Retrospective Cohort Study

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Change of indocyanine green clearance ability and liver function after transcatheter intra-arterial therapies and its impact on outcomes of resectable hepatocellular carcinoma: a retrospective cohort study

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Background: Indocyanine green (ICG) clearance test is a classical measurement of hepatic reserve, which involves surgical safety and patient recovery of hepatocellular carcinoma (HCC). The authors aim to compare effects of hepatic arterial infusion chemotherapy (HAIC) and transcatheter arterial chemoembolization (TACE) on liver function and outcomes of subsequent hepatectomy.

Material and methods: HCC patients receiving HAIC/TACE in SYSUCC with repeated ICG clearance tests were retrospectively enrolled. ICG eliminating rate (ICG-K), ICG retention rate at 15 min (ICG-R15) and ordinary laboratory tests were collected. Peri-therapeutic changes of values were compared between the groups. Propensity score matching (PSM) and inverse probability of treatment weighing (IPTW) were employed to validate findings. Post-hepatectomy liver failure (PHLF), overall survival (OS) and recurrence-free survival (RFS) were analyzed in patients with subsequent curative hepatectomy.

Results: Two hundred and four patients treated with HAIC ($n = 130$) and TACE ($n = 74$) were included. ΔICG-R15 was greater in the HAIC arm before matching (mean, 3.8% vs. 0.7%, $P < 0.001$), after PSM (mean, 4.7% vs. 1.1%, $P = 0.014$) and IPTW (mean, 2.0% vs. –3.6%, $P < 0.001$). No difference was found for ΔALB, ΔALBI, ΔTBIL, ΔALT, ΔAST and ΔPT-INR. Multivariable analyses revealed elder age, cirrhosis, HAIC, greater ΔTBIL and ΔALBI were associated with deteriorating ICG-R15. Among those (105 for HAIC and 48 for TACE) receiving hepatectomy, occurrence of grade B/C PHLF (4.8% vs. 8.3%, $P = 0.616$), OS (median, unreached vs. unreached, $P = 0.94$) and RFS (median, 26.7 vs. 17.1 months, $P = 0.096$) were comparable between the two arms. In subgroup analyses, preoperative HAIC yield superior RFS (median, 26.7 vs. 16.2 months, $P = 0.042$) in patients with baseline ICG-R15 less than or equal to 10%.

Conclusion: Preoperative FOLFOX-HAIC caused apparent impairment of ICG clearance ability than TACE yet comparable impact on liver function and post-hepatectomy outcomes.

Keywords: Hepatectomy, hepatocellular carcinoma, indocyanine green clearance test, liver function, transcatheter intra-arterial therapy

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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Introduction

To date, liver cancer is the sixth most common malignancy and the third leading cause of cancer-related mortality worldwide[1]. In China, its incidence ranks the fourth among malignant tumours, and it is the third most common cause of cancer-related deaths[2]. As the major histological subtype, hepatocellular carcinoma (HCC) accounts for 75–85% of cases of primary liver cancer around the globe[1,3,4]. Liver resection (LR) is the main option of radical therapy for HCC, given technical limitations for tumour ablation and shortage of donors for liver transplantation. However, the proportion of surgical candidates is quite limited (~5–10%), due to the strict criteria of curative LR[5]. The European Association for the Study of the Liver (EASL) conservatively recommends HCC patients with single tumour and preserved liver function as candidates for hepatectomy, whereas the American Association for the Study of Liver Disease (AASLD) holds the resection criteria to stage BCLC 0/A[6,7].

Regarding intermediate and advanced HCC cases, upfront LR didn't confer better survival to patients compared with transcatheter intra-arterial and/or systemic therapies[6–8]. Transcatheter intra-arterial therapies (TRITs) are mainly comprised of transcatheter arterial chemoembolization (TACE) and hepatic arterial infusion chemotherapy (HAIC) with the respect of HCC management[9]. TACE is recommended as the first-line treatment for intermediate-stage HCC[6–8]. It is acknowledged that TACE can achieve prolonged overall survival for intermediate-stage HCC patients with preserved liver function[10], yet its efficacy is largely dependent on tumour burden[11]. As a novel treatment means based on oxaliplatin plus fluorouracil/leucovorin (FOLFOX), HAIC has shown a good efficacy on unresectable large HCC[12,13]. The development of HAIC is supposed to provide new options for neoadjuvant therapy by clinicians[14].

In recent years, neoadjuvant/conversion therapies were widely adopted for a variety of solid tumours, greatly improving patients' survival time and life quality[15–18]. As for HCC, despite nascent by comparison, preoperative therapies including TRITs, radiotherapy and systemic therapy were investigated with the aim to convert unresectable tumours into resectable ones[10,19,20]. The unresectability of HCC can be divided into two categories: technical unresectability and biological unresectability[10]. The former is defined by patient's intolerance to surgical trauma due to their general condition, liver function, or insufficient remnant liver volume (RLV). The latter refers to unimproved efficacy compared with non-surgical treatment. Through conversion therapy, it is likely to reduce tumour burden or other oncological factors and thus to promise sufficient RLV to support patients' recovery in case of postoperative complications, especially post-hepatectomy liver failure (PHLF). For those with surgically resectable yet biologically unresectable HCC, preoperative therapies may contribute to better long-term survival[15].

As mentioned above, either TACE or HAIC has demonstrated favourable anti-tumour efficacy and promising significance for cancer conversion. Despite this, locoregional therapies including TACE and HAIC might adversely impair liver function to a certain degree[14,21]. Liver damage would inevitably increase risks of adverse events. On the other hand, FOLFOX-HAIC could yield higher conversion rate in large HCC than TACE, while whether it achieved more preserved liver function compared with TACE remains unclear[13,22]. When evaluating the feasibility and safety of LR, it is crucial that any radical treatment should not be applied at the expense of severe impairment of liver function for maximation of life expectancy and quality[23]. As a non-invasive method, indocyanine green (ICG) clearance test is a classical tool to evaluate hepatic reserve (HR) and predict PHLF[6–8,24]. The Chinese guidelines have defined prerequisites for LR as follows: Child-Pugh score A, indocyanine green retention rate at 15 min (ICG-15) less than 30%, and CT-based RLV of at least 40% (cirrhotic patients) or 30% (non- cirrhotic patients)[8]. To better tailor neoadjuvant/conversion treatment, it is of great importance to figure out the influence of HAIC or TACE on ICG clearance ability and general liver function. To our best knowledge, no previous research has made such an investigation.

In this study, we aimed to explore how FOLFOX-HAIC or TACE affect ICG clearance ability and liver function. In addition, we preliminarily analyzed survival outcomes of patients who finally received curative hepatectomy.

HIGHLIGHTS

- Acute deterioration of liver function was induced by both FOLFOX-HAIC and transcatheter arterial chemoembolization (TACE), yet could be tolerated and restored in a short term.
- Indocyanine green clearance ability deteriorated more significantly in HAIC-treated patients than TACE. However, other parameters involving liver function showed no difference between the two groups.
- Preoperative FOLFOX-HAIC resulted in comparable overall survival and better recurrence-free survival in patients with benign hepatic reserve than TACE.

Material and methods

Study design and participants

This single-centre retrospective cohort study obtained approval (approval number: B2022-758-01) from ethics committee of Sun Yat-sen University Cancer Center (SYSUCC) and was performed according to ethnical guidelines of Declaration of Helsinki. In addition, it has been registered with the unique identifying number: ChiCTR2300076241, https://www.chictr.org.cn/ show proj.html?proj=208162. We reported this work in line with the STROCSS criteria and provided a completed checklist[25], Supplemental Digital Content 1, http://links.lww.com/JS9/B940.

Clinical information of patients who were first admitted between 1 January 2018 and 31 August 2022 was collected from the medical database of SYSUCC. The flowchart of patient inclusion is shown in Fig. 1. The inclusion criteria were as follows: (1) clinically diagnosed as HCC according to both AASLD and CNLC guidelines[6,7]; (2) underwent FOLFOX-HAIC or TACE as initial treatment for HCC; (3) received at least two ICG tests, before and after TRITs. The exclusion criteria were as follows: (1) pathologically not diagnosed as HCC; (2) combined with other malignancies; (3) received other locoregional treatment between two adjacent ICG clearance tests, e.g., surgery, ablation, radiotherapy; (4) underwent both HAIC and TACE, or other intra-arterial therapy; (5) Incomplete data. Patients were then divided into the HAIC group and the TACE group according to their treatment regimens.

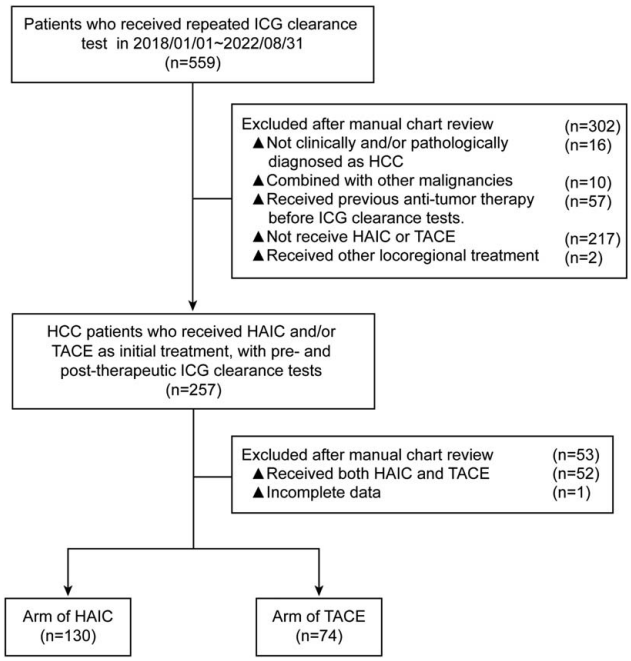

Figure 1. Flowchart of patient selection. HAIC, hepatic arterial infusion chemotherapy; HCC, hepatocellular carcinoma; ICG, Indocyanine green; TACE, transcatheter arterial chemoembolization.

Treatments

Protocols of FOLFOX-HAIC and TACE were previously described[26,27]. Each time after admission, patients routinely received blood tests for assessment of therapeutic contraindications. These tests included complete blood cell count, liver function test, renal function test, cardiac enzymes, coagulation tests, etc. al. Blood tests were also ordinarily performed at 1–3 days and 3–4 weeks after HAIC or TACE. For those who underwent at least two cycles of TRITs, the period between two treatment cycles were generally controlled for around 3–5 weeks. Based on the intraoperative digital subtraction angiography (DSA) and post-treatment reexaminations by enhanced Contrast-enhanced computed tomography (CT) and/or MRI, a multidisciplinary consultation would be organized to evaluate tumour conditions and seize surgical opportunities. All subjects ($n = 204$) included in this study had ICG clearance tests before and after TRITs, while the latter were majorly done before LR ($n = 152$). Postoperative complications were intensively monitored till 30 days after surgery and timely treated if occurred.

Study variables and follow-up

For all variables, baseline levels were defined as the testing results closest to the first TRIT within 7 days. Post-therapeutic levels included laboratory tests after each treatment cycle and before other treatment regimens. The primary outcome was impairment of HR revealed by ICG clearance test compared with baseline. The ICG clearance test was performed by ICG pulse spectrophotometry using a DDG-3300K device (Nihon Kohden) after a dose of 0.5 mg/kg ICG (Yichuang Pharmaceutical Co. Ltd.) dissolved in distilled water was injected through antecubital veins[28]. Two parameters were measured: plasma disappearance rate (ICG-K [/min]) and indocyanine green retention at 15 min (ICG-R15 [%]). For grading of HR deterioration, ICG-R15 $\leq 10\%$, $10\% <$ to $\leq 20\%$, $20\% <$ to $\leq 30\%$, $> 30\%$ indicated normal, mild, moderate and severe deterioration, respectively[29,30]. Secondary outcomes included deterioration of ordinary laboratory values involving liver function in the acute and subacute periods (< 3 d and 25–35 days after treatment, respectively), including total bilirubin (TBIL[μmol/l]), albumin (ALB[g/dl]), alanine aminotransferase (ALT[U/l]), aspartate aminotransferase (AST[U/L]), international normalized ratio of prothrombin time (PT-INR) and albumin-bilirubin (ALBI) scores. ALBI scores were calculated by the following algorithm: $\text{ALBI} = \log_{10}(\text{TBIL})*0.66 + \text{ALB}*(-0.085)$. For ALBI grading, grades 1, 2, 3 corresponds to ALBI score ≤ -2.60, <-2.60 to ≤ -1.39, > -1.39, respectively[31].

For patients who finally underwent LR, PHLF was monitored according to the definition and grading by the International Study Group of Liver Surgery[32]. In addition, overall survivals (OS, defined as the duration between date of surgery and date of death of any cause or lost follow-up) and recurrence-free survivals (RFS, defined as the interval between surgery and date of recurrence or death of any cause or lost follow-up, which occurred first) of these subjects were calculated. Generally, surgical patients discharged from our institution were followed up once every 3 months for the first year and then every 3–6 months for the future years[33]. Enhanced CT and/or MRI were the major tools for tumour surveillance. The date of last follow-up was 28 February 2023.

For the 145 patients who received hepatectomy, future liver remanent (FLR) were calculated using LiverMRDoc (SHUKUN), an artificial intelligence software for three-dimensional reconstruction and segmentation for liver and vessels with their MRI images within 2 months after surgery. Standard liver volume (SLV [ml]) was calculated using the formula: $706.2 \times$ body surface area (BSA [m^2]) $+ 2.4$[34]. The value of dividing FLR by SLV (FLR/SLV) was used to reflect the remaining volume of liver.

Statistical analyses

Unpaired *t*-test was applied to compared homogeneous and normally distributed continuous variables between two groups, otherwise the Wilcoxon rank-sum test was used. For before and after comparison of continuous variables in a single group, paired *t*-test or Wilcoxon signed rank test was applied, depending on data distribution. Categorized variables were compared by χ^2 test or Fisher's exact test, according to the level of measurement. Rank-sum linear correlation and locally weighted regression (LOESS) scatterplots were used to demonstrate the associations of ICG eliminating parameters with other laboratory values. The effects of factors on escalation of impairment grade of ICG clearance ability were assessed using univariable and multivariable logistic regression model. Cumulative OS and RFS were calculated using Kaplan–Meier (K–M) method and compared by Log-rank test. Factors associated with survival were identified using the Cox proportional hazards model. Preoperative ICG-R15 levels, FLR/SLV as well as variables with *P* less than 0.1 in the univariable analyses were further included in multivariable Cox analyses. Besides, candidate variates to be included in multivariate regression models were tested for collinearity. Variates with apparent collinearity were appropriately deleted.

Given the unsatisfying balance of baseline characteristics between the groups, propensity score matching analysis (PSM)

and inverse probability of treatment weighting (IPTW) were applied to validate our findings. The propensity scores were calculated based on a logistic regression model including age, tumour size, vascular invasion, number of therapeutic cycles, time from the closest TRIT to the last ICG clearance test (TII). For PSM, patients in the HAIC and the TACE groups were matched in a 2:1 ratio using the nearest neighbour matching algorithm with a caliper of 0.05 without replacement. For IPTW, patients in the two groups were weighted with inverse propensity scores and inverse of 1 minus the propensity scores, respectively.

In all statistical analyses, a two-tail P less than 0.05 was defined as statistically significant. Statistical analysis was performed using Excel 2019 (Microsoft) and SPSS Statistics software version 22.0 (IBM). Figures were produced using the R package ggplot2 and optimized using Illustrator 2020 (Adobe).

Results

Patient characteristics

A total of 204 consecutive HCC patients met the criteria of this study. The baseline characteristics of the HAIC group ($n = 130$) and the TACE group ($n = 74$) were demonstrated in Table 1. Patients of the HAIC group were characterized with younger age, larger tumour size, more vascular invasion, longer treatment courses, prolonged TII than the TACE group. PSM generated 50 and 35 patients in the HAIC and TACE groups, respectively. ITPW simulated 199 and 258 patients in the HAIC and TACE groups, respectively. After PSM and IPTW, the baseline characteristics of the two groups were better balanced (Table 1).

Before treatment, 10.8% patients (14/130) in the HAIC arm and 20.3% patients (15/74) in the TACE arm were observed with impaired HR (ICG-R15 > 10%) ($P > 0.05$). On multivariable logistic regression analysis, larger tumour size, elevated serum TBIL levels and elevated ALBI scores were independent factors associated with baseline ICG-R15 greater than 10% (Table S1, Supplemental Digital Content 2, http://links.lww.com/JS9/B941).

Liver function and ICG clearance test at baseline and after HAIC or TACE

As shown in Table 2, nearly all parameters were deteriorated in the acute period after the first cycle of TRITs. Levels of TBIL, ALT, AST and PT-INR were restored to baseline levels in the subacute period and afterwards. In contrast, during the treatment cycles, ALB and ALBI scores were continuously impaired compared with baseline.

Significant worsening of ICG clearance ability in the HAIC group was observed before (mean ICG-K, from 0.222 to 0.183; $P < 0.001$) and after PSM (mean ICG-K, from 0.217 to 0.173; $P < 0.001$) (Fig. 2A). In the TACE group, a slighter change was seen in PSM-matched subjects (mean ICG-K: before PSM, from 0.205 to 0.194, $P = 0.053$; after PSM, from 0.217 to 0.203, $P = 0.012$). Before treatment, the proportions of patients with normal clearance ability (ICG-R15 ≤ 10%) were comparable in the HAIC and TACE groups (before PSM, 89.2% vs. 79.7%, $P = 0.062$; after PSM, 86.0% vs. 82.9%, $P = 0.692$) (Table 1; Fig. 2B). After TRITs, a significant rise of impaired ICG clearance ability (ICG-R15 > 10%) was seen in the HAIC group (before PSM, from 10.8 to 34.6%, $P < 0.001$; after PSM, from 14.0 to 40.0%, $P = 0.003$) than the TACE group (before PSM, from 20.3 to 25.7%, $P = 0.434$; after PSM, from 17.1 to 17.1%, $P = 1.000$) (Fig. 2B). The proportion of patients with impaired ICG clearance ability in the HAIC group eventually surpassed the TACE group (before PSM, 34.6% vs. 25.7%, $P = 0.186$; after PSM, 40.0% vs. 17.1%, $P = 0.024$) (Fig. 2B).

Change of ICG-R15 was significantly more marked in the HAIC group than the TACE group before matching (mean, 3.8% vs. 0.7%, $P < 0.001$), after PSM (mean, 4.7% vs. 1.1%, $P = 0.014$) and after IPTW (mean, 2.0% vs. −3.6%, $P < 0.001$) (Table 3). However, no significant difference was found for ΔTBIL, ΔALB, ΔALBI, ΔALT, ΔAST and ΔPT-INR between the two groups (Table 3). The more marked deterioration of serum ALB and ALBI in the HAIC group was observed in the subacute phase after the first cycle. As cycles of treatment increased, injuries of liver function in the HAIC group showed a tendency of gradual recovery (Figure S1, Supplemental Digital Content 3, http://links.lww.com/JS9/B942).

Correlation between ICG clearance ability and laboratory parameters

We further detected whether conventional laboratory indexes were consistent with ICG clearance test in terms of reflecting worsening HR. At baseline, decreased serum ALB (Spearman's $\rho = 0.40$, 95% CI: 0.27–0.51, $P < 0.001$) or increased ALBI scores (Spearman's $\rho = 0.34$, 95% CI: 0.21–0.46, $P < 0.001$) were significantly associated with worse ICG clearance ability (Fig. 3A and B). Multivariate logistic regression showed larger tumour size, elevated serum TBIL levels and decreasing serum ALB levels were independent factors for baseline ICG-R15 greater than 10% in patients with ALBI grade 1 liver function (Table S2, Supplemental Digital Content 4, http://links.lww.com/JS9/B943). However, post to TRITs, correlation between ΔICG-K and ΔALB (Spearman's $\rho = 0.13$, 95% CI: $7.15e^{-3}$ – 0.27; $P = 0.06$) or ΔALBI (Spearman's $\rho = 0.16$, 95% CI: 0.02–0.29; $P = 0.03$) was poor (Fig. 3B-D). LOESS correlation analyses depicted no explicit association between ΔALB/ΔABLI and ΔICG-K/ΔICG-R15 (Fig. 3E). Intriguingly, ΔALB or ΔABLI being equal, variations of ICG-K and ICG-R15 in the HAIC group maintained greater than the TACE group. Upon multivariate logistic regression analyses, elder age [odds ratio (OR), 1.069; 95% CI, 1.028–1.111; $P = 0.001$], cirrhosis (OR, 3.303; 95% CI, 1.373–7.946; $P = 0.008$), HAIC (OR, 4.730; 95% CI, 1.937–11.546; $P = 0.001$), greater ΔTBIL (OR, 1.069; 95% CI, 1.007–1.136; $P = 0.028$) and ΔABLI scores (OR, 2.654; 95% CI, 1.050–6.708; $P = 0.039$) were independent predictors for escalation of impairment degree of ICG clearance ability after TRITs (Table 4).

Outcomes of patients who received hepatectomy

After TRITs, a total of 153 patients (105 of the HAIC group and 48 of the TACE group) finally underwent hepatectomy, and the others received ablation or palliative therapies (Figure S2A-C, Supplemental Digital Content 5, http://links.lww.com/JS9/B944). The baseline characteristics of patients who underwent curative LR were summarized in Table S3, Supplemental Digital Content 6, http://links.lww.com/JS9/B945. There was no inter-group disparity for times of vessel clamping, duration of maximal vessel clamping, intraoperative blood loss and postoperative hospitalization (Table S3, Supplemental Digital Content 6, http://links.lww.com/JS9/B945). No significant difference of occurrence of Grade B PHLF was observed between the two groups (4.8% of

Table 1

Baseline characteristics of patients who underwent transcatheter intra-arterial therapies.

	HAIC ($n=130$)	TACE ($n=74$)	*P*	PSM adjusted *P*	IPTW adjusted *P*
Age, years			<0.001	0.542	0.539
Mean (SD)	52 (10)	57 (11)			
Median (IQR)	53 (45, 60)	59 (52, 67)			
Sex, *n* (%)			0.343	0.569	0.455
Male	118 (90.8)	64 (86.5)			
Female	12 (9.2)	10 (13.5)			
BMI, kg/m^2			0.437	0.772	0.417
Mean (SD)	22.6 (3.6)	22.2 (5.8)			
Median (IQR)	22.5 (20.0–24.6)	23.1 (20.8–25.4)			
BSA, m^2			0.843	0.926	0.806
Mean (SD)	1.75 (0.16)	1.76 (0.17)			
Median (IQR)	1.73 (1.65–1.84)	1.74 (1.63–1.89)			
HBV/HCV infection, *n* (%)	124 (95.4)	71 (95.9)	1.000	1.000	0.239
Cirrhosis, *n* (%)	83 (63.8)	54 (73.0)	0.182	0.206	0.111
Child-Pugh score, *n* (%):			0.161	0.486	0.286
5	114 (87.7)	67 (90.5)			
6	12 (9.2)	7 (9.5)			
7	4 (3.1)	0			
Largest tumour size, cm			<0.001	0.738	0.364
Mean (SD)	8.9 (3.2)	5.5 (2.9)			
Median (IQR)	8.7 (6.8–10.7)	5.0 (3.7–6.2)			
Tumour number, *n* (%)			0.407	0.926	0.545
≤3	108 (83.1)	58 (78.4)			
>3	22 (16.9)	16 (21.6)			
Tumour location, *n* (%)			0.156	0.237	0.353
Right lobe alone	13 (10.0)	3 (4.3)			
Left lobe alone	5 (3.8)	3 (4.1)			
Middle lobe alone	38 (29.2)	16 (21.6)			
Right and middle lobe	61 (46.9)	30 (40.5)			
Left and middle lobe	8 (6.2)	5 (6.8)			
Bilateral	5 (3.8)	10 (13.5)			
Vascular invasion, *n* (%)	69 (53.1)	12 (16.2)	<0.001	0.067	0.073
Extrahepatic metastasis, *n* (%)	12 (9.2)	1 (1.4)	0.055	0.404	0.020
Biliary obstruction, *n* (%)	16 (12.3)	4 (5.4)	0.111	0.752	0.579
Treatment courses			<0.001	0.362	0.647
1–2 courses	83 (63.8)	72 (97.3)			
3–4 courses	44 (33.8)	2 (2.7)			
5 courses and more	3 (2.3)	0			
Combined treatment of HCC, *n* (%)			0.762	0.828	0.019
None	112 (86.2)	67 (90.5)			
Target therapy	8 (6.2)	4 (5.4)			
Immuno-therapy	4 (3.1)	1 (1.4)			
Target and immune therapy	6 (4.6)	2 (2.7)			
TBIL, μmol/l			0.123	0.102	0.343
Mean (SD)	15.7 (8.0)	13.9 (5.3)			
Median (IQR)	14.0 (11.4, 18.4)	13.1 (10.3, 17.0)			
ALB, g/dl			0.761	0.570	0.025
Mean (SD)	42.5 (3.9)	42.7 (3.6)			
Median (IQR)	42.5 (40.1, 44.9)	42.8 (40.3, 45.2)			
ALT, U/l			0.528	0.099	0.387
Mean (SD)	49.1 (35.6)	53.5 (43.1)			
Median (IQR)	40.1 (26.3, 60.1)	44.2 (28.2, 60.1)			
AST, U/l			0.073	0.108	0.494
Mean (SD)	56.2 (32.1)	50.6 (32.7)			
Median (IQR)	46.5 (34.8, 68.2)	39.4 (30.3, 59.8)			
PT-INR			0.601	0.661	0.156
Mean (SD)	1.05 (0.11)	1.05 (0.07)			
Median (IQR)	1.04 (1.00, 1.09)	1.05 (1.01, 1.10)			
TII, weeks			<0.001	0.145	0.792
Mean (SD)	6.4 (3.6)	8.9 (5.8)			
Median (IQR)	5.7 (4.3, 7.0)	6.7 (6.0, 8.2)			

Table 1

(*Continued*)

	HAIC ($n=130$)	TACE ($n=74$)	*P*	PSM adjusted *P*	IPTW adjusted *P*
EHBF, L/min			0.354	0.335	0.589
Mean (SD)	1.111 (0.450)	1.030 (0.397)			
Median (IQR)					
Median (IQR)	1.014 (0.783, 1.406)	0.990 (0.725, 1.258)			
ICG-K, /min			0.060	0.976	0.231
Mean (SD)	0.222 (0.064)	0.205 (0.062)			
Median (IQR)	0.221 (0.177, 0.258)	0.205 (0.160, 0.252)			
ICG-R15, (%)			0.128	0.778	0.127
Mean (SD)	5.4 (6.1)	7.0 (6.7)			
Median (IQR)	3.7 (2.1, 7.0)	4.7 (2.3, 9.1)			
Impairment of hepatic reserve, *n* (%)			0.075	0.810	0.408
Normal (ICG-R15 ≤ 10%)	116 (89.2)	59 (79.7)			
Mild (10% < ICG-R15 ≤ 20%)	11 (8.5)	9 (12.2)			
Moderate (20% < ICG-R15 ≤ 40%)	2 (1.5)	6 (8.1)			
Severe (ICG-R15 > 40%)	1 (0.8)	0			
ALBI scores			0.882	0.845	0.076
Mean (SD)	− 3.03 (0.35)	− 3.02 (0.33)			
Median (IQR)	− 3.02 (− 3.28, − 2.79)	− 2.99 (− 3.27, − 2.75)			
ALBI grading, *n* (%)			0.957	0.222	0.173
1	118 (90.8)	67 (90.5)			
2	12 (9.2)	7 (9.5)			

ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BSM, body surface area; EHBF, effective hepatic blood flow; HAIC, hepatic arterial infusion chemotherapy; ICG-K, plasma disappearance rate of indocyanine green; ICG-R15, indocyanine green retention at 15 min; IPTW, inverse probability of treatment weighting; IQR, interquartile range; PSM, propensity scores matching; PT-INR, international normalized ratio of prothrombin time; TACE, transcatheter arterial chemoembolization; TBIL, total bilirubin; TII, time from the last intra-arterial treatment cycle to the following ICG clearance test.

the HAIC group vs. 8.3% of the TACE group, $P=0.616$) (Figure S2D, Supplemental Digital Content 5, http://links.lww.com/JS9/B944). No Grade C PHLF and perioperative death occurred in both groups.

We further analyzed survival of the 145 patients who received curative LR (97 of HAIC group and 48 of TACE group, Figure S2B5, http://links.lww.com/JS9/B944). The median follow-up time was 20.7 (interquartile range: 9.2–37.4) months. Both groups didn't reach median OS by the end of the follow-up ($P=0.94$, Fig. 4A). Median RFS was 26.7 (95% CI: 15.4–NA) months in the HAIC arm and 17.1 (95% CI: 9.4–40.6) months in the TACE arm ($P=0.096$, Fig. 4B). For patients with baseline normal ICG clearance ability ($n=131$), no difference of OS was observed between the two groups (median OS unreached in both groups, $P=0.42$; Figure S3A, Supplemental Digital Content 7, http://links.lww.com/JS9/B946). Patients of the HAIC group showed better RFS than those of the TACE group, median RFS of 26.7 (95% CI: 15.4–NA) months vs. 16.2 (95% CI: 8.1–25.8) months ($P=0.042$, Figure S3B, Supplemental Digital Content 7, http://links.lww.com/JS9/B946). For patients with preoperatively normal ICG clearance ability ($n=104$), no significant difference of OS was observed (median OS unreached in both groups, $P=0.24$; Figure S3C, Supplemental Digital Content 7, http://links.lww.com/JS9/B946). Patients of the HAIC group showed significantly better RFS than those of the TACE group, median RFS of unreached versus 13.6 months (95% CI: 6.2–25.8 mo) ($P=0.02$, Figure S3D, Supplemental Digital Content 7, http://links.lww.com/JS9/B946). Univariate and multivariate Cox regression analyses identified histological differentiation as an independent prognostic factor for OS (Table S4, Supplemental Digital Content 8, http://links.lww.com/JS9/B947); while preoperative prothrombin time and tumour location were associated with RFS (Table S5, Supplemental Digital Content 9, http://links.lww.com/JS9/B948).

Discussion

HCC is one of the most lethal neoplasms, with more than 50% of cases were presented with advanced diseases at diagnosis, which portends a poor prognosis[3,4]. TACE is the current standard-of-care therapy for intermediate-stage HCC, while FOLFOX-HAIC has shown superiority in patients with large unresectable tumours[6–8,13]. Despite bright prospects brought for neoadjuvant or conversion therapy, effects of TRITs on hepatic functional reserve as well as the outcomes of HCC who received subsequent hepatectomy remain unclear. It lacks consensus on the evaluation of HR of patients who underwent preoperative therapies, which brought challenges for neoadjuvant/conversion TRITs. ICG clearance test is the standard preoperative examination for the assessment of HR in east Asia[6–8,24]. To our best knowledge, this study is the first to demonstrate that FOLFOX-HAIC led to sharper yet tolerable impairment of ICG clearance ability compared with TACE.

There is a variety of tests for the assessment of liver function, including conventional liver function tests, Child-Pugh scoring, ALBI scores and ICG clearance test[35,36]. Among the multiple parameters about liver function, we observed ICG-K, ICG-R15, ALB and ALBI scores were the ones apparently deteriorated after TRITs. In contrast, laboratory values including TBIL, ALT, AST and PT-INR were restored to baseline levels soon after the first treatment cycle. These values, whose performance individually is poor and reflected a temporarily acute loss of liver function[37–39], are superficial compared with ALBI scores and ICG clearance test in evaluating HR. As is well known, ALBI score is a favourable measurement by healthcare scientists due to its objectivity and

Table 2

Laboratory values at baseline and in the acute and subacute phase following each treatment course of HAIC or TACE.

Treatment course	TBIL, μmol/L		Albumin, g/dl		ALT, U/L		AST, U/L		PT-INR		ALBI	
	Mean (SD)		Mean (SD)		Mean (SD)		Mean (SD)		Mean (SD)		Mean (SD)	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)
HAIC group (n=130)												
1A (n=129)	15.6 (8.0)	20.5 (10.7) §	42.5 (3.9)	36.4 (3.4) §	49.3 (35.6)	81.6 (77.8) §	56.4 (32.1)	132.8 (129.6) §	1.03 (0.08)	1.05 (0.11)	-3.02 (0.35)	-2.26 (0.30) §
1S (n=129)	15.7 (8.1)	11.7 (4.7) §	42.5 (4.0)	39.6 (3.7) §	48.8 (35.6)	41.1 (33.3) ¶	56.2 (32.2)	56.4 (41.2)	1.05 (0.11)	1.03 (0.10) ǂ	-3.03 (0.35)	-2.68 (0.35) §
2A (n=127)	15.6 (8.1)	15.1 (7.3)	42.5 (4.0)	35.1 (3.5) §	48.7 (35.5)	58.5 (59.6)	56.4 (32.2)	102.5 (83.6) §	1.04 (0.08)	1.05 (0.09)	-3.03 (0.36)	-2.23 (0.29) §
2S (n=128)	15.6 (8.1)	12.4 (7.0) §	42.5 (4.0)	40.2 (3.2) §	49.1 (35.5)	43.5 (45.2) ¶	56.4 (32.1)	55.6 (48.3)	1.05 (0.08)	1.02 (0.08) §	-3.03 (0.36)	-2.73 (0.32) §
3A (n=47)	16.1 (10.9)	16.7 (11.6)	41.9 (3.9)	34.8 (2.9) §	52.6 (48.0)	50.6 (54.8)	64.2 (36.9)	83.8 (93.3)	1.04 (0.08)	1.03 (0.09)	-2.97 (0.35)	-2.19 (0.26) §
3S (n=46)	16.0 (11.0)	11.6 (5.3) §	41.9 (3.9)	39.4 (3.4) §	52.9 (48.5)	34.1 (29.3) ¶	64.5 (37.3)	46.4 (20.5) ¶	1.06 (0.08)	1.01 (0.07) §	-2.95 (0.35)	-2.59 (0.58) §
4A (n=42)	16.4 (11.4)	13.7 (6.5)	41.7 (3.8)	34.7 (3.3) §	54.9 (50.2)	42.3 (32.9)	66.3 (38.4)	69.2 (26.8)	1.04 (0.09)	1.04 (0.08)	-2.96 (0.33)	-2.17 (0.46) §
4S (n=43)	16.3 (11.3)	11.6 (4.5) §	41.6 (3.9)	40.5 (3.7)	54.2 (49.8)	30.7 (25.1) ¶	65.6 (38.2)	42.9 (24.5) ¶	1.05 (0.08)	0.99 (0.09) §	-2.94 (0.34)	-2.76 (0.33) ¶
Overall change before PSM (n=130)	15.7 (8.0)	12.4 (5.6) §	42.5 (3.9)	40.3 (3.8) §	49.1 (35.6)	40.0 (43.9) §	56.2 (32.1)	52.6 (54.2) ¶	1.05 (0.11)	1.03 (0.09) ¶	-3.03 (0.35)	-2.73 (0.35) §
Overall change after PSM (n=50)	15.5 (5.8)	13.5 (6.5) ǂ	42.8 (4.4)	40.3 (3.9) §	43.1 (26.9)	39.2 (43.5) ǂ	46.0 (27.0)	50.2 (49.0)	1.04 (0.21)	1.04 (0.10)	-3.05 (0.40)	-2.71 (0.26) §
TACE group (n=74)												
1A (n=74)	13.9 (5.3)	25.3 (13.1) §	42.7 (3.6)	38.0 (3.9) §	53.5 (43.1)	167.5 (186.2) §	50.6 (32.7)	237.1 (343.5) §	1.05 (0.07)	1.16 (0.13) §	-3.02 (0.33)	-2.33 (0.37) §
1S (n=72)	14.1 (5.3)	12.7 (4.9) ¶	42.8 (3.6)	41.2 (4.0) ¶	53.9 (43.7)	46.4 (52.1) ¶	51.2 (33.0)	46.7 (41.2) ǂ	1.05 (0.08)	1.06 (0.11)	-3.03 (0.33)	-2.79 (0.38) §
2A (n=8)	16.0 (5.1)	21.6 (11.0)	45.1 (1.6)	38.2 (2.9) §	39.4 (23.1)	187.9 (195.9) ǂ	36.9 (15.6)	229.2 (209.6) ǂ			-3.27 (0.15)	-2.40 (0.21) §
2S (n=8)	16.0 (5.1)	13.3 (2.9)	45.1 (1.6)	41.4 (4.8) ǂ	39.4 (23.1)	220.3 (532.8)	36.9 (15.6)	229.0 (542.6)	1.03 (0.09)	1.03 (0.09)	-3.27 (0.15)	-2.82 (0.40) ǂ
Overall change before PSM (n=74)	13.9 (5.3)	13.1 (5.4)	42.7 (3.6)	40.7 (3.9) §	53.5 (43.1)	62.8 (177.0) ǂ	50.6 (32.7)	64.2 (180.1)	1.05 (0.07)	1.06 (0.10)	-3.02 (0.33)	-2.74 (0.36) §
Overall change after PSM (n=35)	13.5 (4.9)	12.1 (3.8)	43.3 (3.2)	40.8 (3.7) ¶	54.6 (38.2)	49.3 (43.4)	54.0 (27.6)	52.8 (38.5)	1.05 (0.07)	1.07 (0.12)	-3.07 (0.31)	-2.77 (0.33) §

The red and blue colours denote deteriorated and improved liver function compared with baseline respectively, as reflected by each laboratory value; while the black colour refers to no statistical significance. ALBI, albumin-bilirubin score; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HAIC, hepatic arterial infusion chemotherapy; IIQR, interquartile range; nA, within 3 days (acute phase) post to each treatment course. nS, 28–32 days (subacute phase) post to each treatment course; PT-INR, international normalized ratio of prothrombin time; TACE, transcatheter arterial chemoembolization.

ǂ $P < 0.05$ compared with baseline.

¶ $P < 0.01$ compared with baseline.

§ $P < 0.001$ compared with baseline.

sensitivity, providing granular evaluation of HR regardless of tumour stage. The prognostic significance of ALBI grade has been proved for various HCC treatments, including LR, ablation, intra-arterial therapies and systemic therapies[35,40]. Meanwhile, as a test of hepatic synthetic function, serum ALB has a long half-life of ~20 days. As for ICG clearance test, the median TII of the HAIC group and the TACE group was respectively 5.7 (IQR, 4.3–7.0) and 6.7 (IQR, 6.0–8.2) weeks, mainly distributed across

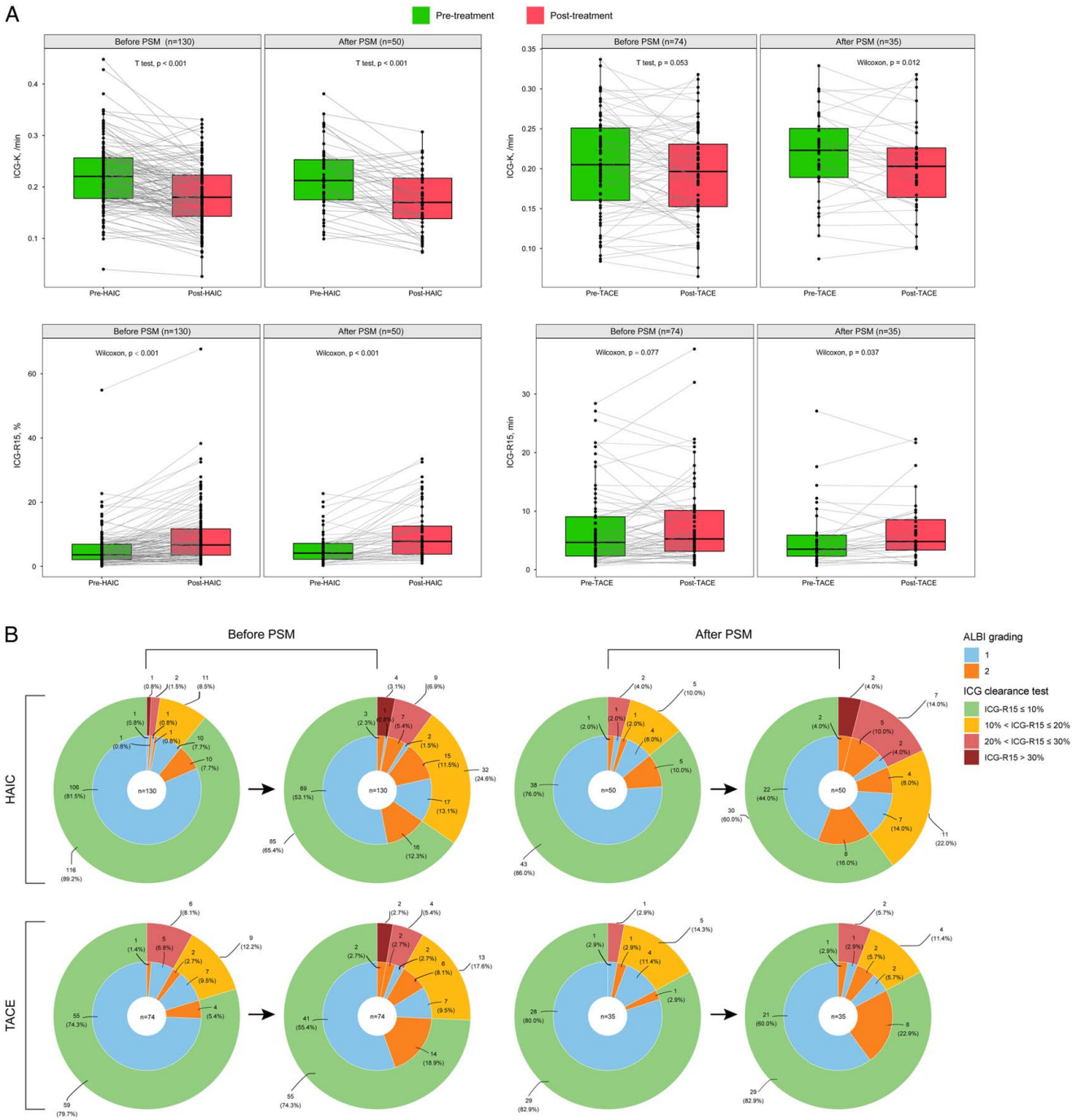

Figure 2. Change of ICG clearance ability and liver function after transcatheter intra-arterial therapies. (A) ICG-K and ICG-R15 before and after FOLFOX-HAIC or TACE. (B) Proportions of patients with unnormal ICG-R15 and ALBI grade 2/3 before and after FOLFOX-HAIC or TACE. ICG-K, plasma disappearance rate of indocyanine green. ALBI, albumin-bilirubin score; HAIC, hepatic arterial infusion chemotherapy; ICG-R15, indocyanine green retention at 15 min; PSM, propensity scores matching; TACE, transcatheter arterial chemoembolization.

subacute phases (Table 1). The deterioration of ICG clearance ability, serum ALB and ALBI scores uniformly indicated somehow chronic impairment of HR in HCC patients after TRITs.

We next investigated the disparity between FOLFX-HAIC and TACE of their effects on HR. However, results from ICG clearance test and ALBI scores diverged from each other. Both ΔALBI scores and ΔALB were comparable between the HAIC and the TACE groups after TRITs, while variation of ICG clearance parameters of the HAIC arm was significantly more substantial than the TACE arm. Possible accounts for this intriguing phenomenon include: (1) HR was indeed superiorly compromised after treatment in the HAIC group versus TACE, since previous research in colorectal liver metastasis confirmed oxaliplatin tends to induce sinusoidal injuries[41]; (2) a misjudgment derived from the fact

Table 3

Change of ICG clearance ability and liver function of patients who underwent transcatheter intra-arterial therapies.

	Before matching			After PSM			After IPTW		
Change of parameters	**HAIC ($n=130$)**	**TACE ($n=74$)**	***P***	**HAIC ($n=50$)**	**TACE ($n=35$)**	***P***	**HAIC ($n=199$)**	**TACE ($n=258$)**	***P***
ΔICG-K, /min	− 0.04 (0.05)	− 0.01 (0.05)	< 0.001	− 0.04 (0.06)	− 0.02 (0.04)	0.027	− 0.02 (0.09)	− 0.20 (0.11)	< 0.001
ΔICG-R15, (%)	3.8 (5.8)	0.7 (4.7)	< 0.001	4.7 (6.6)	1.1 (3.6)	0.014	2.0 (9.9)	− 3.6 (4.6)	< 0.001
ΔTBIL, μmol/l	− 3.2 (8.5)	− 0.8 (5.4)	0.022	− 1.9 (6.8)	− 1.4 (4.2)	0.635	− 2.9 (7.9)	− 1.6 (5.5)	0.384
ΔALB, g/dl	− 2.2 (3.8)	− 2.0 (4.0)	0.318	− 2.5 (4.3)	− 2.4 (4.5)	0.728	− 2.1 (3.9)	− 2.0 (5.0)	0.952
ΔALBI scores	0.29 (0.39)	0.28 (0.41)	0.587	0.34 (0.45)	0.29 (0.43)	0.606	0.30 (0.39)	0.28 (0.46)	0.907
ΔALT, U/l	− 8.2 (57.9)	9.3 (182.4)	0.371	− 3.9 (50.7)	− 5.3 (34.1)	0.758	− 8.8 (56.0)	− 8.7 (128.5)	0.995
ΔAST, U/l	− 3.7 (63.4)	13.6 (184.4)	0.315	4.2 (54.2)	− 1.3 (34.3)	0.658	− 3.2 (63.1)	− 5.6 (131.6)	0.891
ΔPT-INR	− 0.03 (0.17)	0.01 (0.10)	0.022	0.00 (0.20)	0.02 (0.14)	0.314	− 0.03 (0.16)	0.04 (0.16)	0.094

Data are presented as mean (SD) for continuous variables.

ALB, albumin; ALBI, albumin-bilirubin score; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HAIC, hepatic arterial infusion chemotherapy; ICG-K, plasma disappearance rate of indocyanine green; ICG-R15, indocyanine green retention at 15 min; IPTW, inverse probability of treatment weighting; PSM, propensity score matching; PT-INR, international normalized ratio of prothrombin time; SD, standard deviation; TACE, transcatheter arterial chemoembolization; TBIL, total bilirubin.

that ICG was resorbed by tumour tissues, since ICG is a water-soluble anionic compound and has long been applied in real-time navigation for liver surgery[42]; (3) impairment of ICG excretion due to micro-biliary damage, since both TACE and infusion of fluorodeoxyuridine could induce biliary sclerosis and damage[43–46]. Multivariate logistic regression analyses showed larger tumour size and elevated serum TBIL levels (which reflects excretory function of biliary ducts) were independently linked with

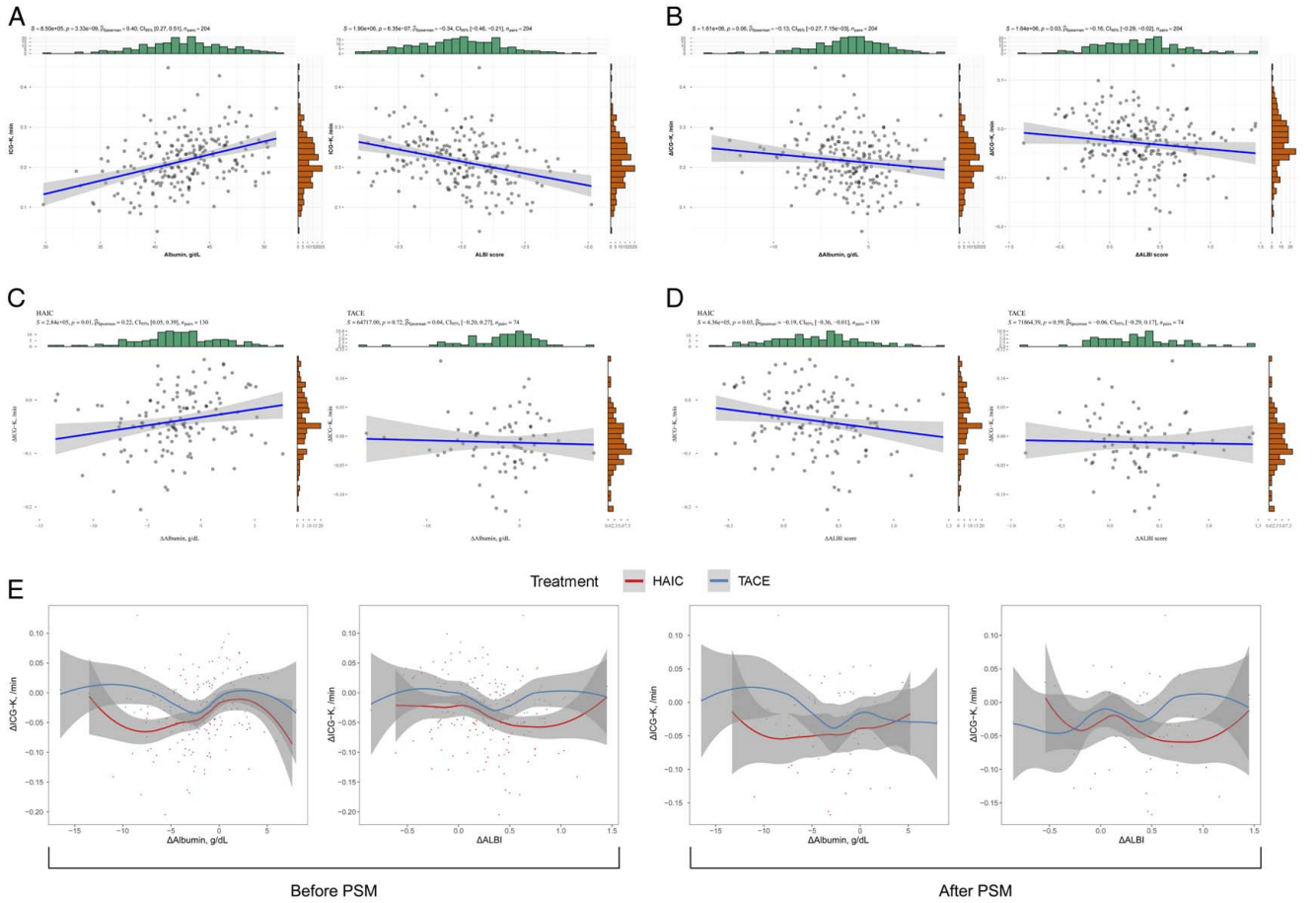

Figure 3. Correlation between ICG delimitating rate and conventional liver functional tests. (A) rank-sum linear correlation between ICG-K5 and serum ALB/ALBI scores in the whole population and FOLFOX-HAIC/TACE groups before treatment. (B) Rank-sum linear correlation between ΔICG-K and ΔALB/ΔALBI in the whole population and FOLFOX-HAIC/TACE groups after treatment. (C) Rank-sum linear correlation between ΔICG-K and ΔALB in the FOLFOX-HAIC and TACE groups after treatment. (D) Rank-sum linear correlation between ΔICG-K and ΔALBI in the FOLFOX-HAIC and TACE groups after treatment. (E) Locally weighted regression scatterplots fitting the association between ΔICG-K and ΔALB/ΔALBI after FOLFOX-HAIC or TACE. ALBI, albumin-bilirubin score; HAIC, hepatic arterial infusion chemotherapy; ICG, Indocyanine green; PSM, propensity scores matching; TACE, transcatheter arterial chemoembolization.

Table 4

Univariate and multivariate logistic regression analyses of baseline predictors associated with escalation of impairment degree of ICG clearance ability following HAIC or TACE.

Variables	OR comparison	UV OR (95% CI)	UV *p* value	MV OR (95% CI)	MV *p* value
Age, years		1.039 (1.008–1.070)	0.014	1.069 (1.028–1.111)	0.001
Sex	Male vs. female	1.705 (0.550–5.283)	0.355		
BMI		1.001 (0.935–1.073)	0.974		
BSA, m^2		0.950 (0.137–6.598)	0.959		
HBV/HCV infection	Yes vs. no	2.986 (0.365–24.448)	0.308		
Cirrhosis	Yes vs. no	3.152 (1.434–6.928)	0.004	3.303 (1.373–7.946)	0.008
Tumor number	>3 vs≤3	0.834 (0.367–1.899)	0.666		
Tumor size, cm		1.003 (0.917–1.097)	0.946		
Tumor location	Overall	NA	0.452		
	Left lobe vs. right lobe	1.760 (0.262–11.835)	0.561		
	Middle lobe vs. right lobe	2.389 (0.779–7.322)	0.128		
	Right and middle vs. right alone	1.600 (0.545–4.700)	0.393		
	Left and middle vs. right alone	0.440 (0.045–4.274)	0.479		
	Bilateral lobes vs. right alone	2.500 (0.224–27.940)	0.907		
Vascular invasion	Yes vs. no	0.955 (0.505–1.805)	0.886		
Extrahepatic metastasis	Yes vs. no	1.253 (0.370–4.250)	0.717		
Biliary obstruction	Yes vs. no	0.670 (0.214–2.101)	0.492		
Treatment	HAIC vs. TACE	2.162 (1.069–4.370)	0.032	4.730 (1.937–11.546)	0.001
Treatment courses	Overall	NA	0.533		
	3~4 vs. 1~2	1.490 (0.727–3.051)	0.276		
	>4 vs. 1~2	1.539 (0.136–17.455)	0.728		
Combined treatment	Overall	NA	0.758		
	Target therapy vs. none	0.546 (0.115–2.581)	0.445		
	Immune therapy vs. none	0.682 (0.074–6.258)	0.735		
	Target and immune-therapy vs. none	1.637 (0.377–7.115)	0.511		
TII, weeks		0.939 (0.861–1.024)	0.155		
ΔTBIL, μmol/L		1.059 (1.002–1.118)	0.042	1.069 (1.007–1.136)	0.028
ΔALB, g/dL		0.965 (0.892–1.045)	0.381		
ΔALT, U/L		1.000 (0.998–1.003)	0.956		
ΔAST, U/L		1.000 (0.997–1.003)	0.775		
ΔPT-INR		0.922 (0.113–7.533)	0.940		
ΔALBI scores		2.475 (1.107–5.532)	0.027	2.654 (1.050–6.708)	0.039
ΔTumor size, cm		0.966 (0.834–1.119)	0.644		

ALB, albumin; ALBI, albumin-bilirubin score; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BSA, body surface area; EHBF, effective hepatic blood flow; HAIC, hepatic arterial infusion chemotherapy; HBV, hepatitis B virus; HCV, hepatitis C virus; ICG, indocyanine green; MV, multivariate; NA, not analyzed; OR, odds ratio; PT-INR, international normalized ratio of prothrombin time; TACE, transcatheter arterial chemoembolization; TBIL, total bilirubin; TII, time from the last intra-arterial treatment cycle to the following ICG clearance test; UV, univariate.

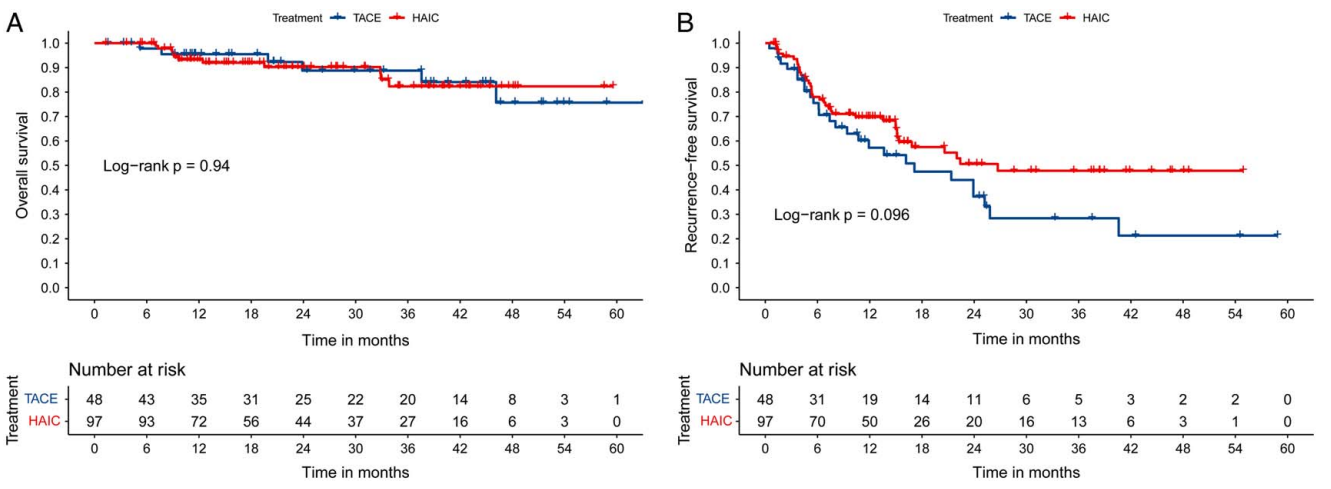

Figure 4. Comparison of cumulative overall (A) and recurrence-free (B) survival curves in patients who underwent neoadjuvant transcatheter intra-arterial therapies and subsequent curative liver resection. HAIC, hepatic arterial infusion chemotherapy; TACE, transcatheter arterial chemoembolization

baseline ICG-R15 greater than 10%. Besides, both HAIC and increasing ΔTBIL were independent factors associated with escalation of deteriorating degree of ICG clearance ability after TRITs. Other factors included old age, cirrhosis and increasing ΔALBI scores, despite ΔALB and ΔALBI didn't explicitly correlate with ΔICG-K. Surely, we didn't suspect the efficacy of either ALBI scores or ICG clearance tests in assessment of liver function. Indeed, before any treatment, ALBI scores were in moderate linear correlation with ICG-K values and strongly associated with impaired ICG clearance ability, consistent with the study by Hiraoka *et al*.[40]. The key of the question is, we speculated that HAIC actually led to a worse deterioration of HR, while the quantification of the changes of liver function by ICG clearance test was disturbed by multiple factors to a certain degree.

Finally, we preliminarily investigate effects of preoperative HAIC or TACE on PHLF and long-term survival of patients who received hepatectomy, since clinical evidence have confirmed that the ICG clearance test is an effective tool for PHLF prediction and establishment of tailored therapeutic strategies[24,30]. In the present study, however, we didn't observe significant difference of occurrence of grade B/C PHLF and OS of patients who underwent curative LR between the HAIC group and the TACE group. With the median follow-up of 20.7 months, the 5-year recurrence rates of the HAIC group after LR were estimated to less than 60%, better than those who underwent purely LR (about 70%)[5–7]. Yet preoperative TACE didn't show such superiority. Univariate and multivariate Cox analyses showed type of preoperative therapies was not independent factor associated with OS or RFS. In subgroup analyses of those with baseline or preoperatively normal ICG-R15, we found preoperative HAIC yield an even better RFS than TACE, despite the larger tumour burden in the HAIC group. FOLFOX-HAIC is an effective and safe regimen in treatment of HCC patients with larger tumour and microscopic vascular invasion (MVI)[13,47], which may defer tumour relapse after curative LR. Briefly, preoperative HAIC was not inferior to TACE in postoperative outcomes, despite its impact on HR.

There are several additional findings in the present study. Notably, we observed liver function didn't exacerbated along repeated FOLFOX-HAIC cycles, which was important for advanced HCC patients who needed a long term of chemotherapy. However, in another study, number of HAIC cycles still showed a positive correlation with postoperative ALBI score and complications[14]. We also found cirrhosis, a typical precancerous disease associated with most cases of HCC oncogenesis and makes liver function fragile, was independently associated with deterioration of HR after transcatheter intra-arterial therapies. What's more, tumours at left liver tended to have poorer RFS after LR.

The present study is inevitably limited by its retrospective nature, small sample size and potential confounders. Although there are currently no standard criteria for the allocation of advanced HCC cases to TACE or HAIC treatment, patients with large tumours (largest diameter $\geq$ 7 cm) or with macrovascular invasion tended to be empirically treated by FOLFOX-HAIC in clinical practice, according to the better survival benefit of these population in previous studies[13,27], which caused the imbalanced tumour biological characteristics of the two groups. Moreover, sufficient data is necessary to determine a clear cut-off value of ICG delaminating ability for those who underwent preoperative FOLFOX-HAIC or TACE. So far, we stuck to the criteria suggested by guidelines for safety evaluation before surgery[6–8], whether or not receiving intra-arterial therapies before. Although TACE is a preferred neoadjuvant/conversion therapy for HCC management especially in East Asia, international consensus has not been reached, let alone the novel application of preoperative FOLFOX-HAIC[19,20]. In view of these, we are looking forward to appropriate powerful prospective studies to resolve the doubts.

Conclusion

FOLFOX-HAIC caused sharper impairment of ICG clearance ability than TACE, yet did not cause superior deterioration in conventional liver function tests, ALBI scores as well as worse outcomes of hepatectomy in patients with HCC. Preoperative FOLFOX-HAIC may yield a better RFS in those who possessed good HR and underwent curative LR. Prospective studies are needed to further confirm the findings.

Ethical approval

This study obtained approval (approval number: B2022-758-01) from ethics committee of the Sun Yat-sen University Cancer Center (SYSUCC) and was performed according to ethnical guidelines of 1975 Declaration of Helsinki. In addition, it has been registered with the unique identifying number: ChiCTR2300076241, https://www.chictr.org.cn/showproj.html?proj=208162.

Consent

This retrospective cohort study has gotten waiver of informed consent from ethics committee of the Sun Yat-sen University Cancer Center (SYSUCC). Patients' privacy will always be protected.

Source of funding

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Author contribution

Conceptualization and design: Y.-X.G. and L.X.; data acquisition: Y.-X.G., Y.-H.T., L.-Y.O.-Y. and L.X.; development of methodology: Y.-X.G., Z.-L.Y., Y.-X.P. and L.X.; analysis and interpretation of data: Y.-X.G. and Z.-L.Y.; drafting the article: Y.-X.G.; figure and Table production: Y.-X.G. and Z.-L.Y.; administrative and technical support: Y.-J.Z., M.-S.C. and L.X.; critical revision and final approval: All authors.

Conflicts of interest disclosure

There are no conflicts of interest.

Research registration unique identifying number (UIN)

1. Name of the registry: Chinese Clinical Trial Registry
2. Unique Identifying number or registration ID: ChiCTR 2300076241

3. Hyperlink to our specific registration: https://www.chictr.org.cn/showproj.html?proj=208162

Guarantor

Li Xu.

Data availability statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Provenance and peer review

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Presentation

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