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Deterioration in liver function after liver-directed therapy for hepatocellular carcinoma measured by cholate clearance

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Summary

Background: Liver-directed therapy (LDT) for hepatocellular carcinoma (HCC) carries a risk of serious liver toxicity, but the risk is not accurately predicted. Our aim is to evaluate the baseline and change in liver function after LDT measured by a potentially more sensitive test than the usual clinical assessment.

Methods: We conducted a prospective cohort study of patients undergoing LDT for HCC. We evaluated cholate clearance at baseline (T0) and 4-10 weeks after (T1) LDT in 11 patients. Hepatotoxicity was defined as the development of a new complication of cirrhosis or an increase in Child score by ≥2 points.

Results: Four patients (36.4%) were Child A and the remainder (63.6%) Child B. Patients were BCLC stage A (63.6%) or BCLC stage B (36.4%). LDT modalities were Transarterial Chemoembolisation (TACE) (45.5%) or external beam radiotherapy (EBRT) (54.5%). From T0 to T1, there was a reduction in oral cholate clearance (4.29 [2.43-15.89] mL/kg/min to 3.58 [2.21-15.68] mL/kg/min, $P = 0.05$) and a trend towards a worsening Disease Severity Index (32.01 [17.11-39.07] vs 33.01 [18.64-40.20], $P = 0.06$); however, there was no significant change in MELD (12 [9-13] vs 11 [10-12], $P = 0.72$), or Child score (7 [5-8] vs 7 [6-8], $P = 0.15$). Hepatotoxicity was observed in 42.9% Child B patients and none of the Child A patients; and in 60.0% patients with a baseline DSI > 35, and none of the patients with DSI < 35.

Conclusions: The dual cholate clearance assay may better define baseline disease severity and may be more sensitive to change in liver function induced by LDT than traditional measures.

1 | INTRODUCTION

Hepatocellular carcinoma (HCC) usually occurs in a background of chronic liver disease, is one of the leading causes of cancer related death worldwide, and the fastest growing cause of cancer related death in men in the United States.[1] Liver-directed therapy (LDT) in the form of transarterial chemoembolisation (TACE), transarterial radioembolisation (TARE) or external beam radiotherapy (EBRT) is the usual treatment for a subgroup of patients, constituting approximately 30%-40% of HCC cases, with unresectable tumours in the absence of extrahepatic disease or vascular invasion.[2]

The premise behind LDT is that therapy would be targeted to the tumour while minimising injury to the non-involved liver. However, while being effective in inducing a tumour response and prolonging survival,[3-5] all modalities of LDT are associated with a risk of hepatotoxicity.[6]

Numerous studies have shown that baseline liver function is the major predictor of hepatotoxicity after LDT.[6-9] Yet, using the clinically available measures of liver function, a well-defined upper limit of liver dysfunction for which the risk of hepatotoxicity outweighs the benefits of LDT is lacking.[9] The current measures of liver function used in clinical practice rely on surrogate markers of liver function obtained upon clinical evaluation and laboratory evaluation of patients with liver disease, rather than a direct measurement of the functional capacity of the liver.

Cholate is a bile acid synthesised and metabolised exclusively by the liver. The dual cholate clearance test (HepQuant -SHUNT®, HQ-SHUNT®) is a functional assay evaluating the hepatic uptake of cholate.[10,11] Cholate clearance was shown to be an independent predictor of the development of future liver-related complications in 227 clinically compensated hepatitis C infected patients with advanced liver fibrosis and cirrhosis, and was found to be more sensitive than the routine clinical assessment in predicting this outcome.[12] Cholate clearance was also found to correlate with the increase in volume of regenerating living donor livers after liver transplant donation.[13] Thus, it appears that the dual cholate clearance assay is capable of detecting subtle abnormalities in liver function that are associated with future significant clinical events.

Therefore, it is plausible that a direct measurement of liver function using HQ-SHUNT® would provide a more sensitive assessment of hepatic reserve prior to LDT and could improve the selection of patients who can safely undergo LDT procedures. The performance of the HQ-SHUNT® assay in the setting of HCC and whether LDT induces a variation in cholate clearance is not known. It is also not known whether the baseline HQ-SHUNT® or change in HQ-SHUNT® is associated with the development of complications of liver disease after LDT.

We hypothesised that LDT would result in a reduction in cholate clearance, as measured by the HQ-Shunt® assay. The goal of the study was to describe the change in dual cholate clearance before and after LDT for in patients with unresectable HCC, and to determine whether the baseline and the change in cholate clearance parameters after therapy are associated with the development of clinical complications of worsening of liver disease after LDT.

2 | METHODS

2.1 | Patient population

Patients with HCC and planned TACE or EBRT were recruited from the multidisciplinary liver tumour clinic at the Hospital of the University of Pennsylvania, between January 2015 and December 2016. The diagnosis of HCC was established according to the American Association for the Study of Liver Disease criteria.[2]

Patients with prior TACE, EBRT or TARE were included if the prior treatment was >4 weeks (TACE) or >12 weeks (TARE or EBRT) prior to enrolment without clinical evidence of liver toxicity. Patients were excluded if they had history of small bowel surgery or disease that may interfere with absorption of oral cholate, history of congestive heart failure or renal dysfunction, portal or hepatic vein thrombosis, Transjugular Intrahepatic Portosystemic Shunt (TIPS), alcohol abuse in the past 6 months, were pregnant or breast feeding, or had an expected survival <6 months. The study was approved by the University of Pennsylvania Institutional Review Board.

2.2 | Cholate clearance assay

The following time points are defined for the purpose of the study:

- Time = T0: between 0 and 6 weeks *before* the date of LDT.
- Time = T1: between 4 and 10 weeks *after* LDT (prior to the next scheduled LDT procedure, if indicated).
- Time = T2: between 12 - 18 weeks *after* the date of LDT.

The following parameters were evaluated at times T0 and T1: history and physical examination, Complete Blood Count, Comprehensive Metabolic Panel, INR, Alpha Fetoprotein, review of tumour characteristics on imaging tests, urine pregnancy test in women of child-bearing age.

The dual cholate clearance test (HQ-SHUNT®) was administered at times T0 and T1 at the Clinical and Translational Research Center of the University of Pennsylvania.

The detailed administration method, and analysis of output data for this assay were previously described.[10,11] Briefly, serum cholate levels are measured at 5, 20, 45, 60, 90 minutes after the oral administration of 40 mg of 2,2,4,4- ^{2}H cholate and simultaneous administration of 20 mg of 24 ^{13}C cholate as an intravenous infusion over 2 minutes. The resulting serum cholate levels were used to calculate the oral and intravenous cholate clearances, cholate shunt (Shunt = AUC(oral)/AUC(IV) × Dose(IV)/Dose(oral)), and the disease severity index (DSI ≈ A × f{[(B − ln(Systemic HFR)) + (C − ln(Portal HFR))]}, where A is a constant for scaling DSI, and B and C are limits

from healthy controls). HFR refers to the Hepatic Filtration Rate of cholate or weight-adjusted cholate clearance.

Test compounds (13C-cholate and d4-cholate) were administered to patients under INDs 65 121 and 65 123. The oral and IV cholate products were formulated by the Penn Investigational Drug Services pharmacy according to the standard operating procedure provided by HepQuant®.

2.3 | Study endpoints

The hepatotoxicity of LDT was assessed at times T1 and T2. For the purpose of this study, treatment-related hepatotoxicity is defined as any of the following: new or worsening ascites (increase in the ascites points described in the Child-Pugh score), new or worsening hepatic encephalopathy (increase in the encephalopathy points in the Child-Pugh score), development of variceal bleeding, development of grade 3 or higher toxicity in serum total Bilirubin, Albumin or INR according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4, May 2009),[14] or increase in Child score by 2 points or more. Patients who met criteria for hepatotoxicity but also had evidence of tumour progression radiographically or with a rising AFP were considered indeterminate for treatment-related hepatotoxicity.

The primary endpoint was the alteration in liver function after LDT, measured by the HepQuant-SHUNT® cholate clearance assay. As an exploratory secondary endpoint, we evaluated the difference in cholate clearance parameters between patients who developed hepatotoxicity by time point T2, and those who did not.

A Wilcoxon Signed Rank test was used to compare continuous variables before and after LDT.

3 | RESULTS

3.1 | Baseline characteristics

Detailed baseline characteristics are listed in Tables 1 and 2.

3.2 | Liver-directed therapy

TACE was performed after selective catheterisation of a third order branch of the hepatic artery. The chemoembolisation mixture consisted of 50 mg doxorubicin and 10 mg mitomycin in 10 mL aqueous solution emulsified in lipiodol. Following delivery of the chemoemulsion, arterial occlusion was achieved by injection of 100-300 micron spheres (Embosphere, Merit Medical, South Jordan, UT). Treatment was delivered to a right hepatic artery branch in four cases (A, B, C, D) and to a left in one case (F).

Radiotherapy was delivered utilising hypofractionated intensity modulated radiation therapy in two patients, stereotactic body radiation therapy (SBRT) in two patients, and proton therapy in two

TABLE 1 Baseline characteristics. Continuous variables are expressed as median (range)

N	11
Female/Male	3/8
African American/ White	2/9
Age, years	61 (51-76)
Etiology of liver disease	HCV: 6/11 (55%) NASH: 3/11 (27%) Alcohol: 2/11 (18%)
Bilirubin, mg/dL	1.5 (0.8-2.1)
Albumin, mg/dL	3.4 (2.5-4.1)
INR[a]	1.3 (1.0-2.6)
History of ascites	Yes: 4/11(36%) No: 7/11 (64%)
History of hepatic encephalopathy	Yes: 4/11 (36%) No: 7/11 (64%)
Child Class	A: 4/11 (36%) B: 7/11 (64%)
Child score	7 (5-9)
MELD score	12 (7-20)
MELD-Na score	12 (7-20)
Number of tumour nodules	2 (1-5)
Largest Tumour size, cm	2.6 (1.2-7.4)
Alpha Foetoprotein (AFP), IU/mL	7 (2-4014)
AFP > 20 IU/mL	3/11 (27%)
Estimated % volume of treated liver[b]	46.5% (19.7%-62.5%)
ECOG performance status	0:6/11 (55%) 1:4/11 (36%) 2:1/11 (9%)
BCLC stage	A: 7/11 (64%) B: 4 /11(36%)

[a]The only patient with INR ≥ 2 was on warfarin for atrial fibrillation.
[b]The % volume of treated liver was estimated using cone beam CT obtained at the time of TACE, or from treatment planning in EBRT cases, as the volume of liver exposed to > 15 Gy divided by total liver volume.

patients. For patients undergoing hypofractionated photon or proton radiation, the mean target prescription dose was 57.5 Gy, with a mean liver dose of 14.2 Gy, with a planning goal of achieving a mean liver dose of < 30 Gy. For the two patients treated with SBRT, the delivered dose was 30 Gy with 864 cc of liver spared of > 15Gy exposure and 50 Gy with 1586 cc spared > 15 Gy, respectively, with a goal of at least 700cc spared.

3.3 | Cholate clearance assays

All 11 patients had a complete dual cholate clearance assay at baseline (T0). Two of 11 patients did not have a complete follow-up assay (T1): in one patient, IV access could not be obtained (patient G); and

TABLE 2 Individual patient data

	Baseline (T0) Child score	T0 MELD score	T0 ECOG	T0 BCLC	T0 AFP (IU/mL)	T0 DSI	Largest tumour size (cm)	N of tumour nodules	Rx	ΔDSI (T0→T1)	ΔChild (T0→T1)	ΔMELD (T0→T1)	ΔAFP IU/mL (T0→T1)	Tumour progression by end of follow up (T2)	Hepatotoxicity by end of follow up (T2)
A	A5	7	0	B	6	17.11	5.7	5	TACE	+1.53	0	0	1	Y[b]	N
B	B8	13	0	A	4	35.87	2.6	3	TACE	—	-1	-3	0	N	N
C	B8	14	1	A	2	35.01	3.3	1	TACE	+1.94	+1	-2	1	Y[b]	N
D	A5	13	0	A	7	26.12	2.4	3	TACE	+3.67	0	-1	0	N	N
E	B9	20[a]	1	A	8	39.07	1.6	3	EBRT	+0.33	+2	+3	3	N	Y
F	B7	10	1	B	4014	38.26	6.3	2	TACE[c]	+1.95	0	+1	-1,963	N	Y
G	B7	9	1	A	9	32.01	2.6	1	EBRT	—	0	-1	-1	N	N
H	A5	13	2	A	4	18.75	2.5	1	EBRT	+1.86	+1	-2	-1	N	N
I	B7	12	0	B	147	37.76	7.4	1	EBRT	-3.98	+3	+4	-120	N	Y
J	B7	10	0	B	5	29.42	2.5	1	EBRT	+3.59	0	+1	0	N	N
K	A6	7	0	A	142	19.55	1.2	2	EBRT	+10.05	0	+2	-99	N	N

[a]Value affected by therapeutic INR on anticoagulation for atrial fibrillation.

[b]Patient A had adrenal metastasis with no progression of hepatic lesions, patient C had a regrowth of a previously treated lesion.

[c]Patient F had TACE to a branch of the left hepatic artery, all other TACE procedures were to a branch of the right hepatic artery.

one patient did not have detectable oral cholate on the follow-up assay (patient B).

The median Portal HFR was 4.29 (range 2.43-15.89) mL/kg/min. The median Systemic HFR was 2.21 (1.61-4.96) mL/kg/min. The median cholate shunt fraction was 60.90 (21.50-76.70) %. The median DSI was 32.01 (17.11-39.07). Figure 1A shows HepQuant®'s function map with individual test results for each patient. Data on historical controls with no liver disease are provided for reference.

3.4 | Change in liver function after LDT

After LDT, there was a significant drop in Portal HFR (4.29 (2.43-15.89) mL/kg/min to 3.58 (2.21-15.68) mL/kg/min, $P = 0.05$) and no significant change in Systemic HFR (2.21 (1.61-4.96) mL/kg/min to 2.45 (1.54-3.12) mL/kg/min, $P = 0.16$). There was a trend towards a worsening disease severity index (DSI) (32.01 (17.11-39.07) vs 33.01 (18.64-40.20), $P = 0.06$). There was no significant change in shunt fraction (60.90 (21.50-76.70) % to 65.90 (19.90-78.50) %, $P = 0.51$).

Eight of the nine patients with complete post-treatment assays had worse cholate clearance parameters after LDT, and one (patient I) had an improvement in parameters (Figure 1B). Patient I developed treatment related hepatotoxicity, yet his cholate clearance parameters improved after therapy. When data are reanalysed, excluding Patient I as an outlier, all parameters indicated worsening liver function, except for the cholate shunt (Portal HFR: 4.42 (2.43-15.89) mg/kg/min to 4.27 (2.21-15.68) mg/kg/min, $P = 0.02$, Systemic HFR: 2.57 (1.61-4.96) mg/kg/min to 2.51 (1.54-3.12) mg/kg/min, $P = 0.01$, DSI: 30.72 (17.11-39.07) to 31.40 (18.64-40.20), $P = 0.02$, shunt fraction 58.90 (23.75-76.70) % to 59.85 (19.9-78.50) %, $P = 0.89$).

Between the baseline cholate clearance assay (T0), and the follow-up assay (T1), there was no difference in median bilirubin (1.5 (0.8-2.1) mg/dL vs 1.8 (0.6-3.0) mg/dL, $P = 0.17$), median INR (1.3 (1.0-2.6) vs 1.2 (1.0-3.1), $P = 0.41$), median MELD score (12 (7-20) vs 11 (7-23), $P = 0.86$), median MELD-Na score (12 (7-20) vs 11 (7-24), $P = 0.79$) or median Child-Pugh score (7 (5-9) vs 7 (5-11), $P = 0.15$). A decrease in median albumin did not reach statistical significance (3.4 (2.5-4.1) mg/dL vs 3.2 (2.4-3.7) mg/dL, $P = 0.06$). The Child-Pugh score increased by at least 1 point in 4/11 patients, and decreased or remained stable in the rest (Figure 2).

3.5 | Treatment-related hepatotoxicity and outcome

Three patients (E, F, I) developed treatment-related hepatotoxicity by the end of study follow-up (T2). Patient E was treated with EBRT for a new 1.6 cm HCC lesion. He developed a 2-point increase in Child score (9 to 11) because of a rise in INR and drop in albumin. He had no evidence of tumour progression on imaging and had only a small fluctuation in AFP (8 to 11 IU/mL). His performance status deteriorated significantly between T0 and T2 (ECOG 1 to ECOG 3) and he received hospice care.
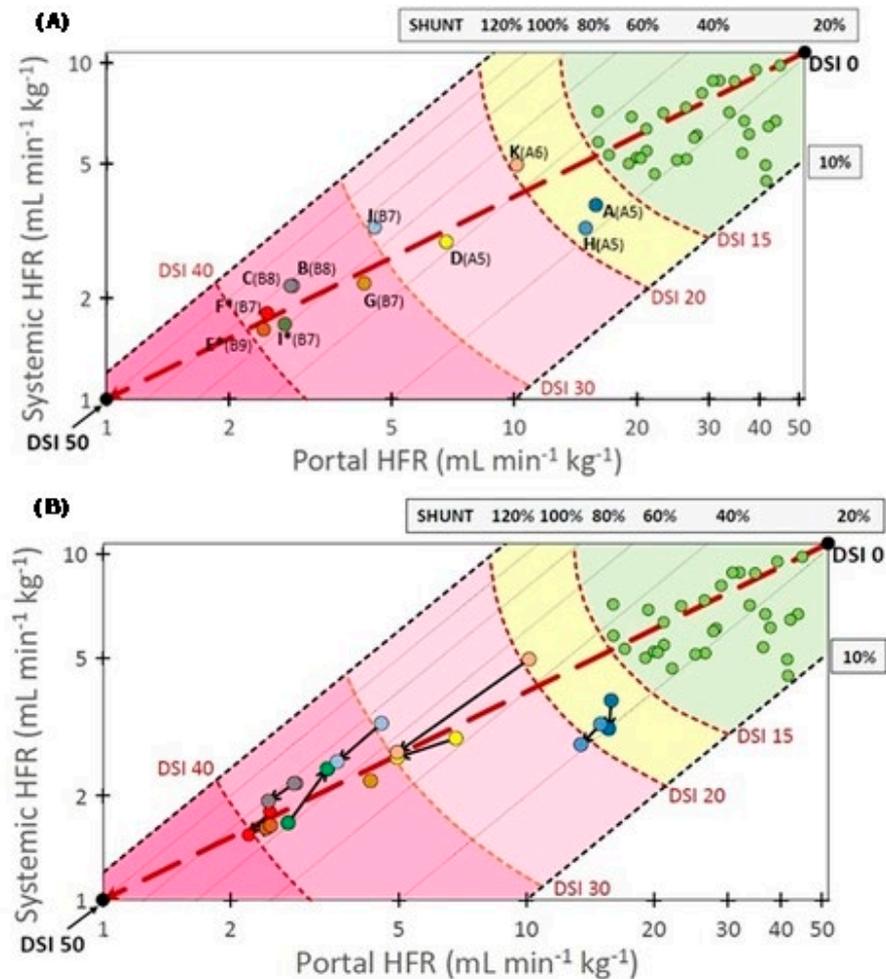
FIGURE 1 A, Baseline cholate clearance parameters with normal controls – Study patients are labelled (A to K) with the corresponding Child class and score noted between parentheses. The asterisks (*) denotes patients with clinical evidence of treatment related hepatotoxicity by the end of follow-up. Unlabelled data points in the upper right hand corner of the diagram represent reference healthy controls without liver disease. The portal hepatic filtration rate (HFR) is the weight-adjusted clearance rate of oral cholate, the systemic HFR is the weight-adjusted clearance rate of intravenous cholate. Disease Severity Index (DSI), ranging from 0 to 50, combines the oral and intravenous clearance data as a measure of liver function and is represented as the diagonal of the diagram. The cholate shunt is an estimate of portosystemic shunting, computed from the ratio of portal and systemic HFR. B, Change in cholate clearance parameters after LDT – Arrows denote the change in cholate clearance parameters between baseline (T0) and 4-10 weeks after LDT (T1). Two patients (B, G) did not have complete assay at time T1. All patients had a reduction in liver function as measured by the dual cholate clearance assay except for one (patient I)

Patient F was treated with TACE for a new diagnosis of HCC with two lesions measuring 6.3 cm and 2.3 cm. He had no clinically evident change in liver function between T0 and T1, but had a marked deterioration with the development of refractory ascites and marked rise in bilirubin (5.0 mg/dL from a baseline of 1.2 mg/dL) at T2. AFP was markedly elevated at baseline (4014 IU/mL), but he had no evidence of vascular invasion or metastatic disease. AFP dropped to 2051 IU/mL after therapy and he had no evidence of tumour progression on imaging. He died of complications of decompensated cirrhosis.

Patient I was treated with EBRT for a re-growth of a single 7.4 cm HCC, treated to satisfaction with TACE 20 weeks prior. He developed new onset ascites, new onset encephalopathy and rise in bilirubin from 1.8 mg/dL to 3.0 mg/dL at time T1. Child-Pugh score increased from a baseline (T0) of 7 to 10 at T1. His AFP dropped from

147 IU/mL to 27 IU/mL. He was referred to hospice due to a marked deterioration in performance status (ECOG 0 to ECOG 3).

Only two patients in the cohort had clinical evidence of tumour progression by time point T2 (Table 2); neither had clinical evidence of deterioration in liver function. On long-term follow-up, three patients eventually received a liver transplant for HCC (patients B, D and K) while the remainder continued to receive palliative therapy for unresectable HCC.

All three patients with treatment-related hepatotoxicity (E, F and I) had Child-Pugh B cirrhosis (1 B9, and 2 B7). There were four additional patients (B, C, G, J) with Child-Pugh B cirrhosis enrolled (2 B8, and 2 B7) who did not have hepatotoxicity, making the proportion of Child B patients affected by hepatotoxicity 42.9%. None of the Child-Pugh A patients developed hepatotoxicity.
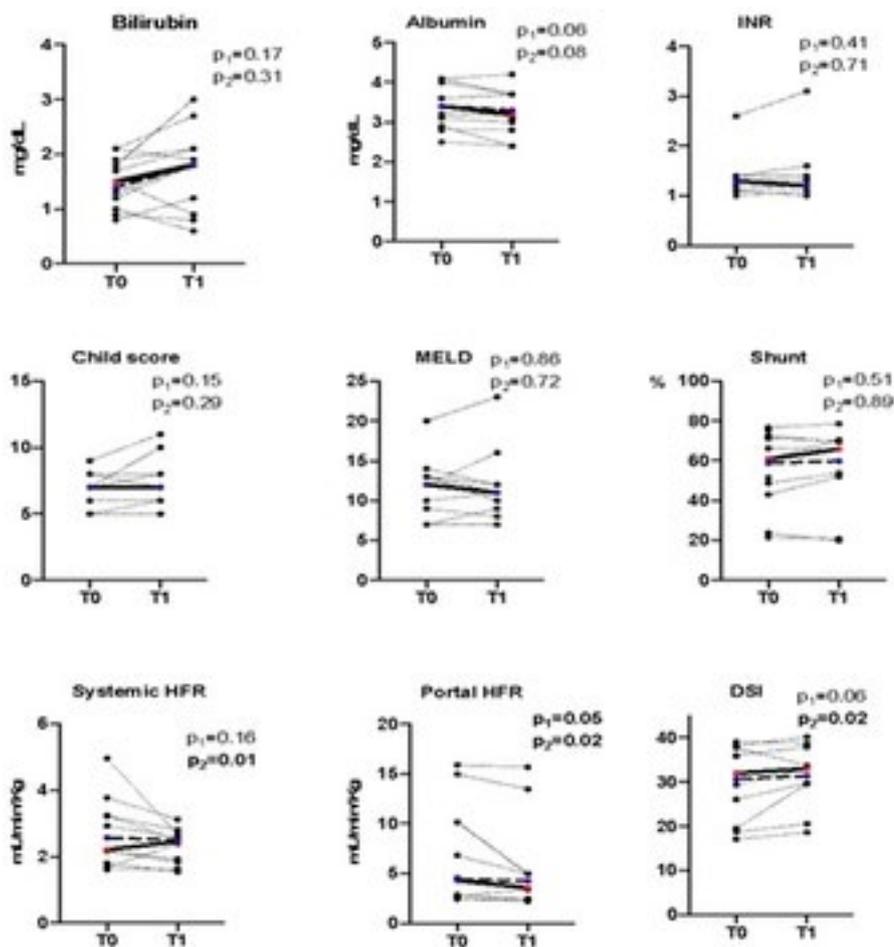
FIGURE 2 Change in cholate clearance and standard liver function assessments between T0 and T1 – the 9 patients with complete assays at T0 and T1 are included in the diagrams below. Individual data points are shown in thin dotted lines. The median change is shown in heavy solid line. We also included the median value when excluding the one outlier case (patient I) in a heavy dashed line. p1 is the P-value for the overall nine patients, p2 excludes the one outlier from the analysis

The three patients with the worst DSI were the three that developed hepatotoxicity (Figure 1B). They were three of the five patients (60%) in the study with a DSI > 35. None of the patients with a DSI < 35 developed hepatotoxicity.

4 | DISCUSSION

A number of quantitative assays of liver function have been described for evaluating liver disease.[11,12] Retention of intravenously administered Indocyanine Green at 15 minutes (ICG-R15) has been used to evaluate liver reserve prior to resection.[15] The ICG-R15 assay showed promise in assisting treatment modulation for safety in a cohort of patients with liver malignancy treated with radiotherapy,[16] but was not directly compared to a detailed standard laboratory and clinical assessment of liver function as an alternative. Similarly, baseline ICG-R15 was evaluated in patients treated with TACE. The available data suggests its ability to predict liver toxicity, though it did not perform better than the standard clinical and laboratory assessment of liver function.[17,18]

Unlike ICG-R15, the novel dual cholate clearance assay HQ-SHUNT® uses both orally administered cholate, undergoing first-pass hepatic metabolism through the portal vein, and intravenously administered cholate metabolised via the systemic blood flow to the liver. Being that the oral and IV cholates are labelled differently for analysis by mass spectroscopy, the assay permits the calculation of separate oral (portal) and intravenous (systemic) cholate clearances, portal-systemic shunt, and combines data from both clearances in the disease severity index (DSI), which provides a global assessment of liver function.

We conducted a pilot study evaluating the dual cholate clearance assay in assessing liver function pre- and post-LDT for HCC. Our 11 patients represented a range of baseline liver function in patients who are potential candidates for LDT, including Child-Pugh A and B patients treated with TACE or with EBRT (Figure 1A). We noted a deterioration in liver function at 4-10 weeks post therapy, measured by the dual cholate clearance assay after LDT in all except one patient of the nine with complete data. A similar change was not consistently detectable using traditional parameters. Both Child score and MELD score increases of any magnitude were only noted in 4 out of 11 patients. Presumably the change in cholate clearance parameters after LDT reflects hepatic injury induced by HCC treatment.

Overall, our data show that LDT for has a measurable effect on liver function that appears to be more readily detectable using the dual cholate clearance assay than by the standard clinical and laboratory assessments of liver function. This deterioration is a reflection of the hepatotoxicity of LDT modalities that limits the ability to utilise them in some patients, despite their effectiveness

in inducing a tumour response. Treatment-related hepatotoxicity, as defined in our study, is a serious complication of LDT for HCC. In fact, of the three patients who met criteria for hepatotoxicity, one died and two were enrolled in hospice care because of deterioration in liver function and performance status by the end of planned clinical follow-up.

All patients with hepatotoxicity had Child-Pugh B cirrhosis at baseline, including two patients with Child score B7 and one patient with B9. Hepatotoxicity was not noted in four other Child B patients, including two Child B7 and two Child B8. It is of interest that the three patients with hepatotoxicity had the worst baseline cholate clearance parameters. All had a DSI > 35, and constituted three of the five patients with a DSI > 35 in this study. Accordingly, it appears that the dual cholate clearance assay may be of value in risk-stratifying Child B patients for LDT. We plan to conduct a larger study, focused on Child B patients, to answer this question.

The study has several limitations. First, it is a small pilot study, so it may not detect small effects, and is also prone to outliers. One patient (Patient I) who had clearance parameters unexpectedly improved after LDT. He had standard clinical and laboratory evidence of liver deterioration after LDT, which should have resulted in worse cholate clearance parameters. Whether, in his particular case, tumour response was responsible for a change in hepatic perfusion that explains the improvement in cholate clearance is unknown. He did have the largest single lesion treated in our cohort (7.4 cm), and it is possible that the change in cholate clearance in his case is measuring both the change in liver function and alteration in liver perfusion induced by tumour necrosis. This effect was not noted among the seven other patients with paired assays and evidence of tumour response, however, though they had smaller tumours. We presented an analysis of cholate clearance using the complete data, as well as an analysis that excludes Patient I as an outlier.

Second, while we detected a change in cholate clearance parameters after LDT, we did not have additional cholate clearance assays beyond 4-10 weeks post-therapy. Therefore, it is not known whether the observed change is reversible. The fact that many HCC patients treated with LDT ultimately require additional treatments, the interpretation of serial assays would be more complicated and we did not feel that it was practical to do so in the context of this pilot trial.

Third, we did not include patients treated with TARE in our study, which is an increasingly common modality of LDT. Our rationale was to limit the number of modalities used in order to facilitate interpretation of the pilot data. We chose TACE as representative of transarterial LDT as it has been historically more commonly used in our centre. There is good rationale for improved evaluation of baseline liver function in patients treated with TARE, where serious toxicity from radiation-induced liver disease has been well-described.[19] We intend to evaluate this in future studies.

Finally, the risk of hepatotoxicity related to LDT would depend not only on liver functional reserve, but also on the volume of liver affected by therapy. We did not find a correlation between the change in liver function measured by the cholate assay and the percentage volume of liver affected by therapy as assessed in our study (change in DSI vs %liver volume, Spearman $\rho = -0.32$, $P = 0.48$). This lack of correlation could be because of our small sample size, and potentially because of the methodology in determining the volume of affected liver by TACE using cone beam CT, which is a rough approximation.

In summary, we describe the first pilot study evaluating the dual cholate clearance test (HepQuant® SHUNT) in patients undergoing LDT for HCC. We plan to use this pilot data to refine planning of a larger study to examine the role of this assay in appropriate patient selection for LDT.

CONFLICT OF INTEREST

MAH serves on the scientific advisory board of Hepquant, LLC. SH is Chief Scientific Officer at Hepquant, LLC. GTE is CEO and Chief Medical Officer at Hepquant, LLC. Other authors have no relevant personal or financial disclosures.

AUTHOR CONTRIBUTIONS

MAH is the guarantor of the article, he designed, conducted the study and drafted the manuscript; AW assisted in drafting the manuscript, provided details of radiotherapy regimens and manuscript edits; BC provided details of chemoembolisation regimens and volumetric analysis; MHL, KAR provided manuscript edits; KAF provided statistical review and manuscript edits; EBJ, GN, MCS, GTE, SH assisted in study design, cholate clearance result interpretation, and provided manuscript edits. All authors approved the final version of the manuscript.

PEER REVIEW

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