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ORIGINAL ARTICLE

# Volume–Function Analysis (LiMAx Test) in Patients with HCC and Cirrhosis Undergoing TACE—A Feasibility Study

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## Abstract

**Background** Transarterial chemoembolization (TACE) is an important therapy for hepatocellular carcinoma (HCC) in cirrhosis. In particular in advanced cirrhosis, post-TACE hepatic failure liver (PTHF) failure may develop. Currently, there is no standardization for the periinterventional risk assessment. The liver maximum capacity (LiMAx) test assesses the functional liver capacity, but has not been investigated in this setting.

**Aims** The aim of this study was to prospectively evaluate periinterventional LiMAx and CT volumetry measurements in patients with cirrhosis and HCC undergoing repetitive TACE.

**Methods** From 06/2016 to 11/2017, eleven patients with HCC and cirrhosis undergoing TACE were included. LiMAx measurements ($n=42$) were conducted before and after each TACE. Laboratory parameters were correlated with the volume–function data.

**Results** The median LiMAx levels before ($276 \pm 166$ µg/kg/h) were slightly reduced after TACE ($251 \pm 122$ µg/kg/h; $p=0.08$). This corresponded to a median drop of 7.1%. Notably, there was a significant correlation between LiMAx levels before TACE and bilirubin (but not albumin nor albumin–bilirubin [ALBI] score) increase after TACE ($p=0.02$, $k=0.56$). Furthermore, a significantly higher increase in bilirubin in patients with LiMAx ≤ 150 µg/kg/h was observed ($p=0.011$). LiMAx levels at different time points in single patients were similar ($p=0.2$).

**Conclusion** In our prospective pilot study in patients with HCC and cirrhosis undergoing multiple TACE, robust and reliable LiMAx measurements were demonstrated. Lower LiMAx levels before TACE were associated with surrogate markers (bilirubin) of liver failure after TACE. Specific subgroups at high risk of PTHF should be investigated. This might facilitate the future development of strategies to prevent occurrence of PTHF.

**Keywords** Cirrhosis · Hepatocellular carcinoma · Liver function · Liver maximum capacity · Transarterial chemoembolization · Volume–function analysis

## Abbreviations

| | |
|---|---|
| ALBI | Albumin–bilirubin |
| ALT | Alanine aminotransferase |
| AFP | Alpha-fetoprotein |
| BCLC | Barcelona Clinic Liver Cancer Classification |
| CPS | Child–Pugh score |
| CT | Computed tomography |
| EV | Embolization volume |
| FLRV | Functional remnant liver volume |
| FRLF | Future remnant liver function |
| HBV | Hepatitis B virus |
| HCC | Hepatocellular carcinoma |
| INR | International normalized ratio |
| LiMAx | Liver maximum capacity |
| LV | Liver volume |
| MELD | Model for end-stage liver disease |
| PBC | Primary biliary cholangitis |
| PTHF | Post-TACE hepatic failure |
| TLV | Total liver volume |
| TuV | Tumor volume (TuV) |

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| | |
|---|---|
| SD | Standard deviation |
| TACE | Transarterial chemoembolization |
| TIPS | Transhepatic intrahepatic portosystemic shunt |
| TKI | Tyrosinkinase inhibitor |

## Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the third most common cancer-dependent death cause worldwide [1]. Transarterial chemoembolization (TACE) is the gold standard palliative therapy in non-resectable Barcelona Clinic Liver Cancer Classification (BCLC) stage B patients and also used for bridging patients to liver transplantation [2]. It is well known that the prognosis depends on tumor burden and liver function capacity. TACE is less effective in patients with extrahepatic spread or macrovascular invasion, and/or decompensated liver disease [2]. Post-TACE hepatic failure (PTHF) is severe complication after TACE. Several scoring systems and algorithms for HCC patients have been evaluated in the past [3]. Child–Pugh stage B or C and serum bilirubin level > 2 mg/dl are considered as risk factors for liver failure after TACE [4, 5]. Currently, the ALBI-[6] and other scores are applied. However, there is still no widely accepted standard risk assessment procedure in patients undergoing TACE.

The liver maximum capacity (LiMAx) test was introduced for the evaluation of the liver function capacity. LiMAx was initially developed and proved beneficial to predict postoperative liver function in patients after hepatectomy [7]. In the further course, it was used to assess the severity of liver cirrhosis and the short-term mortality of cirrhosis patients and HCC patients undergoing hepatectomy [8, 9]. Previous studies found a strong correlation between LiMAx levels and histological severity of liver disease [10] and different clinical stages of cirrhosis [11].

Moreover, we previously evaluated the ability to predict the functional reserve in patients with cirrhosis and transhepatic intrahepatic portosystemic shunt (TIPS) implantation [8].

The aim of this study was to prospectively assess LiMAx in HCC patients with cirrhosis and HCC undergoing repetitive TACE.

## Patients and Methods

### Study Population

The study was reviewed and approved by an institutional research review board (Approval 266/16). Each patient signed a written informed consent for the study and TACE procedure, as well as informed consent to use the clinical data for this research project. All patients evaluated for TACE in our departments between June 2016 and November 2017 were screened for inclusion. Only patients with HCC and cirrhosis were included in the analysis. HCC was diagnosed according to EASL criteria [2]. All patients were discussed in the local tumor board, and TACE was recommended. Since a total bilirubin level > 3.0 mg/dl is considered as a contraindication for TACE in our center, no such patients were enrolled. Age < 18 years, paracetamol allergy, and the inability to perform all the necessary study examinations were exclusion criteria. Before TACE, all patients received a clinical examination including laboratory liver function tests and magnetic resonance as well as computed tomography (CT) imaging of the liver. The following clinical data were analyzed: age, sex, etiology of cirrhosis, Child–Pugh score (CPS), and model for end-stage liver disease (MELD) score. Moreover, the following laboratory values were collected: serum levels of hemoglobin, creatinine, bilirubin, albumin, sodium, international normalized ratio (INR), aminotransferases, white and red blood cell and platelet counts as well as ammonium serum concentrations and alpha-fetoprotein (AFP) levels.

Patients were screened for the occurrence of complications until dismissal and at presentation at the following treatments. The LiMAx measurements were performed $1 \pm 1$ day prior and $1 \pm 1$ day post-TACE treatment to study early changes after TACE. According to the pre-TACE LiMAx value, patients were divided into two groups: higher and lower than 150 µg/kg/h. This cutoff was based on a large study by Stockman et al. [7] where significantly worse outcome for patients after hepatectomy with LiMAx under 150 µg/kg/h was found. The ALBI score was calculated as follows and as previously described [6]: log10 bilirubin [mmol/L] × 0.66) + (albumin [g/L] × (− 0.0852)). ALBI classes were assessed as follows: ALBI score ≤ 2.60 (ALBI grade 1), ≥ 2.60 to ≤ 1.39 (ALBI grade 2), and ≥ 1.39 (ALBI grade 3) according to Johnson et al. [12].

### TACE Procedure

TACE procedures were routinely prepared using analgetic and antiemetic oral medication including dexamethasone, ondansetron, and pethidine. Angiography was performed via a transfemoral route using an appropriate 4 French guiding catheter for catheterization of the celiac trunk or mesenteric artery to evaluate anatomical feasibility. A coaxial 2.7 French microcatheter was used for selective angiography of the hepatic vasculature and to identify segmental hepatic tumor feeding arteries. For chemoembolization, a mixture of 10 ml Lipiodol® Ultra Fluid (Guerbet, France) and 50 mg of doxorubicin was slowly injected to avoid non-target

embolization. A CT scan was conducted in all patients post-TACE to allow for evaluation of embolized liver volume.

## LiMAx Test

Liver tests were performed at the time of inclusion after fasting for a minimum of 3 h. The procedure is based on body weight-adjusted (2 mg/kg) intravenous $^{13}$C-labeled methacetin bolus injection and subsequent injection of 20 ml 0.9% sodium chloride as previously described [13]. Exhaled breath is collected by a distinct two-way face mask and analyzed by means of a special device (Humedics, Berlin, Germany). Herein, we are able to achieve a continuous real-time sampling rate and optimal analysis of delta-over-baseline (DOB) curves of $^{13}CO_2/^{12}CO_2$ ratios. $^{13}$C-methacetin is a substrate of the hepatic CYP1A2 enzyme, which exclusively metabolizes it into paracetamol and $^{13}CO_2$ [14]. Prior to substrate injection, the baseline $^{13}CO_2/^{12}CO_2$ ratio is recorded in the native expired air to calculate the individual baseline. Using the individual $^{13}CO_2/^{12}CO_2$ baseline, the results are not influenced by obstructive pulmonary disease or ventilation. Maximum delta-over-baseline (DOBmax) of the $^{13}CO_2/^{12}CO_2$ ratio was determined by analyzing the continuous DOB curve over a maximum of 60 min, and the LiMAx value is calculated as previously described [13]. The principle of the LiMAx test is illustrated in Fig. 1 (according to Stockmann et al. [13]).

## Liver Volume Reduction and LiMAx Value Drop

Semi-automated liver volumetry was performed using a dedicated medical image viewing and postprocessing software (iNtuition, TeraRecon, NC, USA) pre- and post-TACE CT scans (available in all patients). The total liver volume (TLV) and tumor volume (TuV) were measured before TACE. The embolization volume (EV) was measured directly after TACE. LiMAx was performed 1 day (± 1) before and 1 day (± 1) after TACE treatment. A LiMAx drop was defined as: (LiMAx before TACE – LiMAx after TACE)/LiMAx before TACE *100 [%]. The Liver volume (LV) reduction was defined as: (TLV-TuV)-(TLV-EV)/(TLV-TuV) [%].

## Assessment of Liver Function After TACE

LiMAx and liver function tests (thrombin time, bilirubin, transaminases) were measured at the first day after TACE treatment. Moreover, deterioration in clinical outcome, hospital stay, and post-interventional morbidity according to the Clavien–Dindo classification were recorded. A total bilirubin increase (total bilirubin after TACE – total bilirubin before TACE), albumin decrease (total albumin after

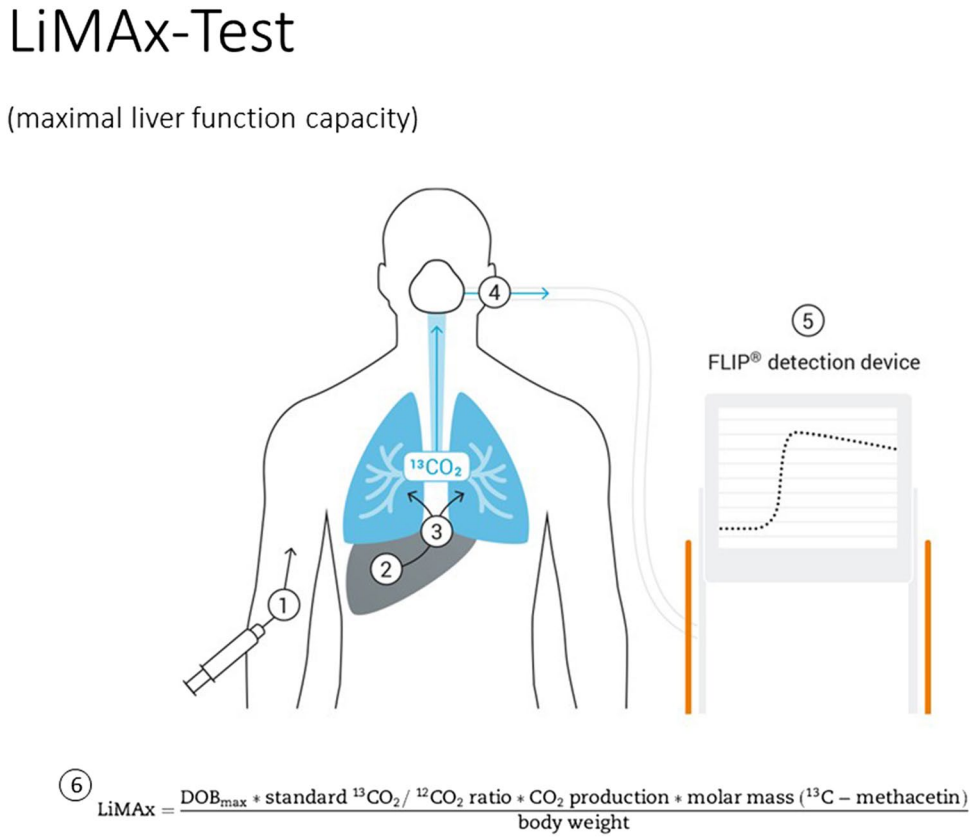


**Fig. 1** Principle of the LiMAx test. The test starts with a body weight-adjusted (2 mg/kg) intravenous $^{13}$C-labeled methacetin bolus injection and a subsequent injection of 20 ml 0.9% sodium chloride (1). $^{13}$C-methacetin is a substrate of the hepatic CYP1A2 enzyme, which is metabolized into paracetamol and $^{13}CO_2$ (2), which is excreted pulmonary (3). Consecutively exhaled air is collected by a facemask (4) and then analyzed in a FLIP ® device according to the following formula (6). Adapted from Stockmann et al. [12]

TACE – total albumin before TACE), and ALBI increase (total ALBI after TACE – total ALBI before TACE) were calculated as surrogate parameters for post-TACE treatment liver function deterioration.

## Statistical Analysis

All variables are described as proportions, means with standard deviations (SD), or medians with interquartile ranges (IQR). Univariate analysis was performed with $Chi^2$-squared test, *t* test or Mann–Whitney U test, according to the distribution of the test variable. The statistical analyses were performed using SPSS 22.0 (SPSS, Munich, Germany). Two-sided p values $< 0.05$ were regarded as statistically significant. Coefficient of variations as well as Friedmann two-factorial rank analysis for repeated measures was used to compare repetitive LiMAx measurements before and after consecutive TACE in the same patient.

## Results

### Baseline Data

The patient baseline characteristics are summarized in Table 1. Twenty-one TACE procedures in 11 patients were included in the analysis. The patients were predominantly male (72%); the median age was 67 (± 11 SD) years. All of the patients had cirrhosis. The most common etiology was alcohol (64%), followed by hepatitis B (18%) and primary biliary cholangitis (18%)-induced cirrhosis. The patients were mostly in an early stage of cirrhosis (Child–Pugh stages: A 82%, B 18%, C 0%; median MELD score 9.9 points ± 4 SD). Most patients were ALBI score grade 1 (81.8%); 2 patients (18.2%) were grade 2. Median LiMAx in the ALBI grade 1 patients was 292 ± 168 µg/kg/h; in ALBI grade 2 patients LiMAx levels were lower (117 ± 37 µg/kg/h), even though not reaching statistical significance ($p = 0.12$). No ALBI grade 3 patients were included.

### HCC and TACE Treatments

Characteristics of the HCCs (Table 2) and TACE treatments (Table 3) are provided. The median size of the largest HCC nodule was 58.4 ± 24 mm. Most patients (87%) were BCLC stage B; 3 patients (13%) were in stage A3. The median TLV was 1755 ± 400 ml; median TuV of the HCCs was 64.5 ± 6 ml. The median EV was 693 ± 400 ml. Most TACE was conducted in a selective lobar approach (70%).

**Table 1** Baseline patients characteristics

| | |
|---|---|
| Age (years) | 67 ± 11 |
| Sex (male) | 8 (72) |
| Child–Pugh stage | |
| A | 9 (82) |
| B | 2 (18) |
| C | 0 |
| ALBI score (mean) | − 3.01 ± 0.4 |
| Total bilirubin before TACE [mg/dl] | 1.22 ± 0.8* |
| Total bilirubin after TACE [mg/dl] | 1.91 ± 1.3* |
| Albumin [mg/dl] | 36.4 ± 4 |
| INR | 1.16 ± 0.2 |
| Creatinine [mg/dl) | 1.05 ± 0.3 |
| Platelets | 102 ± 63 |
| ALT [U/l] | 39.6 ± 20 |
| MELD | 9.9 ± 4 |
| MELD-Na | 11.2 ± 4 |
| Etiology of cirrhosis | |
| Alcoholic | 7 (64) |
| HBV | 2 (18) |
| PBC | 2 (18) |

Unless specified differently, values are given as median and standard deviation (SD), or frequencies and percentages

*$p = 0.001$ vs serum bilirubin before TACE. Significant p-values are indicated in bold

**Table 2** HCC characteristics

| | |
|---|---|
| Largest nodule diameter [mm] | 58.4 ± 24 |
| Number noduli | |
| 1 | 9 (39) |
| 2 | 1 (4) |
| 3 | 5 (22) |
| > 3 | 8 (35) |
| BCLC score | |
| A1 | 0 (0) |
| A2 | 0 (0) |
| A3 | 3 (13) |
| A4 | 0 (0) |
| B | 20 (87) |
| C | 0 (0) |
| D | 0 (0) |
| AFP pre-TACE [µg/l] | 842 ± 2106 |
| TNM T-status prior TACE | |
| T1a | 1 (4) |
| T1b | 2 (9) |
| T2 | 3 (13) |
| T3 | 17 (74) |
| T4 | 0 (0) |

Values are given as median and standard deviation (SD), or frequencies and percentages

Significant *p*-values are indicated in bold

**Table 3** TACE and liver volume–function analysis parameters

| | |
|---|---|
| TLV [ml] | 1755 ± 400 |
| TuV [ml] | 64.5 ± 6 |
| EV [ml] | 693 ± 400 |
| TACE approach (%) | |
| Subsegmental | 0 |
| Segmental | 2 (9) |
| Lobar | 16 (70) |
| Bilobar | 5 (22) |
| LiMAx before TACE [µg/kg/h] | 276 ± 166 |
| LiMAx after TACE [µg/kg/h] | 251 ± 122* |
| LiMAx drop [%] | 7.1 ± 23 |
| LV reduction [%] | 37.5 ± 23 |

Values are given as median and standard deviation (SD), or frequencies and percentages

*$p = 0.08$ versus LiMAx before TACE. Significant $p$-values are indicated in bold

## LiMAx and Function–Volume Analysis Pre- and Post-TACE

The data are provided in Tables 2 and 3. The LiMAx levels pre-TACE correlated with the pre-TACE ALBI score ($p = 0.017$, $k = -0.513$) and albumin ($p = 0.016$, $k = 0.519$) levels, pre-TACE bilirubin (as item of the ALBI score) only ($p = 0.065$, $k = -0.41$) were not significantly correlated with LiMAx levels pre-TACE though. Serum bilirubin levels were significantly higher after (1.91 ± 1.3 SD), than before (median 1.22 mg/dl ± 0.8 SD; $p = 0.001$) TACE. The median LiMAx levels before TACE were 276 ± 166 µg/kg/h; they were slightly reduced after TACE (251 ± 122 µg/kg/h; $p = 0.08$). This corresponded to a median drop of 7.1% of LiMAx levels after TACE. The LV was reduced median 37.5 ± 23% SD. The reduction in LV did not correlate with the drop in LiMAx levels as presented in Fig. 2.

LV reduction (10.7–100%) and change of LiMAx levels (− 37.8% to +40.0%) after TACE varied substantially among the patients and did not correlate significantly ($p = 0.209$, $k = 0.302$). When we compared patients with lower versus those with a higher (LiMAx ≤ 150 µg/kg/h versus > 150 µg/kg/h) LiMAx levels (Table 4), higher bilirubin and INR levels, larger spleen sizes, and lower platelet counts were observed in patients with lower LiMAx levels, which additionally in the setting of TACE confirms the well-known association of reduced LiMAx levels with the increasing stage of cirrhosis.

Notably, there was a significant correlation between LiMAx levels pre-TACE and the bilirubin increase after TACE ($p = 0.019$; Fig. 3). The increase in bilirubin was higher in the group of patients with LiMAx ≤ 150 µg/kg/h (Fig. 4c), whereas no difference could be detected for ALBI score and albumin levels (Fig. 4a and b).

## Repetitive TACE

Most of the patients were treated multiple times ($n = 18$, 78%): one patient was treated 5 times, one 4 times, one 3 times, and 3 patients were treated twice. The longitudinal data of LiMAx measurements in the patient with five treatments are presented in Fig. 5, there was no significant difference between LiMAx levels at different time points ($p = 0.2$), and this could also not be observed in the other patients. Overall, we noticed only few and minor complications post-TACE; 21 Patients (74%) had a normal post-interventional course, in one patient (4%) Clavian–Dindo Grade I, and in five patients (22%) Clavian–Dindo Grade II (mostly acute cholecystitis) morbidity were observed.

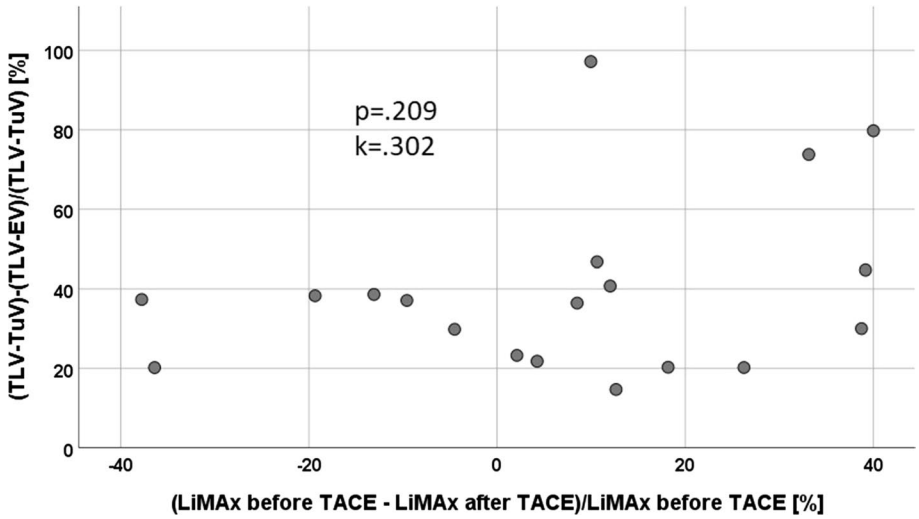


**Fig. 2** Poor correlation of FRLF und FLRV in patients after TACE

**Table 4** Parameters stratified by LiMAx levels ≤/> 150 µg/kg/h. Values are given as median and standard deviation (SD), or frequencies and percentages

| | LiMAx before TACE ≤ 150 µg/kg/h | LiMAx before TACE > 150 µg/kg/h | *p*-Value |
|---|---|---|---|
| Total bilirubin before TACE [mg/dl] | 1.4 ± 0.6 | 0.8 ± 0.6 | **0.01** |
| Total bilirubin after TACE [mg/dl] | 2.2 ± 0.8 | 1.1 ± 0.7 | **0.02** |
| Total bilirubin rise [mg/dl] | 0.81 ± 0.5 | 0.1 ± 0.2 | **0.01** |
| Spleen size [cm] | 18.0 ± 5 | 11.8 ± 3 | **0.004** |
| Platelets count [$10^9$/l] | 70.0 ± 55 | 143.4 ± 42 | **0.01** |
| ALT [U/l] | 76.7 ± 150 | 42.3 ± 21 | 0.31 |
| GGT [U/l] | 148 ± 106 | 264 ± 245 | 0.55 |
| AP [U/l] | 179 ± 100 | 145 ± 73 | 0.19 |
| INR | 1.35 ± 0.1 | 1.01 ± 0.1 | **0.001** |

Significant *p*-values are indicated in bold

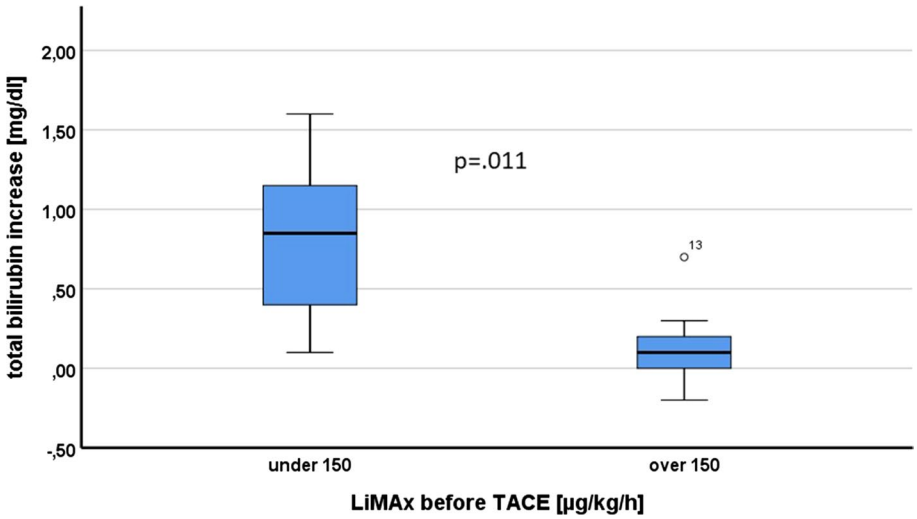


**Fig. 3** Correlation of bilirubin increase after TACE and LiMAx levels before TACE

## Discussion

TACE is the gold standard therapy for patients with HCC in intermediate stages as endorsed by both the guidelines from the European Association for the Study of the Liver (EASL) [2] and the American Association for the Study of Liver Diseases (AASLD) [15, 16]. Two randomized controlled trials confirm the benefit of treatment for those patients in comparison with the best supportive care [17–19]. Post-TACE hepatic failure (PTHF) is one of the major complications after TACE. There are several risk factors for PTHF, including the presence of a portal vein thrombosis, reduced serum sodium and serum albumin levels, increased serum total bilirubin and AFP levels and reduced platelets count and large diameter of HCC [20]. Different scores including those parameters were developed. The ALBI score (albumin–bilirubin grade) [3–5, 21] and the BCLC criteria (based on the CPS [22]) are widely used prognostic markers for PTHF, but still are suboptimal. Therefore, other additional tests were developed in order to reduce the PTHF rate. Huang et al. [23] showed the superiority of the monoethylglycinexylidide test over conventional liver function tests and clinical parameters to predict PTHF. Similarly, Khisti et al. [24] showed a specificity of 87.5% and sensitivity of 90% for the liver function test with indocyanine green clearance to predict PTHF. There are also reports though, showing a non-superiority of the indocyanine green plasma disappearance rate in order to predict PTHF compared to MELD, MELD-Na, and CPS [25]. Still, there is no widely accepted gold standard for the evaluation of the liver function reserve in patients prior TACE treatment.

In this prospective pilot study, the feasibility of LiMAx measurements to assess the pre-TACE liver function was demonstrated. The LiMAx test has been intensively evaluated since its introduction in the year 2009 [13]. It was initially evaluated in hepatectomy patients. Using an algorithm to predict posthepatectomy liver failure, including volume–function analysis [7], a significant improvement in the postoperative liver failure and mortality rate can be achieved as shown by Jara et al. [26]. Since there were some

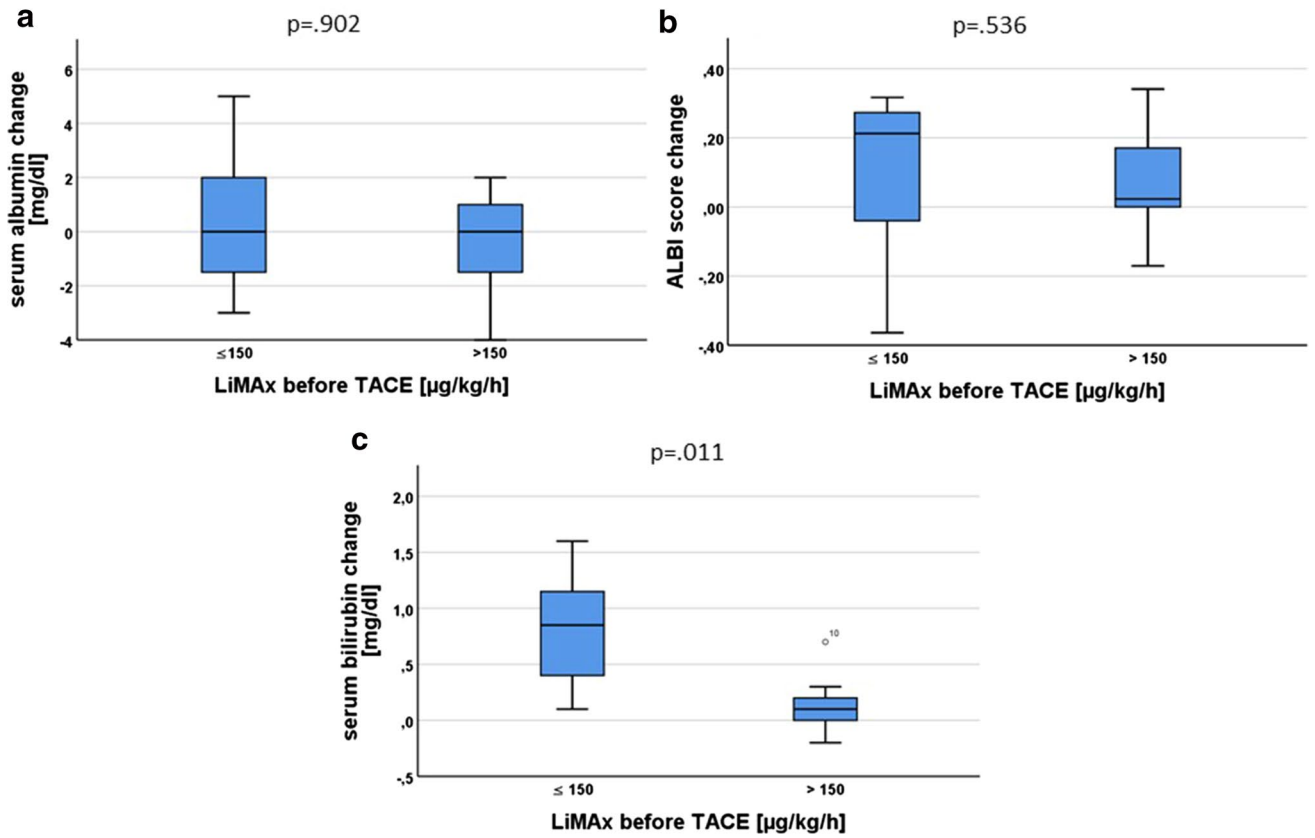


**Fig. 4** **a** Post-TACE albumin change stratified by LiMAx levels. **b** Post-TACE ALBI change stratified by LiMAx levels. **c** Post-TACE bilirubin change stratified by LiMAx levels

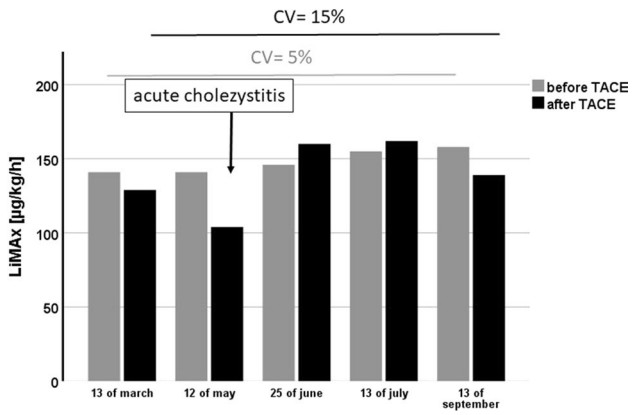


**Fig. 5** Course of LiMAx before and after TACE in the patient with five treatments. There was no significant difference between the single measurements ($p = 0.16$). The coefficient of variations (CV) for the LiMAx before TACE was 15% and after TACE 5%. There was a drop of LiMAx value after the second TACE. This was associated with an episode of acute cholecystitis induced by TACE

considerations regarding an HCC functional status and the feasibility of volume–function analysis in those patients, Blüthner et al. [27] analyzed this algorithm in HCC patients with and without liver cirrhosis, yielding a similar result. As shown by Jara et al. [28], LiMAx can be repeatedly performed even before and after extra-abdominal surgery leading to similar results.

A recent study by Barzakova et al. [29] also investigated LiMAx measurements in a similar approach to our cohort in patients undergoing TACE. Similar reductions to our cohort of LiMAx levels after TACE were found (10.0 versus 7.1%). As the cohort by Barzakova et al. contained > 65% of the patients with no cirrhosis, results can be not compared with our cohort.

In the present study, we found that LiMAx measurements are reliable reproducible in patients with HCC and cirrhosis undergoing multiple TACE treatments. LiMAx levels did not correlate with ALBI levels, likely due to the similar stage of cirrhosis of the included patients. The functional liver volume reduction correlates very well with the drop of liver function measured by LiMAx in hepatectomy patients [13, 30]. LV changes were not correlated with changes of the LiMAx levels in our TACE patients though. We assume that this is due the fact that after TACE, there is no ''real'' liver parenchyma loss, since only portal, but no arterial branches are embolized.

In addition, there is typically no necrosis within the embolized liver after TACE. We thus assume that liver volume analysis prior TACE cannot stratify the risk of post-interventional liver failure, as it is the case in hepatectomy patients [7].

In contrast to ALBI and albumin levels, reduced LiMAx levels were associated with an increase in bilirubin after TACE. Even though this might also reflect changes in vascularization after TACE or other confounders and, therefore, further studies are required, this may indicate that LiMAx could be an important marker to predict PTHF.

Our study has limitations that have to be acknowledged: our cohort size was small, and we had no case of major hepatic failure after TACE. This is due to a rigid selection of TACE candidates regarding preserved liver function. However, in this limited cohort of patients, results showed significant results indicating LiMAx as a robust method for assessment of liver function in cirrhotic liver. Occurrence of PTHF in the follow-up could therefore not be evaluated, and we therefore evaluated surrogate markers, but not clinical endpoints. Additionally, further studies investigating the optimal time point of LiMAx measurements after TACE are required.

We conclude that in our prospective pilot trial, LiMAx measurements before TACE in order to predict PTHF are feasible and safe and show a strong intra-patient correlation with reliable reproducible measurements in repetitive treatments. Lower LiMAx levels before TACE were associated with surrogate markers indicating the liver function drop after TACE. Specific subgroups at high risk of PTHF should be investigated in dedicated future prospective trials. This may facilitate the future development of strategies to prevent the development of PTHF and identify patients at highest risk.

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**Author's contribution** Author's contributions (according to Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Ethical Considerations in the Conduct and Reporting of Research: Authorship and Contributorship, ICMJE): MCR, MM, and FL designed the study; MCR, AS, AM, and MM participated in the acquisition of clinical data, drafted the manuscript, and together with MG, AB and FL analyzed the data and finalized the manuscript, which was then revised by all authors. The final draft of the manuscript has been approved by all authors. The contents of this manuscript are our original work and have not been published, in whole or in part, prior to or simultaneous with our submission of the manuscript.

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## Compliance with Ethical Standards

**Conflict of interest** The authors who have taken part in this study declared that they do not have anything to disclose regarding conflicts of interest with respect to this manuscript.

**Ethical approval** Informed consent was obtained from all individual participants included in the study. The study protocol has been approved by the research institute's committee on human research (Approval 266/16). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.



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