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ORIGINAL ARTICLE

# Scintigraphic liver function and transient elastography in the assessment of patients with resectable hepatocellular carcinoma

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## Abstract

**Background:** Hepatobiliary scintigraphy (HBS) is used to quantify total and regional liver function. Transient elastography (TE) provides a non-invasive alternative to percutaneous biopsy to assess liver fibrosis and cirrhosis. This study aims to determine the correlation between HBS and histopathology of liver parenchyma, and to compare these with TE in patients with resectable hepatocellular carcinoma (HCC).

**Methods:** Patients who underwent surgery for HCC between 2000 and 2016 after preoperative HBS were included. Non-tumorous liver tissue was evaluated for inflammation, steatosis, ballooning, siderosis and fibrosis. Correlation analysis was performed between HBS results and histopathological scoring. These were also compared with TE and surgical outcomes.

**Results:** 71 patients underwent preoperative HBS of whom 24 also had TE. HBS correlated with portal and lobular inflammation as well as fibrosis. TE correlated with portal and lobular inflammation, ballooning and fibrosis. A significant correlation was found between HBS and TE. No association was found with overall postoperative morbidity and mortality.

**Conclusion:** HBS and TE show a moderate to strong correlation. HBS and TE share discriminatory features of histopathological scoring and show a weak to moderate correlation with hepatic inflammation and fibrosis.

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## Introduction

Most patients with hepatocellular carcinoma (HCC) are not eligible for liver transplantation and liver resection offers the only treatment with curative intent in a select group of patients. Major liver resection in these patients with frequent hepatic parenchymal damage harbors the risk of posthepatectomy liver failure (PHLF). The incidence of PHLF after major liver resection is reported to be at least 7% in patients with healthy parenchyma and can reach up to 30% in patients with liver cirrhosis, which is a common condition in patients with HCC.[1]

Since the risks of liver surgery are substantial in HCC patients, adequate staging and risk-assessment are essential. The Barcelona clinic liver cancer (BCLC) staging system is used to guide management of patients with HCC. In very early and early stage tumors (BCLC 0 and A), curative resection is the treatment of choice, when radiofrequency ablation is technically not possible.[2,3] Other classification systems have been used for surgical risk-assessment, including the Child-Pugh classification as the reference standard for clinically classifying patients with liver cirrhosis and the Model For End-Stage Liver Disease (MELD), a scoring system that stratifies the





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severity of end-stage liver disease that is mostly used for liver transplant planning.[4] These scoring systems only provide indirect information on liver function, merely based on clinical parameters and lack the possibility to assess regional liver function.[5]

CT-volumetric analysis is the most widely used technique to preoperatively assess the future remnant liver (FRL), but is increasingly challenged by functional analyses. Liver volume is used as an indirect measure of liver function. A FRL share larger than 25–30% is considered a safe cut-off for liver resection in normal liver parenchyma, whereas at least 40% FRL volume is needed in patients with compromised livers.[6] Estimation of FRL function based on CT-volumetry can therefore be unreliable in patients with undetermined parenchymal quality.[7]

Hepatic uptake and excretory function can be assessed using Technetium-99m ($^{99m}$Tc)-mebrofenin hepatobiliary scintigraphy (HBS). HBS is a dynamic quantitative liver function test that evaluates global, and when combined with SPECT-CT, also regional liver function. HBS has proven to predict the risk of PHLF in a mixed series of patients undergoing major liver resection.[8–15]

Liver parenchymal quality can additionally be assessed using liver stiffness measurement (LSM) techniques, such as transient elastography (TE) carried out with the Fibroscan®. This is a non-invasive alternative to percutaneous biopsy that uses the velocity of shear wave propagation to assess liver elasticity, which has shown to correlate with the grade of fibrosis.[16]

The correlation between liver function measured with HBS, LSM measured with TE and histopathological grading as the gold standard in the assessment of liver parenchymal quality remains undefined in patients with HCC considered for resection. The aim of this study was to compare results of these techniques in a series of patients with HCC who underwent resection and to compare these with surgical outcomes.

## Methods

### Patients

All consecutive patients who underwent surgery for HCC between January 2000 and December 2016 in the Academic Medical Center in Amsterdam and had undergone preoperative risk assessment with HBS and/or TE were included. The diagnosis of HCC was confirmed on histopathological examination of the resection specimen.

Clinical data were obtained from electronic medical records. Patient demographics and surgical outcomes were recorded. Child-Pugh and MELD scores were calculated. Severe postoperative morbidity was defined as any complication of Dindo grade IIIa or higher within 30 days after surgery.[17] PHLF was defined according to International Study Group of Liver Surgery (ISGLS) grade B or C.[18] Postoperative mortality was defined as death within 90 days after surgery. The need for individual informed consent was waived by the institutional review board of the Academic Medical Center. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

### Hepatobiliary scintigraphy

HBS was performed with $^{99m}$Tc-labeled mebrofenin (Bridatec; GE-Amersham Health) which is a suitable agent to assess liver function.[7] This was used to calculate the mebrofenin uptake rate (MUR, %/min) which corresponds with liver function, as described previously.[19]

Dynamic acquisitions were obtained for at least 36 frames of 10 s/frame to calculate the MUR.[7,20] Subsequently, a fast SPECT acquisition centered around the peak of the hepatic time-activity curve was made, providing information on three-dimensional, segmental distribution of liver function. This was combined with low-dose, non-contrast enhanced CT for attenuation correction and anatomical mapping.

To compensate for differences in individual metabolic requirements, the MUR was divided by the body surface area (BSA, $m^2$).[21] The current future remnant liver function (FRLF) cut-off value for a safe resection is set at 2.7%/min/$m^2$.[7]

### Histopathology

Formalin fixed, paraffin embedded liver tissue slides were retrieved from the pathology archives. Hematoxylin and eosin, Perl's Prussian Blue and collagen (Sirius red or Elastica van Gieson) stained slides were used. Microscopic features of non-tumorous liver tissue were evaluated in detail by an experienced liver pathologist (J.V.), blinded to the clinical data.

Non-tumorous liver tissue was evaluated according to the grading system presented in Table 1.[22] For the analysis, two groups were created where no to mild fibrosis was defined as grade A–C and severe fibrosis to cirrhosis was defined as grade D–F.

### Transient elastography (Fibroscan®)

TE was performed with the Fibroscan® (Echosens, Paris, France) using the M- or XL-probe. The probe was positioned in the right midaxillary line, between the ninth to eleventh intercostal space.

Examination with a regular ultrasound was made to make sure that other structures were avoided. A low frequency shear wave of 50 Hz is generated by a mechanical push. This travels through the hepatic tissue where the velocity of wave propagation is measured. According to Young's principle, the velocity is proportional to tissue stiffness (kilopascal, kPa).

The study was only considered successful if there were at least 10 measurements with a success rate of more than 60% and if the interquartile range did not exceed 30% of the median.

### Liver volumetry

Multiphase CT scans (Brilliance 64, Philips, Eindhoven, The Netherlands) were performed prior to every resection. Volumetric




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**Table 1** Grading system of histopathologic features of nontumoral liver tissue

| Histopathological feature of nontumoral liver tissue | Grade |
|---|---|
| Portal inflammation | 0 – none |
| | 1 – mild |
| | 2 – moderate |
| | 3 – severe |
| Lobular inflammation | 0 – no foci |
| | 1 – <2 foci per × 200 field |
| | 2 – 2–4 foci per × 200 field |
| | 3 – >4 foci per × 200 field |
| Interface activity | 0 – none |
| | 1 – mild |
| | 2 – moderate |
| | 3 – severe |
| Steatosis | 0 – <5% of hepatocytes |
| | 1 – 5–33% of hepatocytes |
| | 2–34–66% of hepatocytes |
| | 3 – >66% of hepatocytes |
| Ballooning | 0 – none |
| | 1 – few ballooning cells |
| | 2 – many ballooning cells |
| Siderosis | 0 – none |
| | 1 – ≤25% of hepatocytes |
| | 2–26–50% of hepatocytes |
| | 3–51–75% of hepatocytes |
| | 4 – ≥76% of hepatocytes |
| Fibrosis | A – none |
| | B – perisinusoidal or periportal |
| | C – perisinusoidal and portal/ periportal |
| | D – bridging fibrosis involved in <50% of the portal tracts and/or central veins |
| | E – bridging fibrosis involved in ≥50% of the portal tracts and/or central veins |
| | F – cirrhosis |
| NAFLD activity score (NAS) = grade of steatosis + lobular inflammation + interface activity | 0–2 – no steatohepatitis |
| | 3–4 – borderline steatohepatitis |
| | ≥5 – definite steatohepatitis |

analysis was performed on 3D reconstructions of 5 mm axial slices in portal-venous phase using manual delineation of the FRL. Total liver volume (TLV), tumor volume (TV) and FRL volume (FRLV) were determined. FRL volumetric share (FRLV%) was calculated using the following formula: $FRLV\% = \frac{FRLV}{TLV-TV} \times 100\%$.

### Statistical analysis

Continuous data are expressed as median and interquartile range (IQR) and/or mean and standard deviation (SD) when appropriate. Discrete variables are expressed as absolute numbers and relative frequencies. Differences in parametric data between groups were tested using unpaired t-test and in non-parametric data with the Mann–Whitney U test. Differences in categorical variables were tested using Fisher's exact test. Pearson rank correlation test was used to analyze the correlation between normally distributed variables. A two-sided *P*-value less than 0.05 was considered statistically significant. Statistical analysis was carried out using IBM SPSS Statistics (version 24.0; IBM Corp., New York, USA).

## Results

### Patients

Between January 2000 and December 2016, 127 patients with HCC underwent surgery with the intention of undertaking liver resection. Of these patients, 71 had undergone preoperative HBS of whom 24 patients did also undergo TE. Baseline characteristics are presented in Table 2.

### Histopathology of the non-tumorous liver tissue

Histopathological evaluation of liver resection specimens of all 71 patients is summarized in Table 3.

Based on histopathological grading, 25 (35%) patients had no to mild fibrosis (grade A–C) and 46 (65%) patients had severe fibrosis to definite cirrhosis (grade D–F). The majority of patients (n = 67, 94%) had no or mild steatosis (Grade 0–1).

Furthermore, based on the NAS, 57 (80%) patients had no steatohepatitis and the remaining 14 (20%) had borderline steatohepatitis. No patients had overt steatohepatitis.

### Association between HBS, histopathology and TE

A significant negative correlation was found between mebrofenin uptake rate (MUR, %/min) as determined by HBS with portal inflammation (Pearson r = −0.237, n = 71, $P = 0.047$), lobular inflammation (Pearson r = −0.342, n = 71, $P = 0.003$) and fibrosis grade (Pearson r = −0.314, n = 71, $P = 0.008$). Fig. 1 shows the MUR in patients with no to mild fibrosis compared to patients with severe fibrosis to cirrhosis. MUR was significantly higher in patients with no evident cirrhosis (15.79 (±0.63) vs 14.02 (±0.51) %/min, $P = 0.038$). Steatosis and ballooning, interface activity, NAS and siderosis had no significant correlation with MUR.

Of all the histopathology scoring variables, TE was associated with portal inflammation (Pearson r = 0.523, n = 24, $P = 0.009$), lobular inflammation (Pearson r = 0.533, n = 24, $P = 0.007$), ballooning (Pearson r = 0.578, n = 24, $P = 0.003$) and fibrosis grade (Pearson r = 0.444, n = 24, $P = 0.030$), Table 4.

Furthermore there was a significant correlation between MUR and TE (Pearson r = −0.634, n = 24, $P = 0.001$), Fig. 2.




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**Table 2** Patient demographics and baseline tumor characteristics in 71 patients with HCC with preoperative HBS

| Clinical characteristic and patient demographics | N = 71 |
|---|---|
| Male sex | 51 (72%) |
| Age at resection (median, IQR) | 63 (57–69) |
| BMI (median, IQR) | 24.8 (22.3–27.0) |
| Etiology of underlying disease | |
| Alcohol | 9 (13%) |
| Viral hepatitis[a] | 32 (45%) |
| NASH | 6 (8%) |
| Miscellaneous[b] | 4 (6%) |
| No known risk factors | 20 (28%) |
| Child Pugh (in patients with cirrhosis, n = 34) | |
| A | 33 (97%) |
| B | 1 (3%) |
| MELD-score (median, IQR) | 7 (6–8) |
| Preoperative assessment | |
| HBS | 71 (100%) |
| TE (Fibroscan®) | 24 (34%) |
| American Society of Anesthesiologists (ASA) classification | |
| ASA 1 | 6 (9%) |
| ASA 2 | 41 (58%) |
| ASA 3 | 23 (32%) |
| ASA 4 | 1 (1%) |
| Major resection (3 or more Couinaud segments) | 32 (45%) |
| Minor resection (<3 Couinaud segments) | 37 (52%) |
| No resection | 2 (3%) |
| Resection type | |
| Extended right hemihepatectomy | 4 (6%) |
| Extended left hemihepatectomy | 2 (3%) |
| Right hemihepatectomy | 17 (24%) |
| Left hemihepatectomy | 7 (10%) |
| Segmentectomy (<3 Couinaud segments) | 32 (45%) |
| Local Resection | 7 (10%) |
| No resection | 2 (3%) |

[a] HBV n = 11 (15%), HCV n = 18 (25%), HBV + HCV n = 3 (4%).
[b] Gaucher (n = 1), hemochromatosis (n = 1), auto-immune hepatitis (n = 2).

## FRL volume and function

Of all patients who underwent major liver resection, 28 underwent both preoperative HBS and CT. The median FRLF, corrected for BSA, was 3.4 (IQR 2.7–5.1)%/min/$m^2$ and the median FRLV% was 40.1 (IQR 34.3–60.6)%.

In this cohort, the FRLF and FRLV were not associated with the incidence of severe postoperative morbidity ($P = 0.308$ and $P = 0.516$) or 90-day mortality ($P = 0.962$ and $P = 0.083$). There was a significant correlation between FRLF and FRLV% (Pearson r = 0.654, n = 28, $P < 0.001$), Fig. 2. When analyzing the groups

**Table 3** Histopathology of non-tumorous liver tissue (N = 71)

| Non-tumorous liver parenchymas | N = 71 |
|---|---|
| **Portal inflammation** | |
| None | 0 (0.0) |
| Mild | 24 (34%) |
| Moderate | 33 (46%) |
| Severe | 14 (20%) |
| **Lobular inflammation** | |
| Grade 0: no foci | 22 (31%) |
| Grade 1: <2 foci per × 200 field | 36 (51%) |
| Grade 2: 2–4 foci per × 200 field | 12 (17%) |
| Grade 3: >4 foci per × 200 field | 1 (1%) |
| **Interface activity** | |
| None | 5 (7%) |
| Mild | 59 (83%) |
| Moderate | 7 (10%) |
| Severe | 0 (0%) |
| **Grade of steatosis** | |
| 0: <5% of hepatocytes | 36 (51%) |
| 1: 5–33% of hepatocytes | 31 (44%) |
| 2: 34–66% of hepatocytes | 4 (6%) |
| 3: >66% of hepatocytes | 0 (0%) |
| **Ballooning** | |
| No ballooning cells | 63 (89%) |
| Few ballooning cells | 5 (7%) |
| Many ballooning cells | 3 (4%) |
| **NAFLD activity score (NAS) = grade of steatosis + lobular inflammation + interface activity** | |
| <3: no steatohepatitis | 57 (80%) |
| 3–4: borderline steatohepatitis | 14 (20%) |
| ≥5: steatohepatitis | 0 (0%) |
| **Presence of siderosis** | |
| 0: none | 56 (79%) |
| 1: ≤25% of hepatocytes | 10 (14%) |
| 2: 26–50% of hepatocytes | 2 (3%) |
| 3: 51–75% of hepatocytes | 1 (1%) |
| 4: ≥76% of hepatocytes | 2 (3%) |
| **Fibrosis** | |
| A: none | 4 (6%) |
| B: perisinusoidal or periportal fibrosis | 10 (14%) |
| C: perisinusoidal and portal/periportal fibrosis | 11 (16%) |
| D: bridging fibrosis involved in <50% of the portal tracts and/or central veins | 12 (17%) |
| E: bridging fibrosis involved in >50% of the portal tracts and/or central veins | 8 (11%) |
| F: cirrhosis | 26 (37%) |




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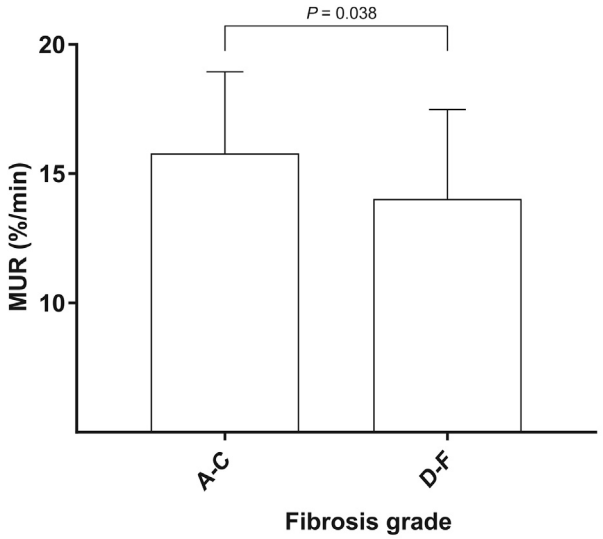


**Figure 1** Plot between MUR and fibrosis grade (mean and SD)

based on the severity of fibrosis, a significant correlation was found between FRLF and FRLV% in patients with no to mild fibrosis but not in patients with severe fibrosis to cirrhosis. (Pearson r = 0.791, n = 16, $P < 0.001$, vs. r = 0.381, n = 12, $P = 0.222$).

### Etiology of underlying liver disease

A total of 20 (28%) patients did not have any risk factors associated with chronic liver disease. Compared to all other groups, these patients had significantly higher MUR (16.11 (±3.43) vs. 13.97 (±3.28) %/min, $P = 0.019$) and on histological assessment, less severe fibrosis. The median fibrosis grades for patients without risk factors was B (IQR A–C) vs. E (IQR D–F) in patients with known risk factors (P < 0.001).

### Surgical outcomes

Outcomes after resection are shown in Table 5. In total, 7 patients developed PHLF of whom 4 patients died within 90 days. Data of these patients is presented in Table 6. The causes of 90-day mortality were liver failure (n = 4), septic shock (n = 2), recurrent disease (n = 1) or cardiac complications (n = 1).

In this cohort, there was no association between TE, MUR and overall severe morbidity and mortality. When comparing the groups based on the grade of fibrosis, no association was found between the histopathological scoring of background parenchyma and morbidity and mortality (Table 7). Patients with less severe fibrosis did undergo lesser resections, which was a statistically significant difference.

## Discussion

In this study we compared liver function measured with $^{99m}$Tc-mebrofenin HBS with morphological assessment of the background liver parenchyma in patients with resectable HCC. Simultaneously, we compared these with liver stiffness, measured with TE. This is the first study to compare these techniques with histopathological grading of the parenchyma. There was a moderate to strong correlation between liver function and TE. Furthermore, there was a weak to moderate negative correlation between MUR and fibrosis, portal and lobular inflammation. Regarding TE, there was a moderate positive correlation with fibrosis, portal and lobular inflammation and ballooning. Considering the strict selection criteria for surgery in patients with HCC, like ineligibility due to insufficient liver function, the population in this cohort is highly selected and relatively homogeneous. This explains why no association was found between liver function, TE and postoperative outcomes.

In the current study, MUR was lower in patients with a higher grade of fibrosis, implicating decreased liver function in these patients. An explanation for these findings could be that in the presence of severe hepatic fibrosis and cirrhosis, microcirculatory changes appear which affect the uptake of mebrofenin in the hepatocytes. Sinusoidal endothelial cells constitute the interface between blood cells and hepatocytes. Their fenestrae and the absence of a basement membrane render them highly permeable.[23,24] In response to chronic changes in the environment that

**Table 4** Correlation between histopathology, MUR and TE

| Pearson Correlation | MUR (%/min) (n = 71) | | TE (kPa) (n = 24) | |
|---|---|---|---|---|
| | Correlation coefficient | *P*-value (2-tailed) | Correlation coefficient | *P*-value (2-tailed) |
| Portal inflammation | –0.237 | **0.047** | 0.523 | **0.009** |
| Lobular inflammation | –0.342 | **0.003** | 0.533 | **0.007** |
| Interface activity | –0.177 | 0.140 | –0.123 | 0.566 |
| Steatosis | –0.012 | 0.921 | –0.029 | 0.894 |
| Ballooning | –0.185 | 0.123 | 0.578 | **0.003** |
| NAS | –0.180 | 0.133 | 0.238 | 0.263 |
| Siderosis | –0.215 | 0.072 | –0.105 | 0.625 |
| Fibrosis | –0.314 | **0.008** | 0.444 | **0.030** |

A two-sided P-value less than 0.05 was considered statistically significant.




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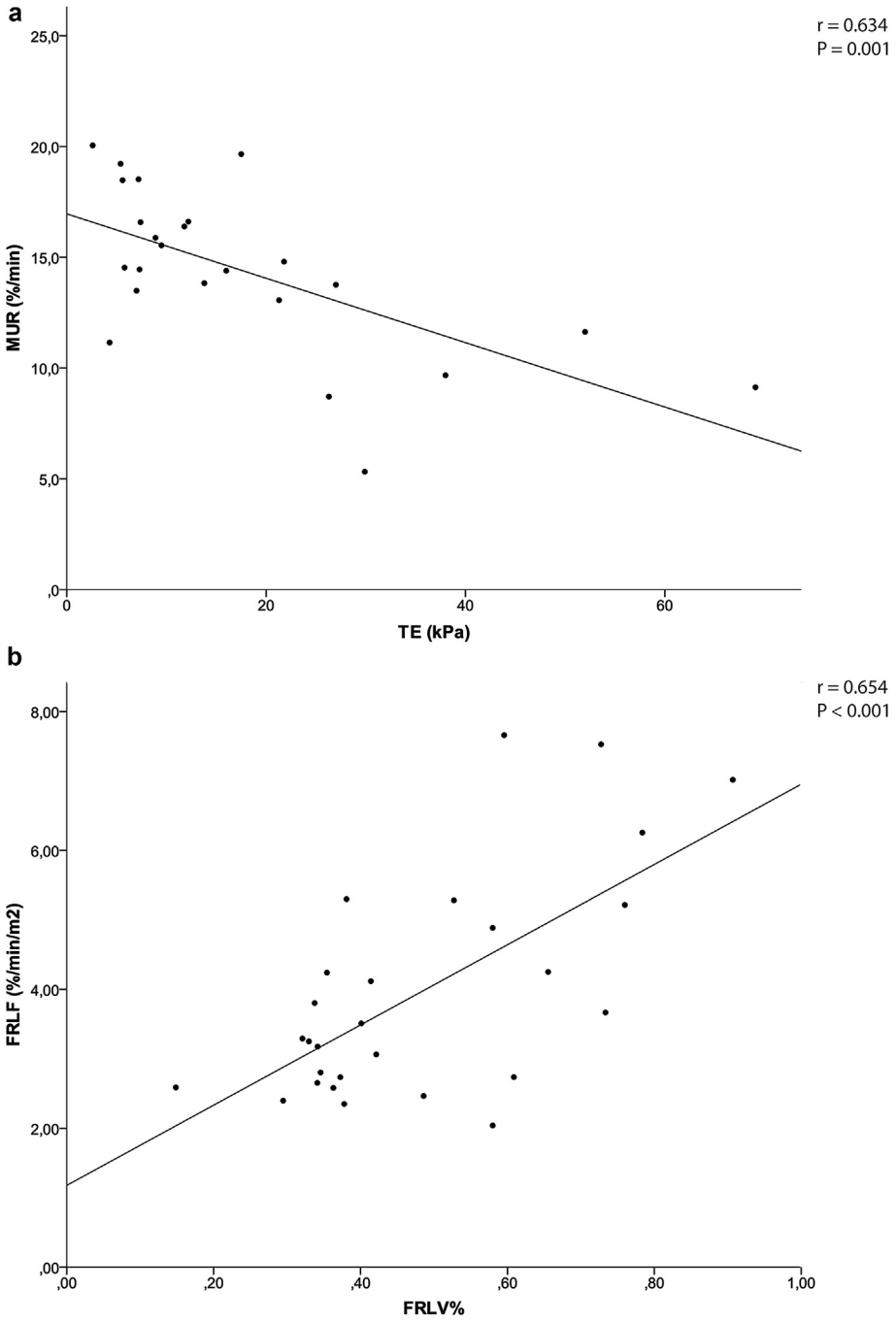


**Figure 2** Scatter-plot comparison showing a significant correlation of MUR (%/min) with TE (kPa) (a) and FRLF (%/min/$m^2$) with FRLV% (%) (b)

lead to fibrosis and cirrhosis, the number of fenestrations decrease.[25] This is accompanied with endothelial dysfunction, remodeling with formation of a basement membrane and vasoconstriction leading to impaired interaction between hepatocytes and sinusoids.[26] These alterations of the hepatic microcirculation likely lead to an impairment in the exchange between blood and hepatocytes, thereby influencing the elimination of drugs.[27] Along with decreased intrinsic function of hepatocytes featured in fibrosis and cirrhosis, the microvascular alterations may further contribute to the lower MUR.[27–29]

The negative correlation between MUR and portal and lobular inflammation can be explained by the expressional patterns of hepatic transporters. These are strictly regulated and influenced by a variety of factors to meet the physiological demands.[30] The




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**Table 5** Outcomes of liver surgery

| | Complications Dindo IIIa or higher | 90 days mortality | PHLF ISGLS (B–C) |
|---|---|---|---|
| All patients (n = 127) | 18 (14.2%) | 8 (6.3%) | 9 (7.1%) |
| Patients with preoperative HBS (n = 71) | 15 (21%) | 8 (11%) | 7 (10%) |
| Major liver resections (n = 32) | 8 (25%) | 6 (19%) | 3 (9%) |
| Minor liver resections (n = 37) | 7 (19%) | 2 (5%) | 4 (11%) |

**Table 6** Characteristic of patients developing posthepatectomy liver failure

| Pt | ISGLS grade | Resection | Etiology | Fibrosis grade | Death within 90 d | Total liver function (%/min) | FRL function[a] (%/min/m$^2$) | Exacerbating factor |
|---|---|---|---|---|---|---|---|---|
| 1 | C | Left hemihepatectomy | Viral hepatitis | B | Yes | 14,8 | 5,3 | 6 L blood loss during resection |
| 2 | C | Right hemihepatectomy | Viral hepatitis | D | Yes | 14,6 | 5,2 | 15 L blood loss due to injury to the vena cava |
| 3 | C | Segmentectomy | Viral hepatitis | E | Yes | 13,6 | | Infected ascites leading to respiratory and kidney failure |
| 4 | C | Right hemihepatectomy | Viral hepatitis | F | Yes | 19,4 | 2,4 | Sepsis with necrotizing pancreatitis |
| 5 | B | Wedge resection | Viral hepatitis | F | No | 9,4 | | Bacterial peritonitis leading to burst abdomen and kidney failure |
| 6 | B | Segmentectomy | Viral hepatitis | F | No | 11,6 | | Bacterial peritonitis leading to hepato-renal syndrome |
| 7 | B | Segmentectomy | Hemochromatosis | F | No | 12,6 | | Bacterial peritonitis and portal vein thrombosis |

[a] Patient 3, 5, 6 and 7 had all undergone (sub)segmentectomies. The exact FRL function could therefore not be calculated with SPECT but clearly represented a surplus.

**Table 7** Surgical outcomes of patients with no to mild fibrosis versus patients with severe fibrosis to cirrhosis

| | Fibrosis grade A–C n = 25 | Fibrosis grade D–F n = 46 | *P*-value |
|---|---|---|---|
| Morbidity Dindo >3a | 5 (20%) | 10 (22%) | 1.000 |
| 90D-mortality | 3 (12%) | 5 (11%) | 1.000 |
| Major resection | 20 (54%) | 12 (26%) | <0.001 |
| Liver failure | 1 (4%) | 6 (13%) | 0.409 |
| MUR (%/min) | 15.8 (±3.2) | 14.0 (±3.5) | 0.038 |

hepatic uptake of mebrofenin is mediated by organic anion transporting protein B1 and B3 and its biliary secretion is mediated by the conjugate export pump Multidrug resistance-associated protein 2 (MRP2). Inflammation has been shown to reduce their expression.[31,32]

Most patients in this series had no cirrhosis while cirrhotic patients had Child-Pugh score A with a median MELD score of 7 (IQR 6–8). Both scoring systems were not able to differentiate between patients with different grades of parenchymal damage. Although liver biopsy is considered the gold standard in the assessment of parenchymal disease, this method has drawbacks in routine application. These include bleeding complications, sampling error, observer variability and apart from being invasive, routine biopsy is costly and time-consuming.[33–35] This underscores the need for less invasive tools that can assess surgical risk in patients with HCC considered for resection.

TE is a noninvasive measurement of liver stiffness. Although quality of evidence was low, a recently published review and meta-analysis showed that TE has superior sensitivity and specificity in detecting liver cirrhosis in patients with chronic hepatitis B virus (HBV) infection, chronic hepatitis C virus (HCV) infection, NAFLD, and alcoholic liver disease.[36] The data presented in this study also demonstrates a good correlation between TE and severity of liver fibrosis and cirrhosis. TE measures liver stiffness using a volume of liver that is approximately 400 mm$^2$, which is 100 times greater in size than a standard liver biopsy, and thus may be more representative of the entire hepatic parenchyma. However, there are circumstances that can cause false elevations in TE measurements including active viral or autoimmune hepatitis, cholestasis or hepatic congestion. Nevertheless, a good correlation was observed in this study between TE and MUR, indicating that sampling




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heterogeneity was limited in this cohort. The correlation between liver stiffness and liver function determined by mebrofenin HBS has also been shown in an earlier study, in which a strong correlation was found between the two techniques[37]

During HBS, after the first dynamic acquisition, a SPECT is acquired. This falls in the phase where the highest amount of the mebrofenin is accumulated in the liver, making it possible to depict the three-dimensional functional distribution.[38] This aids in determining the segmental liver function which is of particular significance when planning resection. Some recent papers have argued that combining total liver function with liver volumetry could be reliable in the prediction of PHLF.[10] CT-volumetry offers an indirect estimation of liver function while liver function measured by HBS has proven more valuable in predicting liver failure than CT-volumetry.[39] In most patients with normal livers, volume correlates with function. However, in patients with compromised livers there is a discrepancy between volume and function while function is also not homogenously distributed in the liver.[40] Also in patients undergoing liver augmenting procedures such as portal vein embolization and ALPPS (Associating Liver Partition and Portal vein Ligation for Staged hepatectomy) a discrepancy between functional and volumetric increase was observed.[13,41,42]

In the present study, the correlation between function and volume was relatively good in patients with no to mild fibrosis (Pearson r = 0.791, P < 0.001) whereas in patients with severe fibrosis to cirrhosis, the correlation was less prominent and not significant (Pearson r = 0.381, $P = 0.222$).

The possibility to evaluate FRL function brings an additional advantage to the use of HBS over TE for surgical planning. In this cohort however, TE had no additional value over HBS in the preoperative workup and selection of patients for liver resection.

Irrespective of etiology, cirrhotic patients have an increased risk of developing HCC. However, 10–20% of HCC develops in patients without cirrhosis.[43] In this cohort, the proportion of patients with cirrhosis that developed HCC is lower than expected from literature. This is explained by the strict selection criteria for curative resection according to the BCLC grading system. Most patients with HCC present with advanced disease, rendering only a small number eligible for curative resection.[44] Furthermore, 20 (28%) patients had no known risk factors associated with HCC. Of these, 4 patients had no signs of fibrosis or cirrhosis on histological examination and most of the remaining patients had less severe fibrosis than patients with known risk factors ($P < 0.001$). These patients had on average higher MUR ($P = 0.019$), as is compatible with less pre-existent parenchymal damage.

Limitation of this study is the highly selected cohort of patients with HCC that were considered resectable. In clinical practice, the majority of patients with advanced fibrosis or cirrhosis are not eligible for surgical treatment due to impaired liver function and/or portal hypertension. Furthermore, the predicted FRL function in this cohort was sufficient enabling all patients to undergo resection, which likely is the reason why no association was found between MUR, TE and postoperative outcomes. The 7 patients that developed PHLF had severe postoperative complications ultimately leading to multi-organ failure including the liver, even in 4 patients that had undergone minor i.e.(sub) segmental liver resection. PHLF has multifactorial etiology and even in patients with sufficient FRL function, the risk of liver failure remains when severe complications occur during or after the resection. This cohort is therefore too small to draw conclusions on the use of HBS to assess suitability for resection. However, HBS has played a role in the selection of patients who had low FRL function to begin with and who were therefore not deemed eligible for resection.

Of note, a recent study showed that low preoperative elasticity measured with TE, was an independent predictor of PHLF for patients undergoing liver resection for HCC.[45] Further limitations of our study are the retrospective design and the small number of patients that underwent LSM (only 24 patients had undergone HBS as well as TE while fibrosis grade varied).

In conclusion, HBS and TE show a moderate to strong correlation. Both liver function measured with $^{99m}$Tc-mebrofenin HBS and liver stiffness measured with TE share discriminatory features of histopathological scoring as the gold standard. TE provides a practical, non-invasive tool to assess the grade of liver fibrosis while HBS has the advantage of assessing both global and regional liver function.

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## Conflicts of interest

None.

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