The value of virtual touch quantification in assessment of liver function reserve in hepatocellular carcinoma patients: a clinical study

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Research Article

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Abstract

Purpose: Quantitative assessment of liver function reserve (LFR) plays an important role in clinical management of hepatocellular carcinoma (HCC) patients. Reduced LFR is closely related to increased level of liver fibrosis. Virtual Touch Quantification (VTQ) is a non-invasive ultrasonic imaging technique. In this study, we aimed to explore the correlation between VTQ parameters and LFR levels in different stages of liver fibrosis.

Methods: From January 2016 to October 2018, 145 hepatocellular carcinoma patients (114 males and 31 females) scheduled for hepatectomy were enrolled in this study. All patients were histopathologically diagnosed and classified into five groups. The VTQ measurement and indocyanine green (ICG) clearance tests were performed following standard presurgical procedures. VTQ parameters and ICG retention values at 15min (ICG-R15) after ICG injection were compared among all staging groups using non-parametric Kruskal-Wallis test. Correlation between VTQ parameters and ICG-R15 was analyzed for all patients and patients within each staging group. We further divide patients into 3 groups by ICG-R15 values: Group 1 (ICG-R15 < 10%), Group 2 (ICG-R15 10%-20%) and Group 3 (ICG-R15 > 20%). The receiver operating characteristic (ROC) in detection of Group 3 patients using VTQ parameters was analyzed.

Results: (1) The ICG R15 values are significantly different among the five-liver fibrosis staging groups (F =7.149, P < 0.001). Moderate correlation was observed between VTQ and ICG R15 values (r = 0.575, p < 0.001) among all patients. (2) VTQ value of Group 2 was significantly higher than that of Group 1 (P = 0.013) and VTQ value of Group 3 was significantly higher than in Group 1 and 2 (P < 0.001; p = 0.005). Classifying a patient to have ICG R15 value greater than 20% (Group 3) given his/her VTQ value is above 1.8 m/s has 100% sensitivity and 78.1% specificity. The area under the ROC is 0.946 (95%CI: 0.895, 0.976, p <0.0001).

Conclusions: Non-invasive measurement of VTQ using ultrasound elastography techniques is a valuable tool for clinician to quantify liver fibrosis and assess liver functional reserve in HCC patients, *in vivo*, which, in turn, helps for the better preoperative planning of HCC patients.

Introduction

Reduced or absent of liver functional reserve (LFR) is one of the major pathophysiologic liver impairments in hepatocellular carcinoma (HCC) patients. Preoperative evaluation of LFR is critical for optimal surgical plan and prognosis in HCC patients. The Indocyanine green (ICG) clearance test is one of the most widely used quantitative methods for assessing LFR[1] levels due to its simplicity, reliability, high sensitivity and specificity. It can be used for pre-surgical planning and prediction of post hepatectomy liver failure[2]. In clinical practice, patients before surgical treatment are injected with ICG. Liver resection areas are then pre-determined based on the ICG retention value at 15 min (ICG R15) after injection according to the following criteria: for ICG-R15 values (1) less than 10%, major hepatectomy was considered possible; (2) 10–19%, removal up to Couinaud's sector was allowed; (3) 20–29%, removal up to Couinaud's single segmentectomy was allowed; (4) 30–39%, only limited resection was indicated; (5) more than 40%, enucleation was the only possible procedure. [3] However, ICG elimination test is dependent on hepatocyte function, liver blood flow and bile secretion. It is also not suitable for patients with obstructive jaundice and iodine allergy. Under such circumstances, alternative tools are needed to assist clinicians for better preoperative LRF assessment.

Loss of LRF is closely related to the development of liver fibrosis[4]. Conventional method for diagnosis of liver fibrosis consists of liver biopsy. Staging (S0-S4) of fibrosis was determined semi-quantitatively using scoring systems such as the Scheuer scoring[5] or Batts-Ludwig scoring [6]. However, as an invasive procedure, liver biopsy suffers from sampling errors, as well as potential complications including bleeding and severe pain. Several noninvasive parameters have been proposed for the diagnosis and assessment of liver fibrosis. Clinical scoring systems including Child-Pugh score and model for end-stage liver disease (MELD) score, liver fibrosis biomarkers including fibrosis index based on four factors (FIB-4) and aspartate transaminase-to-platelet ratio index (APRI) are widely used to assess liver fibrosis and LFR [4, 7, 8].

Hepatic fibrosis is an abnormal accumulation of collagen decomposition and other extracellular matrix components. It is often associated with morphological and elastic property changes in liver., Techniques sensitive to tissue morphology and stiffness, such as ultrasound elastography and magnetic resonance (MR) imaging elastography, can be used for evaluating liver fibrosis and LFR [9]. MR elastography, expensive and the vulnerable to body mass index and liver iron deposition, finds limited use in daily clinical practice[10]. On the other hand, ultrasound elastography is cheaper, repeatable and easy to use, and is increasingly adopted for routine non-invasive liver examinations. Virtual touch quantification (VTQ) is an emerging quantitative US elastography methods for quantitative assessing tissue stiffness by measuring shear-wave speed within tissue. In stiffer tissues, the VTQ is greater. VTQ has previously been used for detecting liver fibrosis[10]. Different cut-off values have been proposed for different conditions. Although previous studies have found significant correlation between elastography parameters and LFR in different stages of liver fibrosis in the laboratory animals, the correlation between VTQ and LFR has not been characterized and validated using clinical data. [11, 12]

In this study, we compared the diagnostic performance of Child-Pugh score, MELD score, APRI, FIB-4 and VTQ in pre-operative evaluation of liver fibrosis and LFR. In addition, we evaluated VTQ in the detection of LFR impairment in different stage of liver fibrosis.

Patients And Methods

Patients

From January 2016 to October 2018, HCC patients received treatment in Department of Hepatobiliary Surgery and scheduled for potential hepatectomy at Nanjing University Medical School Affiliated Nanjing Drum Tower Hospital, were enrolled in this retrospective study. The exclusion criteria were (1) diffuse liver tumors, or the tumor is very large and there's not enough normal liver parenchyma surrounding it (2) elastography examination failure, such as severe cirrhosis and liver atrophy or large volume paracentesis (3) ICG test failure, such as acute cholangitis or obstructive jaundice. Routine liver biochemistry was performed. This study was carried out in accordance with the Declaration of Helsinki and was approved by our hospital’s institutional review board (2021-294-02)

Blood markers and biological examination

Blood samples were obtained from the patient after overnight fasting before surgery. The following routine blood markers were measured: ALT (alanine aminotransferase), AST (aspartate aminotransferase) and PLT (platelet count). The APRI and FIB-4 were calculated using the formula.[13]

$$APRI = \left(\frac{ALT}{ASTULN} * 100 \right) / PLT$$

where ASTULN is the upper limit of the normal AST value (40 IU/L).

$$FIB - 4 = (Age \times AST) / (PLT \times ALT\frac{1}{2})$$

Child-Pugh score was calculated and ranked based on patient’s blood samples and physical condition.[14].End-stage liver disease (MELD) score was calculated.

$$\mathrm{MELD} = 10 \times \{ 0.957 \times \ln(\mathrm{serumcreatinine}) + 0.378 \times \ln(\mathrm{totalbilirubin}) + 1.12 \times \ln(\mathrm{prothrombintime} + 0.643) \}$$

ICG Clearance Test

The ICG clearance test was performed using the DDG-3300K liver reserve function analyzer (Nihon Kohden, Tokyo, Japan) with the patient fasted for 6 hours. For each patient, ICG was administered intravenously at a dose of 0.5 mg/kg. The entire ICG solution was injected to the median cubital vein via the indwelling needle in 10 s. Blood ICG concentrations were monitored before and 5, 10 and 15 min after administration, and ICG R15 is the ratio between the ICG concentration 15 min after injection and the initial concentration. ICG R15 greater than 20% is often considered to be a contraindication to major hepatectomy[3, 15].

VTQ of non-tumor liver tissue

We used a 4C-1 curved array transducer (ACUSON S2000™, Siemens Medical Solutions, USA) to perform both real-time gray-scale imaging and VTQ. All measurements were performed by three observers with at least 10 years of experience in sonographic examination and were blinded to the clinical data.

Patients were placed in a supine position. During real-time gray-scale imaging, we used VTQ to measure the shear wave velocity of the liver using the intercostal approach. The measurements were standardized according to the following protocol[9]: (1) The region of interest (ROI) was acquired 1–2 cm from the capsule of the liver. (2) The location of ROI was placed in the parenchyma of liver to avoid reverberation artifacts and to keep away from “visible” vessels (3) The location of ROI was placed more than 2cm away from tumor. (4) The patients were instructed to hold their breath at the end of expiration. In each patient, five valid VTQ were performed. The results are expressed in m/s. The results were considered reliable when a measurement success rate of at least 60% in 5 acquisition trials was obtained. Besides, the median value was considered representative of the VTQ only if the interquartile range of all validated measurements was within 30% of the median value[16]. **(Fig. 1)**

Histological analysis of non-tumor liver tissue

Liver specimens obtained from surgical were fixed in formalin, embedded in paraffin, and stained with HE trichrome. Non-tumor liver tissue was defined as liver parenchyma greater than 2cm away from the tumor. All specimens of non-tumor liver tissue were analyzed by one experienced pathologist with 15 y of clinical experience who was blinded to the patients’ elastography results and the clinical data. Liver fibrosis staging (S0-S4) was evaluated semi-quantitatively according to the Batts-Ludwig scoring system. Fibrosis was staged on a scale from 0 to 4: stage 0 (S0), no fibrosis, normal connective tissue; stage 1 (S1), portal fibrosis, fibrous portal expansion; stage 2 (S2), periportal fibrosis, periportal or rare portal-portal septa; stage 3 (S3), sepal fibrosis, fibrous septa with architectural distortion; and stage 4 (S4), cirrhosis[6]. **(Fig. 1)**

Statistical analysis

All data were analyzed using the statistical package SPSS (version 18.0, SPSS Inc, Chicago, IL, USA). Continuous variables were expressed as the mean ± standard deviation or median and interquartile. Categorical variables as counts and percentages. Chi-square (χ^2) test or Fisher exact test were used to analyze the categorical variables. Because many of the variables were not normally distributed, the Kruskal-Wallis test was used for comparisons of more than two independent groups.

Spearman or Pearson correlation coefficients were obtained between e Child-Pugh score, MELD score, APRI, FIB-4, VTQ and ICG R15 after performing a normality test. Pearson correlation coefficient was obtained only when two variables showed normal distribution. The interpretation of coefficients was as follows: Correlation coefficients (r) were classified as follows: almost none, $|r| < 0.2$; mild, $|r| = 0.2$-0.4; moderate, $|r| = 0.4$-0.7 and strong, $|r| \geq 0.7$. A two-sided P value < 0.05 was considered statistically significant. [11]

Results

Patient Characteristics

A total of 145 HCC patients scheduled for potential hepatectomy (114 male and 31 females; mean age: 58.6 ± 11.2 years) were retrospectively enrolled; demographic, clinical, and biochemical characteristics of the entire population are shown in **Table 1.**

Table 1

Baseline Characteristics of the Study Population

Variable	Result
No. of patients	145
Men (n, %)	114/78.6
women (n, %)	31/21.4
Age (y)	58.6 ± 11.2
HBsAg n (%)	91/62.8
Final diagnosis	HCC
ALT (U/L)	67.4 (32.2,142.9)
AST (U/L)	39.2 (23.4,76.9)
PLT($\times 10^9$/L)	150.0 (106.0, 195.5)
APRI	0.6 (0.4,1.2)
FIB-4	0.5 (0.3,1.0)
Child-Pugh score	5.2 ± 0.6
MELD score	7.6 ± 1.9
VTQ (m/s)	1.5 ± 0.4
ICG R15 (%)	5.3 (3.5,8.9)

HCC (hepatocellular carcinoma), ALT(Aminotransferase), AST (Aspartate aminotransferase), PLT(Platelets), APRI (aminotransferase-to-platelet ratio index), FIB-4 (fibrosis index based on four factors), MELD (model for end-stage liver disease), VTQ (Virtual Touch Quantification), ICGR15 (indocyanine green retention rate at 15 min)

Correlation analysis of Child-Pugh score, MELD score, APRI, FIB-4, VTQ and ICG R15

The correlations between Child-Pugh score, MELD score, APRI, FIB-4, VTQ and ICG R15 were verified. As Fig. 2 showed moderate correlations between VTQ and ICG R15 values ($r = 0.575$, $p < 0.001$). Mild correlation was observed between Child-Pugh score, MELD score, APRI, FIB-4 and ICG R15 ($r = 0.386, 0.300, 0.233, 0.249$, $p < 0.05$).

Correlation analysis of VTQ and ICG R15 in different stages of liver fibrosis

According to Batts-Ludwig scoring system of liver fibrosis, 145 patients in our study were classified into five groups: S0(n = 35), S1 (n = 29), S2 (n = 19), S3 (n = 19) and S4 (n = 43). The liver biochemistry assay results are shown in Table 2. Except for PLT count, ICG R15 and VTQ, all blood markers and clinical score remained similar among the five histologic groups ($P > 0.05$). A positive correlation was observed between ICG R15 and liver fibrosis staging ($r = 0.357$, $p < 0.001$).

The mean ± std of VTQ values for stages S0–S4 were 1.2 ± 0.2 m/s, 1.3 ± 0.3 m/s, 1.4 ± 0.3 m/s, 1.7 ± 0.4 m/s, 1.9 ± 0.4 m/s, respectively. VTQ significantly differed among the five histologic groups (F = 23.438, P < 0.001). The mean VTQ of S4 was significantly higher than that of S0, S1, S2 (p < 0.05). The mean VTQ of S3 was significantly higher than that of S0 and S1 (p < 0.05).

The mean ICG R15 of stages S0–F4 were 4.3 ± 2.6(%), 5.1 ± 2.7(%), 5.9 ± 2.6(%), 8.2 ± 5.3(%), 10.4 ± 8.7(%), respectively. ICG R15 significantly differed among the five histologic groups (F =7.149, P < 0.001). The mean ICG R15 of S4 was significantly higher than that of S0, S1, S2 (p < 0.05). **(Table 2)**

A positive correlation was observed between VTQ and ICG R15 (r = 0.575, p < 0.001). In S1, S3 and S4 of liver fibrosis staging, the correlation between VTQ and ICG R15 values was moderate (r = 0.442, 0.627, 0.519, p < 0.05). In S0 and S2 of liver fibrosis staging, there is little correlation between VTQ and ICG R15 (p>0.05). **(Fig.2)**

Table 2

Characteristics of HCC patients in different stages of liver fibrosis (n = 145)

Variable	S0 (n=35)	S1 (n=29)	S2 (n=19)	S3 (n=19)	S4 (n=43)	c^2	P value
Sex (male, %)	24/68.5	17/58.6	11/57.8	16/84.2	39/90.6	0.615	0.591
Age (y)	57.2 ± 11.1	58.3 ± 9.4	62.5 ± 12.5	64.4 ± 11.1	55.5 ± 10.8	1.123	0.348
ALT (U/L)	79.7(33.7, 147.9)	63.2(33.1, 145.8)	64.5(51.0, 76.0)	56.7(30.7, 146.5)	64.7(31.4, 112.5)	0.732	0.571
AST (U/L)	46.7(22.4,105.0)	43.8(25.5, 107.3)	37.3(18.7, 61.8)	26.1(21.2, 77.2)	40.2(24.6, 76.2)	1.190	0.318
PLT ($\times10^9$/L)	169.0(142.0, 201.0)	182.0(146.5, 243.5)	155.0(106.0, 176.0)	115.0(73.0, 149.0)	109.0(81.0, 172.0)	**6.586**	**<0.001**
APRI	0.6(0.3, 1.5)	0.5(0.3, 1.4)	0.5(0.4, 0.9)	0.7(0.5, 0.9)	0.8(0.4,1.3)	0.930	0.448
FIB-4	0.4(0.3, 0.9)	0.4(0.3, 0.6)	0.6(0.3, 0.8)	0.7(0.4, 1.8)	0.7(0.4, 1.2)	1.502	0.205
Child-Pugh score	5.2 ± 0.5	5.2 ± 0.7	5.0 ± 0.0	5.3 ± 0.6	5.3 ± 0.8	0.659	0.621
MELD score	7.1 ± 1.2	8.0 ± 3.2	7.2 ± 0.9	7.6 ± 1.4	7.8 ± 1.5	1.182	0.321
ICG R15 (%)	3.9(2.2, 6.0)	4.8(3.0, 7.1)	5.4(4.0,7.0)	7.1(4.4, 10.7)	8.4(4.0, 14.3)	**7.149**	**<0.001**
VTQ (m/s)	1.2 ± 0.2	1.3 ± 0.3	1.4 ± 0.3	1.7 ± 0.4	1.9 ± 0.4	**23.438**	**<0.001**

HCC (hepatocellular carcinoma), ALT(Aminotransferase), AST (Aspartate aminotransferase), PLT(Platelets), APRI (aminotransferase-to-platelet ratio index), FIB-4 (fibrosis index based on four factors), MELD (model for end-stage liver disease), VTQ (Virtual Touch Quantification), ICGR15 (indocyanine green retention rate at 15 min)

Diagnostic performance of VTQ in the detection of patients from different ICG R15 grouping

Previous studies have showed that when ICG-R15 was less than 10%, patients are tolerant of major hepatectomy, while ICG R15 values greater than 20% is often considered to be a contraindication to major hepatectomy. Here we evaluate VTQ in predicting patient's ICG-R15 test outcomes. Accordingly, 145 patients were divided into three groups: Group 1(ICG-R15 < 10%, n = 118), Group 2(ICG-R15 10%-20%, n = 18) and Group 3(ICG-R15 > 20%, n = 8). The mean ± std of VTQ for Group 1-3 were 1.4 ± 0.4 m/s, 1.8 ± 0.4 m/s, 2.4 ± 0.4 m/s respectively. VTQ significantly differed among patients in the three groups (F = 30.664, P < 0.001).

VTQ in Group 2 was significantly higher than in Group 1 (P = 0.013). VTQ in the Group 3 was significantly higher than in Group 1 and 2 (P < 0.001; p = 0.005).

Table 3

Diagnostic performance of VTQ in the detection of patients from different ICG R15 grouping

	Group 1 (R15≤10%) (n=119)	Group 2 (10%<R15<20%) (n=18)	Group 3 R15≥20% (n=8)	c^2	p value
Sex (male, %)	91/76.5	16/88.9	7/87.5	0.908	0.406
Age (y)	58.1 ± 11.1	60.7 ± 12.1	59.5 ± 11.3	0.432	0.65
ALT (U/L)	67.4(32.4,138.3)	82.6(46.0,158.7)	48.1(21.1,172.4)	1.063	0.348
AST (U/L)	37.2(22.2,75.3)	42.4(34.9,119.2)	57.6(24.5,178.2)	1.255	0.288
PLT($\times10^9$/L)	155.0(109.0,199.0)	140.0(105.0,186.0)	84.5(54.5,165.0)	3.210	0.043
APRI	0.5(0.4,1.1)	0.8(0.6,1.5)	1.1(0.4,2.7)	1.657	0.194
FIB-4	0.6(0.3,0.9)	0.6(0.4,1.0)	1.9(1.1,2.9)	11.812	**0.001**
Child-Pugh score	5.1±0.5	5.4±0.9	6.1±1.1	26.637	**0.001**
MELD score	7.5 ± 1.8	8.0 ± 1.2	8.3 ± 2.6	1.199	0.305
VTQ (m/s)	1.4 ± 0.4	1.8 ± 0.4	2.4 ± 0.4	30.664	**0.001**

ICGR15 (indocyanine green retention rate at 15 min), ALT(Aminotransferase), AST (Aspartate aminotransferase), PLT(Platelets), APRI (aminotransferase-to-platelet ratio index), FIB-4 (fibrosis index based on four factors), MELD (model for end-stage liver disease), VTQ (Virtual Touch Quantification),

Diagnostic performance of VTQ in the detection of patients with ICG R15 greater than 20%

The receiver operating characteristic (ROC) curve of VTQ in the detection of patients with ICG R15 greater than 20% was shown in **Fig. 3**. The area under the ROC is 0.946 (95%CI: 0.895, 0.976, p <0.0001). At cut-off value of VTQ, 1.8 m/s, corresponding sensitivity and specificity was 100%, 78.1%, respectively.

Discussion

HCC remains one of the most lethal diseases in the world[17]. Quantification of LFR is of critical concern during pre-surgical planning and prognosis of HCC patients. ICG R15 has been one of the most widely adopted tests for LFR, due to its simplicity, reproducibility and high detection power. Since LFR is closely related to liver fibrosis, LFR can also be indirectly quantified using fibrosis biomarkers. Current gold standard for diagnosing and staging liver fibrosis is liver biopsy. Batts-Ludwig scoring system provides a measure of severity of the hepatitis at the time of biopsy or surgery and also helps in assessing effect of the treatment[6, 18]. Other noninvasive parameters (Child-Pugh score, MELD score, FIB-4) have also been proposed for the diagnosis and assessment of liver fibrosis. VTQ is an emerging noninvasive quantitative imaging technique sensitive to tissue stiffness, which allows for accurate and clinically significant test of liver fibrosis. The purpose of the study was to verify the value of VTQ in assessment of LFR impairment with various liver fibrosis stages and compare its diagnostic performances to other non-invasive biomarkers.

Child-Pugh score and MELD score were initially used to evaluate prognosis in liver cirrhosis and rank candidates for transplantation, and have been recently applied to estimate LFR[7, 19, 20]. World Health Organization recommends the FIB-4 and APRI as non-invasive tools to detect significant fibrosis[4, 21]. In our study, surprisingly, we found that Child-Pugh score, MELD score, APRI, FIB-4 are not significantly associated with LFR (r = 0.386, 0.300, 0.233, 0.249, p < 0.001). This may be a

result of the fact that HCC patients scheduled for hepatectomy in this study have normal or slightly fibrosis, and most of the patients' Child-Pugh score ranged from 5 to 7. Using Child-Pugh score and MELD score, APRI and FIB-4 scores for LFR assessment has also been challenged[??]. Child-Pugh score calculation includes subjective criteria, such as ascites and encephalopathy. And albumin and ascites in the formula are inter-correlated. Serum creatinine levels in the formula of MELD score can be significantly affected by factors like age and gender [19]. According to the formula, AST and ALT could reflect the degree of liver disorder, and PLT could reflect the patient's portal hypertension status. The platelet count can serve as indicators of fibrosis. A low platelet count level was demonstrated to be an unfavorable factor in HCC. Compared to APRI, FIB-4 also take age into consideration. Age is a risk factor to determine the prognosis of patients with HCC.

Moreover, we found histologic grading of fibrosis does not necessarily correlate with ICG R15 ($r = 0.357$, $p < 0.001$). Among the 5 histological groups in our study, the mean ICG R15 of S4 was significantly higher than that of S0, S1, S2 ($p < 0.05$). Differences in other groups were not statistically significant. This means liver fibrosis staging in noncancerous parenchyma may not fully reflect changes in LFR. One potential explanation is that histologic grading of fibrosis may over- or underestimate the disease severity due to the use of a limited liver tissue sample.[12] In fact, the use of liver biopsy to assess the LFR is often avoided in our clinical practice.

This study showed that correlation coefficient between VTQ and ICG R15 was 0.487 ($p < 0.001$). This implied that VTQ value increases as ICG-R15 levels increase, resulting in reduced hepatic clearance and aggravated liver damage. [22]. The correlations between VTQ and ICG R15 values were moderate in S1, S3 and S4 ($r = 0.442, 0.627, 0.519$, $p < 0.05$), whereas little correlations were found between VTQ and ICG R15 in S0 and S2 ($p>0.05$). Sever previous studies have confirmed the correlation between liver stiffness and LFR with relation to liver fibrosis histologic staging in animal models[12, 23]. Our study is the first to demonstrate that liver elasticity, measured by VTQ, is related to reserve function, especially in severe liver fibrosis and cirrhosis, using clinical data. Recent progress that integrates ultrasound elastography technologies into ultrasound systems makes elastography (VTQ) a convenient and economic supplementary approach for clinical assessment for LFR. Furthermore, it has been reported that operative procedures selected according to the liver stiffness, which differed markedly from those expected from the indocyanine green test values, have achieved good clinical outcomes [24].

In clinical practice, ICG-R15 was less than 10% in normal people. Patients with ICG R15 greater than 20% are often considered to be contraindications to major hepatectomy. Accordingly, our patients were divided into three groups: Group 1(ICG-R15 < 10%, n = 118), Group 2(ICG-R15 10%-20%, n = 18) and Group 3(ICG-R15 > 20%, n = 8). VTQ, FIB-4 and Child-Pugh score significantly differed among patients in the three groups ($P < 0.05$). VTQ in Group 2 was significantly higher than that in Group 1 and VTQ in Group 3 was significantly higher than that in Group 1 and 2 ($P < 0.05$). This suggested that VTQ parameters are negatively correlated with LFR. The higher the VTQ value, the worse the LFR. Predicting patients to have ICG R15 greater than 20% and thus to be a contraindication to major hepatectomy given his/her VTQ value is above 1.8 m/s (cut-off) has achieved 100% of specificity and 78.1% of sensitivity.

Several limitations are inherent in the current study. Firstly, our findings were based on a retrospective study with small numbers of patients from a single Chinese hospital. Selection bias may affect the reliability of our results. Our result must be validated by larger, multicentric studies and from a longitudinal analysis. Secondly, VTQ measurement may be affected by several factors, including respiration, precompression and the operator's experience and skills. Several conditions other than liver fibrosis can increase liver stiffness: liver inflammation, steatosis, cholestasis, central venous pressure, and even food intake. Thirdly, LFR also depends on liver volume resection and patient's performance status. Clinically, ICG R15 alone is insufficient to determine LFR.

In conclusions, VTQ showed a moderate positive correlation with ICG R15, which was considered to be an independent standard of LFR. VTQ may be used as an imaging-based quantifiable metric for LFR estimation. VTQ greater than 1.8 m/s suggested poor liver reserve function. Clinicians can use ultrasound elastography technology to measure VTQ and assess LFR to determine if a patient is suitable for surgery; thereby, determining the best type of surgical procedure to be performed.

Abbreviations

HCC: Hepatocellular carcinoma; CEUS: Contrast-enhanced ultrasound; 2DUS:

Two-dimensional ultrasound; TUS: Therapeutic ultrasound; US: Ultrasound; AP:

Arterial phase; LP: Late phase.

Declarations

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None

Authors' contributions

Guarantor of the article: J.Y., W.K.; Designed the study, interpreted data and wrote the manuscript: C.L.; Data Collection: L.G., B.W., H.H., J.Y., Q.Y, L.M. and M.W.;W.K reviewed the results and made critical comments on the manuscript. All authors approved the final version of the manuscript.

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Availability of data and materials

The datasets used and analyzed during the current study are available from

the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was approved by Nanjing Drum Tower Hospital Ethics Committee (2021-294-02)

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests

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Figures

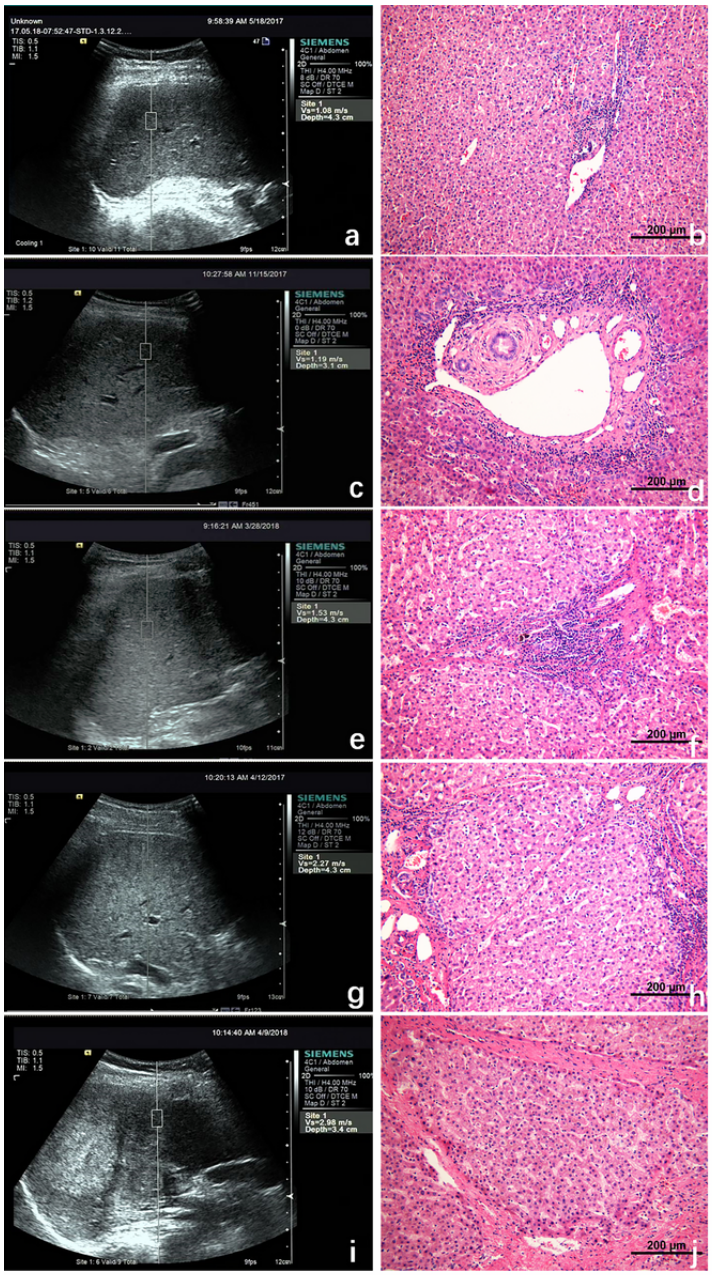

Figure 1

Liver stiffness with different degrees of fibrosis measured using Virtual touch quantification (VTQ) and its relevant indocyanine green retention rate at 15 min (ICG R15). **a & b** (VTQ 1.08m/s, S0, ICG R15 3.6%), **c & d** (VTQ 1.19m/s, S1, ICG R15 2.7%), **e & f** (VTQ 1.53m/s, S2, ICG R15 8.8%), **g & h** (VTQ 2.27m/s, S3, ICG R15 20.4%), **i & j** (VTQ 2.98m/s, S4, ICG R15 23.7%)

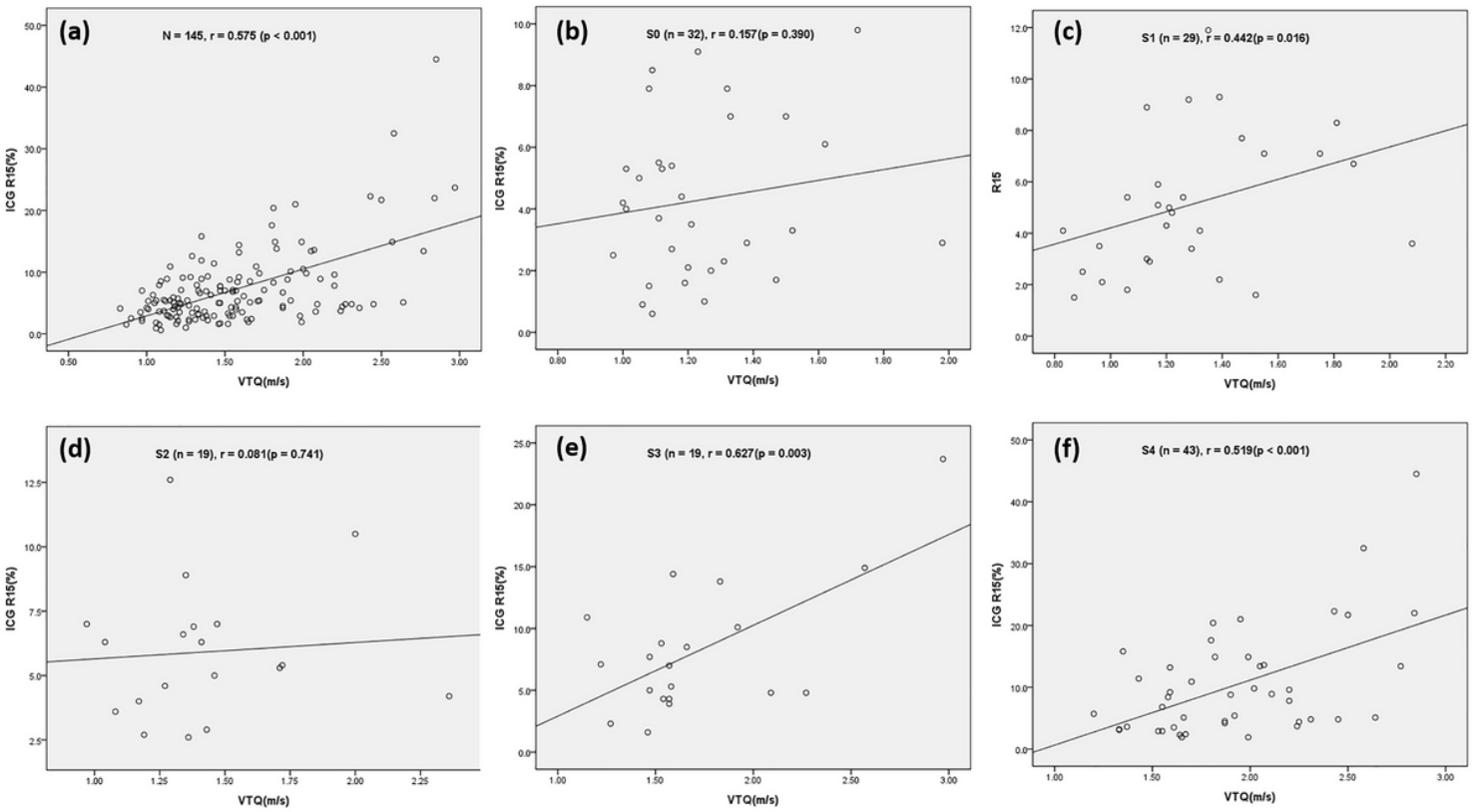

Figure 2

Correlation between Virtual Touch Quantification (VTQ) and indocyanine green retention rate at 15 min (ICG R15) in different stages of liver fibrosis **a** A positive correlation was observed between VTQ and ICG R15 ($r = 0.575$, $p < 0.001$). **b** In S0, there is little correlation between VTQ and ICG R15 ($r = 0.157$, $p = 0.390$). **c** In S1, the correlation between VTQ and ICG R15 was moderate ($r = 0.442$, $p = 0.016$). **d** In S2, there is little correlation between VTQ and ICG R15 ($r = 0.157$, $p = 0.390$). **e** In S3, the correlation between VTQ and ICG R15 was moderate ($r = 0.627$, $p = 0.003$). **f** In S4, the correlation between VTQ and ICG R15 was moderate ($r = 0.519$, $p < 0.001$).

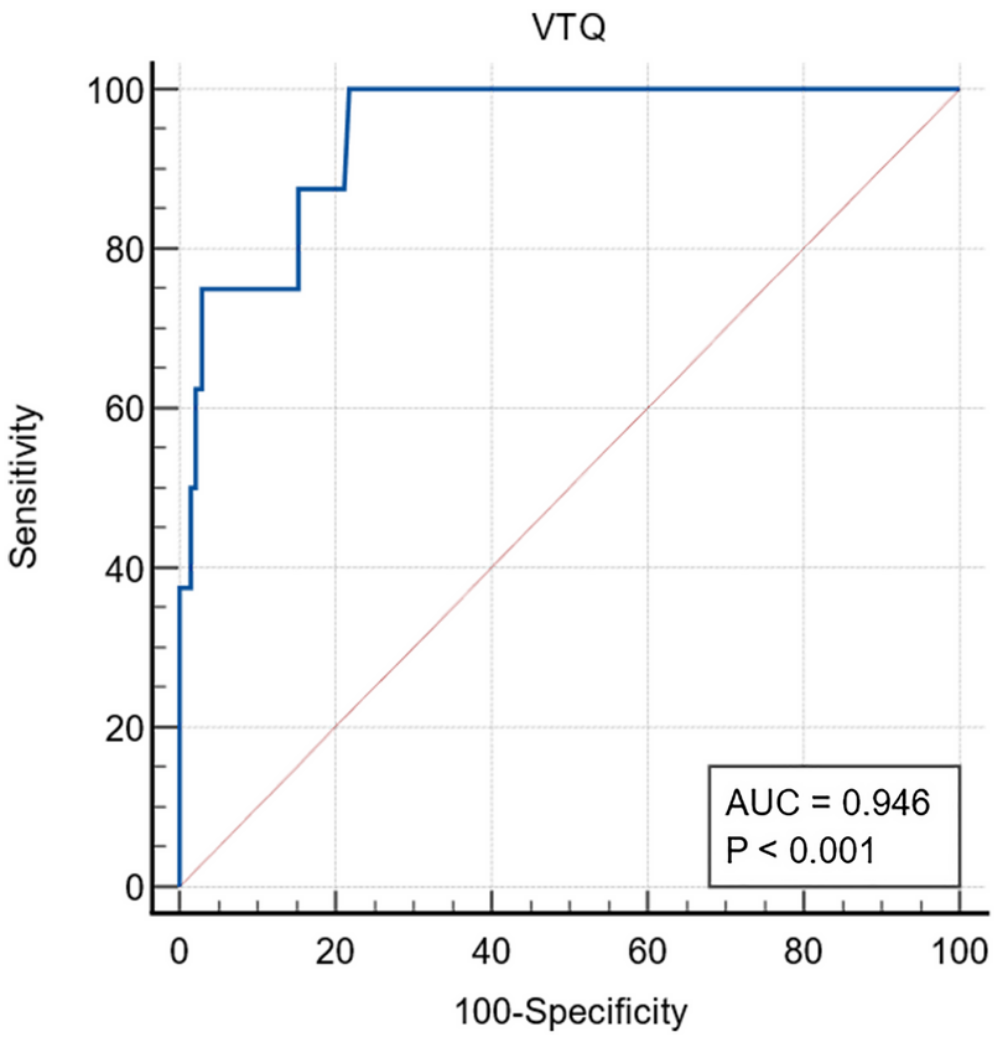

Figure 3

Diagnostic performance of Virtual Touch Quantification (VTQ) in the detection of patients with indocyanine green retention rate at 15 min (ICG R15) greater than 20%.