An Assessment of the Clinical Accuracy of Ultrasound in Diagnosing Cirrhosis in the Absence of Portal Hypertension

Erin M. M. Kelly, MD, Vickie A. Feldstein, MD, Monica Parks, BS, Rebecca Hudock, BS, Dustin Etheridge, BAC, and Marion G. Peters, MD

Dr Kelly is an assistant professor of medicine in the Division of Gastroenterology and Hepatology at the University of Ottawa in Ottawa, Canada. Dr Feldstein is a professor of clinical radiology in the Department of Radiology & Biomedical Imaging at the University of California, San Francisco in San Francisco, California. Ms Parks is a medical student at the University of California, San Francisco. Ms Hudock is a pharmacy student in the Division of Pharmacy at the University of California, San Francisco. Mr Etheridge is an independent statistician in Ottawa, Canada. Dr Peters is a professor of medicine in the Division of Gastroenterology and Hepatology at the University of California, San Francisco.

Address correspondence to:
Dr Erin M. M. Kelly
Division of Gastroenterology and Hepatology
University of Ottawa
The Ottawa Hospital, General Campus
501 Smyth Road W1203, Box 255
Ottawa, Ontario, Canada K1H 8L6
Tel: 613-737-8899, ext 73002
Fax: 613-737-8296
E-mail: ekelly@toh.on.ca

Keywords
Cirrhosis, nodular, ultrasound, fibrosis, liver biopsy

Abstract: Ultrasound is an invaluable tool for the diagnosis of hepatocellular carcinoma and portal hypertension. However, the accuracy of ultrasound in diagnosing cirrhosis in the absence of portal hypertension has not been well studied. Using the specific terms cirrhosis or nodular(ity), a retrospective evaluation was conducted on abdominal ultrasounds performed between 2008 and 2013. Patients with evidence of portal hypertension were excluded from the evaluation. Charts were reviewed for evidence of cirrhosis on liver biopsy performed within 1 year of the ultrasound. Of the 69 patients whose ultrasound findings reported cirrhosis without portal hypertension who underwent liver biopsy, 47 (68%) had histologic evidence of cirrhosis. When patients with advanced fibrosis (F3 or F4) on liver biopsy were included, the sensitivity of the ultrasound improved to 80%. One in 5 biopsies showed only mild to moderate or no fibrosis (F0-F2). Sonographic assessment by experts may falsely suggest or overestimate cirrhosis. In the absence of objective evidence of portal hypertension, caution should be taken in diagnosing cirrhosis based on sonographic interpretation alone.

Ultrasound is an invaluable tool in the management of patients with suspected or known liver disease. Sonography is widely and effectively used for surveillance and screening in patients at risk for hepatocellular carcinoma and for evaluating hepatic vasculature when combined with Doppler ultrasound.[1,2] Additionally, sonography is the most common imaging modality for the assessment of patients with newly diagnosed liver disease. Decompensated cirrhosis with portal hypertension, which manifests through varices, splenomegaly, and ascites, is well demonstrated on ultrasound. In fact, it can sometimes be the first indication of liver disease, prompting further evaluation for diagnosis and treatment. Conversely, abdominal ultrasound imaging may identify liver nodularity, suggesting cirrhosis without overt signs of portal hypertension in otherwise asymptomatic patients. Such imaging findings may lead to an extensive diagnostic evaluation to assess and stage liver

disease, including the use of liver biopsy, which is invasive and expensive. Although it is important to interpret ultrasound images, aiming for high sensitivity in order to minimize the number of false-negative results, it is also necessary to recognize the possibility and consequences of false-positive examinations. A diagnosis of cirrhosis on ultrasound informs and alters the clinical management of patients. Hepatologists caring for patients who have been diagnosed with cirrhosis are recommended to screen for hepatocellular carcinoma with abdominal imaging examinations every 6 months as well as to evaluate for varices with upper endoscopy. The utility of abdominal ultrasound for the diagnosis of cirrhosis in the absence of portal hypertension has not been well validated. We sought to determine the clinical accuracy of abdominal ultrasound in diagnosing cirrhosis in the absence of overt clinical or imaging signs of portal hypertension in patients with liver disease.

Materials and Methods

A retrospective analysis of patients who underwent abdominal ultrasound examinations between July 2008 and June 2013 was ordered by 10 hepatologists at the University of California, San Francisco. Ultrasound reports containing the terms cirrhosis, cirrhotic, nodular, nodularity, fibrosis, irregular, heterogeneous, and/or coarse were identified for further review. Patients were excluded if the ultrasound report documented portal hypertension using the terms ascites, free intraperitoneal fluid, varices, varix, splenomegaly, enlarged spleen, portal hypertension, and/or enlarged portal vein. Of the 1415 reports yielded, 403 were excluded owing to mentions of acute liver failure; post–liver transplant status; varices on upper endoscopy; or no specific mention of liver parenchyma, morphology, or echotexture in the final impression of the dictated ultrasound report. The remaining 1012 reports on 496 patients were further reviewed. Patients with ultrasound reports that described the liver with the term(s) cirrhosis, cirrhotic, nodular, and/or nodularity were then identified, yielding 325 reports. If patients underwent more than 1 ultrasound examination, only the first sonogram suggesting cirrhosis or nodularity was included in the analysis. From these 325 reports, a total of 69 patients underwent liver biopsy as prompted by clinical indications and/or an ultrasound documenting cirrhosis. Liver biopsies performed within 12 months of the index ultrasound were included in the analysis. This study was approved by the University of California San Francisco Institutional Review Board, which also determined that patient-informed consent was not required because the study was retrospective and did not involve any patient contact.

Data Collection

The clinical history, demographics, ultrasound reports, laboratory results, and liver histology of 69 patients were obtained through a review of electronic medical records. Patients were classified by the type of liver disease, including hepatitis B virus, hepatitis C virus, alcoholic liver disease, and nonalcoholic fatty liver disease. Laboratory results within 6 months of the ultrasound examination were collected, and included serum aminotransferases, albumin levels, and platelet counts. If patients had multiple laboratory results during this interval, the values closest to the time of the ultrasound examination were recorded.

Ultrasound Examination

The abdominal ultrasounds were performed at the University of California, San Francisco by registered or certified radiologists using an ACUSON S3000 Ultrasound System (Siemens) with a 4V1 (1-4.5 MHz), 6C2 (2-6 MHz), 18L6 (5.5-18 MHz), and/or 9L4 (4-9 MHz) transabdominal transducer, or a GE Logiq 9 system (General Electric) with a C1-5 (2-5 MHz), S1-5 (1-6 MHz), ML6-15 (5-15 MHz), and/or 9L (2.5-8 MHz) transabdominal transducer. Longitudinal and transaxial ultrasound images of the right and left hepatic lobes were obtained. The examinations were documented using still and cine clip images. The studies included comparison views showing the liver and adjacent right kidney. Additional high-resolution images with high-frequency, linear-array transducers were taken to reveal hepatic morphology and surface contour. Split-screen images were obtained, allowing for direct side-by-side comparison of the liver and spleen.

The ultrasound examinations were read by 1 of 9 experienced radiologists. An attending radiologist with subspecialty expertise in sonography (range, 3-30 years of experience) interpreted the images, documenting the right and left hepatic lobes, and approved the finalized dictated reports. The reports commented on hepatic morphology and echotexture in addition to other observations, such as main portal vein diameter. The collected data were retrieved from the original dictated reports. The conclusions reached by the interpreting radiologist were based on the overall assessment of the liver by the radiologist, conveyed in the finalized dictation. Of note, the ultrasound results reported on in this series were not re-reviewed or reinterpreted, as we sought to determine how accurate the experienced radiologists were in reporting cirrhosis to hepatologists. Additionally, the various sonographic features incorporated in the overall assessment were not individually analyzed. The term nodularity was used by the interpreting radiologist to refer to uneven, undulating liver surface and/or to

Table 1. Clinical Characteristics of Patients Undergoing Abdominal Ultrasound and Liver Biopsy

	Liver Biopsy (N=69)	No Liver Biopsy (N=255)	*P* Value
Median Age, Years (IQR)	58 (53-64)	60 (54-68)	.06
Male Sex (n)	58% (40)	58% (147)	.9
Type of Liver Disease **HBV Infection (n)** **HCV Infection (n)** **ALD/NAFLD (n)**	 31% (17) 49% (27) 3% (3)	 58% (125) 29% (62) 6% (13)	 .003[a]
Median Platelet Count, 10^6 cells/L (IQR); Thrombocytopenia (n)	153 (121-187); 49% (27)	170 (127-215); 40% (83)	.01[a]; .2
Median Serum ALT (IQR)	42 (29-79)	33 (24-59)	.002[a]
Median APRI (IQR)	0.76 (0.39-1.58)	0.52 (0.34-1.13)	.4
Median FIB-4 (IQR)	2.57 (1.67-4.29)	2.36 (1.54-3.85)	<.001[a]
Median Albumin (IQR)	3.9 (3.6-4.3)	4.0 (3.7-4.2)	.2

ALD, alcoholic liver disease; ALT, alanine aminotransferase; APRI, aspartate aminotransferase–to-platelet ratio index; FIB-4, Fibrosis-4; HBV, hepatitis B virus; HCV, hepatitis C virus; IQR, interquartile range; NAFLD, nonalcoholic fatty liver disease.

[a]Statistically significant.

diffuse alteration in hepatic parenchymal echotexture with small nodular areas, and not to describe discrete focal lesions.

Fibrosis Evaluation

Percutaneous liver biopsies were performed using a right lateral, intercostal approach. The right hepatic lobe was sampled with a 17-gauge core aspiration needle (Jamshidi, BD). Liver histology was evaluated for fibrosis using the Batts-Ludwig system.[3] Fibrosis was categorized as no fibrosis (F0), portal fibrosis (F1), septal fibrosis (F2), bridging fibrosis with architectural distortion (F3), and cirrhosis (F4).

Liver fibrosis was also estimated using noninvasive techniques. Aspartate aminotransferase (AST)-to-platelet ratio index (APRI) and Fibrosis-4 (FIB-4) scores were calculated using standard formulas.[4,5] Scoring was defined per standard cutoffs: no fibrosis (APRI, <0.5 or FIB-4, <1.5), moderate fibrosis (APRI, 0.5-1.5 or FIB-4, 1.5-3.25), and significant fibrosis (APRI, >1.5 or FIB-4, >3.25). APRI and FIB-4 values were censored in patients if AST or alanine aminotransferase levels were greater than 10 times the upper limit of normal, or if platelet counts were less than 25,000 × 10^6 cells/L, as these extreme values are unlikely to be due to chronic liver fibrosis and more likely to be caused by acute hepatitis or another disease process. Six patients in this series underwent transient elastography (FibroScan, Echosens); those results are not included in this analysis.

Statistical Analyses

Discrete variables were summarized using frequency, percentages, and standard deviation, whereas continuous variables were summarized using mean and standard deviation (normally distributed data), and median and interquartile range (IQR; nonnormally distributed data). Comparisons between patients with biopsies consistent with cirrhosis and patients with biopsies not showing cirrhosis were made using the student t-test or Mann-Whitney U Test (continuous data), the chi-square test or Fisher exact test (categorical data), and log transformation or nonparametric tests, including the Mann-Whitney U Test (skewed data). The analyses were 2-tailed, with $P<.05$ being considered statistically significant. APRI and FIB-4 scores were analyzed both as continuous variables as well as categorical variables (ie, no fibrosis, moderate fibrosis, and significant fibrosis, based on the definitions given previously). Ultrasound findings were compared to liver biopsy results in addition to other noninvasive markers of fibrosis, including APRI and FIB-4 scores. All data were analyzed using Stata 13 (StataCorp LLC).

Results

A total of 69 patients who met the inclusion criteria and underwent both an abdominal ultrasound and a liver biopsy were included in the analysis. Patients undergoing liver biopsy were predominantly male (58%), and the median age was 58 years (IQR, 53-64 years;

Table 2. Comparison of Select Clinical Characteristics by Fibrosis Scores, Based on Liver Biopsy Findings

	Liver Biopsy Results				
	Low Fibrosis (F0-F2)	**Advanced Fibrosis (F3/F4)**	***P* Value[a]**	**Cirrhosis**	***P* Value[a]**
N	14	55		47	
Median Platelet Count, 10^6 cells/L (IQR)	181 (132-215)	147 (119-176)	.1	136 (117-162)	.1
Median APRI (IQR)	0.76 (0.31-1.28)	0.76 (0.45-1.70)	.6	1.07 (0.47-2.05)	.6
Median FIB-4 (IQR)	2.57 (1.19-3.57)	2.64 (1.77-4.56)	.2	3.76 (1.89-5.67)	.2
Mean Portal Vein Diameter, mm (SD)	11.0 (2.4)	11.3 (1.9)	.7	11.3 (1.9)	.6

APRI, aspartate aminotransferase–to-platelet ratio index; FIB-4, Fibrosis-4; IQR, interquartile range; SD, standard deviation.

[a]Compared to low-fibrosis group.

Table 1). The most common liver diseases among these patients were chronic hepatitis C virus infection (49%), followed by chronic hepatitis B virus infection (31%). Overall, baseline characteristics were similar to those of patients who did not undergo liver biopsy. However, patients who underwent liver biopsy had slightly higher serum alanine aminotransferase levels and were less likely to carry a diagnosis of hepatitis B virus infection compared to patients who did not undergo liver biopsy. The median time between liver biopsy and abdominal ultrasound was 88 days (IQR, 26-179 days).

Comparison of Abdominal Ultrasound and Liver Biopsy for the Diagnosis of Cirrhosis

Among the 69 patients with abdominal ultrasounds that were suggestive of advanced liver disease (using the terms nodularity or cirrhosis), 47 had evidence of cirrhosis on liver biopsy (positive predictive value, 68%). Two-thirds of patients had ultrasounds reporting cirrhosis, and one-third had ultrasounds reporting nodular livers only. There was no significant difference in liver biopsy reports of cirrhosis between patients whose ultrasound reported cirrhosis (68.8%) or nodular liver (66.6%). The number of cases in this analysis did not allow for subanalyses based on liver edge vs parenchymal nodularity or on individual ultrasound reader. Because a percutaneous core biopsy of the liver can sometimes understage fibrosis,[6] a sensitivity analysis was performed, in which liver biopsies that were classified as either F3 or F4 were considered to have advanced fibrosis. Using these criteria, 80% of participants had evidence of advanced liver disease on a liver biopsy that was performed within 12 months of abdominal ultrasound. However, 20% of patients who underwent liver biopsy had no fibrosis or only mild to moderate fibrosis (F0-F2). F0 through F2 was noted on biopsy at similar rates, regardless of whether the ultrasound reported cirrhosis (20%) or nodular liver (20.8%). An analysis was also performed that included patients who underwent liver biopsies within 3 years of the index ultrasound examination. An additional 8 patients had biopsy data reporting the presence of cirrhosis. However, the addition of these patients to the analysis did not change the results.

Comparison of Aspartate Aminotransferase–to-Platelet Ratio Index and Fibrosis-4 Score to Liver Biopsy

The APRI and FIB-4 scores were calculated in 66 of 69 patients (96%). The median APRI was 0.76 (IQR, 0.39-1.58), and the median FIB-4 score was 2.57 (IQR, 1.67-4.29) among this cohort (Table 1). Previously validated cutoffs of APRI greater than 1.5 and FIB-4 scores greater than 3.25 performed poorly in predicting advanced fibrosis or cirrhosis (Table 2). However, patients with cirrhosis on liver biopsy had significantly higher FIB-4 values (P=.02; Table 3).

Evaluation of Other Markers of Advanced Liver Fibrosis

The mean portal vein diameter was similar between patients with cirrhosis (F4), advanced fibrosis (F3/F4), mild to moderate fibrosis (F2), or no fibrosis (F0) on liver biopsy. In all of the patients, the main portal vein was shown to be patent with the direction of flow toward the liver (ie, hepatopetal). Overall, clinical signs of advanced liver disease were low among the patients in this study (29%) but were more likely to be present in patients with advanced fibrosis (18/53; 34%) than in patients with low fibrosis (1/13; 8%; P=.06).

Discussion

Ultrasound is often the first imaging study obtained in the assessment of a patient with liver disease. If cirrhosis

Table 3. Positive Predictive Value of Ultrasound and Noninvasive Markers Compared to Liver Biopsy for the Diagnosis of Advanced Fibrosis or Cirrhosis

	Liver Biopsy Results	
	Advanced Fibrosis (F3/F4)	**Cirrhosis**
N	55	47
Ultrasound Report of Cirrhosis or Nodular(ity) (n=69[a])	80%	68%
APRI >1.5 (n=66[a])	29% (15)	34% (15)
APRI >2 (n=66[a])	21% (11)	25% (11)
FIB-4 >3.25 (n=66[a])	46% (24)	50% (22)
Thrombocytopenia (Platelet Count <120 × 10^6 cells/L) (n=68[a])	28% (15)	28% (13)
Clinical Findings of Cirrhosis (n=66[a])	34% (18)	35% (16)

APRI, aspartate aminotransferase–to-platelet ratio index; FIB-4, Fibrosis-4.

[a]The number of patients from the original cohort of 69 from which the calculation could be made.

is reported, clinicians should initiate a specific evaluation, including upper endoscopy, to assess for esophageal and gastric varices. Abdominal imaging studies every 6 months are recommended in order to screen for hepatocellular carcinoma. In addition, a diagnosis of cirrhosis alters ongoing clinical management, as it results in different durations and types of medical treatment in patients infected with hepatitis C virus and in different long-term treatments in patients infected with hepatitis B virus that may not otherwise be used. If there are no obvious clinical indications of cirrhosis, clinicians who receive an ultrasound report indicating cirrhosis in a patient will often perform a liver biopsy to confirm the diagnosis. Biopsies have been associated with costs, risks, and potential complications; thus, an ultrasound report describing a nodular or cirrhotic liver has significant clinical ramifications.

In this retrospective analysis of patients without evidence of portal hypertension undergoing abdominal ultrasound, morphologic features suggestive of cirrhosis, including nodularity, had moderate utility at predicting advanced liver disease on liver biopsy with a positive predictive value of 68%. It is widely known that ultrasound can lack sensitivity in detecting cirrhosis[7-9]; however, it is not well recognized that false-positive results and overcalls can occur, especially in the absence of conclusive signs of portal hypertension. In 20% of the cases, cirrhosis was reported by ultrasound but was not confirmed by liver biopsy, with no fibrosis (F0) or mild to moderate fibrosis (F1/F2) found. Not surprisingly, this analysis found no correlation between portal vein diameter and the presence of advanced liver disease in patients without evidence of portal hypertension. Prior studies examining the accuracy of Doppler ultrasound in detecting advanced liver disease have revealed inconsistent results.[8,10-16]

In this study, noninvasive serologic markers including APRI, FIB-4 scores, and the presence of thrombocytopenia had modest utility in predicting advanced liver disease, perhaps due to the exclusion of patients with evidence of portal hypertension (including splenomegaly) on ultrasound. Both APRI and FIB-4 scores utilize platelet values to obtain a clinical score, and, therefore, the exclusion of portal hypertension likely contributed to their poor performance in these highly selected individuals. Not surprisingly, clinical features of cirrhosis, including spider angiomas, palmar erythema, gynecomastia, testicular atrophy, and jaundice,[17,18] were largely absent in the group of patients with compensated liver disease. These signs were more prevalent in patients with biopsy-proven advanced fibrosis as compared to patients with low fibrosis. As such, the presence of these features increases the likelihood of having significant fibrosis; however, their absence cannot exclude advanced disease.

Although core biopsy of the liver is the gold standard for the determination and assessment of fibrosis, it is also subject to error. Biopsy fragmentation, small specimen length, and paucity of portal tracts can impact the reliability of disease staging and grading.[19] In this analysis, combining F3 and F4 disease to represent advanced fibrosis on liver biopsy improved the positive predictive value of ultrasound by more than 10%. It is possible that some of the patients who were reported as having F3 disease may have been understaged by liver biopsy and may actually have had cirrhosis. Studies have shown that liver biopsies may be prone to sampling error due to relative patchiness of disease, and may understage fibrosis.[6,20-23]

Newer technologies and modalities have been added to the noninvasive assessment of hepatic fibrosis, including elastography.[24,25] Because only 6 patients in this analysis underwent elastography, the results were not included in this article. If nodularity or cirrhosis is identified and reported on ultrasound, elastography should be considered to confirm and assess the severity of fibrosis prior to determining the need for liver biopsy.

Sonographic findings such as changes in the shape or contour of the liver, parenchymal echotexture, surface nodularity, or signs of portal hypertension have varying sensitivity and specificity for severe fibrosis or cirrhosis,

ranging from 37.5% to 91.1% and 81.5% to 95.0%, respectively.[7-9,26-31] Surface nodularity has been shown to be a reliable marker for advanced liver disease in patients with chronic liver disease undergoing liver biopsy, with sensitivity and specificity of over 90%.[27] However, many of these studies included patients with features of portal hypertension such as varices, ascites, or splenomegaly, making it difficult to separate the impact of surface nodularity in isolation from other concomitant sonographic features of advanced liver disease and portal hypertension.

The assessment and determination of nodularity or cirrhosis on ultrasound is subjective. These parameters are difficult to articulate, define, and objectively measure. This analysis includes false-positive cases, or examples in which the sonographic interpretation erroneously suggested disease. It is worth considering the possible explanations for these apparent overcalls of cirrhosis on ultrasound. Such explanations include the tendency of the interpreting radiologist to consider ultrasound as a screening test in aiming for high sensitivity in detection; the use of newer ultrasound equipment with advanced technology and higher frequency transducers, which reveal subtle alterations in hepatic morphology that were not previously seen; the inexact use of terminology such as nodular or cirrhotic to describe altered hepatic echotexture; and the undue influence of impressions reported on prior examinations or bias introduced by provided clinical history (eg, chronic hepatitis). All of the physicians who interpreted and reported on the abdominal ultrasounds have significant experience and subspecialty expertise in this field. They were not directly surveyed regarding their criteria or threshold for reaching the diagnosis of cirrhosis. Although it would be of interest and utility to assess performance by individual reader, the numbers were too small to allow for useful analysis.

It is important to note the limitations of this analysis. It is a single-center, retrospective analysis, which may introduce bias. The sample size is relatively small at 69, which limits the precision of estimates as well as the ability to perform multivariable analyses to identify factors associated with overdiagnosis of cirrhosis or the accuracy of specific ultrasonographic signs contributing to a definition of cirrhosis by the radiologist. Moreover, only a minority of patients (n=6) had fibrosis measured by transient elastography, which could have been useful as a supplementary estimate of fibrosis within this patient population, with discordant results between ultrasound and liver biopsy. However, we believe that this study is still relevant, as not all clinicians have access to elastography. Additionally, we did not collect information regarding cryoglobulins or caudate lobe hypertrophy for additional assessment of more advanced liver disease.

Conclusion

In this single-center, retrospective review of patients without portal hypertension who were referred for sonographic evaluation of the liver, we found that nodularity or cirrhosis reported by ultrasound had a modest correlation with cirrhosis on liver biopsy, with false positives in up to 20% of patients. However, ultrasound was superior to other noninvasive fibrosis markers, including APRI, FIB-4 scores, and clinical features, in this cohort. Caution should be taken in the interpretation and reporting of these examinations, and terminology should be used judiciously. It is important to highlight to clinicians that if clinical and radiologic data are discordant, then further testing is recommended because ultrasound is not always accurate for diagnosing cirrhosis in the absence of portal hypertension. In addition, clinicians should consider alternative noninvasive means of assessing fibrosis in cases in which portal hypertension is not present.

The authors have no relevant conflicts of interest to disclose.

References

1. Tchelepi H, Ralls PW, Radin R, Grant E. Sonography of diffuse liver disease. *J Ultrasound Med*. 2002;21(9):1023-1032.
2. Martínez-Noguera A, Montserrat E, Torrubia S, Villalba J. Doppler in hepatic cirrhosis and chronic hepatitis. *Semin Ultrasound CT MR*. 2002;23(1):19-36.
3. Batts KP, Ludwig J. Chronic hepatitis. An update on terminology and reporting. *Am J Surg Pathol*. 1995;19(12):1409-1417.
4. Sterling RK, Lissen E, Clumeck N, et al; APRICOT Clinical Investigators. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. *Hepatology*. 2006;43(6):1317-1325.
5. Wai CT, Greenson JK, Fontana RJ, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. *Hepatology*. 2003;38(2):518-526.
6. Jalan R, Harrison DJ, Dillon JF, Elton RA, Finlayson ND, Hayes PC. Laparoscopy and histology in the diagnosis of chronic liver disease. *QJM*. 1995;88(8):559-564.
7. Ong TZ, Tan HJ. Ultrasonography is not reliable in diagnosing liver cirrhosis in clinical practice. *Singapore Med J*. 2003;44(6):293-295.
8. Colli A, Fraquelli M, Andreoletti M, Marino B, Zuccoli E, Conte D. Severe liver fibrosis or cirrhosis: accuracy of US for detection—analysis of 300 cases. *Radiology*. 2003;227(1):89-94.
9. Allan R, Thoirs K, Phillips M. Accuracy of ultrasound to identify chronic liver disease. *World J Gastroenterol*. 2010;16(28):3510-3520.
10. Kim MY, Jeong WK, Baik SK. Invasive and non-invasive diagnosis of cirrhosis and portal hypertension. *World J Gastroenterol*. 2014;20(15):4300-4315.
11. Iacobellis A, Fusilli S, Mangia A, et al. Ultrasonographic and biochemical parameters in the non-invasive evaluation of liver fibrosis in hepatitis C virus chronic hepatitis. *Aliment Pharmacol Ther*. 2005;22(9):769-774.
12. Chen CH, Lin ST, Yang CC, Yeh YH, Kuo CL, Nien CK. The accuracy of sonography in predicting steatosis and fibrosis in chronic hepatitis C. *Dig Dis Sci*. 2008;53(6):1699-1706.
13. Kutcher R, Smith GS, Sen F, et al. Comparison of sonograms and liver histologic findings in patients with chronic hepatitis C virus infection. *J Ultrasound Med*. 1998;17(5):321-325.
14. Bolognesi M, Sacerdoti D, Mescoli C, et al. Different hemodynamic patterns of alcoholic and viral endstage cirrhosis: analysis of explanted liver weight, degree of fibrosis and splanchnic Doppler parameters. *Scand J Gastroenterol*. 2007;42(2):256-262.
15. Berzigotti A, Castera L. Update on ultrasound imaging of liver fibrosis. *J Hepatol*. 2013;59(1):180-182.

16. Berzigotti A, Piscaglia F; EFSUMB Education and Professional Standards Committee. Ultrasound in portal hypertension—part 2—and EFSUMB recommendations for the performance and reporting of ultrasound examinations in portal hypertension. *Ultraschall Med*. 2012;33(1):8-32.
17. Cavanaugh J, Niewoehner CB, Nuttall FQ. Gynecomastia and cirrhosis of the liver. *Arch Intern Med*. 1990;150(3):563-565.
18. Udell JA, Wang CS, Tinmouth J, et al. Does this patient with liver disease have cirrhosis? *JAMA*. 2012;307(8):832-842.
19. Standish RA, Cholongitas E, Dhillon A, Burroughs AK, Dhillon AP. An appraisal of the histopathological assessment of liver fibrosis. *Gut*. 2006;55(4):569-578.
20. Abdi W, Millan JC, Mezey E. Sampling variability on percutaneous liver biopsy. *Arch Intern Med*. 1979;139(6):667-669.
21. Ratziu V, Charlotte F, Heurtier A, et al; LIDO Study Group. Sampling variability of liver biopsy in nonalcoholic fatty liver disease. *Gastroenterology*. 2005;128(7):1898-1906.
22. Olsson R, Hägerstrand I, Broomé U, et al. Sampling variability of percutaneous liver biopsy in primary sclerosing cholangitis. *J Clin Pathol*. 1995;48(10):933-935.
23. Regev A, Berho M, Jeffers LJ, et al. Sampling error and intraobserver variation in liver biopsy in patients with chronic HCV infection. *Am J Gastroenterol*. 2002;97(10):2614-2618.
24. Afdhal NH, Bacon BR, Patel K, et al. Accuracy of fibroscan, compared with histology, in analysis of liver fibrosis in patients with hepatitis B or C: a United States multicenter study. *Clin Gastroenterol Hepatol*. 2015;13(4):772-779.e1-e3.
25. Barr RG, Ferraioli G, Palmeri ML, et al. Elastography assessment of liver fibrosis: Society of Radiologists in Ultrasound consensus conference statement. *Radiology*. 2015;276(3):845-861.
26. Di Lelio A, Cestari C, Lomazzi A, Beretta L. Cirrhosis: diagnosis with sonographic study of the liver surface. *Radiology*. 1989;172(2):389-392.
27. Simonovský V. The diagnosis of cirrhosis by high resolution ultrasound of the liver surface. *Br J Radiol*. 1999;72(853):29-34.
28. Gaiani S, Gramantieri L, Venturoli N, et al. What is the criterion for differentiating chronic hepatitis from compensated cirrhosis? A prospective study comparing ultrasonography and percutaneous liver biopsy. *J Hepatol*. 1997;27(6):979-985.
29. Xu Y, Wang B, Cao H. An ultrasound scoring system for the diagnosis of liver fibrosis and cirrhosis. *Chin Med J (Engl)*. 1999;112(12):1125-1128.
30. Strauss S, Gavish E, Gottlieb P, Katsnelson L. Interobserver and intraobserver variability in the sonographic assessment of fatty liver. *AJR Am J Roentgenol*. 2007;189(6):W320-W323.
31. Gerstenmaier JF, Gibson RN. Ultrasound in chronic liver disease. *Insights Imaging*. 2014;5(4):441-455.