



# Association of advanced hepatic fibrosis and sonographic visualization score: a dual-center study using ACR US LI-RADS

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## Abstract

**Purpose** To evaluate the association between imaging and clinical features and visualization scores, as specified by American College of Radiology (ACR) Ultrasound Liver Imaging Reporting and Data System (LI-RADS), on hepatocellular carcinoma (HCC) screening ultrasound examinations.

**Methods** In this dual-center retrospective study, HCC screening ultrasound reports containing ultrasound elastography measurements (January to September, 2017) were reviewed. Ultrasound point shear wave elastography and 2-dimensional shear wave elastography were used to assess liver stiffness; median shear wave velocity was translated to METAVIR fibrosis scoring, per previously published data. Reports were analyzed for subject age, sex, reason for HCC screening, spleen size, fibrosis scores, and assigned ultrasound visualization scores. Jonckheere–Terpstra trend and Kendall’s tau-*b* coefficient analyses were performed.

**Results** 714 subjects (mean age 55; 51% male, 49% female) were included. 308 (43%) subjects had clinically declared cirrhosis; 406 (57%) did not. Majority (535, 75%) of exams were adequate (Visualization Score A), 156 (22%) moderately limited (Visualization Score B), and 23 (3%) severely limited (Visualization Score C). Increasing spleen size and patient age were associated with worsening visualization scores ( $p < 0.001$ ). Suboptimal visualization was also associated with clinically significant fibrosis ( $\geq F2$ ) by elastography (Kendall’s tau-*b* = 0.181,  $p < 0.001$ ) and clinically declared cirrhosis (Kendall’s tau-*b* = 0.433,  $p < 0.001$ ). There was no association with patient sex.

**Conclusion** Using ACR Ultrasound LI-RADS visualization score assessment, majority (75%) of HCC screening exams were diagnostically adequate, and only 3% were severely limited. Sonoelastographic diagnosis of clinically significant fibrosis, as well as clinical cirrhosis, increased patient age, and spleen size, were associated with greater diagnostic limitations.

**Keywords** Ultrasound · LI-RADS · Hepatocellular carcinoma · Elastography · Visualization score

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This manuscript has not been previously submitted or published elsewhere. A scientific abstract containing similar results is accepted for a digital poster presentation at RSNA 2018.

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## Introduction

Liver cancer was the fourth most common cause of cancer-related deaths in the world in 2015, with mortality rates projected to rise in North America [1, 2]. When diagnosed at an advanced stage, hepatocellular carcinoma (HCC) has a poor prognosis, with limited average survival of less than 1 year [3]. However, if the disease is discovered at an early stage, several treatment options, including surgical resection, chemoembolization, radioembolization, external beam radiation, and liver transplant, can improve mortality. Less than 30% of patients are diagnosed early enough to undergo such treatment [3]. Patients at high risk for developing HCC can be easily identified, and effective

screening and surveillance is paramount to their survival. Most hepatology societies worldwide recommend screening and surveillance with serial ultrasound examinations at least every 6 months [4–6].

In addition to detecting HCC in high-risk populations, ultrasound offers useful anatomic and physiologic information. Imaging features of advanced fibrosis or cirrhosis, including splenomegaly and elevated liver stiffness, can be assessed at the time of screening ultrasound. Ultrasound elastography offers a rapid, non-invasive, relatively inexpensive, and painless method for predicting liver fibrosis in patients with chronic liver disease, and offers useful prognostic information to guide management in those with advanced fibrosis and cirrhosis [7].

Although ultrasound is the recommended screening and surveillance test, only a few published studies address the technical limitations of ultrasound [5, 8], and future work is needed for consensus on the management of patients with suboptimal exams. The American Association of for the Study of Liver Disease (AASLD) states that there is a need to define the performance of ultrasound in surveillance, particularly with regard to specific patient populations [5]. Recent American College of Radiology (ACR) Ultrasound Liver Imaging Reporting and Data System (LI-RADS) guidelines recommend systematic assignment of visualization scores for consistent reporting of exam technical quality among radiologists [4, 9], thus allowing for large-scale, dual-institutional data analysis.

Ultrasound may be affected by many factors, some specific to the patient—such as body habitus, limited acoustic windows, difficulty with breath holding—and some related to the underlying liver disease, such as steatosis resulting in ultrasound beam attenuation [4]. To date, no study has correlated the degree of advanced fibrosis and cirrhosis to technical quality of screening and surveillance ultrasound exams. The aim of our study was to evaluate for association between patient and imaging factors and ultrasound visualization scores, as specified by the ACR Ultrasound LI-RADS guidelines.

## Materials and methods

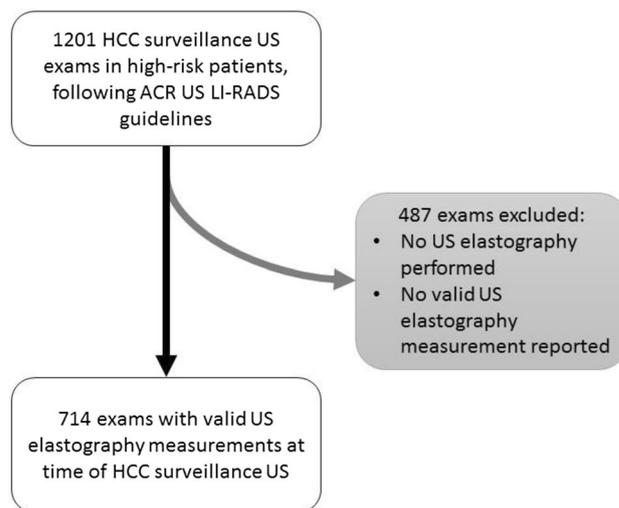
### Materials

This HIPAA-compliant, dual-center retrospective study was approved by two participating institutional review boards, and requirement for informed consent was waived. 1201 HCC screening and surveillance ultrasound reports following the ACR Ultrasound LI-RADS algorithm, from two large academic institutions (Stanford University and University of Michigan), from January to September of 2017, were reviewed. Of these, 487 exams without a

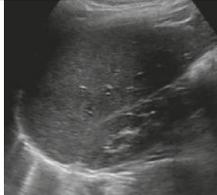
reported ultrasound shear wave elastography measurement—either not concurrently performed or with invalid measurements (IQR/M > 0.30)—were excluded. Final study population included 714 patients undergoing HCC surveillance ultrasound with elastography assessment (Fig. 1). The study included 368 exams from Stanford and 346 from University of Michigan. The average patient age was 55 (range 19–89). 362 (51%) were male; 352 (49%) were female. Patient information, including clinical diagnosis of cirrhosis and type of liver disease, were obtained from the ultrasound order information and electronic medical record review. Visualization scores assigned by the initial interpreting radiologist, according to ACR Ultrasound LI-RADS guidelines (Fig. 2), were used [10]. Spleen length was also recorded.

### Methods

Ultrasound examinations were performed according to recommendations from ACR Ultrasound practice parameters [11]. 17 fellowship-trained radiologists from Stanford and 19 fellowship-trained radiologists from University of Michigan served as the interpreting radiologists. Across both sites, the mean years of post-residency experience was 14.8 years (standard deviation of 2.0 years), and mean clinical time spent on ultrasound was 21.7% (standard deviation of 3.1%). Both institutions utilized structured reporting, as recommended by ACR Ultrasound LI-RADS guidelines [10]. Diagnostic adequacy of ultrasound exams was assessed according to ACR Ultrasound LI-RADS guidelines (Fig. 2). Exams with no or minimal limitations, where the entire or nearly entire liver parenchyma was



**Fig. 1** Flowchart with inclusion and exclusion criteria. Of 1201 exams in high-risk patients undergoing surveillance ultrasound (US) for HCC, only those with concurrent, valid ultrasound elastography measurements were included

Visualization score	Concept	Examples	Image Examples
<b>A. No or minimal limitations</b>	Limitations if any are unlikely to meaningfully affect sensitivity	Liver is homogeneous or minimally heterogeneous Minimal beam attenuation or shadowing Near entire visualization of the liver	 Entire liver is visualized in a 42-year-old female with chronic hepatitis B viral infection and no significant fibrosis by ultrasound (F≤2).
<b>B. Moderate limitations</b>	Limitations may obscure small (< 1 cm) masses	Liver is moderately heterogeneous Moderate beam attenuation or shadowing Some portions of the liver or diaphragm (< 50 %) are not visualized	 Moderately limited exam due to beam attenuation in a 71-year-old female with non-alcoholic fatty liver disease and high risk of cirrhosis by ultrasound (F=4).
<b>C. Severe limitations</b>	Limitations significantly lower sensitivity for focal liver lesions (> 1 cm)	Liver is severely heterogeneous Severe beam attenuation or shadowing Majority of the liver and diaphragm (> 50%) not visualized	 Severely limited exam due to parenchymal heterogeneity in a 64-year-old female with hepatitis C virus cirrhosis and elevated liver stiffness (F=4).

**Fig. 2** Summary of American College of Radiology Ultrasound Liver Imaging—Reporting and Data System visualization scores. Adapted from Fetzer et al. [6]

visualized with homogeneous or minimally heterogeneous echotexture, were assigned Visualization Score A (VIS-A). Exams with moderately limited visualization, where small subcentimeter observations could be obscured, due to intermediate heterogeneity, sound attenuation, or incomplete visualization (greater than 50% of liver visualized), were categorized as Visualization Score B (VIS-B). Severely limited exams, where even larger observations could be obscured, due to severe parenchymal heterogeneity, substantial sound attenuation, or incomplete visualization (less than 50% of liver and/or liver–diaphragm interface visualized), were denoted as Visualization Score C (VIS-C).

In both centers, the ultrasound examinations were performed by ultrasound sonographers trained in elastography. Sonoelastographic measurements of liver stiffness were acquired with ultrasound machines from three vendors: point shear wave elastography from Siemens ACUSON S2000 and Philips Epiq 7, and two-dimensional shear wave elastography from GE Logiq E9, according to Society of Radiologists in Ultrasound guidelines: patients were fasting

for 4–6 h, and the right lobe of the liver was interrogated in the supine position, with breath holding during normal gentle respiration; ten valid measurements were obtained, and only exams with  $IQR/M \leq 0.30$  were considered as valid [7]. Median shear wave velocities were classified into METAVIR fibrosis stages based on cut-off values provided by literature for Siemens: 1.34 m/s for clinically significant fibrosis or  $F \geq 2$ , 1.55 m/s for severe fibrosis or  $F \geq 3$ , and 1.80 m/s for cirrhosis or  $F = 4$  [12]. For Philips and GE, velocity cut-offs from the manufacturer's specifications were used: 1.37 m/s for  $F \geq 2$ , 2.00 m/s for  $F \geq 3$ , and 2.64 m/s for  $F \geq 4$  for Philips; 1.66 m/s, 1.77 m/s, and 1.99 m/s for GE [13].

Trend analyses were performed for association between assigned visualization score and each continuous variable—patient age, liver, and spleen length—and statistical significance was tested with Jonckheere–Terpstra test ( $p$  value 0.05). Kendall's Tau-b correlation test was performed to assess association between visualization score and patient gender, presence or absence of clinical cirrhosis, and presence or absence of moderate fibrosis and

cirrhosis (F0–F1 vs. F2–F4). Trend analyses were performed with Stata, version 15.1; StataCorp LLC, College Station, TX. Chi-square test was also performed to assess for statistically significant difference in the indications for screening and cirrhosis etiology between the two institutions (R Core Team 2018; R Foundation for Statistical Computing, Vienna, Austria.)

## Results

Of the 714 surveillance exams in high-risk patients, cirrhosis was the most common indication for screening, involving 309/714 or 43% of patients, followed by chronic hepatitis B virus infection without cirrhosis, hepatitis C infection without cirrhosis, and non-cirrhotic non-alcoholic fatty liver disease/steatohepatitis (Table 1). Hepatitis B virus infection was most common form of liver disease in the west coast (Stanford), and cirrhosis was most common in the Midwest (University of Michigan); there was a statistically significant difference between the two groups ( $p < 0.0001$ ). In the subset of patients with clinically diagnosed cirrhosis, hepatitis C viral infection was most commonly involved at both institutions (Table 1).

The majority, or 535/714 (75%), of exams were categorized as VIS-A (Fig. 3). 156/714 (22%) of the exams were assigned VIS-B, and 23/714 (3%) of studies were categorized as VIS-C. Of the VIS-A exams, 338/535 (63%) were without clinically significant fibrosis by elastography (F0–F1), and 197/535 (37%) had moderate to high risk for clinically significant fibrosis ( $F \geq 2$ ). Of the VIS-B exams,

64/156 (41%) were F0–F1, and 92/156 (59%) had translated fibrosis scores of  $F \geq 2$ . Of the VIS-C exams, 11/23 (48%) were at low risk for fibrosis, while 12/23 (52%) were with moderate to high risk of fibrosis by sonoelastography (Fig. 4, Table 2). 11/413 (3%) of F0–1 exams and 12/301 (4%) of  $F \geq 2$  exams were severely limited. Reasons for categorization as VIS-B or C were described in 49/179 (25%); of these, the most common reason was severe steatosis (20) (Fig. 5), followed by severe parenchymal heterogeneity [17] (Fig. 6), severe overlying bowel gas [4] (Fig. 7), patient factor such as motion or limited breath holds [2], and limited acoustic window [1].

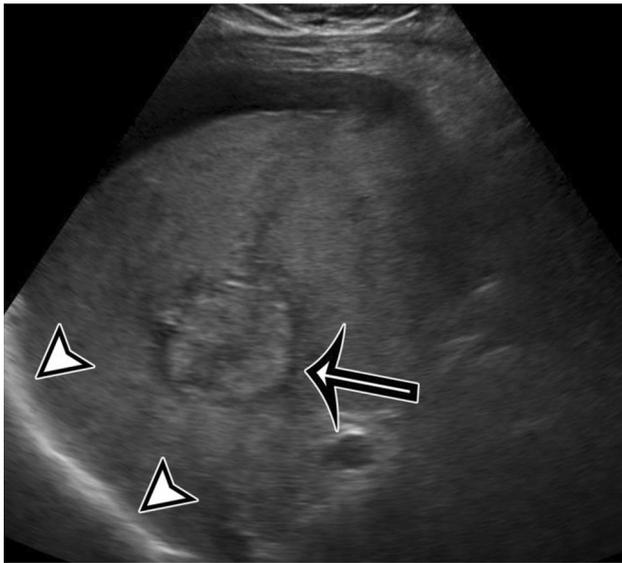
The mean spleen length was 11.3 cm (range 6–25.6 cm) and standard deviation was 3.5. With regard to shear wave elastography measurements, majority (413/714 exams, 58%) had no clinically significant fibrosis, or F0–F1. 123/714 (17%) exams indicated clinically significant fibrosis, fibrosis stage  $F \geq 2$ ; 178/714 (24%) had advanced fibrosis or cirrhosis, F3–F4.

Trend analyses were performed for each of the clinical and ultrasound parameters. There was a non-linear ascending trend with patient age and worsening visualization score, as assessed with Jonckheere–Terpstra test for trend ( $p < 0.0001$ ). There was no association with patient sex (Kendall's tau- $b = 0.020$ ,  $p = 0.597$ ). When the clinical indication for HCC surveillance was grouped into cirrhosis versus other reasons, there was a significant association for those with cirrhosis and poorer visualization scores (Kendall's tau- $b = 0.433$ ,  $p < 0.0001$ ). Spleen size and sonoelastographic evidence of advanced fibrosis were

**Table 1** Number of subjects according to indication for screening, including both cirrhotic and non-cirrhotic conditions

Dominant form of liver disease	Both institutions	Stanford University	University of Michigan
Cirrhosis	309	49	260
Cirrhosis etiology			
Hepatitis C viral infection	100	17	83
Non-alcoholic steatohepatitis	64	8	56
Alcoholic cirrhosis	44	4	40
Autoimmune	19	2	17
Hepatitis B viral infection	19	9	10
Primary biliary cirrhosis	18	6	12
Other	28	0	28
Unknown	19	3	16
Non-cirrhotic liver disease	405	319	86
Chronic hepatitis B viral infection	264	226	38
Chronic hepatitis C viral infection	102	65	37
Non-alcoholic fatty liver disease/non-alcoholic steatohepatitis	14	11	3
Other	25	17	8

Total values for both institutions and each of the two institutions are listed. There was a statistically significant difference in distribution across the two institutions ( $p < 0.05$ )



**Fig. 3** A 46-year-old male with cirrhosis secondary to chronic hepatitis C viral infection. Longitudinal grayscale ultrasound image of the right hepatic lobe demonstrates a heterogeneous, isoechoic mass with refractive edge shadowing (arrow), corresponding to LI-RADS 5 observation on follow-up multiphase CT (not shown). The diaphragm is visualized in its entirety (arrowheads), and the exam was assigned a visualization score A. There is mild ascites, and median shear wave velocity measurements (not shown) corresponded to F4

assessed for association with suboptimal visualization. There was a non-linear ascending trend between spleen size and visualization scores (Jonckheere–Terpstra test for trend,  $p < 0.001$ ) (Fig. 8). There was a significant association between clinically significant fibrosis (F2–F4) and

**Table 2** Distribution of translated fibrosis stages per visualization score; percentages per visualization score category are provided

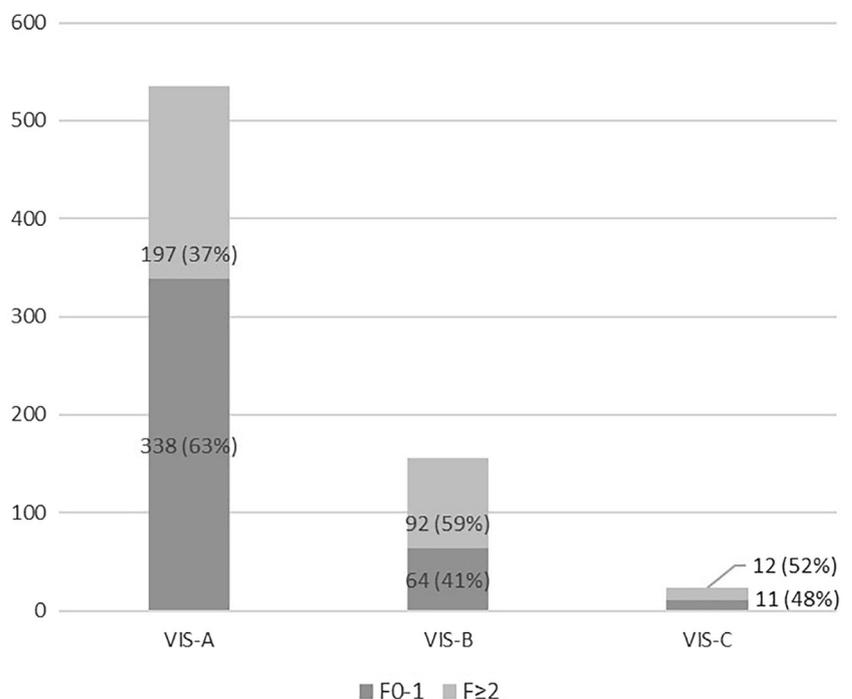
F score	VIS-A (%)	VIS-B (%)	VIS-C (%)
F0–1	338 (63)	64 (41)	11 (48)
F ≥ 2	85 (15)	34 (22)	4 (18)
F ≥ 3	48 (9)	24 (15)	3 (13)
F = 4	64 (12)	34 (22)	5 (22)

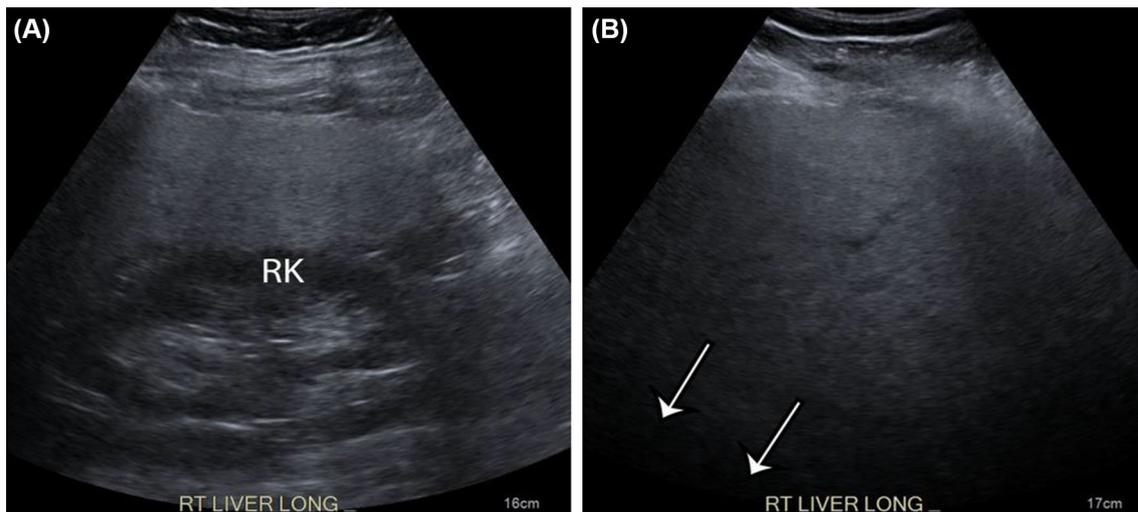
worsening visualization score (Kendall’s tau- $b = 0.181$ ,  $p < 0.0001$ ).

**Discussion**

Using the recently introduced ACR Ultrasound LI-RADS categorization scheme for ultrasound screening and surveillance, we found that the sonoelastographic diagnosis of clinically significant fibrosis, clinically diagnosed cirrhosis, increasing patient age, and spleen size were associated with greater diagnostic limitations. Visualization scores in HCC surveillance are somewhat analogous to breast density categories for ACR Breast Imaging Reporting and Data System in that both convey the expected sensitivity of the exam. For example, sensitivity of mammograms for breast cancer can vary from 85.7 to 88.8% in patients with entirely fatty tissue compared to 62.2–68.1% in patients with extremely dense tissue

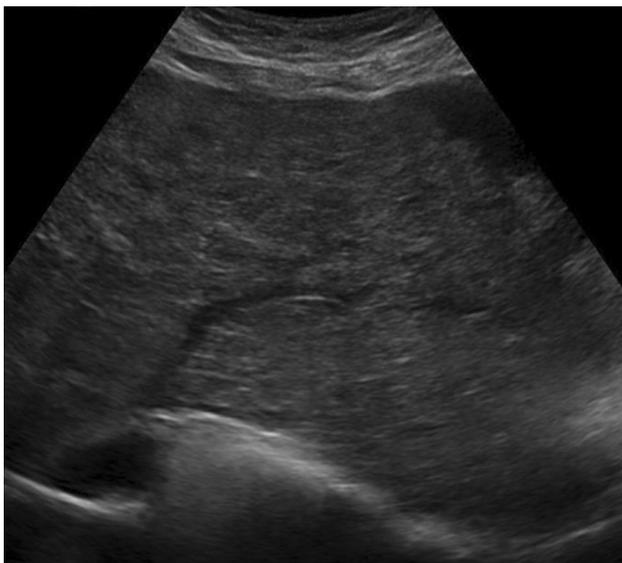
**Fig. 4** Number (%) of exams with low risk (F0–1) versus moderate to high risk (F2 or greater) for clinically significant fibrosis based on shear wave elastography velocities, per visualization score category





**Fig. 5** **a** 43-year-old female with cirrhosis, secondary to non-alcoholic steatohepatitis with severely limited visualization exam, score C, due to marked beam attenuation limiting visualization of deeper portions of the liver. **a** Grayscale sonographic images of the right liver demonstrate that the liver is hyperechoic in appearance

relative to the renal cortex (RK). **b** Longitudinal grayscale view shows non-visualization of greater than 50% of the diaphragm (arrows). Shear wave velocity (not shown) was suggestive of advanced fibrosis or cirrhosis (F4)



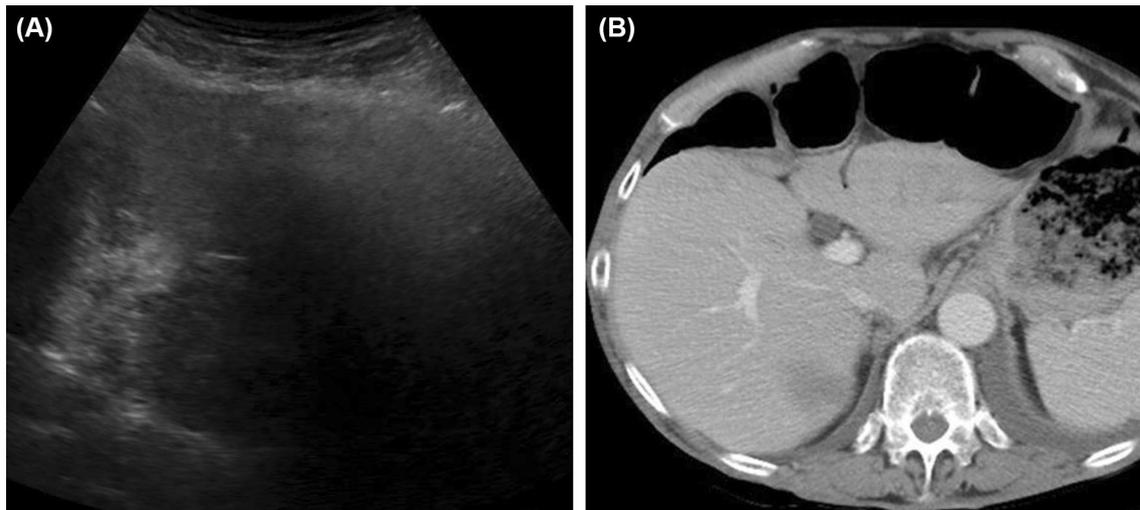
**Fig. 6** **a** 58-year-old male with cirrhosis secondary to hepatitis B virus undergoing ultrasound surveillance. Transverse grayscale image of the left lobe of the liver shows moderately heterogeneous hepatic parenchyma, which was given a visualization score B. Shear wave velocity (not shown) was suggestive of advanced fibrosis or cirrhosis (F4)

[14, 15]. To our knowledge, this is the first study to evaluate for factors contributing to ultrasound exam quality across two institutions according to ACR Ultrasound LI-RADS scheme.

Prior meta-analyses have reported that the sensitivity of ultrasound HCC detection ranges from 60 to 95% [3, 16]. In comparison, magnetic resonance imaging and computed tomography (CT) sensitivities are reported to be 76–88%

and 63–74%, respectively—[5, 16, 17]. However, in a more recent meta-analysis of ultrasound surveillance in cirrhotic patients, the pooled sensitivity of ultrasound for detecting HCC was found to be 85% at any stage, but only 47% for early-stage HCC, increasing to 63% with inclusion of AFP [18]. In this same study, pooled sensitivity of CT was 62% for early-stage HCC, and not significantly different from ultrasound. The broad range in reported ultrasound performance may in part be due to the fact that surveillance exams were not stratified according to visualization scores. Stratification by underlying parenchymal characteristics could allow for a more nuanced understanding of screening efficacy, again analogous to the concept of density in breast imaging.

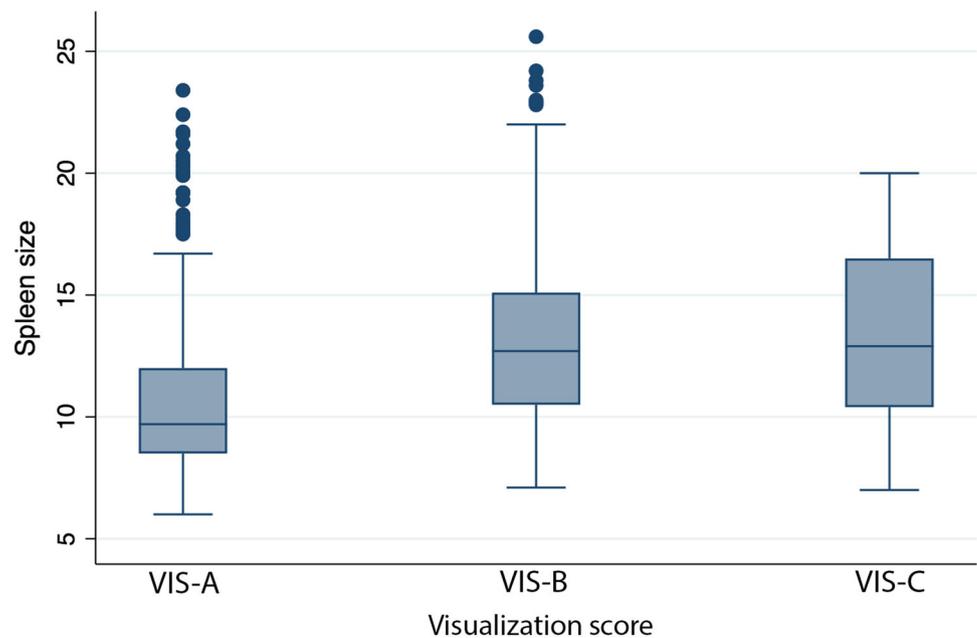
Ultrasound is a dynamic exam that may be affected by many factors, such as large body habitus, obscuration by overlying rib shadows or bowel gas, patient inability to breath-hold, or ultrasound beam attenuation by parenchymal heterogeneity from steatosis or fibrosis [4, 8]. A recent paper by Simmons et al. [8], retrospectively reviewed 941 patients for technical limitations and found 20% of their exams to be likely or definitely inadequate technical quality. Their study, however, did not use the ACR Ultrasound LI-RADS categorization, so a direct comparison to our study is limited. Moreover, they included both inpatients and emergency department patients, which may have diminished exam quality due to superimposed comorbidities and patient's clinical status at the time of examination. Indeed, current recommendations do not advocate surveillance in an inpatient or emergency department setting. In addition, Child–Pugh C cirrhotic



**Fig. 7** A 41-year-old male with alcoholic cirrhosis. **a** Grayscale transverse view of the liver shows limited visualization of the left lobe of the liver secondary to overlying bowel gas. **b** Corresponding CT

image demonstrates colonic interposition anterior to the left hepatic lobe which likely contributed to limitations from bowel gas

**Fig. 8** Boxplot for spleen size for each visualization score category. Horizontal line denotes median, boxes represent 25th and 27th percentiles



patients were included in their study but are not currently part of the recommended AASLD surveillance population due to the limited life expectancy [5, 8].

There were several limitations in our study. First, although this was a dual-institution study, we had a relatively small number of exams categorized as visualization C. This may partly be due to the fact that Ultrasound LI-RADS has only been in existence for a short period of time and we limited our review to those with elastography measurements and Ultrasound LI-RADS visualization categorization. This was necessary in order to understand how elastography stiffness may correlate with liver visualization. A second limitation of our study is that our population

may be skewed towards a lower prevalence of cirrhosis than expected in the overall HCC screening population. Since we only reviewed screening and surveillance exams with elastography measurements, our population included non-cirrhotic hepatitis C patients being evaluated for the presence of fibrosis or cirrhosis while being screened for HCC. However, many other countries and some institutions in the United States routinely include patients with Hepatitis C and stage 3 fibrosis for HCC surveillance. Additionally, the association with patient body habitus or body-mass index was not assessed. Finally, we did not have a gold standard for correlation of ultrasound elastography measurements. Liver biopsy is invasive and not routinely performed for all

patients with chronic liver disease [19]; thus this is an unavoidable limitation. We did not apply disease-specific thresholds for elastography interpretation but rather, we used generalized cut-off values of clinically significant fibrosis versus no clinically significant fibrosis. This is because various etiologies of underlying liver disease may have different thresholds for specific fibrosis staging; while studying a more homogeneous population would yield improved stratification, we chose not to do this because it would not represent normal clinical practice and moreover would significantly limit the number of patients studied even with multiple participating institutions.

In conclusion, in our dual-center experience, the majority (75%) of HCC screening and surveillance ultrasound exams are diagnostically adequate with no or minimal limitations, or VIS-A. Only 3% had severe limitations. Although numerous studies on HCC surveillance ultrasound are available, there is limited data on the diagnostic quality of ultrasound. We believe our study provides meaningful information, that in most cases, ultrasound provides sufficient images, as per ACR Ultrasound LI-RADS Visualization Score assessment. Sonoelastographic diagnosis of clinically significant fibrosis, as well as clinical cirrhosis, increased patient age, and spleen size, were associated with greater diagnostic limitations in the subset of subjects with suboptimal visualization. Identifying factors contributing to limited visualization can lead to future improvements in ultrasound scan protocols, technology, and technique for HCC surveillance in high-risk patients. Further work is underway to assess the impacts of visualization on diagnostic sensitivity for HCC.

## Compliance with ethical standards

**Ethical approval** IRB approval was obtained, and the requirement for written consent was waived.

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