Can acoustic radiation force imagine of the liver and spleen predict the presence of gastroesophageal varices?

Abstract

Aim
To determine whether acoustic radiation force imaging (ARFI) of the liver/spleen could be used in patients with cirrhosis to predict the presence of gastroesophageal varices (GOVs).
Materials and Methods
58 patients with cirrhosis who were currently undergoing 6 monthly ultrasound scans for hepatoma surveillance and who were due to have oesophagogastroduodenoscopy (OGD) within 6 months of their ultrasound were recruited. During routine ultrasound the patient's liver and spleen were also assessed using ARFI. Other clinical parameters (platelet count, spleen size and transient elastography measurements) were also collected. Logistic regression was used to determine which variables were significantly associated with presence or absence of varices univariably and multivariably.
Results
14 patients (24%) had GOVs. Patients with GOVs had higher ARFI measurements in the liver and spleen than patients without GOVs (liver - 2.39 vs 2.13, spleen – 2.89 vs 2.82) but these results were not statistically significant (Odds ratio (95% CI) 1.75 (0.82, 3.91) and 1.12 (0.33, 3.97) respectively). The platelet/splenic ratio, in comparison, was associated with presence or absence of GOVs in multivariate analysis (Odds ratio (95% CI) 0.32 (0.008 – 0.91)).
Conclusion
Although patients with GOVs had overall higher ARFI liver and spleen results, this was not statistically significant. As such, ARFI cannot yet replace OGD in predicting GOVs in patients with this patient group.

Introduction

Patients with liver cirrhosis are at risk of developing portal hypertension due to a combination of increased resistance to flow from fibrosis, regenerative nodules and intrahepatic vasoconstriction. Portal hypertension can subsequently lead to the formation of portosystemic collaterals. Up to 50% of patients with cirrhosis develop oesophageal or gastric varices (GOVs). The risk of bleeding of GOV is 5-15% per year, depending on size of the varices so early diagnosis is important to enable treatment [1-4].

Currently the reference standard for determining the presence of GOVs is oesophagogastroduodenoscopy (OGD). Although an accurate technique, OGD is time consuming, semi-invasive and can be poorly tolerated by patients. There have been moves, therefore, to investigate the potential of non-invasive indicators of GOVs. These include transient elastography (TE) [5] and platelet count [3]. The latter has been combined with spleen length to give a platelet count to spleen length ratio (PSR) with promising results [6-9]. Recent guidelines produced by the Baveno VI Consensus Workshop suggest that patients with a liver stiffness <20 kPa on TE and with a platelet count >150,000 have a very low risk of having varices requiring treatment, and can avoid screening endoscopy[2]. Other groups are not in consensus with this - European Guidelines by the European Association for the Study of the Liver and the Latin American Association for the Study of the Liver suggest that non-invasive methods should not replace OGD at the present time[3].

Acoustic radiation force impulse imaging (ARFI), also known as Virtual Touch quantification elastography, is a relatively new ultrasound-based imaging technique used to assess the elasticity of tissue. ARFI is based on the principle of using an ultrasound probe to apply a focused ultrasound radiation force to a tissue. This force causes tissue displacement depending on the properties of the tissue and the effects of this displacement is mapped by an ultrasound machine. The displacements in the tissue correspond inversely to the stiffness of the tissue[10]. ARFI is performed with an ultrasound machine with additional software capabilities.

ARFI is at least comparable to TE in the diagnosis of liver cirrhosis [11] and recent guidelines suggest that it is the most cost effective option for units that do not already have a Fibroscan machine [12]. What is less well understood is how well ARFI can predict the presence and severity of GOVs.

ARFI has been used to study stiffness in the liver (LS) and spleen (SS). Some studies have demonstrated that LS [13] and SS [14-16] measured with ARFI can predict the presence of GOVs, but other studies have demonstrated that neither LS or SS could reliably replace OGD in confirming or excluding GOVs[17, 18]. ARFI is currently not widely performed in the UK and the reliability in the UK patient population is not yet known.

If ARFI were to prove accurate in the detection of GOVs it has several potential advantages over TE. ARFI is obtained using a standard B-mode ultrasound machine, meaning that the liver or spleen is directly visualised and then sampled. The area of assessment is selected by a trained operator under direct visualisation, rather than blind using body surface landmarks. This is particularly useful in patients who are obese or patients with ascites. This is reflected in the fact that the risk of failure to obtain a value is reportedly less for ARFI as compared with TE - 2.9% vs. 6.4%[19]

Patients at risk of GOVs due to underlying cirrhosis require B-mode ultrasound to look for various factors – for example ascites, portal vein patency and spleen size. In addition, most patients with compensated cirrhosis also undergo regular ultrasound to assess for the presence of hepatocellular carcinoma (HCC) as per European guidelines[20]. As such ARFI, rather than being a new study which would require another patient attendance, could be provided at the time of the patient's routine ultrasound scan, which has potential time and cost saving implications.

The aim of this study was to define the utility of ARFI scanning in the non-invasive screening for GOVs in cirrhotic patients who have been enrolled in a HCC surveillance programme. The primary objective was to determine whether ARFI of the liver and spleen, performed during regular HCC surveillance ultrasound, could predict the presence and severity of GOVs on routine OGD performed as part of normal standard of care within 6 months of the ARFI scan. The secondary objective of the study was to compare the accuracy of ARFI with that of other more established parameters currently performed on all patients, specifically TE and PSR.

Materials and Methods

Ethical approval was obtained from the authors' Trust Research and Development Department. Patients were prospectively selected. All patients who were due to have an outpatient ultrasound scan for hepatoma surveillance whilst the study was ongoing (April 2015 – August 2016) were assessed for eligibility by a Consultant Radiologist and Consultant Hepatologist. This was done by review of the patients' medical and radiology records.

Inclusion Criteria

- >18 years old
- Able to provide written informed consent
- Patients with cirrhosis – either biopsy proven or diagnosed based on clinical, biochemical and radiological investigations.
- Patients currently undergoing six monthly ultrasound for surveillance for hepatoma
    - In cirrhotic patients - Child-Pugh stage A and B scores 5-7
- Patients who have had, or are due to have, OGD, TE and platelet assessment within 6 months of the ultrasound
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Exclusion Criteria

- Unable to provide consent
- Patients currently on treatment for portal hypertension (including beta-blockers)
- Patients with portal vein thrombosis or ascites (as detected on any form of imaging, including ultrasound scan)
- Child-Pugh stage B score >7 or C (as these patients are not suitable for regular ultrasound surveillance).

Those who were suitable based on inclusion and exclusion criteria were contacted by letter and sent a patient information sheet to read before their appointment. Consent was then obtained when the patient came for their ultrasound scan. Data regarding patient age, gender, Child-Pugh score, platelet count, transient elastography measurement, current treatment for portal hypertension and OGD findings (presence and severity of GOVs) were collected.

Scan procedure

ARFI was performed during the patients' routine ultrasound appointment for HCC surveillance. The ultrasound scans were performed using a Siemens Acuson S2000 machine. Scans were performed by the Lead Ultrasound Sonographer or by one of two Consultant Radiologists with a specialist interest in hepatobiliary imaging. All the operators performing ARFI had undergone specific training on its use. The scan was performed to the following protocol:

- Scan the liver to look for signs of HCC
- Scan the portal vein to look for direction of flow and patency
- Scan the spleen and measure the spleen to look for enlargement and to enable later PSR measurement
- ARFI scan:
    - Place a 1 x 0.5cm region of interest in the liver, at least 1cm below the liver capsule, with a maximum depth of 8cm, not directly adjacent to a blood vessel
    - Perform a total of 10 valid measurements in the liver
    - Assess the spleen as above
    - Perform a total of 5 valid measurements in the spleen

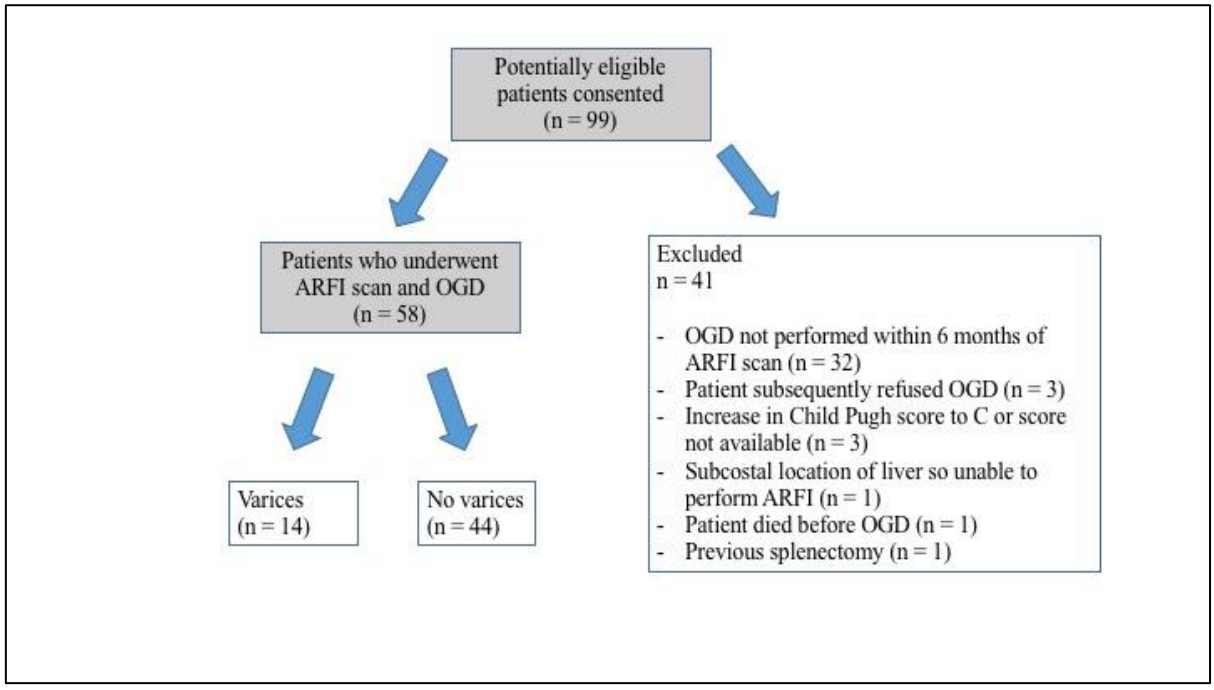
Statistical analysis

Due to the exploratory objectives of this study and the study duration limitations power analysis to determine a minimum required sample size was not performed. Instead a sample of convenience was used.

Logistic regression was used to determine which variables were significantly associated with presence or absence of GOVs, univariably and multivariably. Variables were selected for inclusion in the parsimonious multivariable model according to backwards selection via Akaike's Information Criteria. Missing data was replaced with the median for that covariate.

Results

99 patients had ultrasound scans booked for HCC surveillance during which they consented to the ARFI study. Of those, 41 patients were subsequently excluded (see flow chart, Figure 1.), leaving 58 eligible patients.



There were 20 (34%) females and 38 (66%) male participants in the study. The mean age was 59yrs.

The cause of the patients' underlying liver disease is summarized in table 1.

Table 1: Cause of liver disease

Cause of liver disease	Number of patients (% of total)
Alcoholic liver disease	22 (38%)
Hepatitis C	17 (29%)
Nonalcoholic fatty liver disease	8 (14%)
Hepatitis B	3 (5%)
Primary biliary cirrhosis	2 (3%)
Alcoholic liver disease and hepatitis B	2 (3%)
Cystic fibrosis related liver disease	1 (2%)
Cryptogenic cirrhosis	1 (2%)
Nonalcoholic fatty liver disease and autoimmune hepatitis	1 (2%)
Nonalcoholic fatty liver disease and hepatitis B	1 (2%)

14 patients (24%) had GOVs on OGD. All patients had low risk varices. This meant that we could not perform analysis of low vs. high GOVs.

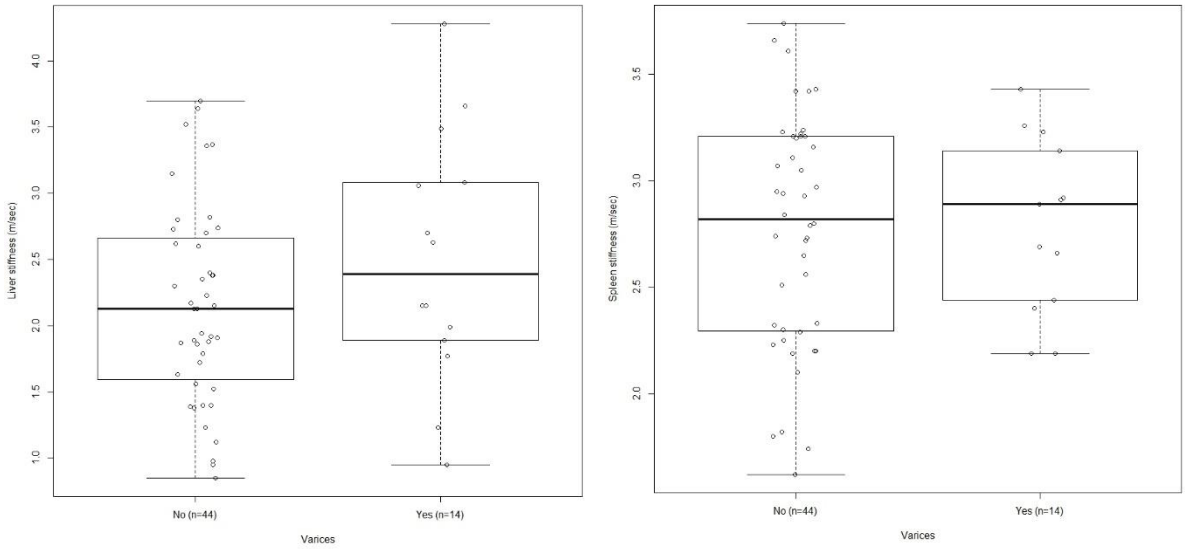
Missing data was replaced with the median for that covariate. This applied to one patient in whom ARFI of the spleen could not be performed and 20 patients who's fibroscan result was not within 6 months of the OGD.

The results for the relationship between the different investigations and the presence or absence of GOVs is found in table 2. ARFI liver and ARFI spleen were not significantly different across the presence or absence of GOVs, though results were generally higher in those with GOVs (Figure 2). The only investigations that were significantly different across the presence of GOVs were spleen size and PSR.

Table 2: Population characteristics, median (IQR) unless otherwise stated

Investigation	No Varices n=44	Varices n=14	Total n=58	p-value
ARFI Liver (m/s)	2.13 (1.61, 2.64)	2.39 (1.92, 3.08)	2.15 (1.73, 2.72)	0.23
ARFI Spleen (m/s)	2.82 (2.30, 3.21)	2.89 (2.44, 3.14)	2.84 (2.32, 3.21)	0.99
Spleen Size (mm)	107.0 (93.0, 126.3)	127.5 (110.0, 139.50)	111.0 (97.0, 128.8)	***0.02***
Platelet Count (x 10^9/l)	149.5 (125.0, 191.5)	120.0 (92.5, 140.3)	135.5 (116.2, 189.5)	0.05
Platelet to Spleen Ratio	1.38 (1.06, 1.74)	0.85 (0.73, 1.25)	1.30 (0.93, 1.71)	***0.02***
Fibroscan (kPa)	21.1 (8.8, 35.1)	26.3 (20.9, 52.5)	21.9 (9.1, 35.7)	0.40

Figures 2: Box plots demonstrating relationship between ARFI results and presence or absence of GOVs. (a) liver stiffness, (b) spleen stiffness



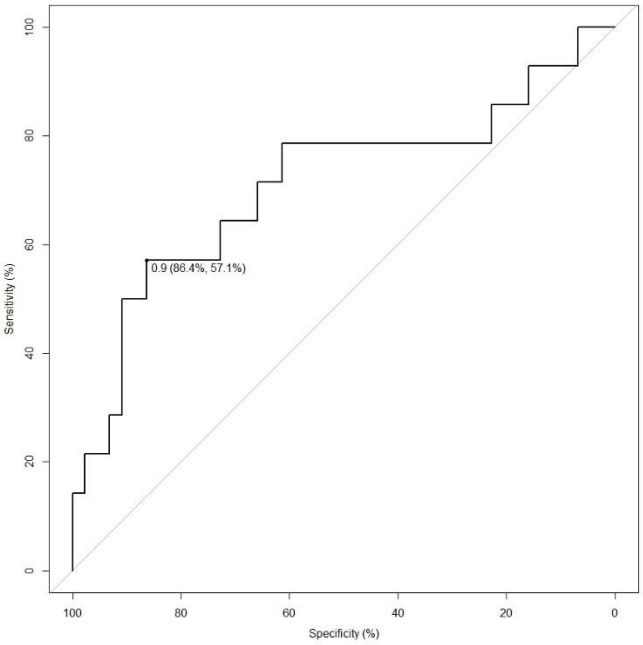
The results of the univariable model can be found in table 3. No variables were significantly associated with the presence of GOVs.

Table 3: Univariable Analysis

Investigation	p-value	Odds Ratio (95% Confidence Interval)
ARFI liver	0.15	1.75 (0.82, 3.91)
ARFI spleen	0.85	1.12 (0.33, 3.97)
Platelet to spleen ratio	0.06	0.32 (0.08, 0.91)
Fibroscan	0.39	1.01 (0.98, 1.05)

According to the multivariable model, only PSR was significantly associated with presence or absence of GOVs. The odds ratio (with 95% confidence interval) was 0.32 (0.008 – 0.91). ROC curve analysis can be seen in figure 3 and provided an area under the curve of 0.711. A sensitivity of 57.1% and specificity of 86.4% was obtained using the optimum cut off of 0.9.

Figure 4: ROC curve for platelet to spleen ratio



Discussion

ARFI

This study aimed to determine whether ARFI could be used as an alternative to OGD in detecting GOVs in a different patient population to that previously studied. The results demonstrated that patients with GOVs had higher mean LS and SS results but that this was not significant.

Theoretically LS should correspond with portal venous pressure as resistance to blood flow is proportional to liver stiffness. Later in portal hypertension, however, there is proportional increase in portal venous flow and splanchnic vasodilation which cannot be measured by ARFI or indeed other methods of LS measurement. This is why SS has been proposed as a more reliable marker, with more promising results.

Several studies have demonstrated that measuring LS or SS with ARFI may be useful in predicting GOVs.

In a Japanese study by Takuma et al [14], 340 patients with cirrhosis of mixed aetiology were studied. SS was superior to LS in predicting GOVs and high risk GOVs. The AUROC values for predicting GOVs using SS were 0.933 and high risk GOVs 0.930. Using a cut off of 3.18m/s for GOVs and 3.30m/s for high risk GOVs gave NPVs of 98.4% and 99.4% and PPVs of 61.0% and 47.8% respectively. Thus according to this study SS could be useful as a "rule out" test. Another study, performed in Italy, found similar results. The study by Rizzo et al [15] on 54 patients with newly diagnosed Hepatitis C related cirrhosis demonstrated that SS was significantly higher in patients with GOVs compared with those without GOVs, AUROC 0.959. Using 3.1m/s as the optimum cut off gave NPV 96% and PPV 90%.

In a further study from China, Ye et al [16] also found that SS could potentially predict GOVs. They studied 73 patients with hepatitis B cirrhosis who underwent OGD and ARFI LS and SS. They found that SS, but not LS, demonstrated significant linear correlation with GOV grade. The AUROCs of SS for predicting the presence of GOVs and grade 3 GOVs were 0.83 and 0.83, respectively. Using cutoff values of 3.16 m/s for predicting the presence of GOVs gave sensitivity 84.1%; specificity, 81.0% and 3.39 m/s and for grade 3 gave sensitivity 78.9% and specificity 78.3%.

In another study in Japan by Morishita et al [13] of 135 patients with HCV related cirrhosis, LS measured with ARFI was moderately good at predicting presence and severity of GOVs. AUROC

values for diagnosis of EV presence and high-risk EVs by ARFI were 0.890 and 0.868 respectively. Optimum cut off of for GOV presence was 2.05 m/s with gave NPV 81% and PPV 78 % and for high-risk GOVs was 2.39 m/s gave NPV 89% and PPV 69 %. This group did not study SS.

In contrast to the above studies other studies found that LS and SS was not as useful in predicting GOVs. In a Japanese study by Mori et al [17], 33 patients with chronic hepatitis C were studied. Neither LS nor SS demonstrated significant association with GOVs, which is in keeping with the results of this current study.

A larger German study by Vermehren et al [18] demonstrated that, in 166 patients with cirrhosis of mixed aetiology ARFI SS correlated better than LS with the presence of large GOVs but the AUROC was unsatisfactory at 0.58. With a cut off of 3.04m/s they demonstrated NPV of 81% and PPV of 40%.

In a study performed in Romania by Bota et al [19] on 145 patients with cirrhosis of mixed aetiology LS and SS were significantly higher in patients with grade 2 or 3 GOVs. The AUROC for each was unsatisfactory, however. For SS AUROC was 0.578. Using a cut off of 2.55m/s, NPV 89.4% and PPV 47.6%. For LS AUROC was 0.596. Using a cut off of 2.25m/s gave NPV 85.7% and PPV 49.5%.

As such, the current study demonstrated similar results to some of the previous studies, but differed from others. One of the potential reasons why the results of the current study differ from some of the previous studies that did show ARFI may be useful in predicting GOVs is the patient group studied. The patients in the current study all had early stage cirrhosis (Child-Pugh stage A and B scores 5-7) consequently none of the patients had grade 2 or 3 GOVs. This may indicate that ARFI may be more useful in advanced stages of liver cirrhosis, but perhaps less useful in early stage. Takuma et al performed subgroup analysis which suggested that ARFI is useful in both early and late cirrhosis, however [14]. Sub group analysis demonstrated that the AUROCs of SS for predicting GOVs were high, both in compensated (Child–Pugh class A) (0.934) and decompensated cirrhosis (Child–Pugh class B and C) (0.936). Furthermore, they found that AUROCs of SS for predicting high-risk GOVs were also high, regardless of compensated (0.921) or decompensated cirrhosis (0.934).

Another potential reason for the difference in the results of the current study compared to some other published studies is the difference in patient population. Some of the previous studies have included only patients with hepatitis B [16] or hepatitis C [13, 15, 16] whilst others studied patients with mixed aetiologies, as in our patient population [14, 18, 19].

Future studies would be useful to help to determine whether other variables, for example liver disease aetiology, make ARFI more or less useful in predicting GOVs.

PSR and TE

In this study spleen size and PSR was demonstrated to be potentially useful in predicting GOVs. This is in keeping with several published studies and a recent meta analysis [21].

This study found that TE in our patient group could not predict the presence of GOVs. This is in contrast to the Baveno VI consensus guidelines that suggest that "Patients with a liver stiffness <20 kPa and with a platelet count >150,000 have a very low risk of having varices requiring treatment, and can avoid screening endoscopy". Reasons for this difference may include the previously discussed factors of selecting only patients with compensated cirrhosis in the study.

Limitations

There were some limitations to this study. There was a relatively small sample size. In addition, technique for LS differed slightly from guidelines that have subsequently been published [22]. In this study the left and right lobes of the liver were studied, whereas consensus guidelines published after this study had commenced suggest that ARFI is more reliable in the right lobe. In addition, as ARFI was performed during the same appointment as routine HCC surveillance (for which patients are not routinely fasted), the patients were not fasted for the ARFI study. The aforementioned consensus guidelines suggest that patients should be fasted.

Future considerations

ARFI is still a relatively new technique and has not been studied as widely as other non-invasive methods. With further research into the potential utility of ARFI in different patient groups it is possible that it could be used in the diagnosis of portal hypertension, in particular GOVs. Given that the Baveno VI [2] guidelines already suggest a threshold for TE, it may be possible that a similar ARFI threshold could be suggested in future.

Other potential considerations are of novel combinations of other non-invasive investigations with ARFI which could potentially improve upon the diagnostic abilities of ARFI when used on its own [19, 23].

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