Received:
03 May 2018

Revised:
21 July 2018

Accepted:
20 August 2018

<https://doi.org/10.1259/bjr.20180401>

Cite this article as:

Madhusudhan KS, Kilambi R, Shalimar, Sahni P, Sharma R, Srivastava DN, et al. Measurement of splenic stiffness by 2D-shear wave elastography in patients with extrahepatic portal vein obstruction. *Br J Radiol* 2018; **91**: 20180401.

FULL PAPER

Measurement of splenic stiffness by 2D-shear wave elastography in patients with extrahepatic portal vein obstruction

¹KUMBLE SEETHARAMAMADHUSUDHAN, MD, FRCR, MAMS, ²RAGINIKILAMBI, MS, MCh, ³SHALIMAR, MD, DM, ²PEUSHSAHNI, MS, MCh, ¹RAJUSHARMA, MD, MAMS, ¹DEEP NARAYANSRIVASTAVA, MD and ¹ARUN KUMARGUPTA, MD

¹Department of Radiodiagnosis, All India Institute of Medical Sciences, New Delhi, India

²Department of Gastrointestinal Surgery, All India Institute of Medical Sciences, New Delhi, India

³Department of Gastroenterology, All India Institute of Medical Sciences, New Delhi, India

Address correspondence to: Dr Kumble Seetharama Madhusudhan
E-mail: drmadhuks@gmail.com

Objective: To assess the accuracy of splenic stiffness (SS) measured by 2D-shear wave elastography (SWE) for predicting variceal bleeding in the patients with extrahepatic portal vein obstruction (EHPVO).

Methods: 52 patients with EHPVO (mean age: 22.29 years; 26 each males and females) were included in the study after obtaining approval from the institute ethics committee. All patients initially underwent upper gastrointestinal endoscopy followed by ultrasonography, including 2D-SWE on the Aixplorer Supersonic Imagine scanner. The SS was measured through the anterior abdominal wall and an average of three measurements was taken. The SS was then compared with clinical symptoms, variceal grade, and other ultrasonography (USG) parameters. USG parameters were also compared with variceal grade.

Results: The mean SS was 44.92 ± 12.35 kPa. There was no significant difference in the mean SS of patients with

high grade varices (44.30 kPa; $n = 25$) from those with low grade varices (46.91 kPa; $n = 20$). The ROC analysis showed a poor area under the curve of 0.477 for the prediction of high grade varices by the SS. The SS did not show any significant correlation with other ultrasonography parameters except splenic size, with which there was a weak but significant correlation. The measurement of SS by 2D-SWE was reliable and Cronbach's alpha was 0.905.

Conclusion: The SS measured by 2D-SWE is not an accurate predictor of variceal grade and thus bleeding in patients of EHPVO.

Advances in knowledge: EHPVO is a vascular pathology with most patients showing splenomegaly and preserved liver function. Although, elastography of spleen has been shown to be useful in patients with cirrhosis for predicting portal hypertension, it does not seem to be helpful in patients with EHPVO.

INTRODUCTION

Extrahepatic portal vein obstruction (EHPVO) is a vascular pathology developing from chronic thrombosis of the extrahepatic portal vein, with or without the involvement of the intrahepatic portal vein branches, the superior mesenteric vein, and the splenic vein.¹ The chronic thrombosis results in attenuation and fibrosis of the portal vein along with the development of multiple collaterals at the porta hepatis (cavernomatous transformation of the portal vein). These patients usually present in the chronic stage and an etiology is not identified in most of these patients.¹ EHPVO is a common cause of pre-hepatic (non-cirrhotic) variety of portal hypertension which most often presents with gastrointestinal hemorrhage.² Since it is a pre-hepatic disease, the liver parenchyma is usually normal and the liver function tests are preserved.^{3,4} The portal hypertension leads

to the development of esophageal varices, portosystemic collaterals, and splenomegaly. Ultrasonography with color Doppler is highly accurate in the diagnosis of EHPVO and CT scan or MRI are routinely not necessary.¹

Splenic enlargement, due to congestion, is seen in majority of the cases with portal hypertension and has been shown to correlate with the severity of esophageal varices and liver disease in patients with cirrhosis of the liver, especially when combined with platelet count.^{5,6} There is also an increase in the splenic stiffness (SS) in these patients and its measurement by sono-elastography has shown good correlation with portal hypertension, esophageal varices, and hepatic decompensation in cirrhotic patients.⁷⁻¹¹ Thus, SS measurement by elastography is becoming increasingly

used for the prediction of portal hypertension in patients with liver cirrhosis.

Various techniques of elastography include strain elastography, transient elastography, acoustic radiation force impulse imaging or point shear wave elastography (point SWE), and 2D-SWE.¹² Strain elastography is operator-dependent and is better for focal diseases. Transient elastography is widely used for diffuse liver disease, but usefulness is limited in obese patients and patients with ascites. Point SWE and 2D-SWE shows the point or area from which stiffness is measured due to the presence of greyscale image. The latter is better as larger area can be evaluated.^{12,13}

There is only one study in the literature, which has evaluated the SS using transient elastography in EHPVO and has shown some correlation with hematemesis.¹⁴ No study in the literature has used 2D-SWE for the evaluation of SS in the patients of EHPVO. With this background, we aimed to evaluate the accuracy of SS measured by 2D-SWE in the predication of esophageal variceal grade and bleeding.

METHODS AND MATERIALS

This prospective observational study was approved by the Institute Ethics Committee and a detailed informed consent was obtained from all patients prior to inclusion in the study. 52 patients with chronic EHPVO (without an identifiable portal vein), confirmed on ultrasonography, were included in the study. After the initial clinical evaluation, laboratory investigations were performed which included liver function tests (alanine transaminase, aspartate transaminase, serum bilirubin, alkaline phosphatase, and serum albumin), platelet count, and HBsAg and anti Hepatitis C Virus antibodies (markers of hepatitis B and hepatitis C viruses, respectively). Patients with positive markers for chronic viral hepatitis, liver stiffness of more than 7 kPa on fibroscan, those on beta-blocker treatment and with previous history of endoscopic treatment for varices were excluded from the study. All the included patients were subsequently evaluated with upper gastrointestinal endoscopy (UGIE) and ultrasonography (USG) within an interval of 7 days. On UGIE, the presence and the grade of esophageal varices, the presence of red color sign, portal hypertensive gastropathy, and fundal varices and the extension of the varices into the lesser curve of the stomach were assessed. Any bleeding varices when present were treated at the same time.

Ultrasonography was done on the Aixplorer machine (Super-sonic Imagine, Aix-en-Provence, France) with SC6-1 convex transducer, after an overnight fast. Initially, greyscale and color Doppler evaluation were done followed by 2D-SWE. On the greyscale USG, size and echotexture of the liver, caliber of intrahepatic and extrahepatic bile ducts, size of the spleen, and the presence of ascites were noted and on the Doppler study, diameter and patency of the splenic, portal, superior mesenteric and left renal veins, and the presence of collaterals (at porta, lienorenal, gallbladder wall) were evaluated. Subsequently, SWE of the spleen was done. There is no standard examination protocol described for measuring the SS. Researchers have performed it through the intercostal space with either in suspended respiration

or after deep inspiration.^{15,16} Here, the SS was measured with the patient in supine position and with the transducer placed on the anterior abdominal wall (as all had splenomegaly), overlying the spleen. The SWE box (40 × 40 mm) was placed on the splenic parenchyma, about 2 cm away from the capsule and avoiding vessels whenever possible (Figure 1). The SWE image was frozen when there was homogeneous color filling in the SWE box, after asking the patient to hold his breath for 3–5 s. Subsequently, a circular region of interest–Q box–of size 1 cm in diameter was placed on the most homogeneous area within the SWE box to obtain quantitative information of tissue elasticity in kilopascals (kPa) (Figure 1). The measurement was considered reliable when the standard deviation (SD) was less than 10% of the mean SS as suggested by the manufacturer. If not, the measurement was repeated. Three such reliable measurements were recorded for each patient from three different areas of spleen and the median value was calculated. The measurements were considered valid when the interquartile range (IQR)/median was <30%.

or after deep inspiration.^{15,16} Here, the SS was measured with the patient in supine position and with the transducer placed on the anterior abdominal wall (as all had splenomegaly), overlying the spleen. The SWE box (40 × 40 mm) was placed on the splenic parenchyma, about 2 cm away from the capsule and avoiding vessels whenever possible (Figure 1). The SWE image was frozen when there was homogeneous color filling in the SWE box, after asking the patient to hold his breath for 3–5 s. Subsequently, a circular region of interest–Q box–of size 1 cm in diameter was placed on the most homogeneous area within the SWE box to obtain quantitative information of tissue elasticity in kilopascals (kPa) (Figure 1). The measurement was considered reliable when the standard deviation (SD) was less than 10% of the mean SS as suggested by the manufacturer. If not, the measurement was repeated. Three such reliable measurements were recorded for each patient from three different areas of spleen and the median value was calculated. The measurements were considered valid when the interquartile range (IQR)/median was <30%.

Statistical evaluation of the results was done using SPSS v. 17 (SPSS Inc, Chicago, IL). Descriptive statistics was used to summarize patient characteristics. Correlation of the SS with the clinical, endoscopic, and various ultrasonography parameters was done using Chi square test, Pearson correlation coefficient, Mann-Whitney U, and Kruskal-Wallis tests. Intraclass correlation coefficient was calculated to assess the reliability of SWE in the measurement of SS. A *p*-value of less than 0.05 was considered significant.

RESULTS

A total of 52 patients (mean age: 22.3 years; 26 males, 26 females) were included in the study. The mean duration of presenting complaints was 7.15 years. Hematemesis was the most common presentation, seen in 39 (75%) of the patients. High grade esophageal varices were seen in 25 (48.1%) patients, low grade varices in 20 (38.5%), and no varices were seen in 7 (13.5%) patients. Color Doppler USG showed portal cavernoma in 48 (92.3%) patients and a patent splenic vein in 45 (86.5%) patients. Intrahepatic portal vein branches were not seen in any of the patients.

None of the patients had prothrombotic state or myeloproliferative disorder. All cases were idiopathic and no cause for EHPVO could be identified in any of these patients. The details of the patient characteristics and data are summarized in Table 1.

The mean SS was 44.92 ± 12.35 kPa. The mean IQR was 3.7 kPa (Q1–43.03 kPa; Q3 – 46.4 kPa) with mean IQR/median ratio of 10.77%. The mean SS in patients with high grade varices ($n = 25$) was 44.30 kPa and those with low grade varices ($n = 20$) was 46.91 kPa, with no significant difference between the two groups ($p = 0.48$). The patient group which had no varices on UGIE had a mean SS of 41.44 kPa. The mean SS in patients with Grade I ($n = 2$), Grade II ($n = 18$), Grade III ($n = 11$), and Grade IV ($n = 14$) esophageal varices were 37.40 kPa, 47.96 kPa, 41.72 kPa,

Table 1. Demographic parameters and results of patients

Parameters	EHPVO ($n = 52$)
Mean age (years)	22.29 (13–50)
Sex (male:female)	26:26
Symptoms	
Mean duration (years)	7.15 (1–18)
Hematemesis (n)	39 (75%)
Pain (n)	23 (44.2%)
Lump (n)	20 (38.5%)
Jaundice (n)	15 (28.8%)
UGIE	
Esophageal varices – median grade	2 (0–4)
High grade (n)	25 (48.1%)
Low grade (n)	20 (38.5%)
No varices (n)	7 (13.5%)
Red cherry sign (n)	14 (26.9%)
Portal hypertensive gastropathy (n)	30 (57.7%)
Lesser curve extension (n)	14 (26.9%)
Laboratory investigations	
Total bilirubin (mg/dL)	2.18 (0.4–15.5)
Serum alkaline phosphatase (IU / L)	245.78 (102 – 659)
Serum AST (IU / L)	48.37 (15 – 256)
Serum ALT (IU / L)	45.33 (14 – 154)
Serum albumin (g/dL)	4.29 (3.1–5.7)
Platelet count ($\times 10^3$ /microL)	100.42 (27 – 337)
Ultrasonography	
Mean SS (kPa)	44.92 (25.4–75.6)
Portal cavernoma (n)	48 (92.3%)
Patent splenic vein (n)	45 (86.5%)
Splenic vein diameter (mean)	4.69 mm (1–9 mm)
Left renal vein diameter (mean)	7.69 mm (5–17 mm)
Spleen size (mean)	18.89 cm (11.7–25.8 cm)

EHPVO, extrahepatic portal vein obstruction; SS, splenic stiffness; UGIE, upper gastrointestinal endoscopy;

Figure 2. Boxplot showing the spread of the splenic stiffness values in groups with different grades of esophageal varices. Significant overlap in the SS values are seen between the groups.

and 46.34 kPa, respectively (Figure 2), with no significant difference between the groups ($p = 0.52$). Further, the mean SS was not significantly different in patients who presented with hematemesis ($n = 39$; 45.79 kPa) from those without ($n = 13$; 42.32 kPa), with a p -value of 0.77. The area under the receiver operating characteristic curve for the prediction of high grade varices by the SS was a poor 0.477, suggesting that the SS is not useful. There was also no significant difference in splenic size, splenic vein diameter, left renal vein diameter, and platelet count between patients with high and low grade esophageal varices. Multivariate analysis showed no significant correlation between SS, spleen size, and splenic vein diameter and the grade of esophageal varices. There was a weak but significant correlation between the SS and the size of the spleen ($r = 0.326$; $p = 0.018$). The SS did not show any significant correlation with the duration of the disease ($p = 0.35$; $r = -0.13$), splenic vein diameter ($r = 0.25$; $p = 0.09$), and left renal vein diameter ($r = -0.231$; $p = 0.1$). The details of the results and comparison are shown in Tables 2 and 3.

The SS could be measured in all the patients (as all were performed through anterior abdominal wall). The reliability of the three measurements of SS in each patient was assessed by intraclass correlation coefficient which showed a Cronbach's alpha value of 0.905 ($p < 0.001$).

DISCUSSION

Hematemesis, due to the rupture of esophageal varices, is the most common clinical presentation of EHPVO.² Although, variceal bleeding in patients of EHPVO is usually well-tolerated, assessment is necessary to avoid morbidity and rare cases of mortality.¹⁷ Esophageal varices are routinely evaluated by UGIE, which is invasive, causes discomfort to the patient and is associated with a very low risk of perforation.^{18,19} Thus a search for an accurate non-invasive modality for predicting the presence and grade of esophageal varices is on. Measurement of liver stiffness

Table 2. Comparison of parameters between high grade and low grade varices groups

Mean value of parameters	High grade varices (<i>n</i> = 25)	Low grade varices (<i>n</i> = 20)	<i>p</i> - value
Splenic stiffness (kPa)	44.30	46.91	0.48
Duration of symptoms (years)	6.0	7.6	0.24
Platelet count ($\times 10^3$ microL ⁻¹)	107.67	95.71	0.58
Splenic vein diameter (mm)	9.45	9.95	0.45
Left renal vein diameter (mm)	7.72	7.75	0.97
Spleen size (cm)	19.2	18.5	0.47

in patients of EHPVO is of limited use as most of these patients do not show any liver fibrosis and studies have shown that liver stiffness in these patients are either similar to or only little different from healthy population.^{4,14} Measurement of the SS, on the other hand may be useful. Promising results of SS measurement are seen in patients with chronic liver disease and it has shown to be useful in predicting variceal bleeding in this subgroup.⁷⁻¹¹ Some studies evaluating the role of SS by SWE in portal hypertension and liver disease have shown variable results.^{15,20-23} Since splenomegaly occurs in portal hypertension of any etiology, we hypothesized that measuring the SS in patients of EHPVO also should correlate with the degree of esophageal variceal dilation and thus, portal hypertension.

The results in the present study were contradictory to the proposed hypothesis. The SS did not show any correlation with the presence or absence of hematemesis or the grade of esophageal varices. In one study on the measurement of the SS in the patients of EHPVO, the authors showed significantly higher SS in the patients with variceal bleed than those without bleed (60.4 vs 30.3 kPa; $p = 0.01$).¹⁴ They however did not correlate the SS with the grade of esophageal varices. In a preliminary study at our institute, we found no significant correlation between the SS and the intra-operative portal pressure in the patients of EHPVO, suggesting that the stiffness of spleen may not be directly related to the extent of portal hypertension.²⁴ Presence of spontaneous lieno-renal portosystemic shunts is thought to reduce the portal hypertension and the grade of esophageal varices.²⁵ We tried to assess this by comparing the SS with the caliber of the left renal vein [(LRV), which dilates in the presence of a spontaneous shunt]. Although, there was a weak inverse correlation (r

= -0.231) between the SS and the diameter of LRV, it was not significant ($p = 0.1$). Similarly, the size of LRV was not significantly different between patients with high grade and low grade varices (7.72 vs 7.75 mm respectively; $p = 0.97$).

Various pathological changes occur in the spleen of patients of portal hypertension.²⁶⁻²⁸ These include angiogenesis, fibrogenesis, widening of the Billroth's cords leading to an increase in the fibroblasts and the fibrillary connective tissue, increase in the white pulp, perivascular phlebosclerosis, capsular thickening, sinus hyperplasia, increase in trabeculations, and increase in the macrophages. Thus, the SS is not only determined by the extent of splenic congestion but also by these hyperplastic and fibroblastic changes. Moschcowitz showed that these changes are more advanced in patients with long standing portal hypertension, which is seen in EHPVO.²⁶ In view of these complex pathological changes in the spleen of patients with portal hypertension, it needs to be investigated if these changes progressively occur just as a result of persistent portal hypertension or if the severity is related to the degree of portal hypertension. It may be possible that these changes do not directly correlate with the severity of portal hypertension due to the fact that some of the studies on the measurement of SS in cirrhotic patients have not shown consistent and accurate results in predicting the severity of esophageal varices and portal hypertension.²⁹⁻³¹ The same could presumably be true for the patients of EHPVO too.

Since low grade varices rarely bleed, there was another discrepancy in the study. Out of the 75% ($n = 39$) of patients with history of hematemesis, only 48.1% ($n = 25$) had high grade varices and the remaining 14 patients had low grade varices. This could be because most of the patients had a long clinical history and the episode of hematemesis was long before presentation, when the portal hemodynamics could have changed.

There are sporadic studies in literature evaluating the role of non-invasive markers of portal hypertension in the patients of EHPVO. Liver stiffness in EHPVO has been evaluated by two studies, but with conflicting results, as one showed significant difference between patients of EHPVO and healthy population and the other showing no significant difference.^{4,14} Although, splenomegaly and low platelet count are seen in patients of EHPVO, only one study is available which showed no significant difference in spleen size and platelet count between bleeders and non-bleeders.¹⁴ Similar results were found in the present study.

Table 3. Comparison of splenic stiffness with various other ultrasonography parameters

Correlation between SS and the following	Pearson correlation coefficient (<i>r</i>)	<i>p</i> -value
Duration of disease	-0.133	0.348
Grades of esophageal varices	0.079	0.540
Splenic vein diameter	0.250	0.098
Left renal vein diameter	-0.231	0.100
Splenic size	0.326	0.018 ^a

SS, splenic stiffness;

^aIndicates significance at p -value.

A study by Sharma et al, showed that the liver stiffness in patients with non-cirrhotic portal fibrosis (NCPF; a disease similar to EHPVO) was higher than healthy population, but significantly lower than in cirrhotics and thus may help differentiate Child's A cirrhosis from NCPF.³² More studies are thus needed to evaluate the role of non-invasive markers of portal hypertension in the patients of EHPVO.

There were a few limitations in our study. The numbers were small and thus results may not be representative. We did not measure the invasive variceal or portal pressure, which would have helped in validating our results. Biopsy of the spleen

was not done in any of our patients. Spleen histology might be useful for assessing parenchymal changes which can be correlated with SS measurements.

In conclusion, this was a preliminary study evaluating the usefulness and reliability of the SS through 2D-SWE in predicting the severity of portal hypertension in the patients of EHPVO. It showed that the SS is not accurate for prediction of endoscopic variceal grade. In view of complex pathological changes occurring in the spleen of patients of EHPVO, further studies are necessary to provide conclusive evidence.

REFERENCES

1. Sarin SK, Sollano JD, Chawla YK, et al. Members of the APASL working party on portal hypertension. Consensus on extrahepatic portal vein obstruction. *Liver Int* 2006; **26**: 512–9.
2. Webb LJ, Sherlock S. The aetiology, presentation and natural history of extrahepatic portal venous obstruction. *Q J Med* 1979; **48**: 627–39.
3. Sarin SK, Agarwal SR. Extrahepatic portal vein obstruction. *Semin Liver Dis* 2002; **22**: 543–58. doi: <https://doi.org/10.1055/s-2002-23206>
4. Madhusudhan KS, Sharma R, Kilambi R, Shylendran S, Shalimar S, Sahni P, et al. 2D shear wave elastography of liver in patients with primary extrahepatic portal vein obstruction. *J Clin Exp Hepatol* 2017; **7**: 23–7. doi: <https://doi.org/10.1016/j.jceh.2016.12.001>
5. Colli A, Gana JC, Yap J, Adams-Webber T, Rashkovan N, Ling SC, et al. Platelet count, spleen length, and platelet count-to-spleen length ratio for the diagnosis of oesophageal varices in people with chronic liver disease or portal vein thrombosis. *Cochrane Database Syst Rev* 2017; **4**: CD008759. doi: <https://doi.org/10.1002/14651858.CD008759.pub2>
6. Berzigotti A, Seijo S, Arena U, Abalde JG, Vizzutti F, García-Pagán JC, et al. Elastography, spleen size, and platelet count identify portal hypertension in patients with compensated cirrhosis. *Gastroenterology* 2013; **144**: 102–11. doi: <https://doi.org/10.1053/j.gastro.2012.10.001>
7. Takuma Y, Nouse K, Morimoto Y, Tomokuni J, Sahara A, Takabatake H, et al. Portal Hypertension in Patients with Liver Cirrhosis: Diagnostic Accuracy of Spleen Stiffness. *Radiology* 2016; **279**: 609–19. doi: <https://doi.org/10.1148/radiol.2015150690>
8. Ma X, Wang L, Wu H, Feng Y, Han X, Bu H, et al. Spleen stiffness is superior to liver stiffness for predicting Esophageal varices in chronic liver disease: a meta-analysis. *PLoS One* 2016; **11**: e0165786. doi: <https://doi.org/10.1371/journal.pone.0165786>
9. Takuma Y, Morimoto Y, Takabatake H, Toshikuni N, Tomokuni J, Sahara A, et al. Measurement of spleen stiffness with acoustic radiation force impulse imaging predicts mortality and hepatic decompensation in patients with liver cirrhosis. *Clin Gastroenterol Hepatol* 2017; **15**: 1782–90. doi: <https://doi.org/10.1016/j.cgh.2016.10.041>
10. Giunta M, Conte D, Fraquelli M. Role of spleen elastography in patients with chronic liver diseases. *World J Gastroenterol* 2016; **22**: 7857–67. doi: <https://doi.org/10.3748/wjg.v22.i35.7857>
11. Ye XP, Ran HT, Cheng J, Zhu YF, Zhang DZ, Zhang P, et al. Liver and spleen stiffness measured by acoustic radiation force impulse elastography for noninvasive assessment of liver fibrosis and esophageal varices in patients with chronic hepatitis B. *J Ultrasound Med* 2012; **31**: 1245–53.
12. Dietrich CF, Bamber J, Berzigotti A, Bota S, Cantisani V, Castera L, et al. EFSUMB guidelines and recommendations on the clinical use of liver ultrasound elastography, update 2017 (Short Version). *Ultraschall Med* 2017; **38**: 377–94. doi: <https://doi.org/10.1055/s-0043-103955>
13. Srinivasa Babu A, Wells ML, Teytelboym OM, Mackey JE, Miller FH, Yeh BM, et al. Elastography in chronic liver disease: modalities, techniques, limitations, and future directions. *Radiographics* 2016; **36**: 1987–2006. doi: <https://doi.org/10.1148/rg.2016160042>
14. Sharma P, Mishra SR, Kumar M, Sharma BC, Sarin SK. Liver and spleen stiffness in patients with extrahepatic portal vein obstruction. *Radiology* 2012; **263**: 893–9. doi: <https://doi.org/10.1148/radiol.12111046>
15. Pawluś A, Inglot M, Chabowski M, Szymańska K, Inglot M, Patyk M, et al. Shear wave elastography (SWE) of the spleen in patients with hepatitis B and C but without significant liver fibrosis. *Br J Radiol* 2016; **89**: 20160423. doi: <https://doi.org/10.1259/bjr.20160423>
16. Leung VY, Shen J, Wong VW, Abrigo J, Wong GL, Chim AM, et al. Quantitative elastography of liver fibrosis and spleen stiffness in chronic hepatitis B carriers: comparison of shear-wave elastography and transient elastography with liver biopsy correlation. *Radiology* 2013; **269**: 910–8. doi: <https://doi.org/10.1148/radiol.13130128>
17. Sarin SK, Khanna R. Non-cirrhotic portal hypertension. *Clin Liver Dis* 2014; **18**: 451–76. doi: <https://doi.org/10.1016/j.cld.2014.01.009>
18. Berzigotti A, Bosch J, Boyer TD. Use of noninvasive markers of portal hypertension and timing of screening endoscopy for gastroesophageal varices in patients with chronic liver disease. *Hepatology* 2014; **59**: 729–31. doi: <https://doi.org/10.1002/hep.26652>
19. Wolfsen HC, Hemminger LL, Achem SR, Loeb DS, Stark ME, Bouras EP, et al. Complications of endoscopy of the upper gastrointestinal tract: a single-center experience. *Mayo Clin Proc* 2004; **79**: 1264–7. doi: <https://doi.org/10.4065/79.10.1264>
20. Lucchina N, Recalini C, Macchi M, Molinelli V, Montanari M, Segato S, et al. Point shear wave elastography of the spleen: its role in patients with portal hypertension. *Ultrasound Med Biol* 2018; **44**: 771–8. doi: <https://doi.org/10.1016/j.ultrasmedbio.2017.11.019>
21. Jansen C, Bogs C, Verlinden W, Thiele M, Möller P, Görtzen J, et al. Shear-wave

- elastography of the liver and spleen identifies clinically significant portal hypertension: A prospective multicentre study. *Liver Int* 2017; **37**: 396–405. doi: <https://doi.org/10.1111/liv.13243>
22. Grgurevic I, Puljiz Z, Brnic D, Bokun T, Heinzl R, Lukic A, et al. Liver and spleen stiffness and their ratio assessed by real-time two dimensional-shear wave elastography in patients with liver fibrosis and cirrhosis due to chronic viral hepatitis. *Eur Radiol* 2015; **25**: 3214–21. doi: <https://doi.org/10.1007/s00330-015-3728-x>
 23. Elkrief L, Rautou PE, Ronot M, Lambert S, Dioguardi Burgio M, Francoz C, et al. Prospective comparison of spleen and liver stiffness by using shear-wave and transient elastography for detection of portal hypertension in cirrhosis. *Radiology* 2015; **275**: 589–98. doi: <https://doi.org/10.1148/radiol.14141210>
 24. Madhusudhan KS, Kilambi R, Shalimar PS, Pal S, Sharma R, Srivastava DN. Evaluation of splenic stiffness in patients of extrahepatic portal vein obstruction using 2D shear wave elastography: comparison with intra-operative portal pressure. *J Clin Exp Hepatol* 2017;Epub ahead of print. DOI. doi: <https://doi.org/10.1016/j.jceh.2017.12.002>
 25. Zardi EM, Uwechie V, Caccavo D, Pellegrino NM, Cacciapaglia F, Di Matteo F, et al. Portosystemic shunts in a large cohort of patients with liver cirrhosis: detection rate and clinical relevance. *J Gastroenterol* 2009; **44**: 76–83. doi: <https://doi.org/10.1007/s00535-008-2279-1>
 26. Moschcowitz E. The pathogenesis of splenomegaly in hypertension of the portal circulation; congestive splenomegaly. *Medicine* 1948; **27**: 187–222. doi: <https://doi.org/10.1097/00005792-194805000-00002>
 27. Mejias M, Garcia-Pras E, Gallego J, Mendez R, Bosch J, Fernandez M. Relevance of the mTOR signaling pathway in the pathophysiology of splenomegaly in rats with chronic portal hypertension. *J Hepatol* 2010; **52**: 529–39. doi: <https://doi.org/10.1016/j.jhep.2010.01.004>
 28. Bolognesi M, Merkel C, Sacerdoti D, Nava V, Gatta A. Role of spleen enlargement in cirrhosis with portal hypertension. *Dig Liver Dis* 2002; **34**: 144–50. doi: [https://doi.org/10.1016/S1590-8658\(02\)80246-8](https://doi.org/10.1016/S1590-8658(02)80246-8)
 29. Zyklus R, Jonaitis L, Petrenkienė V, Pranculis A, Kupčinskas L. Liver and spleen transient elastography predicts portal hypertension in patients with chronic liver disease: a prospective cohort study. *BMC Gastroenterol* 2015; **15**: 183. doi: <https://doi.org/10.1186/s12876-015-0414-z>
 30. Procopet B, Berzigotti A, Abalde JG, Turon F, Hernandez-Gea V, García-Pagán JC, et al. Real-time shear-wave elastography: applicability, reliability and accuracy for clinically significant portal hypertension. *J Hepatol* 2015; **62**: 1068–75. doi: <https://doi.org/10.1016/j.jhep.2014.12.007>
 31. Singh S, Eaton JE, Murad MH, Tanaka H, Iijima H, Talwalkar JA. Accuracy of spleen stiffness measurement in detection of esophageal varices in patients with chronic liver disease: systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2014; **12**: 935–45. doi: <https://doi.org/10.1016/j.cgh.2013.09.013>
 32. Sharma P, Agarwal R, Dhawan S, Bansal N, Singla V, Kumar A, et al. Transient elastography (fibroscan) in patients with non-cirrhotic portal fibrosis. *J Clin Exp Hepatol* 2017; **7**: 230–4. doi: <https://doi.org/10.1016/j.jceh.2017.03.002>