



Usefulness of Splenic Stiffness Measurement for Predicting Esophageal Varices in Chronic Liver Disease

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Abstract

Background: Chronic parenchymal liver disease and their complications are major source of morbidity and mortality. One of such complication is bleeding from esophageal varices due to portal hypertension. Other major complications are ascites hepatic encephalopathy. But major cause of death in chronic liver disease is bleeding from esophageal varices. Early diagnosis of clinically significant portal hypertension (>10mmHg) and varices is of greater.

Patients are asymptomatic in early stages. Most of the patients will be diagnosed with varices only at later stages during routine screening or during bleeding manifestations. Hence its detection at a later stage will have higher mortality rate. But varices are effectively treatable before results in bleeding, hence it is important to diagnose accurately at an early stage³ and hence the appropriate treatment can be undertaken to reduce both morbidity and mortality.

Current methods of screening for esophageal varices is upper gastrointestinal endoscopy which is an invasive. Hence a noninvasive technique is needed to prevent unnecessary interventions and costly procedures in low-risk patients and lead to an appropriate start of primary prophylaxis in high-risk patients.

Materials and Method: Designed as diagnostic test evaluation among patients with chronic parenchymal liver disease who came for follow up in Department of Radiodiagnosis. One ninety five patients evaluated and findings were correlated prospectively with their upper gastrointestinal endoscopy results.

Results: Optimal cut off value for differentiating between No varices vs positive varices is 9.15 kpa with 95% CI and that of no varices, grade 1 varices vs grade 2, grade 3 varices is 11.3 kpa, No varices, grade 1 varices, grade 2 vs grade 3 varices is 12.3kpa all with 95% CI(p=0.00)

Conclusion: Spleen Ultrasound shear wave elastography can be used as a predictor for the presence of esophageal varices.

Ultrasound shear wave elastography of spleen helps in predicting the grades of esophageal varices

Keywords: Esophageal varices, Gastrointestinal endoscopy, Shear wave elastography, Splenic stiffness.

Introduction

Chronic parenchymal liver disease and their complications are major source of morbidity and mortality. One of such complication is bleeding from esophageal varices due to portal hypertension. Other major complications are ascites hepatic encephalopathy. But major cause of death in chronic liver disease is bleeding from esophageal varices. Early diagnosis of clinically significant portal hypertension (>10mmHg) and varices is of greater importance in the management of chronic liver disease and in the prevention of liver-related morbidity and mortality.¹

Patients are asymptomatic in early stages. Most of them will be diagnosed of having varices only at later stages during routine screening or during bleeding manifestations.² Hence its detection at a later stage will have higher mortality rate. But varices are effectively treatable before results in bleeding, hence it is important to diagnose accurately at an early stage³ and hence the appropriate treatment can be undertaken to reduce both morbidity and mortality.

Current methods of screening for esophageal varices is upper gastrointestinal endoscopy which is an invasive, expensive and require special experience for doctors and the patient's compliance causing discomfort for patients, time consuming for patients as well as doctors.⁴ Hence a noninvasive technique is needed to prevent unnecessary interventions and costly procedures in low-risk patients and lead to an appropriate start of primary prophylaxis in high-risk patients.

Esophageal varices are one of the portosystemic anastomotic site. These are dilated sub mucosal veins in distal esophagus.⁵ This happens due to portal hypertension (most commonly a result of cirrhosis), resistance to portal blood flow, and increased portal venous blood inflow. The most common fatal complication of cirrhosis is variceal rupture; the severity of liver disease correlates with the presence of varices and risk of bleeding.⁶ Splenomegaly is a common finding in patients with cirrhosis and noncirrhotic portal

hypertension, and is commonly because of blood congestion, increased portal pressure, augmented resistance to splenic vein outflow, and increased angiogenesis and fibrogenesis which results in increase in splenic stiffness. Spleen stiffness correlates with hepatic fibrosis and portal hypertension in patients with chronic liver disease.⁷ Published studies have suggested that spleen stiffness measurement can be used to predict the presence and size of esophageal varices in patients with chronic liver disease with high diagnostic accuracy.⁸ The aim of present study is to evaluate the role of spleen stiffness in patients with cirrhosis in predicting esophageal varices by shear wave elastography.

Aim and Objectives

- 1) To assess the efficacy of splenic stiffness by shear wave elastography in patients with chronic liver disease in predicting esophageal Varices.
- 2) To find out whether there is any additional advantage by the same in predicting grades of varices.

Materials and Method

A prospective study (Diagnostic test evaluation) was conducted in the Department of Radiodiagnosis, Government Medical College, Kottayam for a period of 12 months from August 2018 to September 2019 on an average of 195 patients. Adult patients with cirrhosis based on imaging (ultrasound or Computed Tomography) findings were included. Patients with ongoing hemorrhage are not considered as eligible, and other exclusion criteria were, portal vein thrombosis, intrahepatic malignancy, and previous or current treatment for portal hypertension (beta-blocker therapy, transjugular intrahepatic portosystemic shunt, and balloon-occluded retrograde transvenous obliteration).

After obtaining ethical clearance from Human ethical committee of the institution the study was commenced

After the procedure is explained to the patient and getting informed consent. Patients underwent an upper abdomen ultrasound. All patients underwent shear wave elastography examination by using a curvilinear transducer (bandwidth, 1-6 MHz)) in High resolution ultrasound with colour doppler GE machine and shear wave elastography [LOGIC E9].

Splenic stiffness will be measured using the intercostal approach at a single intercostal space with the best visualization of spleen in the left upper quadrant, they will be studied either supine or by lying in the right lateral decubitus position with left arm extended above the head during breath holding for a few seconds per each measurement. Different positioning for the spleen was to obtain the maximum scanning area and avoid air shadowing from the lung. A 10x5-mm region of interest (ROI) box is placed on the spleen parenchyma without large blood vessels or abnormal lesions. Region of interest (placed within the center of the rectangular region of interest) for analysis will be positioned within 0.5–2 cm, from the capsular surface of the spleen.

Special attention will be paid to avoid any focal lesion, vessels, or artifacts from nearby lung air. The mean value of the 12 measurements will be calculated and represented as splenic stiffness value. Splenic stiffness is expressed as shear wave velocity in kilopascals or youngs modulus. The final results were correlated with gastrointestinal endoscopy to assess the presence of esophageal varices. Grades of varices is classified based on westaby classification.

Data of each patient were obtained entered in MS Excel and analysed with SSPS16. The cut off point was calculated by plotting ROC Curve.

Results

In our study group of 195 patients with clinical or biochemical evidence of chronic parenchymal liver disease 133 has splenomegaly and 62 has no splenomegaly.

Out of 195 patient studied 148 had varices. Among them 58 patients had Grade 1 varices,46 patients had grade 2 varices,44 patients had grade 3 varices.



Figure 1: Shear wave elastography

Statistical analysis revealed following findings

Table 1: Spleen size and varices

	No varices	Varices present	
No splenomegaly (<12cm)	32	30	62
Splenomegaly (>12cm)	15	118	133
Total	47	148	195

Table 2: Mean value of splenic stiffness in study population

	Mean elastography value in kpa	Standard deviation
No varices	8.5	1.5
Varices positive	12.5	2.49
Grade 1 varices	10.7	1.27
Grade 2 varices	11.8	1.51
Grade 3 varices	15.5	1.58

Table 3: Optimal cut off values of spleen elastography measured with AUROC curve

	Optimal cut off value (kpa)	Sensitivity% (95% CI)	Specificity% (95% CI)	Positive predictive value% (95% CI)	Negative predictive value% (95% CI)
No varices vs positive varices	9.15	96.6	70.2	91.0	86.8
No varices, grade 1 varices vs grade 2, grade3 varices	11.3	77.8	83.8	78.8	81.9
No varices, grade 1 varices, grade 2 vs grade3 varices	12.3	97.7	80.8	55.8	99.1

P=0.00

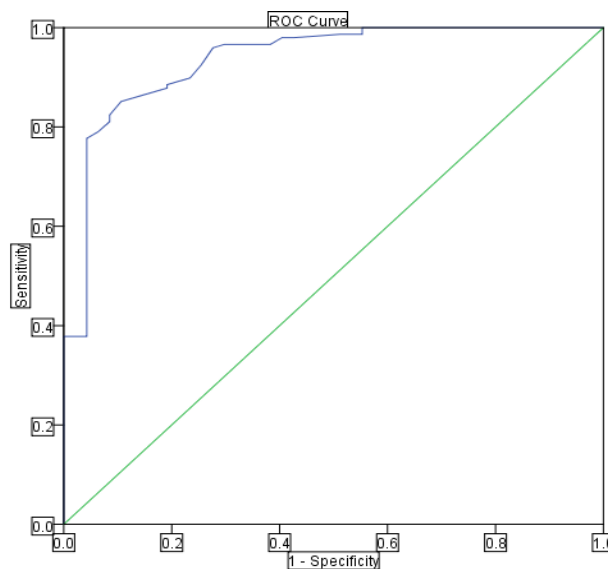


Figure 2: AUROC curves of No varices vs positive varices

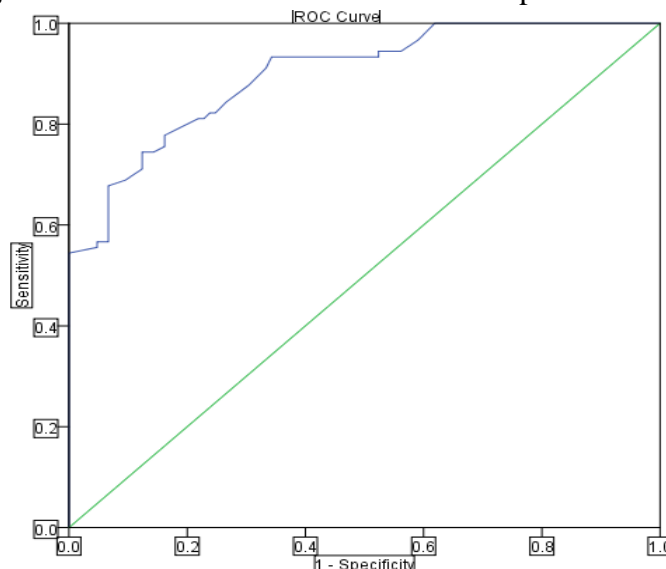


Figure 3: AUROC curves No varices, grade 1 varices vs grade 2, grade 3 varices

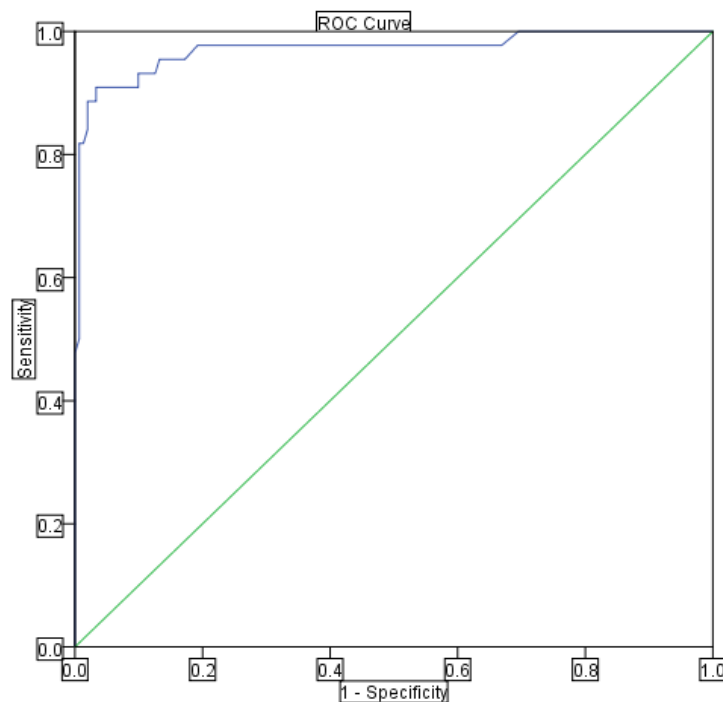


Figure 4: AUROC curves of No varices, grade 1 varices, grade 2 vs grade 3 varices

Study to find the efficacy of splenic elastography in predicting the presence of esophageal varices in patient with chronic liver disease studying 195 subjects shows ultrasound shear wave elastography have sensitivity, specificity, PPV and NPV are 96.6%, 70.2%, 91.0% and 86.8% respectively ($p=0.00$) in this study. It is comparable with previous studies and statistically significant.

Optimal cut off value for differentiating between No varices vs positive varices is 9.15 with Sensitivity % (95% CI), Specificity % (95% CI), PPV, NPV of 96.6%, 70.2%, 91.0%, 86.8% respectively,

No varices, grade 1 varices vs grade 2, grade 3 varices is 11.3 with Sensitivity% (95% CI), Specificity% (95% CI), PPV, NPV of 77.8%, 83.8%, 78.8%, 81.9% respectively.

No varices, grade 1 varices, grade 2 vs grade 3 varices is 12.3 with Sensitivity % (95% CI), Specificity % (95% CI), PPV, NPV of 97.7%, 80.8%, 55.8%, 99.1 % respectively ($p=0.00$).

It is comparable with previous studies and statistically significant

Discussion

Normal adult spleen is concavoconvex shaped organ that lies between the fundus of the stomach and the diaphragm, its long axis in the line of the left 10th rib. The diaphragmatic surface is convex. Spleen usually situated between the ninth and eleventh ribs. The inferomedial surface also called visceral surface has gentle indentations where it comes into contact with the stomach, left kidney, pancreas, and splenic flexure. The spleen is suspended by the splenorenal ligament, the phrenicocolic ligament, and the gastrosplenic ligament. Weight of organ is related to the patient's age and gender, less than 150g. Decreases in size and weight with advancing age, increases slightly during digestion and vary in size according to the nutritional status of the body. Liver has dual blood supply from portal vein (80%) and the hepatic artery (20%). The portal triad contains a branch of the portal vein, hepatic artery, and bile duct. The main portal vein maximum diameter of 13 mm divides into right and left branches. It originates behind the neck of the pancreas where it is classically formed by the confluence of the superior mesenteric and splenic veins. It also receives blood from the inferior mesenteric, gastric, and cystic veins

Portal pressure increases as a consequence of an increased resistance to flow due to architectural distortion of the liver secondary to fibrous tissue and regenerative nodules in chronic liver disease results in development of porto systemic collaterals

Spleen is surrounded by a capsule composed of dense fibrous tissue, elastic fibers, and smooth muscle. Trabeculae of smooth muscle and fibroelastic tissue extends from capsule into the splenic parenchyma. Trabeculae contain blood and lymph vessels and nerves. Spleen is a highly vascular organ. The splenic artery divides into trabecular arteries located within the trabeculae entering the splenic parenchyma. Small arterioles branch from the trabecular arteries and enter the red pulp where they become central arterioles which are surrounded by lymphoid tissue. Smaller arterioles arises from the central arterioles and feed the white pulp. These terminate in the marginal sinus at the junction of the white pulp and the marginal zone, some of which terminate within the marginal zone, and a few extend beyond the white pulp to terminate in the red pulp.

Red Pulp

Composed of a three dimensional meshwork of splenic cords and venous sinuses. The splenic cords are composed of reticular fibers, reticular cells, and associated macrophages

White Pulp

Subdivided into the Periarteriolar lymphoid sheaths, the follicles, and the marginal zone and is composed of lymphocytes, macrophages, dendritic cells, plasma cells, arterioles, and capillaries in a reticular framework similar to that found in the red pulp

Most common liver disease encountered in general clinic are is chronic parenchymal liver disease. Patients with cirrhosis will develop clinically significant portal hypertension when hepatic venous pressure gradient (HVPG) ≥ 10 mmHg.⁹ There is increased resistance to portal blood flow which is key factor for development of portal hypertension in liver cirrhosis. There are many of portal hypertension

related complications, and esophageal varices major cause of morbidity and mortality. As hepatic fibrosis progresses, hemodynamic and pathologic changes can be both found in the spleen. The results of a previous study demonstrated that the size of the spleen increased as liver fibrosis progressed and was more apparent in the late stages. The density changes of spleen with splenomegaly due to tissue hyperplasia, angiogenesis, and fibrogenesis, as well as portal and splenic congestion. As severity of portal hypertension increases patients are more likely to present with variceal bleeding and recurrent variceal bleeding from esophageal varices.

Gastroesophageal varices are noted in around half of patients with cirrhosis and its presence correlates with severity of disease; only 40% of Child A patients have varices, 85% of Child C patients.¹⁰

Role of Endoscopy in Cirrhosis¹¹

Endoscopy has undergone a period of rapid expansion with numerous and specialized modalities that are of increasing value in the investigation and management of the patient with liver disease. Role of endoscopy in liver disease is both diagnostic and interventional. Patients with liver disease can be challenging to sedate, and the complexity of endoscopy in liver disease continues to increase with rising numbers of patients with a liver transplant, and the advent of new endoscopic modalities such as capsule endoscopy and endoscopic ultrasound (EUS). Pharmacodynamics are altered in advanced liver disease as a result of changes in hepatic conjugation and oxidation, shunting, decreased protein binding and an increased volume of distribution.¹⁵ Common agents used for sedation Midazolam, Pethidine and fentanyl all these are metabolized in liver so its clearance is diminished hence propofol, an anesthetic agent that is widely used in endoscopy, which is unaffected by cirrhosis. Coagulopathy and thrombocytopenia are common in patients with chronic liver disease. Diagnostic endoscopy is a low-risk procedure and

safe in patients with altered coagulation.¹² High-risk endoscopic therapeutic procedures have a significantly increased risk of hemorrhage and, as such, coagulopathy should be treated with Platelet and FFP transfusions.

Common endoscopic diagnosis in cirrhosis patients includes peptic ulcer disease, Gastroesophageal varices, gastric antral vascular ectasia, Portal hypertensive gastropathy. Gastric varices are less prevalent than esophageal varices and less prone to bleeding.¹³

Early prediction of development of esophageal varices and appropriate timely management reduces morbidity and mortality for patients with cirrhosis to greater extent. American Association for the Study of the Liver (AASLD) suggest endoscopic surveillance for all cirrhotic patients and also endoscopic follow up in varices negative patients.¹⁴ Hence upper gastrointestinal endoscopy is tedious and invasive procedure, there is need for alternate noninvasive technique to predict gastroesophageal varices for both patients and doctors, one such method is elastography which is simple, less time consuming, and easily available. Mechanical properties of this spleen stiffness is quantified by shear wave elastography

Spleen is visualized better when scanned in lower left intercostal spaces at various degrees of inspiration to maximize the window to the spleen and Swept posteriorly and anteriorly to view the entire volume of the spleen in coronal oblique plane. Curvilinear transducers are used for examination of the spleen as for the other abdominal organs. A high-frequency linear array transducer can be used for more detail¹⁵

Elastographic techniques are promising tools developed in the recent decade in patients with chronic liver disease as non-invasive test for evaluation of tissue stiffness. Most commonly used is Liver stiffness measurement using transient elastography, it is widely accepted and validated method. It predicts the severity and prognosis of liver disease, few studies shows that its diagnostic accuracy can be affected by the presence of some confounders, such as liver cell

inflammation and cholestasis. It has limited performance in case high body mass index, narrow intercostal space, or ascites. liver elastography measures hepatic fibrosis which only deals with the fixed component of portal hypertension related to intrahepatic resistance but it does not take into account the dynamic component related to hyperdynamic splanchnic circulation and portal venous blood flow which is major cause of development of esophageal varices. Spleen is another organ affected by hyper dynamic splanchnic circulation. Hence spleen elastography has been proposed as an alternative method to predicts complications related to cirrhosis like presence of esophageal varices.

Two types of ultrasound elastography techniques are used, one is Transient elastography and other is using Acoustic radiation force impulse.¹⁶

Transient elastography

An dedicated ultrasound transducer probe used to produce vibrations of mild amplitude and low frequency, inducing an elastic shear wave that propagates through the underlying tissues. Pulse-echo acquisitions are made and velocity is measured. Velocity is directly related to the tissue stiffness. The stiffer the tissue, the faster the shear wave propagates. Major disadvantages of TE are requires a dedicated device, the region of interest cannot be chosen, it cannot be performed in patients with ascites and can be difficult to obtain in patients with obesity.

Acoustic radiation force impulse techniques

Shear wave elastography²⁰

Elastographic technique recently developed and integrated allows the quantitative assessment stiffness, providing measurements of shear-wave velocity within a small region (fixed ROI size 0.5 cm × 1.5 cm), its localization can be monitored by real-time B-mode ultrasound. Results may be expressed in units of shear-wave velocity (m/s) or converted into units of Young's modulus (kPa) into several conventional ultrasound machines. Advantages includes positioning the region of interest where to take measurements with an adequate ultrasound window, can be performed in

presence of ascites, obesity or narrow intercostal spaces.

Stiffness is measured in a bidimensional rather than in a single small point as in transient elastography. Its failure rate is significantly lower than that of transient elastography.

Magnetic resonance elastography

It provides full anatomic information, organ coverage and low inter scan variability

Laure Elkrief, MD et al, did study that shows Shear-wave elastography (SWE) has an excellent technical success rate; it is far better than that of transient elastography (TE) for both liver stiffness (LS) and spleen stiffness (SS) measurements (97% and 97% vs 44% and 42%, respectively; $P, .001$) in patients with advanced cirrhosis.¹⁷

Bota S et al (2010) included 82 subjects shows cut-off value of >2.51 m/s of SS, ARFI had 85.2% Se, 91.7% Sp, 95.8% PPV, 73.3% NPV, 87.1% for predicting liver cirrhosis but could not predict the presence or severity of esophageal varices, also the risk of variceal bleeding.¹⁸

Calvaruso V et al, shows that spleen transient elastography was more accurate in predicting grade 2/grade 3 oesophageal varices (AUROC: 0.82, cut-off: 54.0 kPa, sensitivity: 80%, specificity: 70%).¹⁹

Conclusion

Ultra sound shear wave elastography of spleen helps in predicting the presence of esophageal varices in patients with chronic parenchymal liver disease.

Ultrasound shear wave elastography of spleen helps in predicting the grades of esophageal varices

In predicting the presence of esophageal varices in patient with chronic liver disease optimal cut off of 9.15 kpa have sensitivity, specificity, PPV and NPV are 96.6%, 70.2%, 91.0% and 86.8% respectively ($p=0.00$) in this study. It is comparable with previous studies and statistically significant.

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References

1. Kim, Hwi Young et al. "The Role of Spleen Stiffness in Determining the Severity and Bleeding Risk of Esophageal Varices in Cirrhotic Patients." *Medicine* vol. 94,24 (2015): e1031. doi:10.1097/MD.0000000000001031
2. Herrera, Jorge L, and Reynaldo Rodríguez. "Medical Care of the Patient With Compensated Cirrhosis." *Gastroenterology & hepatology* vol. 2,2 (2006): 124-133.
3. Patch, D, and L Dagher. "Acute variceal bleeding: general management." *World journal of gastroenterology* vol. 7,4 (2001): 466-75. doi:10.3748/wjg.v7.i4.466.
4. Karatzas, Andreas et al. "Non-invasive screening for esophageal varices in patients with liver cirrhosis." *Annals of gastroenterology* vol. 31,3 (2018): 305-314. doi:10.20524/aog.2018.0241
5. Balwant Singh Gill et al. Pathophysiology and management of esophageal varices in current practice 14th International Conference on Gastro Education September 06-07, 2018 London, UK.
6. Nusrat, Salman et al. "Cirrhosis and its complications: evidence based treatment." *World journal of gastroenterology* vol. 20,18 (2014): 5442-60. doi:10.3748/wjg.v20.i18.5442
7. Dajti E, Ravaioli F, Colecchia A, Marasco G, Vestito A, Festi D. Liver and Spleen Stiffness Measurements for Assessment of Portal Hypertension Severity in Patients

- with Budd Chiari Syndrome. *Can J Gastroenterol Hepatol.* 2019;2019: 1673197. Published 2019 Jan 2. doi:10.1155/2019/1673197
8. Ma, Xiaowen et al. "Spleen Stiffness Is Superior to Liver Stiffness for Predicting Esophageal Varices in Chronic Liver Disease: A Meta-Analysis." *PLoS one* vol. 11,11 e0165786. 9 Nov. 2016, doi:10.1371/journal.pone.0165786
9. Suk, Ki Tae. "Hepatic venous pressure gradient: clinical use in chronic liver disease." *Clinical and molecular hepatology* vol. 20,1 (2014): 6-14. doi:10.3350/cmh.2014.20.1.6
10. Nusrat, Salman et al. "Cirrhosis and its complications: evidence based treatment." *World journal of gastroenterology* vol. 20,18 (2014): 5442-60. doi:10.3748/wjg.v20.i18.5442
11. Krystallis, Christoforos et al. "Update of endoscopy in liver disease: more than just treating varices." *World journal of gastroenterology* vol. 18,5 (2012): 401-11. doi:10.3748/wjg.v18.i5.401
12. Zullo, Angelo et al. "Gastrointestinal endoscopy in patients on anticoagulant therapy and antiplatelet agents." *Annals of gastroenterology* vol. 30,1 (2017): 7-14. doi:10.20524/aog.2016.0096
13. Gjeorgjievski, Mihajlo, and Mitchell S Cappell. "Portal hypertensive gastropathy: A systematic review of the pathophysiology, clinical presentation, natural history and therapy." *World journal of hepatology* vol. 8,4 (2016): 231-62. doi:10.4254/wjh.v8.i4.231
14. Piekarska, Anna et al. "Surveillance for portal hypertension in the course of liver cirrhosis." *Clinical and experimental hepatology* vol. 4,2 (2018): 49-54. doi:10.5114/ceh.2018.75954
15. Rumack C. Diagnostic ultrasound. St. Louis: Elsevier Mosby 20th September 2017.
16. Zullo, Angelo et al. "Gastrointestinal endoscopy in patients on anticoagulant therapy and antiplatelet agents." *Annals of gastroenterology* vol. 30,1 (2017): 7-14. doi:10.20524/aog.2016.0096
17. Laure Elkrief, MD Pierre-Emmanuel Rautou, MD, PhD et al. Prospective Comparison of Spleen and Liver Stiffness by Using Shear-Wave and Transient Elastography for Detection of Portal Hypertension in Cirrhosis, radiology.rsna.org
18. Bota S, Sporea I, Sirli R et al. Spleen assessment by Acoustic Radiation Force Impulse Elastography (ARFI) for prediction of liver cirrhosis and portal hypertension, PMID:21203598.
19. Calvaruso V, Bronte F, Conte E, Simone F, Craxì A, Di Marco V. Modified spleen stiffness measurement by transient elastography is associated with presence of large oesophageal varices in patients with compensated hepatitis C virus cirrhosis. *J Viral Hepat* 2013; 20: 867-874 [PMID: 24304456 DOI: 10.1111/jvh.12114]
20. Jaehyung Park, Heejin Kwon, Jinhan Cho, Jongyoung Oh et al. Is the spleen stiffness value acquired, using acoustic radiation force impulse (ARFI) technology, predictive of the presence of esophageal varices in patients with cirrhosis of various etiologies, DOI: 10.11152/mu.2013.2066.181.sff