Ultrasound in Med. & Biol., Vol. 46, No. 7, pp. 1641–1650, 2020

0301-5629/$ - see front matter

https://doi.org/10.1016/j.ultrasmedbio.2020.04.007

● *Original Contribution*

THE ROLE OF SPLEEN AND LIVER ELASTOGRAPHY AND COLOR-DOPPLER ULTRASOUND IN THE ASSESSMENT OF TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT FUNCTION

Mariangela Giunta,* Vincenzo La Mura,†,‡ Clara Benedetta Conti,* Giovanni Casazza,§ Giulia Tosetti,† Daniele Gridavilla,* Simone Segato,* Antonio Nicolini,¶ Massimo Primignani,† Pietro Lampertico,† and Mirella Fraquelli*

* Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, UOC Gastroenterologia ed Endoscopia, Milan, Italy; † Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, UOC Medicina Generale, Emostasi e Trombosi, Milan, Italy; Dipartimento di Scienze Biomediche per la Salute, Università degli Studi di Milano, Milan, Italy; Centro di Ricerca Coordinata "A.M. e A. Migliavacca" per lo Studio e la Cura delle Malattie del Fegato, Milan, Italy; ‡ Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, UOC Gastroenterologia ed Epatologia, Milan, Italy; § Dipartimento di Scienze Biomediche e Cliniche "L. Sacco", Universita' degli Studi di Milano, Milan, Italy; and ¶ Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, UOC Radiologia, Milan, Italy

(*Received* 18 *November* 2019; *revised* 11 *March* 2020; *in final from* 9 *April* 2020)

Abstract—The reference standard for assessing transjugular intrahepatic portosystemic shunt (TIPS) function is venography with portosystemic pressure gradient (PPG) measurement. This procedure is invasive and expensive; thus, we assessed the feasibility, reproducibility and diagnostic accuracy of color-Doppler ultrasound (CDUS) and spleen and liver stiffness (LS) measurements for identifying TIPS dysfunction. Twenty-four patients (15 undergoing TIPS placement and nine undergoing TIPS revision) consecutively underwent CDUS examination and LS and spleen stiffness (SS) determination by transient elastography (TE) and point shear-wave elastography (pSWE). All parameters were taken before TIPS placement/revision (1–15 d before) and 24 h after, just before revision by venography. pSWE inter-observer agreement was assessed by intra-class correlation coefficient (ICC). CDUS and elastographic data were correlated (Pearson coefficient) with pressure gradients (hepatic venous pressure gradient [HVPG], PPG). Main determinants of TIPS dysfunction were investigated by linear regression. Forty-nine paired examinations were performed in total: 49 (100%) SS reliable measurements by pSWE and 38 (88%) by TE. The ICC for pSWE values was 0.90 (95% confidence interval [CI] 0.81–0.94). SS values significantly correlated with HVPG and PPG ($R = 0.51$, $p = 0.01$). The area under the Receiver-Operating Characteristic (AUROC) curve of SS for diagnosing TIPS dysfunction was 0.86 (95% CI 0.70–0.96) using a 25 kPa cutoff. At multivariate analysis, the flow direction of the intrahepatic portal vein branches and SS values were independently associated to TIPS dysfunction. The intrahepatic portal vein branches flow direction and SS value are two simple, highly sensitive parameters accurately excluding TIPS dysfunction. SS measurement by pSWE is feasible, reproducible and both positively and significantly correlates with HVPG and PPG values. (E-mail: mfraquelli@yahoo.it)

Key Words: **Transjugular intrahepatic portosystemic shunt, Elastography, Spleen stiffness, Liver stiffness, Color-Doppler ultrasound.**

INTRODUCTION

The transjugular intrahepatic portosystemic shunt (TIPS) is an established procedure in the treatment of portal hypertension complications, including bleeding from esophageal varices, refractory ascites, hepatic hydrothorax and hepatorenal and hepatopulmonary syndromes (Fagiuoli et al. 2017). TIPS placement successfully reduces the portosystemic pressure gradient (PPG) in more than 90% of cases (Rössle et al. 1994; Cello et al. 1997; Sanyal et al. 1997). However, TIPS dysfunction,

Address correspondence to: Mirella Fraquelli, Gastroenterology and Endoscopy Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Via F. Sforza 35, 20122 Milan, Italy. E-mail: mfraquelli@yahoo.it

defined as a PPG of 12 mm Hg (Garcia-Tsao et al. 1985; Casado et al. 1998), is a common short- and mid-term complication of the procedure and leads to recurrence of the portal hypertension complication. When promptly identified, shunt thrombosis or stenosis may be successfully treated before the recurrence of gastrointestinal bleeding or ascites; thus, these patients require close follow-up to detect and correct TIPS dysfunction. There are no consensus guidelines or protocols for the management of post-TIPS placement, and even the timing of screening has not yet been standardized.

Currently, venography and pressure measurement are the reference standards for assessing TIPS dysfunction, but they are invasive and expensive. Therefore, in many centers venography is used only as a secondary test, and Doppler ultrasound (US) is usually the primary tool used for screening TIPS dysfunction because it is non-invasive, readily available, repeatable and relatively low-cost compared with other imaging modalities. No consensus exists about the optimal sonographic screening protocol, and many different US parameters have been applied to assess the patency and function of TIPS with variable results (Chong et al. 1993; Ferral et al. 1993; Longo et al. 1993; Surratt et al. 1993; Feldstein et al. 1994; Foshager et al. 1995; Kanterman et al. 1997; Abraldes et al. 2005). Despite the number of studies that assessed the accuracy of color-Doppler ultrasound (CDUS) in the evaluation of TIPS patency, US parameters are not adequately standardized yet.

Recently, several non-invasive elastographic techniques have been developed and ascertained for accuracy in assessing the severity of liver fibrosis and portal hypertension in patients with chronic liver diseases. Recently, a rapid change of liver stiffness (LS) has been demonstrated after variceal ligation and TIPS implantation (Piecha et al. 2018). However, on considering the promising results of spleen stiffness (SS) in the assessment of portal hypertension (Calvaruso et al. 2013; Sharma et al. 2013; Fraquelli et al. 2014; Singh et al. 2014; Stefanescu et al. 2014; Wong et al. 2019), thanks to its good correlation with hepatic venous pressure gradient (HVPG) values (Colecchia et al. 2012; Sharma et al. 2013), in the last few years, some authors have examined the variations of spleen elastography in patients undergoing TIPS placement and hypothesized that this parameter might have a useful predictive value in determining TIPS function. In particular, two previous preliminary studies (Gao et al. 2012; Ran et al. 2013) showed that SS measured by Acoustic Radiation Force Impulse (ARFI) has a significant correlation with portal vein pressure and that the reduction in PPG after TIPS correlates with the reduction of SS. A further study (Gao et al. 2016) proved the application of splenic shear-wave elastography in monitoring TIPS function during a 12-mo follow-up. All the patients showed SS reduction after a successful revision of TIPS. Interestingly, in the study by Novelli et al. (2015), after the TIPS placement and effective reduction of PPG below 12 mm Hg, the SS value decreased in 58% of patients. At variance, in the remaining 42% of the patients SS increased in spite of lower portal pressure when the competitive internal shunts were embolized. The authors speculated that this finding suggests a potential risk of recurrent variceal bleeding.

More recently, two prospective Italian and Chinese studies (De Santis et al. 2018; Han et al. 2017) and a retrospective German study (Buechter et al. 2018) have showed that SS measured by ARFI and transient elastography (TE), respectively, positively correlates with pre-TIPS HVPG values and significantly decreases after TIPS. In addition, Attia et al. (2019) have demonstrated that SS is superior to LS (both measured by ARFI and Child-Pugh score) as a non-invasive surveillance tool for evaluating patients with clinically significant portal hypertension (HVPG $\geq$10 mm Hg) before TIPS.

All these studies, albeit conducted on small numbers of patients, suggest that SS may be a predictive marker of TIPS status: SS decreases because of portal pressure reduction and its measurement can complement conventional sonography for patients undergoing TIPS.

None of the previous studies has simultaneously assessed the role of CDUS and elastographic parameters. Thus, the aim of our study was to assess the accuracy of CDUS parameters and LS and SS, as assessed both by TE and ARFI (point shear-wave elastography [pSWE]) in the evaluation of TIPS function. In greater detail, the aims of the present study were:

- To assess the feasibility and reproducibility of splenic pSWE in patients undergoing TIPS placement or revision;
- To measure any change of LS and SS after TIPS placement or revision;
- To evaluate the correlation between CDUS or elastographic findings and HVPG and PPG values before and after TIPS placement;
- To assess the diagnostic estimates of CDUS and LS and SS for the identification of TIPS dysfunction and to identify any variables independently associated with TIPS dysfunction.

MATERIAL AND METHODS

The experimental protocol was approved by the local institutional review board (IRB), and the informed consent for the study was obtained from all the patients in accordance with the World Medical Association's 2008 Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. The privacy rights of patients were always observed.

Patients

All patients referred for TIPS and portal hypertension complications to the hepatology unit of our hospital from January 2017 to June 2018 were consecutively enrolled over an 18-mo period. The study protocol was approved by the local ethics committee, and all the patients gave their written informed consent.

All the patients underwent CDUS examination, liver and splenic measurement by pSWE and TE 1−15 d before TIPS placement or revision and 24 h after, just before revision by venography; the pSWE measurements were performed by two investigators (M.F. and M.G.) well trained in elastographic techniques. TE was performed by another expert operator (B.C.).

The inclusion criteria were all indications to TIPS placement or TIPS revision, given by the multidisciplinary team. The exclusion criteria were all conditions that did not meet the inclusion criteria. Demographic, clinical, biochemical, CDUS and elastographic data were collected for every patient.

CDUS examinations

A physician with at least 3 y experience in sonography performed all the sonographic examinations using an iU22 US scanner (Philips Healthcare, Bothell, Washington, USA). In all the patients, we measured the spleen size, the direction and flow velocity of the main portal vein. In the patients with TIPS, we evaluated the direction of flow (hepatopetal vs. hepatofugal) of the main portal vein and intrahepatic portal vein branches (hepatopetal vs. hepatofugal), and we measured the flow velocity in the shunt at two sites (proximal and distal).

The CDUS parameters analyzed and considered as pathologic were: the presence of a hepatofugal direction of flow in the main portal vein, a flow velocity of the main portal vein slower than 30 cm/s, a hepatopetal direction of flow in the intrahepatic portal vein branches and a flow velocity in the TIPS <90 cm/s and/or >190 cm/s.

Liver pSWE

Liver pSWE was performed by two investigators (MF and MG), expert in elastographic techniques and blind to radiologic data. LS was measured using iU22 US equipment with a convex broadband probe and the ElastPQ module. This technique generates shear waves in the liver using radiation force from a targeted US beam. The US machine monitoring the shear-waves propagation by a Doppler-like US technique, ultimately measures the shear-wave velocity, which is displayed in m/s or in kPa through Young modulus $E = 3$ (vS2.q), where E is Young modulus, vS is the shear-wave velocity and q is the tissue density. The measurements were performed in the right lobe of the liver through intercostal approach, with the patient lying supine with the right arm in maximal abduction. Using a real-time B-mode picture, the rater selected a vessel-free area at least 1.5 cm below Glisson capsule, where a fixed region of interest (ROI) sized 0.5 cm x 1.5 cm was outlined by moving a trackball. The maximum penetration depth of pSWE was 7 cm. The patients were instructed to hold their breath in an indifferent position while the rater pressed a button that launched the data acquisition. Only the examinations with at least 10 validated measurements expressed in kPa were considered reliable. In addition, the median value of successful measurements was considered as representative of the LS in any given patient only if the inter-quartile range (IQR) of all validated measurements was less than 30% of median values.

Splenic pSWE

In the 29 paired examinations, the splenic pSWE measurements were performed by two investigators (M.F. and M.G.). An iU22 US scanner with the shear-waves generation capability was used to measure SS by a calculated Young modulus estimate based on the shear-wave velocity.

The patient was placed in the right lateral decubitus position to measure SS through the intercostal approach. The splenic pSWE was measured as the patient held his or her breath for a few seconds. The splenic pSWE was sampled in the splenic parenchyma at a 2-cm depth from the splenic capsule in a region free of visible vessels. The size of the ROI for measuring splenic pSWE was 10 cm x 5 mm. The mean shear-wave velocity value of the spleen was calculated as the average of these measurements.

The splenic pSWE was measured twice: once 1−15 d before TIPS placement or revision and then the day after both procedures. For 7 patients referred for TIPS revision, we could not perform sonographic and elastographic measurements after TIPS revision because the patients were non-compliant or had not given their consent to examination.

Liver TE

The measurements were performed by an independent investigator (B.C.) who had already gained 3 y experience in TE measurements and was blind to clinical, US and elastographic data. Excellent intra- and inter-observer agreement on TE measurement has already been reported in the literature (Fraquelli et al. 2007; Boursier et al. 2008).

TE was performed on patients in a fasting state on the same day after pSWE. The medium probe was used for all the patients. The right lobe of the liver was targeted through the intercostal space access while the patient was lying in the dorsal decubitus position with the right arm in maximal abduction. The rate of successful measurements was calculated as the ratio between the number of valid measurements and the total number of measurements. The results were expressed as a median value of the total

measurements in kPa. Only the examinations with at least 10 validated measurements and a success rate of at least 60% were considered reliable. In addition, the median value of successful measurements was considered as representative of LS in any given patient only if the IQR of all the validated measurements was less than 30% of the median values (Ziol et al. 2005).

Splenic TE

The procedures were performed by the same investigator who had performed LS measurements (B. C.) and was blind to pSWE data. S-TE was performed after the scanning of the splenic parenchyma through left-hand side intercostal space access, while the patient lay in the ventral decubitus position with his or her left arm in maximal abduction. The medium probe was used for all the patients. The tip of the probe transducer was placed in a previously US targeted point, where the spleen parenchyma had previously been identified. The adequate total number of valid measurements, success rate and IQR were the same as for the LS-TE examination. The lack of valid shots was defined as SS-TE failure.

The investigator who performed splenic TE had received prior training of 50+ S-TE measurements.

Venography, TIPS placement and TIPS revision

TIPS placement was performed in the interventional unit of the department of radiology. A polytetrafluoroethylene (PTFE)-covered stent (10-mm diameter Gore Viatorr TIPS Endoprosthesis, Putzbrunn, Germany) was placed between the right hepatic vein and right portal vein in 15 patients. In a patient affected by Budd-Chiari syndrome a transcaval shunt was used. The HVPG before TIPS placement and the PPG after it were measured. The HVPG was determined by the measurement of the pressure gradient between the wedged and free hepatic venous pressures. The PPG was determined by subtracting the inferior vena cava pressure value from that of the portal vein pressure. Good hemodynamic response was defined as a reduction of PPG down to less than 12 mm Hg. In addition to TIPS placement, the radiologist looked for the presence of possible competitive portosystemic collateral veins with the aim of possible embolization.

Venography and PPG measurement were performed on the patients undergoing TIPS revision.

TIPS dysfunction was considered as the presence of venographic morphologic defect (intra-stent thrombosis or stenosis) or when PPG was greater than or equal to 12 mm Hg. In these cases, radiologic revision, using percutaneous transluminal angioplasty (PTA) balloons and/or with additional stents, was performed. The PPG was again measured after TIPS revision.

Statistical Analysis

The quantitative variables (*i.e.* the velocity of the main portal vein, intra-shunt proximal and distal velocity, liver and spleen TE, liver and spleen pSWE and HVPG or PPG) were expressed as mean value and standard deviation. The inter-rater agreement of the splenic pSWE measurements was evaluated by intra-class correlation coefficient (ICC). Agreement was classified as poor (ICC = 0.00–0.20), fair (ICC = 0.20–0.40), moderate (ICC = 0.40–0.75) or substantial to excellent (ICC $>$ 0.75) (Bland and Altman 1986; Fleiss 1986). The linear correlation between liver and splenic pSWE and HVPG or PPG in patients with and without TIPS dysfunction was evaluated by the Pearson correlation coefficient (r).

The diagnostic accuracy of liver and splenic pSWE in identifying TIPS dysfunction was assessed using venographic and/or manometric data as the reference standard. Sensitivity, specificity and positive and negative likelihood ratios (LR+ and LR−) with 95% CI were calculated for every parameter.

Receiver-operating characteristic (ROC) curve analysis was performed, and the area under the ROC curve (AUROC), along with 95% CI, was calculated as an indicator of the overall accuracy of liver and splenic pSWE. As to pSWE, we arbitrarily decided to use the measurement performed by the first rater. For TIPS dysfunction, the value maximizing the Youden index (sensitivity + 1 − specificity) was selected as the best cutoff value. The obtained cutoff values were used to assess the splenic pSWE inter-observer clinical concordance. The agreement between the two operators in classifying each patient above or below the obtained cutoff values (*i.e.* in predicting TIPS function vs. dysfunction) was calculated by the Cohen kappa coefficient.

Finally, logistic regression analysis was performed to identify the variables significantly associated with TIPS dysfunction. CDUS parameters (velocity in the main portal vein, intrashunt proximal and distal velocity, flow direction in the intrahepatic portal branches) and SS by pSWE were considered potential predictors of TIPS dysfunction. Firstly, univariate analysis was carried out on each of the above reported determinants. Subsequently, only the variables that had resulted as statistically significant at univariate analysis were considered for multivariate analysis.

The study was conducted and written according to the Standards for Reporting Studies of Diagnostic Accuracy. All statistical analyses were performed with SAS statistical software (release 9.4; SAS Institute Inc., Cary, North Carolina, USA).

RESULTS

Thirty-four consecutive patients referred for TIPS placement or revision were initially recruited. Five of these patients did not undergo TIPS placement (two

patients for technical reasons, another 2 patients moved to a different city or country and 1 patient did not consent to the procedure). Five other patients who underwent early TIPS as rescue therapy for acute bleeding owing to gastroesophageal varices were also excluded.

The remaining 24 patients were enrolled in the study: 15 patients underwent TIPS placement, and 9 patients underwent TIPS revision. The main indications for TIPS placement were refractory ascites (7 patients) and variceal bleeding (6 patients). A patient underwent TIPS placement because of both refractory ascites and variceal bleeding and another for refractory ascites in Budd-Chiari syndrome. Indications for TIPS revision in 9 patients included scheduled invasive revision at 1 y in 4 patients and clinical evidence of shunt dysfunction in 5 patients (persistence of ascites or large varices). The etiology of portal hypertension and the other clinical and demographic characteristics of the 24 patients enrolled are summarized in Table 1.

On the 24 enrolled patients, the following were performed:

- On the 15 patients who underwent TIPS placement, we performed 15 CDUS and elastographic examinations (considered as index examinations) before and 15 index examinations 1 d after TIPS placement;
- On the 9 patients who underwent TIPS revision, we performed 11 index examinations before TIPS revision (1 patient underwent three TIPS revisions, so we performed three index examinations before each TIPS revision) and only two index examinations after TIPS revision because seven patients withdrew their consent.

Table 1. Main clinical and demographic characteristics of 24 consecutive patients who underwent color-Doppler ultrasound examination and liver and spleen stiffness measurement by point shear-wave elastography and transient elastography

Patients characteristics	
Male, n (%)	17 (71)
Age, median, range (y)	58 (22–80)
BMI (kg/m^2)	25 (19.7–35)
Etiology of portal hypertension, n (%)	
ETOH	8 (33)
HCV	3 (12)
NASH	3 (12)
Budd-Chiari syndrome	3 (1)
PBC	2 (8)
Mixed	5 (21)
Child-Pugh, n (%)	
A, B, C	5 (21), 18 (75), 2 (13)
Indication for TIPS placement, n (%)	
Refractory ascites	7 (47)
Secondary prophylaxis of varices bleeding	6 (40)
Both, other	2 (13)
PPG value, n (%)	
≥12 mm Hg	13 (38)
<12 mm Hg	21 (62)

BMI, body mass index; ETOH, ethanol; HCV, Hepatitis C virus; NASH, non alcoholic steatohepatitis; PBC Primary biliary cholangitis; PPG, portosystemic pressure gradient; TIPS, transjugular intrahepatic portosystemic shunt.

Overall, we carried out 49 paired examinations (*i.e.* 49 pairs of data consisting of each non-invasive examination result being coupled with the venographic examination result: 34 pairs from patients who had TIPS already in place and 15 from patients before TIPS placement). The analysis of the study was conducted by examining the data of these procedures.

A flow chart of the patients and study design is provided in Figure 1.

Feasibility and reproducibility of liver and spleen TE and pSWE measurements

Among the 49 paired examinations, there were 14 (28%) indeterminate liver TE measurements, of which 10 were failures (no valid data) and four were unreliable measurements (not valid for SR <60% and/or IQR >30%). The reason of such indeterminate results was related to the presence of ascites. There were 11 (22%) indeterminate SS measurements; half of those cases were related to failures and the other half to unreliable examinations. In such cases, the main reason of unsuccessful results was again related to the presence of ascites or to a high body mass index.

All the 49 liver and splenic pSWE measurements were reliable in spite of any presence of ascites (0% of unreliable results). Regarding the reproducibility of splenic pSWE measurements, splenic pSWE was performed by two blinded operators for 29 examinations, and their inter-observer agreement, expressed as ICC, was 0.90 (0.81–0.94) (Fig. 2).

Correlation between liver and spleen elastography values and HVPG/PPG values

In the whole group of 49 examinations, LS values did not significantly correlate with HVPG/PPG values ($r = 0.19$, p = NS, not significant) whereas SS values significantly and positively correlated with HVPG/PPG values ($r = 0.51$, $p = 0.01$) (Fig. 3).

Among the 17 patients who underwent CDUS and elastographic examinations before and after TIPS placement (15 patients) or TIPS revision (2 patients), statistically significant differences in PPG ($p = 0.05$), portal vein velocity ($p = 0.033$) and splenic pSWE measurements ($p = 0.019$) were observed before and after TIPS placement or TIPS revision, while there was no statistically significant difference in LS as measured by pSWE ($p = 0.888$) (Fig. 4).

Venographic, CDUS and elastographic data referring to TIPS dysfunction

Among the 24 patients who underwent TIPS placement or TIPS revision, PPG decreased below 12 mm Hg

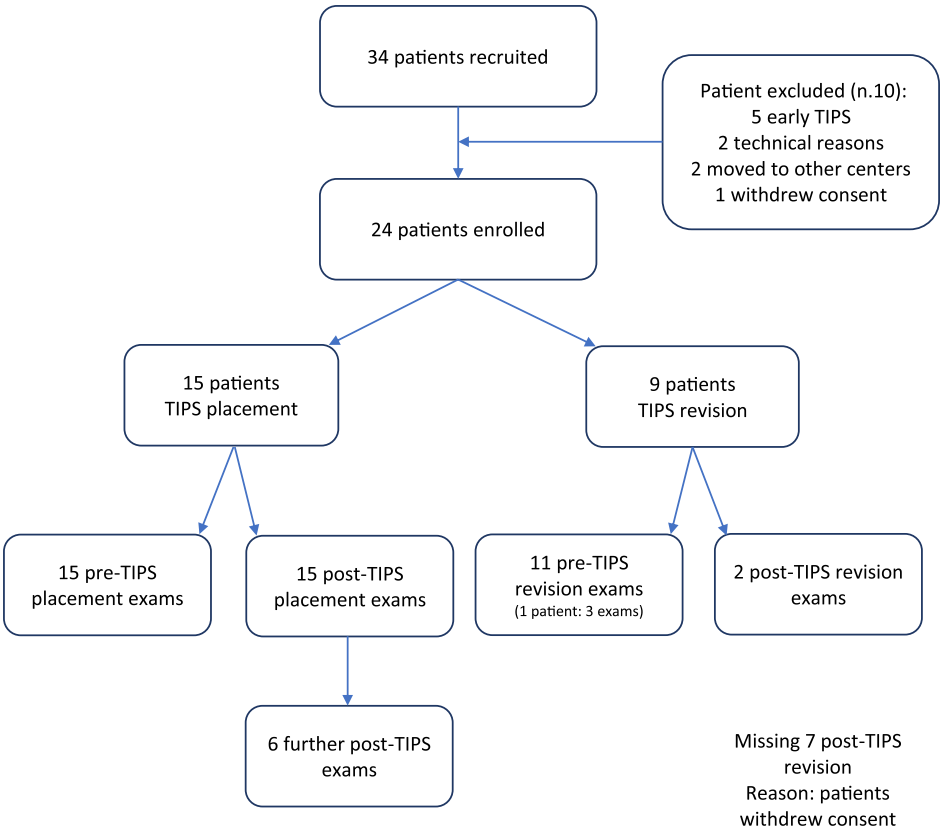

Fig. 1. Patients flow chart. The image explains in detail the phases of the study.

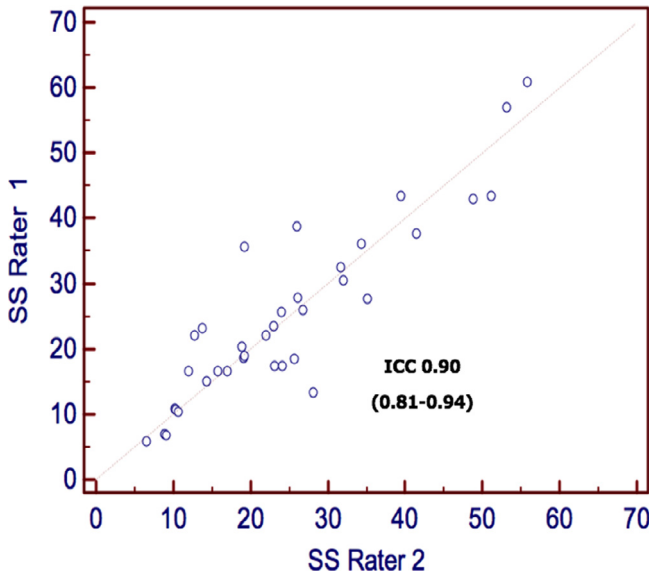

Fig. 2. Spleen stiffness inter-observer agreement. The graph represents the inter-observer agreement of the spleen stiffness, measured by point shear-wave elastography (pSWE), between the two operators in the overall cohort of the 24 patients.

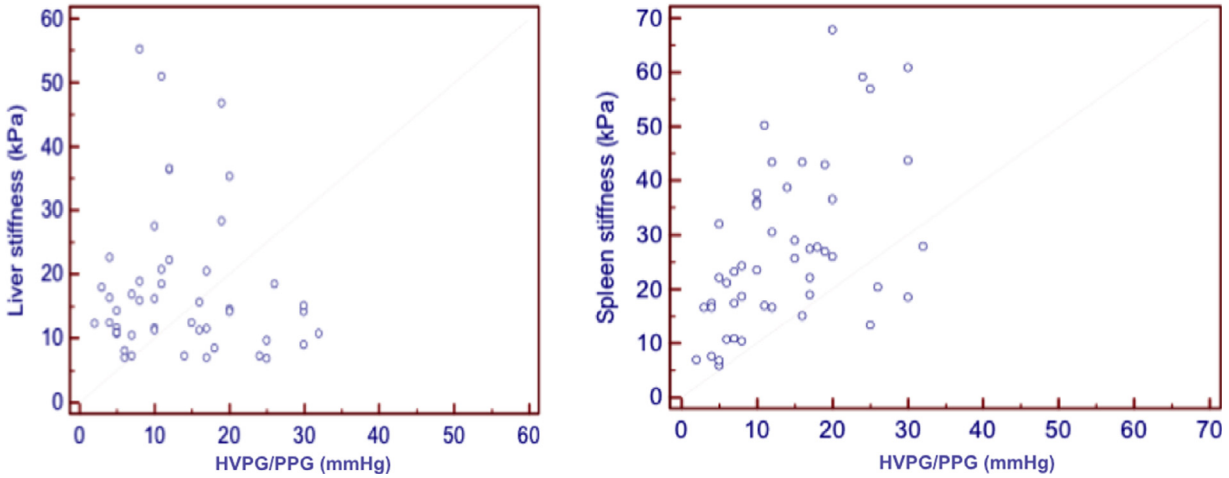

Fig. 3. Correlation between elastography data and hepatic venous pressure gradient (HVPG). The graphs represent the correlation between liver or spleen elastography values, measured by point shear-wave elastography (pSWE) (kPA), and the HVPG/PPG values (mm Hg).

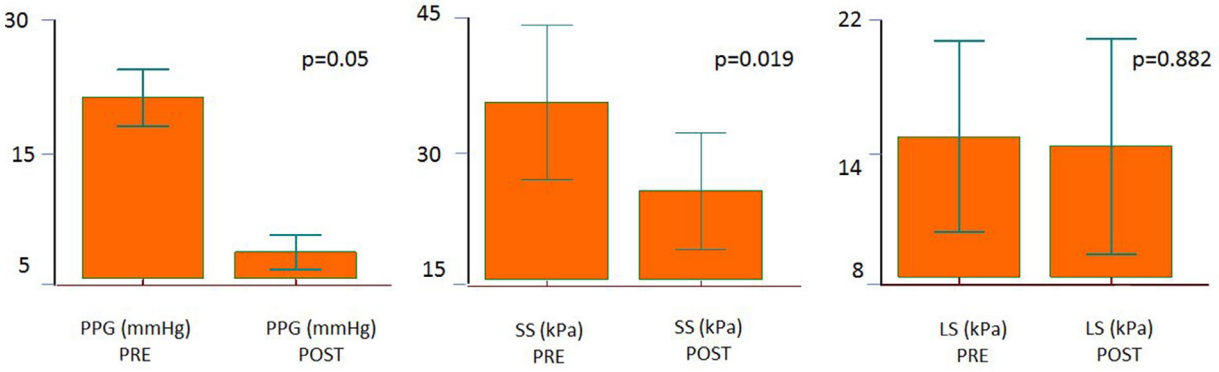

Fig. 4. Hepatic venous pressure gradient (HVPG) and elastographic measurements before and after transjugular intrahepatic portosystemic shunt (TIPS) placement or revision. The graphs represent the mean portal pressure gradient (mm Hg) or the liver or the splenic stiffness (kPa) measured by point shear-wave elastography (pSWE) in 17 patients before and after TIPS placement or TIPS revision.

in 21 patients (87.5%). In 3 cases, the PPG values remained between 13 mm Hg and 15 mm Hg.

Among the 34 TIPS revision cases, venographic examination showed 21 cases of TIPS function (61.7%) in which no morphologic defects were evidenced by venography and by PPG value of <12 mm Hg, and 13 cases of TIPS dysfunction (38.2%). The PPG values were ≥12 mm Hg in 4 cases, there was shunt stenosis or thrombosis in 3 cases, and both shunt stenosis and thrombosis occurred in 6 cases.

Diagnostic accuracy of mean portal vein velocity and liver and spleen elastography in predicting TIPS dysfunction

The 24 patients enrolled in our study underwent a total of 34 paired examinations to evaluate TIPS function. Every paired examination included the index test (which comprised CDUS, liver and spleen elastography) and the reference standard, which comprised venography and PPG measurement. In 21 cases the reference standard demonstrated TIPS function, whereas in the remaining 13 cases it showed TIPS dysfunction (Table 2). These 13 examinations included four examinations where PPG was ≥12 mm Hg, three examinations where thrombosis or stenosis of the stent was detected (and then treated with PTA balloons and/or stents) and six examinations showing both venographic defect and PPG of ≥12 mm Hg.

At univariate analysis, the variables that were significantly related to TIPS dysfunction were: the hepatopetal blood flow direction in the intrahepatic portal vein branches ($p = 0.004$) and high SS values (Table 3 provides the diagnostic performance values). In particular, by applying a 25 kPa cutoff value to predict TIPS dysfunction, sensitivity was 86%, specificity was 92%, LR+ was 11, LR− was 0.10 and the AUROC was 0.86 (95% CI 0.70–0.96).

Table 2. Color-Doppler ultrasound and elastographic variables correlated to transjugular intrahepatic portosystemic shunt dysfunction

Parameters	TIPS Functioning (total n = 21 patients)	TIPS Dysfunction (total n = 13 patients)	*p* Value
Hepatopetal portal flow direction	19	8	0.04
Portal vein maximal velocity (cm/s)	7	3	0.52
Shunt maximal flow velocity (proximal) (cm/s)	6	1	0.14
Shunt maximal flow velocity (distal) (cm/s)	6	3	0.72
Hepatofugal flow direction in the intrahepatic portal veins branches	20	4	0.0006
Liver stiffness pSWE (kPa) (mean ± SD)	17.5 ± 12.5	22.9 ± 12.5	0.22
Spleen stiffness pSWE (kPa) (mean ± SD)	18.1 ± 9.3	32.7 ± 9.1	0.0001
Portal vein maximal velocity (mean ± SD)	35.2 ± 17.3	22.5 ± 11.2	0.02

pSWE, point shear-wave elastography; SD, standard deviation. TIPS, transjugular intrahepatic portosystemic shunt.

Table 3. Operative characteristics of color-Doppler ultrasound and elastographic parameters significantly related to transjugular intrahepatic portosystemic shunt dysfunction for 24 consecutive patients who underwent color-Doppler ultrasound, point shear-wave elastography and venography

Variable	Cutoff	Sens (%)	Spec (%)	LR+	LR−	AUROC (95% CI)
Portal vein velocity (cm/s)	19	90	61	2.3	0.15	0.75 (0.57–0.88)
Intrahepatic portal vein branches flow direction (hepatopetal vs. hepatofugal)	-	70	95	14	0.3	-
Spleen stiffness (kPa)	25	86	92	11.1	0.10	0.86 (0.70–0.96)

AUROC, area under the receiver-operating characteristic curve; CI, confidence interval; LR+, positive likelihood ratio; LR−, negative likelihood ratio, Sens, sensitivity; Spec, specificity.

At multivariate analysis, the variables that were significantly related to TIPS dysfunction were: the blood flow direction of intrahepatic portal vein branches ($p = 0.02$) and SS values ($p = 0.01$). The overall diagnostic accuracy of the model was excellent (AUROC = 0.90).

DISCUSSION

The role of TIPS in the treatment of portal hypertension complications is well established. Placing PTFE-coated stents, instead of bare metal ones, has significantly improved the long-term patency of TIPS and decreased the rate of TIPS dysfunction from 44% to 15% (Boyer and Haskal 2005). Despite that, because TIPS dysfunction is often asymptomatic, an accurate screening test is needed to confirm shunt patency. The reference standard to assess TIPS function is venography with PPG measurement: evidence of a reduction of PPG to less than 12 mm Hg is considered the pressure target, especially with patients who have bleeding as an indication (Fagiuoli et al. 2017).

An ideal non-invasive screening tool should have high sensitivity and negative predictive values to rule out patients with well-functioning TIPS, with a good degree of confidence, and safely to spare these patients venography. CDUS has been extensively studied for measuring intra-stent and main portal vein flow velocities and flow direction in the intrahepatic portal vein branches, which has been shown to be a reliable qualitative indicator of TIPS malfunction (Fagiuoli et al. 2017).

In addition, recent data has indicated the promising role of SS in the assessment of portal hypertension thanks to its good correlation with HVPG values. Several studies have demonstrated the good diagnostic accuracy of SS, particularly in ruling out the presence of esophageal varices (Boyer and Haskal 2005; Colecchia et al. 2012; Calvaruso et al. 2013; Sharma et al. 2013; Fraquelli et al. 2014). More recently, several preliminary studies (Gao et al. 2012; Ran et al. 2013; Novelli et al. 2015; Gao et al. 2016; Han et al. 2017; De Santis et al. 2018; Buechter et al. 2018) have shown a progressive significant reduction of SS values after successful TIPS implantation.

When considering all such data, we have hypothesized that a non-invasive assessment of SS, alone or combined with CDUS findings, would provide a useful predictive value in evaluating TIPS function.

The first relevant result of our study is that SS, as estimated by pSWE, is feasible for most patients with portal hypertension, which differs from TE, which has shown a high rate of unreliable measurements and failures mainly because of the presence of ascites. Second, we have obtained a good inter-observer agreement for SS measurements, as expressed by a high ICC of 0.90. The optimal feasibility and good reproducibility of pSWE, also in patients with ascites, is an important achievement for clinical practitioners.

Moreover, we have achieved interesting results by analyzing spleen elastographic measurements. At variance from mean LS values, the mean SS values significantly decreased after TIPS placement. An explanation of this finding can be the presence of the stent inside the hepatic parenchyma, which can create, at least in the very first 24-h period, a kind of compression leading to increased LS. It is also plausible that TIPS placement has more impact on the reduction of venous congestion in the spleen than in the liver because of the inherent hemodynamic differences between the two organs. The reduction of mean SS after TIPS placement/revision supports the idea that SS reflects the portal vein pressure better than LS. Our data shows that, in the whole group of 49 examinations, SS values significantly and positively correlated with HVPG/PPG values, whereas LS values did not. The absence of a significant correlation between LS and HVPG is in line with previous data from the literature, according to which, when HVPG values exceed 10−12 mm Hg (which is the threshold of clinically significant portal hypertension and varices development) the portal pressure becomes largely independent from liver fibrosis: therefore, the ability of LS to predict HVPG is not optimal, while SS better reflects the hemodynamic changes that occur in cirrhotic patients (Hirooka et al. 2011; Stefanescu et al. 2011).

The most interesting results of this study have emerged from the multivariate analysis results. Among all the CDUS parameters, the most accurate one was the flow direction in the intrahepatic portal vein branches, while among the elastographic data the best parameter was SS as measured by pSWE.

As concerns the CDUS parameters, the finding of a reversal of the blood flow direction (from hepatofugal to hepatopetal) within the intrahepatic portal vein branches, as a relevant predictor of TIPS dysfunction, is in line with previous data (Albrades et al. 2005). Interestingly, the performance of other CDUS parameters (*i.e.* direction and flow velocity of the main portal vein and flow velocity in the shunt, proximal and distal), more difficult to obtain and less reproducible, was not significantly related to TIPS function.

Both the flow direction within the intrahepatic portal vein branches and SS values have shown very good positive and negative likelihood ratios (LR) for TIPS dysfunction.

From our data, the best cutoff value of SS, to maximize sensitivity and specificity, is 25 kPa with 86% sensitivity and 92% specificity.

Of note, according to the multivariate analysis results, combining the two parameters leads to an overall diagnostic accuracy increase. In fact, the AUROC (0.86 for SS alone) increased to 0.90 when the flow direction within the intrahepatic portal vein branches was added to the model.

The multivariate analysis has confirmed the strong association between TIPS dysfunction with SS values >25 kPa and a hepatopetal flow direction in the intrahepatic portal vein branches.

This study also has some limitations, such as the relatively small sample size, which makes it difficult to generalize our findings, and the lack of follow-up clinical data on most of the patients participating in the study. However, the data obtained is promising, and therefore further studies on SS in large populations of patients with TIPS dysfunction and long-term follow-up after TIPS placement should be encouraged.

In conclusion, our results suggest that spleen pSWE can be used quantitatively to assess SS as an indicator of TIPS function. The assessment of the blood flow direction in the intrahepatic portal vein branches is a rapid and easy parameter to obtain, and this is the best predictor of TIPS dysfunction among the echo CDUS parameters. The combination of the two simple parameters (measured by CDUS and elastography), identified as independent predictors of TIPS dysfunction at multivariate analysis, is highly sensitive, which accurately enables TIPS dysfunction to be ruled out.

Conflict of interest disclosure—The authors declare no competing interests.

REFERENCES

Abraldes JG, Gilabert R, Turnes J, Nicolau C, Berzigotti A, Aponte J, Bru C, Bosch J, García-Pagán JC. Utility of color Doppler ultrasonography predicting tips dysfunction. Am J Gastroenterol 2005;100:2696–2701.

Attia D, Rodt T, Marquardt S, Hinrichs J, Meyer BC, Gebel M, Wacker F, Manns MP, Potthoff A. Shear wave elastography prior to transjugular intrahepatic portosystemic shunt may predict the decrease in hepatic vein pressure gradient. Abdom Radiol (NY) 2019;44:1127–1134.

Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986;1:307–310.

Boursier J, Konate A, Guilluy M, Gorea G, Sawadogo A, Quemener E, Oberti F, Reaud S, Hubert-Fouchard I, Dib N, Calès P. Learning curve and interobserver reproducibility evaluation of liver stiffness measurement by transient elastography. Eur J Gastroenterol Hepatol 2008;20:693–701.

Boyer TD, Haskal ZJ. American Association for the Study of Liver Diseases practice guidelines: The role of transjugular intrahepatic portosystemic shunt creation in the management of portal hypertension. J Vasc Interv Radiol 2005;16:615–629.

Buechter M, Manka P, Theysohn JM, Reinboldt M, Canbay A, Kahraman A. Spleen stiffness is positively correlated with HVPG and decreases significantly after TIPS implantation. Dig Liver Dis 2018;50(1):54–60 Jan.

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.

Casado M, Bosch J, García-Pagán JC, Bru C, Bañares R, Bandi JC, Escorsell A, Rodríguez-Láiz JM, Gilabert R, Feu F, Schorlemer C, Echenagusia A, Rodés J. Clinical events after transjugular intrahepatic portosystemic shunt: Correlation with hemodynamic findings. Gastroenterology 1998;114:1296–1303.

Cello JP, Ring EJ, Olcott EW, Koch J, Gordon R, Sandhu J, Morgan DR, Ostroff JW, Rockey DC, Bacchetti P, LaBerge J, Lake JR, Somberg K, Doherty C, Davila M, McQuaid K, Wall SD.

Endoscopic sclerotherapy compared with percutaneous transjugular intrahepatic portosystemic shunt after initial sclerotherapy in patients with acute variceal hemorrhage: A randomized, controlled trial. Ann Intern Med 1997;126:858–865.
Chong WK, Malisch TA, Mazer MJ, Lind CD, Worrell JA, Richards WO. Transjugular intrahepatic portosystemic shunt: US assessment with maximum flow velocity. Radiology 1993;189:789–793.
Colecchia A, Montrone L, Scaioli E, Bacchi-Reggiani ML, Colli A, Casazza G, Schiumerini R, Turco L, Di Biase AR, Mazzella G, Marzi L, Arena U, Pinzani M, Festi D. Measurement of spleen stiffness to evaluate portal hypertension and the presence of esophageal varices in patients with HCV-related cirrhosis. Gastroenterology 2012;143:646–654.
De Santis A, Nardelli S, Bassanelli C, Lupo M, Iegri C, Di Ciesco CA, Forlino M, Farcomeni A, Riggio O. Modification of splenic stiffness on acoustic radiation force impulse parallels the variation of portal pressure induced by transjugular intrahepatic portosystemic shunt. J Gastroenterol Hepatol 2018;33:704–709.
Fagiuoli S, Bruno R, Debernardi Venon W, Schepis F, Vizzutti F, Toniutto P, Senzolo M, Caraceni P, Salerno F, Angeli P, Cioni R, Vitale A, Grosso M, De Gasperi A, D'Amico G, Marzano A, AISF TIPS Special Conference. Consensus conference on TIPS management: Techniques, indications, contraindications. Dig Liver Dis 2017;49:121–137.
Feldstein VA, LaBerge JM. Hepatic vein flow reversal at duplex sonography: A sign of transjugular intrahepatic portosystemic shunt dysfunction. AJR 1994;162:839–841.
Ferral H, Foshager MC, Bjarnason H, Finlay DE, Hunter DW, Castañeda-Zúñiga WR, Letourneau JG. Early sonographic evaluation of the transjugular intrahepatic portosystemic shunt (TIPS). Cardiovasc Intervent Radiol 1993;16:275–279.
Fleiss JL. The design and analysis of clinical experiments. New York: John Wiley and Sons; 1986.
Fraquelli M, Rigamonti C, Casazza G, Conte D, Donato MF, Ronchi G, Colombo M. Reproducibility of transient elastography in the evaluation of liver fibrosis in patients with chronic liver disease. Gut 2007;56:968–973.
Fraquelli M, Giunta M, Pozzi R, Rigamonti C, Della Valle S, Massironi S, Conti CB, Aghemo A, Ronchi G, Iurlo A, Primignani M, Conte D, Colombo M. Feasibility and reproducibility of spleen transient elastography and its role in combination with liver transient elastography for predicting the severity of chronic viral hepatitis. J Viral Hepat 2014;21:90–98.
Foshager MC, Ferral H, Nazarian GK, Castañeda-Zúñiga WR, Letourneau JG. Duplex sonography after transjugular intrahepatic portosystemic shunts (TIPS): Normal hemodynamic findings and efficacy in predicting shunt patency and stenosis. Am Roentgenol 1995;165:1–7.
Garcia-Tsao G, Groszmann RJ, Fisher RL, Conn HO, Atterbury CE, Glickman M. Portal pressure, presence of gastroesophageal varices and variceal bleeding. Hepatology 1985;5:419–424.
Gao J, Ran HT, Ye XP, Zheng YY, Zhang DZ, Wang ZG. The stiffness of the liver and spleen on ARFI Imaging pre and post TIPS placement: A preliminary observation. Clin Imaging 2012;36:135–141.
Gao J, Zheng X, Zheng YY, Zuo GQ, Ran HT, Auh YH, Waldron L, Chan T, Wang ZG. Shear wave elastography of the spleen for monitoring transjugular intrahepatic portosystemic shunt function: A pilot study. J Ultrasound Med 2016;35:951–958.
Han H, Yang J, Zhuge YZ, Zhang M, Wu M. Point shear wave elastography to evaluate and monitor changing portal venous pressure in patients with decompensated cirrhosis. Ultrasound Med Biol 2017;43:1134–1140.
Hirooka M, Ochi H, Koizumi Y, Kisaka Y, Abe M, Ikeda Y, Matsuura B, Hiasa Y, Onji M. Splenic elasticity measured with real-time tissue elastography is a marker of portal hypertension. Radiology 2011;261:960–968.
Kanterman RY, Darcy MD, Middleton WD, Sterling KM, Teefey SA, Pilgram TK. Doppler sonography findings associated with transjugular intrahepatic portosystemic shunt malfunction. AJR Am J Roentgenol 1997;168:467–472.
Longo JM, Bilbao JI, Rousseau HP, García-Villareal L, Vinel JP, Zozaya JM. Transjugular intrahepatic portosystemic shunt: Evaluation with Doppler sonography. Radiology 1993;186:529–534.
Novelli PM, Cho K, Rubin JM. Sonographic assessment of spleen stiffness before and after transjugular intrahepatic portosystemic shunt placement with or without concurrent embolization of portal systemic collateral veins in patients with cirrhosis and portal hypertension: A feasibility study. J Ultrasound Med 2015;34:443–449.
Piecha F, Paech D, Sollors J, Seitz HK, Rössle M, Rausch V, Mueller S. Rapid change of liver stiffness after variceal ligation and TIPS implantation. Am J Physiol Gastrointest Liver Physiol 2018;314:G179–G187.
Ran HT, Ye XP, Zheng YY, Zhang DZ, Wang ZG, Chen J, Madoff D, Gao J. Spleen stiffness and splenoportal venous flow: Assessment before and after transjugular intrahepatic portosystemic shunt placement. J Ultrasound Med 2013;32:221–228.
Rössle M, Haag K, Ochs A, Sellinger M, Nöldge G, Perarnau JM, Berger E, Blum U, Gabelmann A, Hauenstein K. The transjugular intrahepatic portosystemic stent-shunt procedure for variceal bleeding. N Engl J Med 1994;330:165–171.
Sanyal AJ, Freedman AM, Luketic VA, Purdum PP, 3rd, Shiffman ML, Cole PE, Tisnado J, Simmons S. Transjugular intrahepatic portosystemic shunts compared with endoscopic sclerotherapy for the prevention of recurrent variceal hemorrhage: A randomized, controlled trial. Ann Intern Med 1997;126:849–857.
Sharma P, Kirnake V, Tyagi P, Bansal N, Singla V, Kumar A, Arora A. Spleen stiffness in patients with cirrhosis in predicting esophageal varices. Am J Gastroenterol 2013;108:1101–1107.
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;12:935–945.
Stefanescu H, Grigorescu M, Lupsor M, Procopet B, Maniu A, Badea R. Spleen stiffness measurement using Fibroscan for the noninvasive assessment of esophageal varices in liver cirrhosis patients. J Gastroenterol Hepatol 2011;26:164–170.
Stefanescu H, Procopet B, Platon Lupsor M. Modified spleen stiffness measurement: A step forward, but still not the solution to all problems in the noninvasive assessment of cirrhotic patients. Letter to editor; J Viral Hepat 2014;21(7):54.
Surratt RS, Middleton WD, Darcy MD, Melson GL, Brink JA. Morphologic and hemodynamic findings at sonography before and after creation of a transjugular intrahepatic portosystemic shunt. AJR Am J Roentgenol 1993;160:627–630.
Wong GL, Liang LY, Kwok R, Hui AJ, Tse YK, Chan HL, Wong VW. Low risk of variceal bleeding in patients with cirrhosis after variceal screening stratified by liver/spleen stiffness. Hepatology 2019;70:971–981.
Ziol M, Handra-Luca A, Kettaneh A, Christidis C, Mal F, Kazemi F, de Lédinghen V, Marcellin P, Dhumeaux D, Trinchet JC, Beaugrand M. Noninvasive assessment of liver fibrosis by measurement of stiffness in patients with chronic hepatitis C. Hepatology 2005;41:48–54.