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**Ultrasound liver elastography beyond liver fibrosis assessment**

Ferraioli G *et al*. LS beyond fibrosis

Giovanna Ferraioli, Richard G Barr

**Giovanna Ferraioli,** Dipartimento di Scienze Clinico-Chirurgiche, Diagnostiche e Pediatriche, Medical School University of Pavia, Pavia 27100, Italy

**Giovanna Ferraioli,** Clinical Sciences and Infectious Diseases Department, Fondazione IRCCS Policlinico S Matteo, University of Pavia, Pavia 27100, Italy

**Richard G Barr,** Northeastern Ohio Medical University, Rootstown, Oh 44272, United States

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**Corresponding author:** **Giovanna Ferraioli**, **MD, Academic Research, Doctor,** Clinical Sciences and Infectious Diseases Department, Fondazione IRCCS Policlinico S Matteo, University of Pavia, Viale Camillo Golgi 19, Pavia 27100, Italy. giovanna.ferraioli@unipv.it

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**Abstract**

Several guidelines have indicated that liver stiffness (LS) assessed by means of shear wave elastography (SWE) can safely replace liver biopsy in several clinical scenarios, particularly in patients with chronic viral hepatitis. However, an increase of LS may be due to some other clinical conditions not related to fibrosis, such as liver inflammation, acute hepatitis, obstructive cholestasis, liver congestion, infiltrative liver diseases. This review analyzes the role that SWE can play in cases of liver congestion due to right-sided heart failure, congenital heart diseases or valvular diseases. In patients with heart failure LS seems directly influenced by central venous pressure and can be used as a prognostic marker to predict cardiac events. The potential role of LS in evaluating liver disease beyond the stage of liver fibrosis has been investigated also in the hepatic sinusoidal obstruction syndrome (SOS) and in the Budd-Chiari syndrome. In the hepatic SOS, an increase of LS is observed some days before the clinical manifestations; therefore, it could allow an early diagnosis to timely start an effective treatment. Moreover, it has been reported that patients that were successfully treated showed a LS decrease, that reached pre-transplantation value within two to four weeks. It has been reported that, in patients with Budd-Chiari syndrome, LS values can be used to monitor short and long-term outcome after angioplasty.

**Key words:** Liver stiffness; Shear wave elastography; Heart failure; Liver congestion; Hepatic sinusoidal obstruction syndrome; Fontan circulation; Budd Chiari syndrome; Valvular diseases

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**Core tip:** An increase of liver stiffness (LS) has been reported in patients with liver congestion. It is a “confounding factor” for the evaluation of liver fibrosis. However, in the setting of right-sided heart failure LS seems directly influenced by central venous pressure and can be used as a prognostic marker to predict cardiac events. It should be emphasized that heart failure “per se” may lead to irreversible liver disease. The potential role of LS in evaluating liver disease beyond the stage of liver fibrosis has been investigated also in the hepatic sinusoidal obstruction syndrome and in the Budd-Chiari syndrome.

**INTRODUCTION**

Several guidelines have indicated that liver stiffness (LS) assessed by means of ultrasound shear wave elastography (SWE) can safely replace liver biopsy in several clinical scenarios, particularly in patients with chronic viral hepatitis[1-3]. SWE techniques assess the biomechanical properties of tissue by applying a stress – externally or directly into the body – that generates a tissue deformation and the generation of shear waves whose speed of propagation is directly associated to the stiffness, *i.e.*, in stiffer tissue the shear wave speed is higher. SWE includes transient elastography (TE) and acoustic radiation force impulse (ARFI) techniques. With TE, the stress that generates the shear wave is applied externally on the skin and the measurement is performed in a fixed region of interest (ROI); the system does not give a B-image. With the ARFI based techniques, the shear waves are generated by the push-pulse of a focused ultrasound beam directly into the body. The B-mode image is used to locate the best area for LS measurement. The measurement is performed in a small fixed ROI without an elasticity image, as in point SWE (pSWE), or in a larger ROI in which the elasticity values are color-coded, as in two-dimensional SWE (2D-SWE).

In addition to fibrosis, there are some factors or clinical conditions that may lead to a LS increase. They are known as “confounding factors” for fibrosis staging: liver inflammation, whose indirect biomarkers are the transaminases values; acute hepatitis; obstructive cholestasis; liver congestion; infiltrative liver diseases[1,2,4].

The first report of a LS increases due to liver congestion dates back to 2008[5]. The authors describe the case of a patient, infected with hepatitis C virus after two heart transplants, who had heart failure and showed a very stiff liver – 44.3 kPa at TE – with signs of cardiac hepatopathy but without liver cirrhosis at histology. One year after another heart transplant, a liver biopsy showed that there was a significant improvement of the cardiac hepatopathy, and the TE value was 3.8 kPa, *i.e.*, within the normal range.

Since that report, several studies have investigated the role of the LS in patients with congestive heart disease and without a primary liver disease.

This article analyses the available literature on the role of the SWE techniques beyond liver fibrosis assessment.

**HEART DISEASES**

Any pathology affecting the right heart may determine an increase of the pressure in the right atrium pressure, the inferior vena cava and the hepatic veins. The liver is covered by a poorly distensible capsule; therefore, hepatic congestion may lead to an increase of stiffness.

***Congestive heart disease***

Heart failure is a major health problem, with a considerable risk of morbidity and mortality. In patients with congestive heart disease, right heart catheterization is the gold standard to measure central venous pressure (CVP). However, the procedure is invasive, not readily available and not useful for following up patients. An indirect noninvasive parameter of the right atrial pressure (RAP), recommended by the guidelines of the American Society of Echocardiography, is the inferior vena cava diameter > 21 mm together with the collapse of the vessel < 50%[6].

In patients with right-sided heart failure, the LS measurement could be a useful parameter that can be repeated over short periods of time. The pivotal study reporting that the LS is directly influenced by CVP was published in 2010 by Millonig *et al*[7]. They showed that the clamping of the inferior vena cava in landrace pigs significantly increased the LS, and this effect reversed after reopening the vessel. Moreover, in a small group of patients with decompensated congestive heart disease, they found a decrease of the LS in the subjects who responded to the treatment. The decrease of the LS in patients with congestive heart disease who had a clinical improvement after treatment was confirmed in another small series[8].

It has been reported that the LS, estimated with TE, could be an indirect marker of the RAP in patients with right-sided heart failure[9]. After excluding patients with organic liver disease, it was found that there was a high correlation between LS and RAP assessed with right heart catheterization (r = 0.95), and the regression equation to predict RAP was (-5.8 + 6.7 × natural logarithm of LS value). The authors found that a LS cut-off value of 10.6 kPa identified RAP > 10 mmHg with sensitivity and accuracy higher than the echocardiographic parameter mentioned above (sensitivity 0.85 *vs* 0.56, accuracy 0.90 *vs* 0.74, *P* < 0.05 for both). However, it should be highlighted that 16 of the 105 (15.2%) patients that were screened were excluded. This is not a negligible percentage and may raise concern on the applicability of the technique in this setting. On the other hand, it should be highlighted that congestive heart disease may lead to organic liver disease, and this latter may be a “confounder” when the LS is used to non-invasively assess the central venous pressure. For that reason, it is of outmost importance to exclude cases with suspected organic liver disease in research studies.

The same group assessed the prognostic value of the LS by TE in a series of hospitalized patients with heart failure[10]. Of the 226 patients that were screened, 55 (24.3%) were excluded (37 for organic liver disease and 18 for invalid LS measurement). The LS was assessed before discharge in the remaining 171 patients, who were stratified into three groups on the basis of the LS value: Group 1: ≤ 4.7 kPa, corresponding to a RAP of 4.6 mmHg on the basis of the regression equation found in their previous study[9]; Group 2: 4.7 to ≤ 6.9 kPa, estimated RAP 6.9 mmHg; Group 3: > 6.9 kPa, estimated RAP ≥ 7.0 mmHg. The authors found that the patients in Group 3 were in advanced New York Heart Association functional class and that they had a significantly higher risk of death or readmission to the hospital for heart failure than those in the other two groups. The LS value was able to predict cardiac events with a hazard ratio of 1.13 per 1-kPa increase.

Another study evaluated the prognostic value of the LS in a series of patients with acute decompensated heart failure[11]. One hundred and fifty-four patients were enrolled, but 27 of them were excluded due to the presence of other factors that could likely increase the LS and 22 dues to invalid LS measurement or because they were lost to follow-up. Using an arbitrary LS value of 8.8 kPa by TE, the remaining 105 patients were divided into two groups. In a median follow-up period of about five months, it was found that cardiac events, *i.e.*, death or readmission to hospital, occurred in 54% of patients with LS ≥ 8.8 kPa and 25% of patients with LS < 8.8 kPa (*P* = 0.001). After adjusting for age, sex, and indices related to organ congestion, a LS ≥ 8.8 kPa was still significantly associated with cardiac events.

The LS as a marker of clinical outcome in patients with acute decompensated heart failure was also evaluated in a series of 149 patients in whom TE was performed in the first two days of admission to the hospital and on the day of discharge[12]. It is reported that, overall, the patients presented a significant decrease of the LS during the hospitalization and that a LS value > 13 kPa on admission and a LS value > 5 kPa at discharge was associated with an increased risk of one-year all-cause death or readmission to the hospital.

Using a pSWE technique in patients with heart failure, it was shown that the changes in LS in patients with heart failure significantly correlated with changes in CVP in multivariate analysis, and that an LS cut-off value of 7 kPa could predict a CVP > 10 mmHg with 89.6% sensitivity and 87.5% specificity[13,14]. Another group reported that a high LS value on admission was an independent determinant of worse clinical outcomes in patients with acute decompensated heart failure[15].

The LS cutoffs obtained in these clinical studies are reported in Table 1.

All the published studies confirm that the LS can be a marker of congestive heart failure; however, it is not yet clear what cutoff value should be used to define the risk of adverse cardiac events. In fact, this value ranges from > 5 kPa to 8.8 kPa. It is worth mentioning that the “rule of 5” proposed by the Baveno VI consensus on portal hypertension has proposed that LS value with TE up to 5 kPa may exclude liver fibrosis[16].

It should also be emphasized that there is an interaction between the liver and the heart: heart failure and liver disease often co-exist, and heart failure “per se” may lead to irreversible liver disease. Therefore, in some cases, the increase in LS may be due to both liver congestion and liver disease, even when other etiologies of primary liver disease are excluded**[**17]. On this regard, it is worth mentioning that liver biopsy data were not available in the majority of the cited articles.

In a small series of patients with end-stage chronic heart failure who underwent left ventricular assist device implantation (28 patients, liver biopsy performed in 16 of them), it was reported that the LS values were affected both by the central venous congestion and the histologic changes of the liver[18]. On the other hand, in patients with severe heart failure who require a left ventricular assist device, it has been observed that the incidence of major adverse events was lower when the LS was ≤ 12.5 kPa[19].

***Congenital heart diseases and valvular diseases***

In a study that included both children (*n* = 60) and adults (*n* = 36) with congenital heart diseases, it was found that the LS significantly correlated with CVP (r = 0.75) [20]. When the two subgroups were analyzed separately, the correlation was significantly higher in the adults (r = 0.68 in children *vs* r = 0.84 in adults, *P* < 0.0001). Overall, the area under the receiver operating characteristic (AUC) curve of the LS for identifying a CVP > 10 mmHg was 0.97 and the optimal cut-off value of LS for detection of the CVP > 10 mmHg was 8.8 kPa, with 92% sensitivity and 96% specificity.

The LS with a 2D-SWE technique was measured in 79 patients aged < 20 years with congenital heart diseases and without liver disease who underwent cardiac catheterization[21]. Thirty-four (43.0%) of them had Fontan physiology. As observed in adult patients with heart failure, the CVP was the only factor that independently and significantly correlated with the LS (r = 0.78). This quite strong correlation was present also in the subgroups of patients with biventricular disease and those who underwent the Fontan procedure.

In a series of 131 patients with various degrees of tricuspid valve regurgitation secondary to left-sided heart valve disease, it was found that the individuals with severe regurgitation had higher LS than those with moderate regurgitation[22]. Moreover, the LS values were associated with the parameters that non-invasively assess the severity of tricuspid regurgitation, such as the area of the regurgitant orifice, the right atrial pressure, and the inferior vena cava diameter.

The change over time of the LS value was assessed in a series of 32 consecutive patients undergoing surgery for valve replacement or repair[23]. All patients had tricuspid valve regurgitation secondary to left-sided heart valve disease. It was reported that the LS decreased significantly at three months after surgery, from 8.4 kPa to 6.0 kPa (*P* = 0.03).

The LS cutoffs obtained in these studies are reported in Table 1.

***Fontan circulation***

The Fontan operation[24] was proposed for the surgical repair of tricuspid atresia and it still is the palliative standard procedure for patients with univentricular physiology.

Advances in the surgical techniques and in the management of patients with Fontan circulation have led to a longer survival of Fontan-palliated patients who may reach adulthood in the majority of cases. However, the altered hemodynamics lead to disfunction of several organs, especially the liver. In fact, cardiac cirrhosis is quite common in Fontan-palliated patients during their adulthood.

Using a 2D-SWE technique, a study has shown that, in patients with Fontan circulation, the LS correlated with the stage of histopathologic fibrosis, and there was a significantly higher LS (15.6 kPa *vs* 5.5 kPa, *P* < 0.0001) than in healthy controls[25]. Using TE, a study reported a significant correlation between the stage of fibrosis and the interval of time since the Fontan surgery, with a sharp increase in the number of patients with significant liver fibrosis at 5 years after the operation[26].

It is worth mentioning that the Fontan procedure *per se* leads to a significant increase in the LS due to hepatic congestion[27,28]. This increase persists chronically; therefore, it could be a confounding factor for the evaluation of liver fibrosis[27]. In a small series (9 children; age range, 3.5-5.6 years), it was observed that the LS increased from 6.2 kPa ± 1.5 kPa in the preoperative period to 11.2 kPa ± 4 kPa at a mean follow-up of 4 mo[28]. To overcome this limitation in the use of the LS as a marker of fibrosis, the recent update of the Society of Radiologists in Ultrasound consensus (Barr RG, Stephanie R, Wilson SR, Rubens D, Garcia-Tsao G, Ferraioli G). Update to the Society of Radiologists in Ultrasound Liver Elastography Consensus Statement] has proposed that each subject becomes his/her own control, using the percentage of the stiffness changes over time to evaluate the efficacy of the treatment or the progression of disease in this or similar settings.

**LIVER DISEASES**

LS assessment is a reliable and non-invasive method for the staging of liver fibrosis in several clinical scenarios and it is an accepted biomarker of portal hypertension[1,2,4,16,29,30]. The potential role of the LS in evaluating liver disease beyond the stage of liver fibrosis has been investigated in the hepatic sinusoidal obstruction syndrome (SOS) and in the Budd-Chiari syndrome.

***Hepatic SOS***

Hepatic SOS, previously named hepatic veno-occlusive disease, is caused by a toxic damage to the hepatic sinusoidal endothelial cells[31]. It may occur after hematopoietic stem cell transplantation and has been associated with the use of oxaliplatin in patients with colorectal liver metastases. It has also been observed after the ingestion of alkaloid toxins, or after high-dose radiation therapy[31]. SOS is a potentially life-threatening disease, which can lead to hepatic congestion and sinusoidal portal hypertension[32]. The diagnosis is based on clinical criteria including weight gain, hepatomegaly, ascites, and jaundice[32].

In 2011, Fontanilla *et al*[33] reported an increase of the LS assessed by a pSWE technique (2.75 m/s and 2.58 m/s) in two adult patients diagnosed with SOS. They observed that the LS decreased, reaching normal values, after successful treatment.

The potential role of LS assessment in this setting has been investigated in rat models of acute and severe SOS or chronic, mild and reversible SOS[34]. In both SOS models, the LS values were significantly higher than in the matched control rats. In the chronic and reversible SOS models there was a significant decrease of the LS after a treatment-free period of two weeks.

The role of the LS in predicting SOS syndrome has been investigated in a series of 25 pediatric patients who received hematopoietic stem cell transplant and in whom the LS by pSWE technique was assessed at three scheduled time points[35]. Five of them developed SOS. Respect to the patients who did not develop SOS, they showed a significant increase of LS at day + 5 and at day + 14 after transplant. The LS increase occurred on average 9 and 11 d before clinical and conventional ultrasound diagnosis of SOS. Therefore, a LS increase seems to be an early marker of SOS development, allowing an early diagnosis and the possibility to timely start an effective treatment.

Similar findings were observed in a series of 78 adult patients who underwent hematopoietic stem cell transplantation[36]. The median baseline LS value assessed by TE was 4.2 kPa. Four patients (5.1%) presented SOS, and in all of them the LS showed a significant increase, respect to baseline values, 2-12 d before the clinical manifestation of SOS. The three patients that were successfully treated with defibrotide showed a decrease of the LS, which reached pre-transplantation value within two to four weeks after the diagnosis of SOS, whereas in the patient with severe SOS who died 20 d after the diagnosis of SOS there was not any decrease of the LS.

***Budd-chiari syndrome***

Budd-Chiari syndrome is due to the obstruction to the hepatic venous outflow which can be due to several conditions.

The role of the LS in monitoring short and long-term outcome after angioplasty was assessed in a series of 25 patients with Budd-Chiari syndrome[37]. There was a significant decrease of the LS values within 24 hours after intervention, from 62.8 kPa to 26.3 kPa. There was also a significant difference between the LS values obtained at 24 h and those at 3 mo after treatment (26.3 kPa *vs* 20.9 kPa; *P* = 0.003).

Likewise, in another series of 32 patients with Budd-Chiari syndrome successfully treated with angioplasty, a significant decrease of the LS two days after the treatment, from 35.2 (10.6) kPa to 20.1 (5.5) kPa, was observed[38]. The patients were followed up for six months. Respect to baseline values, there was a significant decrease at three months; thereafter the LS values remained stable even though still in the cirrhotic stage.

In a case report, the LS together with the pulsed Doppler waveform of the hepatic veins was used to follow-up, at three-month intervals, a patient who presented re-stenosis of the inferior vena cava after balloon dilation. A sharp increase of the LS (from 14.3 kPa to 20.5 kPa) and a monophasic pattern of the hepatic vein flow at pulsed Doppler were markers of re-stenosis, confirmed by X-ray venography[39].

**CONCLUSION**

SWE techniques have largely been used for the assessment of the LS related to liver fibrosis, and their use in the clinical practice is now accepted by guidelines. Several studies have shown that, beyond liver fibrosis assessment, the LS is a useful parameter for the evaluation of liver congestion that occurs in case of right-sided heart failure, some congenital and valvular diseases, hepatic SOS or Budd-Chiari syndrome. In these scenarios, the LS assessment may also play a role in monitoring changes over time; therefore, it could be a marker of clinical outcome.

**REFERENCES**

1 **Ferraioli G**, Wong VW, Castera L, Berzigotti A, Sporea I, Dietrich CF, Choi BI, Wilson SR, Kudo M, Barr RG. Liver Ultrasound Elastography: An Update to the World Federation for Ultrasound in Medicine and Biology Guidelines and Recommendations. *Ultrasound Med Biol* 2018; **44**: 2419-2440 [PMID: 30209008 DOI: 10.1016/j.ultrasmedbio.2018.07.008]

2 **Dietrich CF**, Bamber J, Berzigotti A, Bota S, Cantisani V, Castera L, Cosgrove D, Ferraioli G, Friedrich-Rust M, Gilja OH, Goertz RS, Karlas T, de Knegt R, de Ledinghen V, Piscaglia F, Procopet B, Saftoiu A, Sidhu PS, Sporea I, Thiele M. EFSUMB Guidelines and Recommendations on the Clinical Use of Liver Ultrasound Elastography, Update 2017 (Short Version). *Ultraschall Med* 2017; **38**: 377-394 [PMID: 28407654 DOI: 10.1055/s-0043-103955]

3 **European Association for Study of Liver**; Asociacion Latinoamericana para el Estudio del Higado. EASL-ALEH Clinical Practice Guidelines: Non-invasive tests for evaluation of liver disease severity and prognosis. *J Hepatol* 2015; **63**: 237-264 [PMID: 25911335 DOI: 10.1016/j.jhep.2015.04.006]

4 **Barr RG**, Ferraioli G, Palmeri ML, Goodman ZD, Garcia-Tsao G, Rubin J, Garra B, Myers RP, Wilson SR, Rubens D, Levine D. Elastography Assessment of Liver Fibrosis: Society of Radiologists in Ultrasound Consensus Conference Statement. *Ultrasound Q* 2016; **32**: 94-107 [PMID: 27233069 DOI: 10.1097/RUQ.0000000000000209]

5 **Lebray P**, Varnous S, Charlotte F, Varaut A, Poynard T, Ratziu V. Liver stiffness is an unreliable marker of liver fibrosis in patients with cardiac insufficiency. *Hepatology* 2008; **48**: 2089 [PMID: 19003902 DOI: 10.1002/hep.22594]

6 **Rudski LG**, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, Solomon SD, Louie EK, Schiller NB. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr* 2010; **23**: 685-713; quiz 786-8 [PMID: 20620859 DOI: 10.1016/j.echo.2010.05.010]

7 **Millonig G**, Friedrich S, Adolf S, Fonouni H, Golriz M, Mehrabi A, Stiefel P, Pöschl G, Büchler MW, Seitz HK, Mueller S. Liver stiffness is directly influenced by central venous pressure. *J Hepatol* 2010; **52**: 206-210 [PMID: 20022130 DOI: 10.1016/j.jhep.2009.11.018]

8 **Colli A**, Pozzoni P, Berzuini A, Gerosa A, Canovi C, Molteni EE, Barbarini M, Bonino F, Prati D. Decompensated chronic heart failure: increased liver stiffness measured by means of transient elastography. *Radiology* 2010; **257**: 872-878 [PMID: 20935077 DOI: 10.1148/radiol.10100013]

9 **Taniguchi T**, Sakata Y, Ohtani T, Mizote I, Takeda Y, Asano Y, Masuda M, Minamiguchi H, Kanzaki M, Ichibori Y, Nishi H, Toda K, Sawa Y, Komuro I. Usefulness of transient elastography for noninvasive and reliable estimation of right-sided filling pressure in heart failure. *Am J Cardiol* 2014; **113**: 552-558 [PMID: 24315116 DOI: 10.1016/j.amjcard.2013.10.018]

10 **Taniguchi T**, Ohtani T, Kioka H, Tsukamoto Y, Onishi T, Nakamoto K, Katsimichas T, Sengoku K, Chimura M, Hashimoto H, Yamaguchi O, Sawa Y, Sakata Y. Liver Stiffness Reflecting Right-Sided Filling Pressure Can Predict Adverse Outcomes in Patients With Heart Failure. *JACC Cardiovasc Imaging* 2019; **12**: 955-964 [PMID: 29361489 DOI: 10.1016/j.jcmg.2017.10.022]

11 **Saito Y**, Kato M, Nagashima K, Monno K, Aizawa Y, Okumura Y, Matsumoto N, Moriyama M, Hirayama A. Prognostic Relevance of Liver Stiffness Assessed by Transient Elastography in Patients With Acute Decompensated Heart Failure. *Circ J* 2018; **82**: 1822-1829 [PMID: 29669970 DOI: 10.1253/circj.CJ-17-1344]

12 **Soloveva A**, Kobalava Z, Fudim M, Ambrosy AP, Villevalde S, Bayarsaikhan M, Garmash I, Naumenko M. Relationship of Liver Stiffness With Congestion in Patients Presenting With Acute Decompensated Heart Failure. *J Card Fail* 2019; **25**: 176-187 [PMID: 30721735 DOI: 10.1016/j.cardfail.2019.01.020]

13 **Yoshitani T**, Asakawa N, Sakakibara M, Noguchi K, Tokuda Y, Kamiya K, Iwano H, Yamada S, Kudou Y, Nishida M, Shimizu C, Amano T, Tsutsui H. Value of Virtual Touch Quantification Elastography for Assessing Liver Congestion in Patients With Heart Failure. *Circ J* 2016; **80**: 1187-1195 [PMID: 27026257 DOI: 10.1253/circj.CJ-15-1200]

14 **Demirtas AO**, Koc AS, Sumbul HE, Koca H, Icen YK, Demirtas D, Pekoz BC, Ardıc LM, Koc M, Kucukosmanoglu M. Liver stiffness obtained by ElastPQ ultrasound shear wave elastography independently determines mean right atrial pressure. *Abdom Radiol (NY)* 2019; **44**: 3030-3039 [PMID: 31154483 DOI: 10.1007/s00261-019-02083-3]

15 **Omote K**, Nagai T, Asakawa N, Kamiya K, Tokuda Y, Aikawa T, Fukushima A, Noguchi K, Kato Y, Komoriyama H, Nishida M, Kudo Y, Iwano H, Yokota T, Anzai T. Impact of admission liver stiffness on long-term clinical outcomes in patients with acute decompensated heart failure. *Heart Vessels* 2019; **34**: 984-991 [PMID: 30523443 DOI: 10.1007/s00380-018-1318-y]

16 **de Franchis R**; Baveno VI Faculty. Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension. *J Hepatol* 2015; **63**: 743-752 [PMID: 26047908 DOI: 10.1016/j.jhep.2015.05.022]

17 **Xanthopoulos A**, Starling RC, Kitai T, Triposkiadis F. Heart Failure and Liver Disease: Cardiohepatic Interactions. *JACC Heart Fail* 2019; **7**: 87-97 [PMID: 30553904 DOI: 10.1016/j.jchf.2018.10.007]

18 **Potthoff A**, Schettler A, Attia D, Schlue J, Schmitto JD, Fegbeutel C, Strüber M, Haverich A, Manns MP, Wedemeyer H, Gebel M, Schneider A. Liver stiffness measurements and short-term survival after left ventricular assist device implantation: A pilot study. *J Heart Lung Transplant* 2015; **34**: 1586-1594 [PMID: 26169664 DOI: 10.1016/j.healun.2015.05.022]

19 **Nishi H**, Toda K, Miyagawa S, Yoshikawa Y, Fukushima S, Kawamura M, Saito T, Yoshioka D, Daimon T, Sawa Y. Novel method of evaluating liver stiffness using transient elastography to evaluate perioperative status in severe heart failure. *Circ J* 2015; **79**: 391-397 [PMID: 25492039 DOI: 10.1253/circj.CJ-14-0929]

20 **Jalal Z**, Iriart X, De Lédinghen V, Barnetche T, Hiriart JB, Vergniol J, Foucher J, Thambo JB. Liver stiffness measurements for evaluation of central venous pressure in congenital heart diseases. *Heart* 2015; **101**: 1499-1504 [PMID: 26085526 DOI: 10.1136/heartjnl-2014-307385]

21 **Terashi E**, Kodama Y, Kuraoka A, Ishikawa Y, Nakamura M, Sagawa K, Ishikawa S. Usefulness of Liver Stiffness on Ultrasound Shear-Wave Elastography for the Evaluation of Central Venous Pressure in Children With Heart Diseases. *Circ J* 2019; **83**: 1338-1341 [PMID: 31019158 DOI: 10.1253/circj.CJ-18-1313]

22 **Chen Y**, Seto WK, Ho LM, Fung J, Jim MH, Yip G, Fan K, Zhen Z, Liu JH, Yuen MF, Lau CP, Tse HF, Yiu KH. Relation of Tricuspid Regurgitation to Liver Stiffness Measured by Transient Elastography in Patients With Left-Sided Cardiac Valve Disease. *Am J Cardiol* 2016; **117**: 640-646 [PMID: 26718231 DOI: 10.1016/j.amjcard.2015.11.030]

23 **Chon YE**, Kim SU, Park JY, Kim DY, Ahn SH, Han KH, Chon CY, Lee S. Dynamics of the liver stiffness value using transient elastography during the perioperative period in patients with valvular heart disease. *PLoS One* 2014; **9**: e92795 [PMID: 24670988 DOI: 10.1371/journal.pone.0092795]

24 **Fontan F**, Baudet E. Surgical repair of tricuspid atresia. *Thorax* 1971; **26**: 240-248 [PMID: 5089489 DOI: 10.1136/thx.26.3.240]

25 **Kutty SS**, Peng Q, Danford DA, Fletcher SE, Perry D, Talmon GA, Scott C, Kugler JD, Duncan KF, Quiros-Tejeira RE, Kutty S; Liver Adult-Pediatric-Congenital-Heart-Disease Dysfunction Study (LADS) Group. Increased hepatic stiffness as consequence of high hepatic afterload in the Fontan circulation: a vascular Doppler and elastography study. *Hepatology* 2014; **59**: 251-260 [PMID: 23913702 DOI: 10.1002/hep.26631]

26 **Friedrich-Rust M**, Koch C, Rentzsch A, Sarrazin C, Schwarz P, Herrmann E, Lindinger A, Sarrazin U, Poynard T, Schäfers HJ, Zeuzem S, Abdul-Khaliq H. Noninvasive assessment of liver fibrosis in patients with Fontan circulation using transient elastography and biochemical fibrosis markers. *J Thorac Cardiovasc Surg* 2008; **135**: 560-567 [PMID: 18329470 DOI: 10.1016/j.jtcvs.2007.09.039]

27 **DiPaola FW**, Schumacher KR, Goldberg CS, Friedland-Little J, Parameswaran A, Dillman JR. Effect of Fontan operation on liver stiffness in children with single ventricle physiology. *Eur Radiol* 2017; **27**: 2434-2442 [PMID: 27752831 DOI: 10.1007/s00330-016-4614-x]

28 **Deorsola L**, Aidala E, Cascarano MT, Valori A, Agnoletti G, Pace Napoleone C. Liver stiffness modifications shortly after total cavopulmonary connection. *Interact Cardiovasc Thorac Surg* 2016; **23**: 513-518 [PMID: 27316659 DOI: 10.1093/icvts/ivw186]

29 **Paternostro R**, Reiberger T, Bucsics T. Elastography-based screening for esophageal varices in patients with advanced chronic liver disease. *World J Gastroenterol* 2019; **25**: 308-329 [PMID: 30686900 DOI: 10.3748/wjg.v25.i3.308]

30 **Berzigotti A**. Non-invasive evaluation of portal hypertension using ultrasound elastography. *J Hepatol* 2017; **67**: 399-411 [PMID: 28223101 DOI: 10.1016/j.jhep.2017.02.003]

31 **Fan CQ**, Crawford JM. Sinusoidal obstruction syndrome (hepatic veno-occlusive disease). *J Clin Exp Hepatol* 2014; **4**: 332-346 [PMID: 25755580 DOI: 10.1016/j.jceh.2014.10.002]

32 **Ravaioli F**, Colecchia A, Alemanni LV, Vestito A, Dajti E, Marasco G, Sessa M, Pession A, Bonifazi F, Festi D. Role of imaging techniques in liver veno-occlusive disease diagnosis: recent advances and literature review. *Expert Rev Gastroenterol Hepatol* 2019; **13**: 463-484 [PMID: 30895833 DOI: 10.1080/17474124.2019.1588111]

33 **Fontanilla T**, Hernando CG, Claros JC, Bautista G, Minaya J, Del Carmen Vega M, Piazza A, Méndez S, Rodriguez C, Arangüena RP. Acoustic radiation force impulse elastography and contrast-enhanced sonography of sinusoidal obstructive syndrome (Veno-occlusive Disease): preliminary results. *J Ultrasound Med* 2011; **30**: 1593-1598 [PMID: 22039033]

34 **Park SH**, Lee SS, Sung JY, Na K, Kim HJ, Kim SY, Park BJ, Byun JH. Noninvasive assessment of hepatic sinusoidal obstructive syndrome using acoustic radiation force impulse elastography imaging: A proof-of-concept study in rat models. *Eur Radiol* 2018; **28**: 2096-2106 [PMID: 29218616 DOI: 10.1007/s00330-017-5179-z]

35 **Reddivalla N**, Robinson AL, Reid KJ, Radhi MA, Dalal J, Opfer EK, Chan SS. Using liver elastography to diagnose sinusoidal obstruction syndrome in pediatric patients undergoing hematopoetic stem cell transplant. *Bone Marrow Transplant* 2020; **55**: 523-530 [PMID: 29335626 DOI: 10.1038/s41409-017-0064-6]

36 **Colecchia A**, Ravaioli F, Sessa M, Alemanni VL, Dajti E, Marasco G, Vestito A, Zagari RM, Barbato F, Arpinati M, Cavo M, Festi D, Bonifazi F. Liver Stiffness Measurement Allows Early Diagnosis of Veno-Occlusive Disease/Sinusoidal Obstruction Syndrome in Adult Patients Who Undergo Hematopoietic Stem Cell Transplantation: Results from a Monocentric Prospective Study. *Biol Blood Marrow Transplant* 2019; **25**: 995-1003 [PMID: 30660772 DOI: 10.1016/j.bbmt.2019.01.019]

37 **Mukund A**, Pargewar SS, Desai SN, Rajesh S, Sarin SK. Changes in Liver Congestion in Patients with Budd-Chiari Syndrome following Endovascular Interventions: Assessment with Transient Elastography. *J Vasc Interv Radiol* 2017; **28**: 683-687 [PMID: 28153486 DOI: 10.1016/j.jvir.2016.11.091]

38 **Wang HW**, Shi HN, Cheng J, Xie F, Luo YK, Tang J. Real-time shear wave elastography (SWE) assessment of short- and long-term treatment outcome in Budd-Chiari syndrome: A pilot study. *PLoS One* 2018; **13**: e0197550 [PMID: 29847588 DOI: 10.1371/journal.pone.0197550]

39 **Nakatsuka T**, Soroida Y, Nakagawa H, Okura N, Sato J, Akahane M, Sato M, Yatomi Y, Abe O, Tateishi R, Koike K. Utility of hepatic vein waveform and transient elastography in patients with Budd-Chiari syndrome who require angioplasty: Two case reports. *Medicine (Baltimore)* 2019; **98**: e17877 [PMID: 31702657 DOI: 10.1097/MD.0000000000017877]

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**Table 1 Congestive heart disease: Liver stiffness cutoffs obtained in clinical studies**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Etiology** | **Ref.** | **Endpoint** | **Number of enrolled patients** | **SWE technique** | **Number of invalid measurements** | **Liver stiffness cutoff** | **Notes** |
| HF | Taniguchi *et al*[9] | Detecting RAP > 10 mm Hg | 89 adults | TE | 9 (10.1%) | ≥ 10.6 kPa | 85% sensitivity; 93% specificity |
| HF | Taniguchi *et al*[10] | Risk of death or readmission to hospital | 189 adults | TE | 18 (9.5%) | ≥ 6.9 kPa | HR per 1-kPa increase: 1.13 (1.09-1.17) |
| HF + “controls” | Demirtas *et al*[14] | Detecting RAP > 10 mm Hg | 60 adults with HF undergoing CRT + 60 adults without HF undergoing PM implantation | pSWE | None | > 7 kPa | 89.6% sensitivity; 87.5% specificity |
| Acute HF | Saito *et al*[11] | Risk of death or readmission to hospital | 154 adults (excluded: *n* = 49) | TE | 10 (among excluded patients) | ≥ 8.8 kPa | HR: 2.71 (1.43-5.43) |
| Acute HF | Soloveva *et al*[12] | Risk of one-year all-cause death or readmission to hospital | 172 adults (outcome data: *n* = 145) | TE | 16 (9.3%) | > 13 kPa on admission and > 5 kPa at discharge | HR per 1 kPa increase: 1.03 (1.00-1.06) |
| HF in patients requiring a left ventricular assist device | Nishi *et al*[19] | Incidence of major adverse events | 30 adults | TE | None | > 12.5 kPa | AUC: 0.82 |
| Congenital heart diseases | Jalal *et al*[20] | Detecting CVP > 10 mmHg | 60 children + 36 adults | TE | None | > 8.8 kPa | 92% sensitivity; 96% specificity |

HF: Heart failure; TE: Transient elastography; RAP: Right atrial pressure; HR: Hazard ratio; pSWE: Point shear wave elastography; CRT: Cardiac resynchronization therapy; PM: Pacemaker; AUC: Area under the curve; CVP: Central venous pressure.