MULTIPARAMETRIC ULTRASOUND IN LIVER DISEASES: AN OVERVIEW FOR THE PRACTICING CLINICIAN

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LIST OF ABBREVIATIONS:

2DSWE - two-dimensional shear-wave elastography

ARFI - acoustic radiation force impulse

AUROC - area under the receiver operating characteristic curve

CEUS- contrast enhances ultrasound

CT - computed tomography

FLL - focal liver lesions

HCC - hepatocellular carcinoma

HPVG- hepatic venous pressure gradient

kPa - kilopascal

LEMP - liver elastography malignany prediction score

LR – likelihood ratio

LSM - liver stiffness measurement

MPUS- multiparametric ultrasound

MRI - magnetic resonance imaging

NPV - negative predictive value

PPV- positive predictive value

pSWE- point shear vawe elastography

RTE - real time elastography

SD - standard deviation

SSM- spleen stiffness measurement

TE - transient elastography

US - abdominal ultrasound

ABSTRACT

Ultrasound (US) is usually the first and most commonly used tool in the diagnostic algorithm for liver disease. It is widely available, non-invasive and offers a real-time assessment of the liver in several anatomic planes, using different US modalities such as greyscale imaging, Doppler, elastography and contrast-enhanced ultrasound. This multiparametric ultrasound (MPUS) provides more information of the examined structures and allows for a faster and more accurate diagnosis, usually at the point-of-care, thus reducing the requirement for some invasive and more expensive methods. Current data on the MPUS in hepatology are summarized in this review, mostly focused on its use for non-invasive staging of liver fibrosis, detection and classification of portal hypertension and oesophageal varices, prognosis in chronic liver diseases and characterisation of focal liver lesions (FLL). Based on the available data we propose practical algorithms for clinical use of MPUS in chronic liver disease and FLL.

KEY WORDS: Ultrasonography, Doppler, Elasticity Imaging Techniques, Liver Diseases

LEARNING POINTS:

- Multiparametric liver ultrasound (MPUS) is used to assess aetiology, stage, complications and prognosis of patients with chronic and some acute liver diseases, as well as to characterize focal liver lesions (FLL).
- Greyscale ultrasound provides morphological informations: presence of the signs of cirrhosis, steatosis, portal hypertension (highly specific, but with modest sensitivity) and FLL (good sensitivity, lower specificity).
- Doppler is very useful to assess the aetiology of portal hypertension.
- Elastography allows for non-invasive staging of liver fibrosis, ruling-out high-risk oesophageal varices, prognostication and characterisation of FLL.
- Contrast enhanced ultrasound is highly (≥90%) accurate to differentiate benign from malignant liver tumours.

1. Introduction

Ultrasound (US) is usually among the first and most commonly used diagnostic tools in the diagnostic algorithm for liver disease. It is widely available, non-invasive, harmless, relatively inexpensive and offers a real-time assessment of the liver, on several tomographic planes, using different US imaging modalities because of which, the term multiparametric US has been introduced [1]. Whereas modalities such as greyscale (B-mode) imaging and Doppler are available on all US machines, newer and more sophisticated devices offer the additional option of elastography and contrast-enhanced ultrasound (CEUS). By using various imaging modalities, a multidimensional view of the structure of interest is provided and more information is obtained, which increases the diagnostic reliability and allows for a faster and more accurate diagnosis, usually at the point-of-care **(Figure 1).** This simplifies and shortens the duration of the diagnostic algorithm as other potentially harmful (such as CT and/or liver biopsy) and usually long-waiting procedures (MRI) can be avoided, eventually leading to savings and the greater availability of diagnostic methods for patients who really need them.

2. Greyscale (B-mode) ultrasound of the liver

This is a classical mode of US imaging used to analyse the morphology of the liver and other abdominal organs. This method estimates the shape, size, contours and parenchymal structure, as well as the presence of focal lesion in the liver. Morphological changes to the liver's vascular system (vessel diameter, patency, the presence of solid intraluminal lesions, neoplastic infiltrations/thrombosis) and biliary tree (dilation and/or strictures of the bile ducts) can also be assessed. This allows for an early differentiation of the cause of the liver lesion as due to cholestatic disease (dilatation of the biliary tree), infiltrative disease (focal liver lesions) or parenchymal disease (if none of the above is present) and vascular changes can be seen, such as thrombosis of the portal vein or of the hepatic veins. US is usually the first method used to detect liver tumours but lacks specificity since it is often not easy to characterize a liver tumour on the basis of B-mode imaging alone. The clinical background is important in this respect since the pre-test probability of having a malignant tumour is completely different in patients with underlying cirrhosis or known/suspected malignant disease, as opposed to the incidental finding of a focal liver lesion in an otherwise healthy liver and individual. US has been recommended as the screening tool for hepatocellular carcinoma (HCC) in patients with cirrhosis, with a reported pooled sensitivity of 94% for any stage, but less impressive 63% sensitivity for early stage HCC [2]. In cases of parenchymal disease, further attempts should be directed towards defining the stage of liver disease, which refers mostly to being able to rule-in the morphological features of cirrhosis: coarse and more echogenic parenchyma, rounded edges, nodular external borders and the interface of hepatic veins and hypertrophy of the caudate lobe [3,4]. However, one should be aware that US has a low sensitivity and a high specificity for cirrhosis in patients with a chronic liver disease, meaning that the absence of typical morphological features does not exclude the presence of cirrhosis, whereas their presence is highly specific in this clinical setting [5]. US can be

used to detect a fatty liver when >20% of the hepatocytes have been fatty transformed and the liver then becomes more echogenic (brighter) as compared to the right kidney cortex [6]. Several scoring systems have been used to semi-quantitatively assess the severity of steatosis based on US imaging [7], whereas newer technological solutions enable more precise quantitative assessments of steatosis [8,9].

US examinations of other abdominal organs may provide additional information that is useful to a comprehensive assessment of liver disease. Morphological features of the spleen are of major interest since it is enlarged in most cases of cirrhosis. Ascites resulting from cirrhosis decompensation can also be found (bearing in mind that ascites is not exclusively present in cirrhotic patients, but it may also occur in partients with peritoneal carcinomatosis and otherwise healthy liver). In portal hypertension secondary to cirrhosis portal vein becomes dilated (>12.5–13 mm), as does the splenic vein, coupled with the loss of the respiratory variation in diameter [5]. Hepatic veins become narrower with an irregular interface due to the nodular transformation of the surrounding liver parenchyma. The progressively increased arterial blood supply to the liver is mirrored by the dilated hepatic artery (>3 mm). Colateral porto-systemic pathways may be detected as well such as recanalized paraumbilical vein, dilated left gastric vein or collateral vessels in the splenic hilum (the later sometimes form spleno-renal shunt) [10].

3. Doppler of the hepato-portal system

The haemodynamic assessment of hepatic portal circulation using Doppler US provides valuable information regarding the stage of liver disease as well as the potential cause of portal hypertension (PH). In typical cases of cirrhosis, one can observe a decreased mean velocity in the portal vein (<15 cm/s) [11] with an increase in the resistive index of the hepatic artery (RI>0.7)[12]. At the same time, the spectral analysis of the hepatic veins reveals decrease in blood flow pulsatility, i.e., the dampening of the triphasic Doppler waveform pattern to biphasic and even monophasic. These changes reflect an increase in liver stiffness as a consequence of fibrous tissue accumulation and the architectural remodelling of the liver, which also leads to increased resistance to blood flow through the liver and the formation of arteriovenous and veno-venous intraparenchymal shunts [13]. In advanced stages of cirrhosis, a reversal of the portal flow direction occurs from hepatopetal to hepatofugal. This sign is not frequently observed but is highly specific to severe liver cirrhosis and portal hypertension in the context of chronic liver disease. Again, the presence of these signs is highly specific, but their absence may not be used to reliably rule-out PH [10]. The concept of liver cirrhosis as a procoagulant condition has been well appreciated in recent years as it has become evident that the incidence of portal vein thrombosis increases with the deterioration of the liver function observed with the highest frequency among patients on the waiting list for transplantation. Portal vein thrombosis is readily diagnosed using Doppler US upon demonstration of echogenic material in the portal vein lumen, along with the absence of blood flow. One should be mindful of the Doppler angle since, in cases where US waves are vertical to the longitudinal axis

of the portal vein (which also applies to all other blood vessels), a false absence of blood flow may be observed. A long-standing thrombosis may result in the formation of a cavernoma, which usually engulfs the extrahepatic biliary ducts [14]. Important changes occur in the splenic circulation as the result of splenic congestion and histological remodelling, leading to the increased resistance to the arterial inflow, which is reflected in the increased resistive and pulsatility indices (RI>0.6 and PI>1) of the intraparenchymal branches of the splenic artery [15,16].

4. Liver elastography

This modality has been available for the last 15 years and operates through measuring the liver stiffness [17]. The hallmark of a chronic liver disease is the accumulation of the fibrous tissue that makes the liver stiffer. Therefore, a healthy liver is soft, whereas a cirrhotic liver is stiff. In turn, it is possible to determine the stage of the liver fibrosis by measuring the liver stiffness and, thus, avoiding a liver biopsy [18]. The basic principle of elastography is that a mechanical (compressive) or an enforced acoustic impulse that passes through the liver tissue acts as a wavefront that causes minimal displacement of the tissue. This leads to the formation of shear waves in the liver tissue, which spread faster in a stiff medium (i.e., fibrotic liver). There are several types of US elastography [19] that differ in terms of the technological solutions applied and the final output they provide. The basic classification is that of qualitative or strain elastography and quantitative elastography or elastometry. Qualitative elastography assesses only the relative liver stiffness based on the difference in tissue deformation using mechanical compression and therefore it is difficult to make comparisons between patients. This is the reason why this method has not been widely accepted by the hepatology community for the assessment of fibrosis. All other methods are quantitative and based on the measurement of the velocity of shear waves. These may be further classified based on whether they use mechanical or US probes to transmit exciting impulses into the liver, whether they provide underlying greyscale images of the liver and whether elasticity imaging is also provided **(Table 1)** [19]. The first method introduced into clinical practice, and probably the most popular, is transient elastography (TE), known under the commercial name of Fibroscan. [17]. This is a mono-dimensional method in which a simultaneous US representation of the investigated tissue (liver/spleen) cannot be obtained. Other methods have integrated the elastography module into the conventional abdominal probes. This enables a morphological analysis of the organ in the greyscale with a superimposed measuring box in which the liver stiffness is measured. In point shear wave elastography (pSWE), the measuring box is small in size and there is no visible elastogram. If the measuring box is larger and has a visible elastogram (every point in the elastogram is colour-coded and represents different shear wave speeds), the method is called two-dimensional shear wave elastography (2DSWE).

Table 1. Current methods of quantitative ultrasound elastography based on shear waves.

In order to avoid unreliable results it is recommended to repeat several measurements from the same spot and to calculate median value, standard deviation and interquartile range (IQR). Ten measurements from the same area are recommended for the Fibroscan and pSWE, whereas three to five measurements are recommended for the 2DSWE. Generally, measurements with IQR/median<30% are considered reliable [20]. Elastographic measurements are performed through intercostal spaces over the anterior part of the right liver lobe to avoid transmission of the compression by the US probe, in a neutral position of breathing and while the patient suspends their breathing for three to four seconds. Other conditions besides fibrosis can increase liver stiffness (such as liver congestion in right-sided heart failure, cholestasis, severe liver inflammation with liver infiltrated by inflammatory cells and tissue oedema, infiltration by other cells/compounds such as tumours, amyloidosis, etc.), leading to the overestimation of the fibrosis stage. In overweight patients there is an increase in the distance between the skin surface, i.e., the probe, and the liver. Consequently, the transmission of the exciting impulse and the analysis of the shear waves is more difficult, leading to an unreliable or even a failed liver stiffness measurement (LSM). This limitation has led to the development of a special probe for the Fibroscan that has a deeper penetration (XL probe) and enables more reliable LSM in overweight patients (especially with regard to the skin to liver capsule distance (SCD)≥25 mm).

Elastographic method	**Abbrevia-tion**	**Comercial name (Manufacturer)**	**Source of shear waves**	**Presence of Ultrasound image of the liver**	**Colour–coded elastogram displayed in real-time**
Transient Elastography	TE	VCTE (Echosens)	Mechanical vibrator	No	No
Point Shear Wave Elastography	pSWE	ElastPQ (Philips) QElaXto (Esaote) S-shearwave (Samsung) STQ (Mindray) SWM (Hitachi) VTQ (Siemens)	Enforced acoustic power (ARFI)	Yes	No
Two Dimensional Shear Wave Elastography	2DSWE	2D-SWE.GE (General Electric) ElastQ (Philips) SSI (Supersonic Imagine) STE (Mindray) ToSWE (Toshiba/Cannon)	Enforced acoustic power (ARFI)	Yes	Yes

Elastography is used in the following situations in hepatology:

1. Staging of liver fibrosis
2. Establishing the diagnosis of clinically significant portal hypertension (CSPH) and high-risk oesophageal varices (HRV)
3. Characterization of liver tumours
4. Prognosis of the clinical outcomes for chronic liver disease.

4.1. Staging of liver fibrosis

Most data have been accumulated using TE and several meta-analyses results of the cut-off values and the diagnostic performance of the method used to differentiate between the stages of liver fibrosis. Accordingly, the area that is below the receiver operating curves (AUROC) for significant fibrosis (F≥2 according to the METAVIR classification) is 0.84–0.86. For cirrhosis (F=4), the AUROC was reported to be in the range of 0.93–0.96. From this, one can conclude that TE is more reliable for diagnosing cirrhosis (the correct classification in 80–98% of the cases) than it is for significant fibrosis [21]. The chances of the correct staging of liver fibrosis using the over-the-threshold measurement of liver stiffness (7.3kPa for F≥2 and 15kPa for F=4) are 92% and 72%, respectively. This means that this method is very reliable when used to rule in significant fibrosis but is not reliable for cirrhosis [18]. In other words, almost 30% of cases diagnosed as cirrhosis are actually false positive. On the other hand, the method is very reliable for ruling-out cirrhosis, with a very low number of false negative results (6%) following stiffness measurements with values below the established threshold. In contrast, TE is not reliable for ruling out significant fibrosis, with a very high number of false negative results (up to 45%). The cut-off values for certain stages of liver fibrosis differ depending on the aetiology and are not the same in viral hepatitis, non-alcoholic fatty liver disease, cholestatic liver diseases, etc. All these observations of the diagnostic performance of elastography for fibrosis-staging hold true for other elastography methods, i.e., pSWE and 2DSWE. In terms of diagnostic accuracy of 2DSWE (by Supersonic Shear Imaging) recent meta-analysis of individual data revealed the following LSM cut-off values (AUROCs in parentheses): 7.1 kPa (0.86), 9.2 kPa (0.91) and 13 kPa (0.93) for significant, advanced fibrosis and cirrhosis respectively, with an exemption for the patients with chronic hepatitis B in whom corresponding values of LSM (AUROC) were somewhat lower 7.1 kPa (0.91), 8.1 kPa (0.93) and 11.5 kPa (0.96) [22]. Reported optimal cut-off values (AUROCs) of LSM by pSWE as represented with ElastPQ were respectively 7.04 kPa (0.88) , 8.83 kPa (0.91) , and 9.11 kPa (0.91) [23].

4. 2. Establishing the diagnosis of clinically relevant portal hypertension and high-risk oesophageal varices

Portal hypertension (PH) is an important complication of chronic liver disease and determines the clinical outcome of the disease [24]. Measuring the hepatic venous pressure gradient (HPVG) is an invasive method that is performed in a small number of hepatology centres. This is the reason why non-invasive methods for establishing the severity of PH are being researched. Complications of PH (oesophageal varices

(EV), ascites, encephalopathy) occur when the HVPG >10mmHg and this is considered to be a clinically significant portal hypertension (CSPV). Values of the HVPG from 6–10mmHg are considered subclinical PH [25]. A diagnosis of CSPH is usually established following endoscopically proven EV, or splenomegaly or portosystemic collateralization, as revealed by an abdominal US. Around 30% of patients with CSPH do not develop EV or other signs of CSPH, yet these are not excluded from the adverse clinical outcomes and, therefore, it is important to diagnose and manage PH in good time. Elastography can help in assessing the severity of PH. Studies have shown that a combined LSM and platelet count can reliably differentiate between patients with CSPH and high-risk oesophageal varices (HRV). Most data on this issue have been accumulated from studies on viral hepatitis, especially chronic hepatitis C. According to the Baveno VI consensus, CSPH may be assumed in patients with an LSM >20–25 kPa, whereas the combination of an LSM <20 kPa and a platelet count >150 000 may be used to safely rule out HRV [26]. By using these criteria, the risk of missing HRV is around 2% and 21% of endoscopies can be avoided, as revealed by the studies that followed [27]. The Baveno criteria were later extended to propose LSM<25kPa + platelet counts > $110x10^9$/L, according to which, only 1.6% of cases with HRV are not recognized and 40% of gastroscopies have been avoided [28]. The spleen stiffness measurement (SSM) has recently been demonstrated as an independent predictor of HRV, with a cut-off value of ≤46 kPa that reliably excludes HRV. Combined with the Baveno VI criteria, an SSM algorithm was able to avoid endoscopy in 43.8% of patients with <5% risk of missing HRV [29]. Nevertheless, due to inconsistent results with the SSM reported in previous studies, these encouraging data should be further validated before any firm recommendations may be given [30].

4.3. Characterization of liver tumours

Different types of liver tumours differ in their stiffness as the result of different histological structure. Most of the data accumulated to date have demonstrated that malignant tumours are stiffer than benign tumours. However, it should be noticed that various elastography methods have been used and the results were usually expressed as the mean stiffness of the whole tumour or its parts [31-33]. With the introduction of 2DSWE, a more complex analysis of the tumour's elastographic features has become possible, including the analysis of the ratio between the stiffness of the tumour and the surrounding liver parenchyma as well as the stiffness variability within the tumour. This is important since it appreciates the clinical background at which certain tumours arise. For instance, hepatocellular carcinoma (HCC) commonly develops in cirrhotic livers and both the tumour and the non-infiltrated liver may be assessed by elastography during the same examination [34]. By using this approach liver elastography malignancy prediction (LEMP) score has recently been proposed and it was able to differentiate between benign and malignant tumours in 96.1% of cases [35]. This algorithm overcomes the limitations of elastography when only mean tumour stiffness is used. For example, HCC and focal nodular hyperplasia (FNH) have comparable mean stiffness, yet, in most cases, the surrounding liver parenchyma in HCC patients

is stiff (cirrhotic), whereas in FNH patients it is soft (healthy). In addition, the heterogeneity of tumour stiffness is appreciated and is also incorporated into the LEMP formula. A more simplified approach uses only dichotomized values of mean tumour stiffness (14 and 32.5 kPa) with a 96% negative and positive predictive value for malignancy, which is applicable in 55.6% of the patients, whereas 44.4% remain in the "grey zone" between these cut-off points [35]. Although innovative, this elastographic approach to FLL is time consuming, and should be validated in independent cohort.

4.4. Prognosis of the clinical outcome for chronic liver disease

It has been demonstrated that higher liver stiffness is accompanied by a worse prognosis [36]. Patients with LSM<9.5–10 kPa have a 4–5% chance of adverse clinical outcomes in the next three to five years [37,38]. For every 1 kPa above these values, the chance of an adverse outcome increases by 5% and patients with LSM >20 kPa have significantly diminished survival figures (positive predictive value 20%, negative predictive value 97%!). The prognostic predictive value of liver stiffness has also been confirmed with methods other than TE. In patients with compensated cirrhosis baseline LSM≥21.5 kPa by 2DSWE-SSI was associated with 3.4-fold (*P*=0.026) higher risk of liver-related events [39]. Longitudinal studies with repeated LSM have demonstrated worse clinical outcomes in patients with an increase in LSM by TE (>1kPa/year for patients with hepatitis C or >1.5 kPa for patients with primary sclerosing cholangitis) [40,41].

5. Assessment of liver steatosis

Different liver diseases are accompanied by the accumulation of fat in the liver but this is the most prominent histological feature of alcoholic and non-alcoholic fatty liver disease (NAFLD). NAFLD is becoming the leading cause of chronic liver disease with estimates of around 25% of the European population affected by this condition [42]. This disease is defined by the presence of more than 5% of fatty transformed hepatocytes [43]. Clinical impact of the severity (amount) of liver steatosis has been controvesial issue [44]. [45]. Whereas higher grades of steatosis, as assessed non-invasively by controlled attenuation parameter (CAP>220 dB/m), independently predicted worse clinical outcomes in patients with compensated advanced chronic liver disease (cACLD) of mixed aetiology in one study, the other study failed to demonstrate this association [46,47] Nevertheless, significant increase in the risk of cardiovascular events was reported in patients with higher grades of liver steatosis [48]. Therefore, knowledge of the severity of the liver steatosis appears to be clinically relevant. Grey scale US has insufficient sensibility to detect initial grades of liver steatosis but CAP can accomplish this during an elastographic assessment by Fibroscan device. CAP measures ultrasound attenuation at the central frequency simultaneously with the LSM and within the same region of interest [49]. According to the meta-analysis [8], the reported cut-off values of CAP (dB/m with the respective AUROCs) were 238 (0.82) for mild steatosis (S1, 5–33% fatty transformed hepatocytes), 259 (0.88) for moderate

steatosis (S2, 33–66% fatty transformed hepatocytes) and 290 (0.94) for severe steatosis (S3, >66%). With regard to the reliability criteria, the CAP IQR should be<40 dB/m. In patients with a higher body mass index (especially BMI>30 kg/m^2) and higher fibrosis stages (F3–4), CAP tends to overestimate the grade of the steatosis [50] and, vice versa, the fibrosis stage tends to be overestimated (high risk of false positive F2–4) at higher CAP values (>300 dB/m) [51]. Recently, a new method of acoustic structure quantification (ASQ) has been demonstrated to reliably quantify liver steatosis [9], but requires independent validation. This method is attractive since it has been incorporated into classical US machine and, therefore, avoids the need for a dedicated device.

6. Contrast-enhanced ultrasound

This method is based on the intravenous application of sulphur hexafluoride diluted in a saline solution that creates microbubbles smaller than red blood cells, which allows them to pass through the smallest blood vessels [52,53]. The phospholipid layer of the hexafluoride reflects US waves that are, in turn, captured by the US transducer to create an image of the investigated structure. This examination has to be performed using a low mechanical index of the US waves; otherwise, the microbubbles would be destroyed. The contrast is eliminated in 15 minutes through breathing, making it applicable even in patients with kidney dysfunction who cannot use the iodine contrast agents used for CT imaging. The application of sulphur hexafluoride is contraindicated in patients with unstable cardiopulmonary conditions, and not recommended during pregnancy or breastfeeding [54,55].

Contrast-enhanced ultrasound (CEUS) is used for the characterization of focal liver lesions (FLL), especially liver tumours. The basic principle for this indication relies on the dual blood supply to the liver (around 70% of the blood volume provided by the portal vein and 30% by the hepatic artery). Following intravenous contrast injection, microbubbles enter the liver through the hepatic artery and then gradually through the portal vein. This temporal dynamics of contrast enhancement may be divided into three phases: the arterial phase (15–30 seconds after the contrast injection), the portal venous phase (30–120 seconds after the contrast injection) and the late phase that begins >120 seconds after the contrast injection [52]. By analysing the dynamics of the contrast flow and the time it takes for the contrast to leave the focal lesion, one can differentiate between benign and malignant FLL and even predict the histological type of tumour. The contrast is retained throughout the late phase in benign FLL, whereas it disappears (it is “washed-out”) from the malignant lesions during the venous or late phase. The pattern of the contrast’s entrance and distribution during the arterial phase helps to predict the histological subtype of the lesion within the benign/malignant categories. For example, haemangioma have a characteristic peripheral nodular enhancement in the arterial phase with progressive centripetal filling, whereas in focal nodular, hyperplasia enhancement starts in the central part of the lesion with centrifugal progression. Both of these lesions retain the contrast and do not demonstrate the washout phenomenon. Hepatocellular carcinoma is rapidly and

completely enhanced in the arterial phase, which is followed by a more delayed washout, typically occurring in the late phase, whereas most metastatic tumours reveal rapid washout early in the portal venous phase. CEUS is highly accurate in differentiating malignant from benign lesions with sensitivity that exceeds 90% and specificity in the range of 83–90% [54-57]. Additionally, the presence of hyperenhancement in arterial phase followed by washout phenomenon has been used as reliable criterion to differentiate benign (blunt thrombosis) from malignant (infiltrative) portal vein thrombosis [58]. When CEUS was used to follow up patients resected for colorectal cancer, 151% more metastases were detected in 69% more patients as compared to the conventional B-mode US [59].

CEUS has even been used to assess the severity of PH and this was based on the transit time of the US contrast through the liver. The best diagnostic performance for diagnosing severe PH (HVPG≥12 mmHg) was obtained using the intrahepatic transit time (ITT, cut-off value 6 sec, sensitivity 92%, specificity 89%, AUROC 0.94), which is the difference between the hepatic vein arrival time (HVAT) and hepatic artery arrival time (HAAT) [60]. Another approach relies on automated graph analysis of dynamic CEUS reflecting the degree of organization of the hepatic microvascular network that was reported in a pilot study to correlate to the severity of PH in cirrhosis [61].

7. Conclusion

Ultrasound is a sophisticated point-of-care method that allows for very precise assessments of patients with liver disease using different modalities of US examinations, provided state-of-the-art equipment, qualified operators and patient's body habitus that are adequate for the good visualization of the investigated structures. Under these conditions, US may be reliably used to assess the stage, complications and prognosis of patients with chronic and some acute liver diseases, as well as to characterize FLL. A simplified practical algorithms on the clinical use of MPUS in diffuse chronic liver diseases and FLL are proposed in **Figures 2 and 3**. Proper clinical use of US can shorten the duration of the diagnostic algorithm in liver diseases, as well as reduce the requirement for other, usually invasive and more expensive methods.

References

1. Sidhu P. Multiparametric Ultrasound (MPUS) Imaging: Terminology Describing the Many Aspects of Ultrasonography. Ultraschall in der Medizin 2015; 36(4):315-317.

2. Singal A, Volk ML, Waljee A et al. Metaanalysis: surveillance with ultrasound for early-stage hepatocellular carcinoma in patients with cirrhosis. Aliment Pharmacol Ther 2009;30:37–47

3. Vessal S, Naidoo S, Hodson J et al. Hepatic Vein Morphology- A New Sonographic Diagnostic Parameter in the Investigation of Cirrhosis? *J Ultrasound Med 2009*; *28:1219–1227.*

4. Alempijevic T, Bulat V, Djuranovic S et al. Right liver lobe/albumin ratio: contribution to non-invasive assessment of portal hypertension. World J Gastroenterol. 2007 Oct 28;13(40):5331-5

5. **Allan R, Thoirs K, Phillips M. Accuracy of ultrasound to identify chronic liver disease. World J Gastroenterol. 2010 Jul 28;16(28):3510-20.**

6. Hernaez R, Lazo M, Bonekamp S, et al.. Diagnostic accuracy and reliability of ultrasonography for the detection of fatty liver: a meta-analysis. Hepatology. 2011 Sep 2;54(3):1082-1090.

7. Van Werven JR, Marsman HA, Nederveen AJ, et al. Assessment of hepatic steatosis in patients undergoing liver resection: comparison of US, CT, T1-weighted dual-echo MR imaging, and point-resolved 1H MR spectroscopy. Radiology 2010; 256: 159-68.

8. Wang Y, Fan Q, Wang T, et al. Controlled attenuation parameter for assessment of hepatic steatosis grades: a diagnostic meta-analysis. Int J Clin Exp Med 2015; 8: 17654-63.

9. Son JY, Lee LY , Yi NJ, et al. Hepatic Steatosis: Assessment with Acoustic Structure Quantification of US Imaging. Radiology 2016; 278:257–264 Toshiba

10. **Berzigotti A, Piscaglia F. Ultrasound in portal hypertension--part 1. Ultraschall Med. 2011; 32(6):548-68.**

11. Zironi G, Gaiani S, Fenyves D et al. Value of measurement of mean portal flow velocity by Doppler flowmetry in the diagnosis of portal hypertension. J Hepatol 1992; 16: 298–303

12. Piscaglia F, Donati G, Serra C et al. Value of splanchnic Doppler ultrasound in the diagnosis of portal hypertension. Ultrasound Med Biol 2001; 27: 893–899

13. Grgurevic I, Boozari B, Kujundzic M, Brkljacic B. Color Doppler ultrasound of the liver circulation. Lijec Vjesn. 2009 Jul-Aug;131(7-8):211-7.

14. Grgurevic I, Kujundzic M, Banic M, et al. Subtypes and clinical significance of common bile duct varices in portal vein thrombosis: diagnosis and follow-up by Doppler US and EUS. Abdom Radiol (NY). 2016 Mar;41(3):476-84.

15. Bolognesi M, Sacerdoti D, Merkel C, et al. Splenic Doppler impedance indices: Influence of different portal hemodynamic conditions. Hepatology 1996; 23(5): 1035-1040

16. Piscaglia F, Donati G, Serra C, et al. Value of splanchnic Doppler ultrasound in the diagnosis of portal hypertension. Ultrasound Med Biol. 2001 Jul;27(7):893-9.

17. Sandrin L, Fourquet B, Hasquenoph J-M, et al. Transient elastography: a new noninvasive method for assessment of hepatic fibrosis. Ultrasound Med Biol 2003 ;29(12):1705–13.

18. Tsochatzis E, Gurusamy K, Ntaoula S, et al. Elastography for the diagnosis of severity of fibrosis in chronic liver disease: a meta-analysis of diagnostic accuracy. J Hepatol 2011; 54(4):650–9.

19. Bamber J, Cosgrove D, Dietrich CF, et al. EFSUMB guidelines and recommendations on the clinical use of ultrasound elastography. Part 1: Basic principles and technology. Ultraschall Med 2013;34(2):169–84.

20. **Dietrich CF, Bamber J, Berzigotti A, et al. EFSUMB guidelines and recommendations on the clinical use of liver ultrasound elastography, update 2017 (long version). Ultraschall in der Medizin-European Journal of Ultrasound. 2017; 38 (4):e16-e47.**

21. Friedrich-Rust M, Poynard T, Castera L. Critical comparison of elastography methods to assess chronic liver disease. Nature Reviews Gastroenterology & Hepatology 2016; 13: 402–411.

22. Herrmann E, de Lédinghen V, Cassinotto C, et al. Assessment of biopsy-proven liver fibrosis by two-dimensional shear wave elastography: An individual patient data-based meta-analysis. Hepatology. 2018 Jan;67(1):260-272. doi: 10.1002/hep.29179. Epub 2017 Nov 15.

23. Ferraioli G, De Silvestri A, Reiberger T, et al. Adherence to quality criteria improves concordance between transient elastography and ElastPQ for liver stiffness assessment — a multicenter retrospective study. Digestive and Liver Disease 2018: https://doi.org/10.1016/j.dld.2018.03.033

24. Ripoll C, Groszmann R, Garcia-Tsao G, et al. Hepatic venous pressure gradient predicts clinical decompensation in patients with compensated cirrhosis. Gastroenterology 2007; 133 (2): 481–8.

25. Bosch J, Abraldes JG, Berzigotti A, García-Pagan JC. The clinical use of HVPG measurements in chronic liver disease. Nat. Rev. Gastroenterol. Hepatol 2009; 6 (1): 573–82.

26. De Franchis R. EXPANDING CONSENSUS IN PORTAL HYPERTENSION Report of the Baveno VI Consensus Workshop: stratifying risk and individualizing

care for portal hypertension. J. Hepatol 2015; 63 (3): 743–52.

27. Maurice JB, Brodkin E, Arnold F, et al. Validation of the Baveno VI criteria to identify low risk cirrhotic patients not requiring endoscopic surveillance for varices. J. Hepatol. 2016 ;65(5):899-905.

28. Augustin S. Augustin S, Pons M, et al. Expanding the Baveno VI criteria for the screening of varices in patients with compensated advanced chronic liver disease. Hepatology 2017;66(6):1980-1988.

29. Colecchia A, Ravaioli F, Marasco G, et al. A combined model based on spleen stiffness measurement and Baveno VI criteria to rule out high-risk varices in advanced chronic liver disease. Journal of Hepatology 2018; 69(2): 308 - 317

30. Singh S, Eaton JE, Murad MH, et al. Accuracy of Spleen Stiffness Measurement in Detection of Esophageal Varices in Patients With Chronic Liver Disease: Systematic Review and Meta-analysis. Clinical Gastroenterology and Hepatology 2014; 12:935–945.

31. Masuzaki R, Tateishi R, Yoshida H, et al. Assessing liver tumor stiffness by transient elastography. Hepatol Int. 2007;1:394–7.

32. Ying L, Lin X, Xie Z-L, et al. Clinical utility of acoustic radiation force impulse imaging for identification of malignant liver lesions: a meta-analysis. Eur Radiol. 2012; 22: 2798–805.

33. Wang J, Ai H, Guo L, et al. Application of Real-Time Tissue Elastography with a Low Frequency Convex Array Probe: A Noninvasive Approach to Differential Diagnosis of Liver Tumors. ISRN Hepatol. 2014; Article ID 378243. doi: 10.1155/2014/378243.

34. Singal AG, El-Serag HB. Hepatocellular carcinoma from epidemiology to prevention: translating knowledge into practice. Clin Gastroenterol Hepatol. 2015 Nov;13(12):2140-51.

35. **Grgurevic I, Bokun T, Salkic NN, et al. Liver elastography malignancy prediction score for noninvasive characterization of focal liver lesions. Liver Int. 2018; 38(6): 1055-63.**

36. Singh S, Fujii LL, Murad MH, et al. Liver stiffness is associated with risk of decompensation, liver cancer, and death in patients with chronic liver diseases: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 2013; (12):1573-84

37. Vergniol J, Foucher J, Terrebonne E, et al. Noninvasive tests for fibrosis and liver stiffness predict 5-year outcomes of patients with chronic hepatitis C. Gastroenterology 2011;140(7):1970–9.

38. Pang JXQ, Zimmer S, Niu S, et al. Liver Stiffness by Transient Elastography Predicts Liver-Related Complications and Mortality in Patients with Chronic Liver Disease. PLoS ONE 2014; 9(4): e95776. oi:10.1371/journal.pone.0095776

39. Grgurević I, Bokun T, Mustapić S, et al. Real-time two-dimensional shear wave ultrasound elastography of the liver is a reliable predictor of clinical outcomes and the presence of esophageal varices in patients with compensated liver cirrhosis. Croat Med J 2015; 56(5):470–81.

40. Pons M, Simón-Talero M, Millán L, et al. Basal values and changes of liver stiffness predict the risk of disease progression in compensated advanced chronic liver disease. Dig Liver Dis 2016; 48(10):1214–9.

41. Corpechot C, Gaouar F, El Naggar A, et al. Baseline values and changes in liver stiffness measured by transient elastography are associated with severity of fibrosis and outcomes of patients with primary sclerosing cholangitis. Gastroenterology 2014;146(4):970-9

42. Bellentani S. The epidemiology of non-alcoholic fatty liver disease. Liver Internationl 2017, 37: 81-84. doi:10.1111/liv.13299

43. Buzzetti E, Pinzani M, Tsochatzis EA. The multiple-hit pathogenesis of non-alcoholic fatty liver disease (NAFLD). Metabolism - Clinical and Experimental , Volume 65 , Issue 8 , 1038 - 1048

44. Angulo P, Kleiner DE, Dam-Larsen S, et al. Liver Fibrosis, but No Other Histologic Features, Is Associated With Long-term Outcomes of Patients With Nonalcoholic Fatty Liver Disease. Gastroenterology , Volume 149 , Issue 2 , 389 – 397. doi: 10.1053/j.gastro.2015.04.043. Epub 2015 Apr 29.

45. Everhart JE, Lok AS, Kim HY, et al. HALT-C Trial Group. Weight-related effects on disease progression in the hepatitis C antiviral long-term treatment against cirrhosis trial. Gastroenterology 2009;137:549-557.

46. Margini C, Murgia G, Stirnimann G, et al. Prognostic Significance of Controlled Attenuation Parameter in Patients With Compensated Advanced Chronic Liver Disease. Hepatology Communications 2018, 2: 929-940. doi:10.1002/hep4.1201

47. Scheiner B, Steininger L, Semmler G, et al. Controlled attenuation parameter (CAP) does not predict hepatic decompensation in patients with advanced chronic liver disease. Liver Int. 2018 Aug 14. doi: 10.1111/liv.13943. [Epub ahead of print]

48. Pisto P, Santaniemi M, Bloigu R, et al. Fatty liver predicts the risk for cardiovascular events in middle-aged population: a population-based cohort study. BMJ Open 2014; 4:e004973.

49. Sasso M, Beaugrand M, de Ledinghen V, et al. Controlled attenuation parameter (CAP): a novel VCTE guided ultrasonic attenuation measurement for the evaluation of hepatic steatosis: preliminary study and validation in a cohort of patients with chronic liver disease from various causes. Ultrasound Med Biol 2010;36(11):1825—35.

50. Wong VWS, Petta S, Hiriart JB, et al. Validity criteria for the diagnosis of fatty liver by M probe-based controlled attenuation parameter. Journal of Hepatology 2017, Volume 67 , Issue 3 , 577 - 584

51. Petta S, Wong VW, Cammà C, et al. Improved noninvasive prediction of liver fibrosis by liver stiffness measurement in patients with nonalcoholic fatty liver disease accounting for controlled attenuation parameter values. Hepatology 2017 , 65: 1145-1155. doi:10.1002/hep.28843

52. **Claudon M, Dietrich CF, Choi BI, et al. Guidelines and Good Clinical Practice Recommendations for Contrast Enhanced Ultrasound (CEUS) in the Liver – Update 2012. Ultrasound Med Biol 2013;39(2):187–210.**

53. European Medicines Agency. SonoVue. Available from: http://www.ema.europa.eu/docs/hr_H

54. Strobel D, Seitz K, Blank W, et al. Contrast-enhanced Ultrasound for the Characterization of Focal Liver Lesions – Diagnostic Accuracy in Clinical Practice (DEGUM multicenter trial). Ultraschall der Medizin - Eur J Ultrasound 2008;29(5):499–505.

55. Friedrich-Rust M, Klopffleisch T, Nierhoff J, et al. Contrast-Enhanced Ultrasound for the differentiation of benign and malignant focal liver lesions: a meta-analysis. Liver Int 2013;33(5):739–55.

56. Grgurevic I, Bokun T, Huzjan R, et al. Characterization of liver tumors by contrast enhanced ultrasound: single centre experience. Liječ vjesn 2018; 140: 150-155.

57. Sporea I, Martie A, Bota S, et al. Characterization of focal liver lesions using contrast enhanced ultrasound as a first line method: a large monocentric experience. J Gastrointestin Liver Dis 2014;23(1):57–63

58. Danila M, Sporea I, Popescu A et al. Portal vein thrombosis in liver cirrhosis - the added value of contrast enhanced ultrasonography. Med Ultrason. 2016

Jun;18(2):218-33. doi: 10.11152/mu.2013.2066.182.pvt.

59. Bernatik T, Schuler A, Kunze G, et al. Benefit of Contrast-Enhanced Ultrasound (CEUS) in the Follow-Up Care of Patients with Colon Cancer: A Prospective Multicenter Study. Ultraschall in Med 2015; 36(06): 590-593. DOI: 10.1055/s-0041-107833

60. Jeong WK, Kim TY, Sohn JH, et al. Severe Portal Hypertension in Cirrhosis: Evaluation of Perfusion Parameters with ContrastEnhanced Ultrasonography. PLoS ONE 2015; 10(3): e0121601. doi:10.1371/journal.pone.0121601

61. Amat-Roldan I, Berzigotti A, Gilabert R, Bosch J. Assessment of Hepatic Vascular Network Connectivity with Automated Graph Analysis of Dynamic Contrast-enhanced US to Evaluate Portal Hypertension in Patients with Cirrhosis: A Pilot Study. Radiology. 2015;277:268–76.

TABLES AND FIGURES

Figure 1. Multiparametric ultrasound of a patients with compensated liver cirrhosis following successfull treatment of chronic hepatitis C, now under scheduled 6-month ultrasound (US) surveillance for hepatocellular carcinoma (HCC). **A**-typical morphological features of cirrhosis on greyscale US with coarse parenchyma and

irregular interface of hepatic veins; **B**-Small hypoechoc focal lesion (2.45 cm) on the surface of segment IV; **C**-Blood vessel in the centre of the lesion was detected by power Doppler. Spectral analysis of the signal from the vessel revealed arterial flow; **D**-Portal vein was patent with normal hepatopedal direction of the blood flow, with decreased velocity (time averaged mean velocity, TAMV 9.9 cm/s); **E**-High liver stiffness (24 kPa) and **F**-high spleen stiffness (52 kPa) were measured by 2DSWE-SSI (in keeping with cirrhosis and clinically significant portal hypertension (CSPH); LSM by TE in the same patient was 23.1 kPa, Platelet count was $130x10^9$/L and he had large oesophageal varices on endoscopy); **G**-Contrast enhanced ultrasound revealed hyperenhancement of the focal lesion in the arterial phase; **H**-incomplete wash-out of the contrast from the lesion in the portal-venous phase, and **I**-hypoenhancement (wash-out phenomenon) in the delayed phase, typical for HCC. All these US modalities were performed during the same visit, at the same US machine (Supersonic Aixplorer). Final conclusion based on MPUS examination was that patient had small HCC on the background of compensated liver cirrhosis with CSPH.

Figure 2. Proposed simplified practical algorithm on the clinical use of multiparametric ultrasound in diffuse chronic liver disease.

Figure 3. Proposed simplified practical algorithm on the clinical use of multiparametric ultrasound in focal liver lesions.

Table 1. Current methods of quantitative ultrasound elastography based on shear waves. ARFI=Acoustic Radiation Force Impulse, ElastPQ= Elastography Point Quantification; ElastQ=Elastography Quantification; SSI=Supersonic Shear Imaging; STE= Sound Touch Quantification; STQ= Sound Touch Elastography; SWM=Shear Wave Measurement; VTQ= Virtual Touch Quantification; VCTE= Vibration controlled transient elastography.

KEY REFERENCES:

1. Allan R, Thoirs K, Phillips M. Accuracy of ultrasound to identify chronic liver disease. World J Gastroenterol. 2010 Jul 28;16(28):3510-20.

2. Berzigotti A, Piscaglia F. Ultrasound in portal hypertension--part 1. Ultraschall Med. 2011; 32(6):548-68.

3. Dietrich CF, Bamber J, Berzigotti A, et al. EFSUMB guidelines and recommendations on the clinical use of liver ultrasound elastography, update 2017 (long version). Ultraschall in der Medizin-European Journal of Ultrasound. 2017; 38 (4):e16-e47.

4. Grgurevic I, Bokun T, Salkic NN, et al. Liver elastography malignancy prediction score for noninvasive characterization of focal liver lesions. Liver Int. 2018; 38(6): 1055-63.

5. Claudon M, Dietrich CF, Choi BI, et al. Guidelines and Good Clinical Practice Recommendations for Contrast Enhanced Ultrasound (CEUS) in the Liver – Update 2012. Ultrasound Med Biol 2013;39(2):187–210.

QUESTIONS AND ANSWERS (T=true; F=false)

1. Single most accurate morphological sign of cirrhosis by greyscale ultrasound is:

a) Hypertrophy of caudate lobe (F)
b) Presence of ascites (F)
c) Splenomegaly (F)
d) Nodular liver surface/nodular interface of hepatic veins (T)
e) Hyperechoic liver parenchyma (F)

2. In patients with chronic liver diseases Doppler is best used to:

a) Noninvasively assess the stage of liver fibrosis (F)
b) Quantify the severity of portal hypertension (F)
c) Assess the aetiology of portal hypertension (T)
d) Assess the haemodynamic response of portal hypertension to drugs (F)
e) Rule in the presence of high risk esophageal varices (F)

3. Elastography for noninvasive staging of liver fibrosis:

a) Is best used to rule-out the presence of cirrhosis (T)
b) Is best used to rule-out the presence of significant fibrosis (≥2) (F)
c) Is best used to rule-in the presence of cirrhosis (F)

d) The results of liver stiffness measurements are interchangable when obtained by differents elastography methods (F)
e) The results of liver stiffness measurements are not influenced by the histological severity of the necroinflammation within the liver (F)

4. Which of the following criteria used to rule-out the presence of high-risk esophageal varices by transient elastography may spare the highest number of unneccessary upper gastrointestinal endoscopies:

a) Liver stiffness<20 kPa (and Platelets' count>150x10^9/L) (F)
b) Spleen stiffness<46 kPa (F)
c) a+b (T)
d) Liver stiffness<28 kPa (F)
e) Liver stiffness<27kPa and Spleen stiffness<38 kPa (F)

5. Which of the following statements is not true for contrast-enhanced ultrasound of the liver:

a) It has excellent diagnostic performance to differentiate between benign and malignant focal liver lesions (T)
b) Presence of wash-out phenomenon in the portal-venous or late phase is the hallmark of malignancy of focal liver lesions (T)
c) It may be used to differentiate benign from malignant portal vein thrombosis (T)
d) It is not recommended during pregnancy or breastfeeding (T)
e) Should not be used in patients with chronic renal failure (F)

RESEARCH QUESTIONS

- Clinical relevance of quantification of liver steatosis by ultrasound methods
- Diagnostic performance of ultrasound elastography methods other than transient elastography for grading portal hypertension and prognostication
- Use of elastography to assess the haemodynamic response to medicamentous treatment of portal hypertension.
- Use of contrast enhanced ultrasound to noninvasively quantify the severity of portal hypertension and its response to medicamentous treatment

CONTRIBUTORSHIP STATEMENT

Ivica Grgurevic: conception of the manuscript, acquisition, analysis and interpretation of data, drafting the manuscript, final approval of the version to be published, responsible for the overall content as guarantor.

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