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# Capacity of shear wave telephotography in the diagnosis of diffuse liver disease

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#### **Abstract**

Liver fibrosis is a process that is developed by a result of chronic liver disease progression, and if this process is not stopped, cirrhosis or hepatocellular carcinoma (HCC) develops. Fibrous and cirrhotic changes in the liver cause damage to the structure of the liver, disruption of function, and complications that endanger human life and lead to a fairly high percentage of lethality. This is why the diagnosis of diffuse liver disease at an early stage is a fundamental issue in modern radiology. Modern imaging techniques which are newly introduced in practice, ultrasound telephotography is used to diagnose liver fibrosis. Based on this method it is possible to detect the altered elasticity of liver tissue in a non-invasive way and to determine the degree of fibrosis. Early diagnosis of the disease and its timely treatment lead to a better prognosis. The aim of the literature review is to present the capabilities of shear wave telephotography in diagnosing and evaluating liver fibrosis. We have researched and reviewed the relevant scientific literature, and briefly summarized existing knowledge on the results of two-dimensional shear wave elastographic study in hepatology. The results of the study revealed the undoubted advantages and high reliability of shear wave telephotography, as well as showed its limitations. Our literature review confirms an important role of shear wave telephotography in the diagnosis of diffuse liver diseases and outlines aspects of future research to further improve this diagnostic method.

KEYWORDS: liver fibrosis; liver cirrhosis; ultrasound; elastography; shear-wave telephotography

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## Introduction

Cirrhosis is the 11th most common cause of death in the world, and liver cancer is the 16th leading cause of death. Combined, they account for 3.5% of death [1]. There are many factors involved in the development of liver fibrosis, but the most important are 3 factors: alcohol misuse, chronic viral infection (HBV and HCV), and metabolic syndrome, which can lead to nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) [2]. It has been found that liver fibrosis is a reversible process with timely detection and appropriate treatment but if it turns into cirrhosis the reversal process becomes unreliable [3].

Liver fibrosis changes or the process stabilizes with timely treatment. Accurate diagnosis and differentiation of liver fibrosis stages are essential to determine the prognosis and risks of the disease, to plan progression monitoring and therapeutic measures [4]. Biopsy, which provides important information about histomorphological changes, is considered to be the gold standard for the diagnosis and assessment of chronic liver disease [5,6]. Liver biopsy has significant advantages in detecting and determining liver fibrosis, but this method also has got some limitations [4]. Liver biopsy requires adherence to ethical issues and most importantly this procedure is an invasive intervention that can lead to various complications or even death [7]. These limitations have led to the further development and introduction of new non-invasive approaches, which has already drastically reduced need for liver biopsy. In recent years an alternative of liver biopsy is offered in the form of telephotography, which is characterized by non-invasiveness, objectivity and quantitative characteristics [4]. One such method that is widely used to diagnose hepatic fibrosis is Transinent Elastography (TE) (Fibroscan, Echosens, Paris, France), ultrasonography-based elastographic method that determines tissue elasticity by measuring the velocity of shear waves generated by mechanical shocks in the parenchyma [4,8,9].

TE – can be used for recurrence, disease monitoring and event prediction. The results are discussed in detail and its reliability is high. The procedure takes a few minutes. It is technically easy to perform. But TE data is difficult to obtain in overweight patients when the body mass index is BMI>28 kg/m². The data may be unreliable also during ascites [4,10] and in the pleura while existing large amounts of fluid [11]. In such cases, two-dimensional shear wave telephotography (2D SWE) is used to detect fibrosis, which is not concerned by this restriction. Based on the studies there is determined, that it provides important information about liver fibrosis. Therefore, 2D SWE is a reliable and current research method in modern radiology [12]. Number of publications and guidelines published in recent years indicates dynamics of this research



Non-invasive diagnostics are safer and more acceptable to the patient, their use is increasing and the number of biopsies has been drastically reduced in some countries, especially for the routine evaluation of hepatitis B and C [8,13]. European Federation for societies for ultrasound in Medicine and Biology recommended the SWE that the last one assess the degree of liver stiffness in patients with CLD secondary to hepatitis especially hepatitis C [11].

#### 1. Liver fibrosis

Liver fibrosis is a pathophysiological process, which is based on the development of chronic liver diseases. Chronic damage to liver tissue results in cell damage and in response to it regeneration develops – abnormal recovery processes. Cell necrosis and degeneration followed deposition of extracellular matrix and collagen. Deposition of extracellular matrix and collagen follow after cell necrosis and degeneration [3,14]. Cells damaged during chronic inflammation of the liver secrete certain mediators that ensure the accumulation of inflammatory cells. This process activates the cells that contribute to the development of fibrosis [3].

Damaged hepatocytes activate hepatic stellate cells (HSCs) and differentiate them into myofibroblasts (MFBs). A large number of extracellular matrix (ECM) accumulations begins. Prolongation of this process over time leads to replacement and spread of fibrous tissue in the liver tissue [2,3]. ECM structure change results in a change of stiffness, which is measured in some physical techniques of non-invasive study of liver fibrosis [8].

The progression of fibrosis is not a homogeneous process and changes over time. The development of fibrosis at an early stage proceeds at a slower rate with a small increase in collagen content [15]. According to recent studies, hypoxia is an important factor contributing to the progression of fibrosis. The processes that develop during liver fibrosis may further enhance the degree of hypoxia. Excessive deposition of ECM and the development of liver fibrosis leads to an increase in vascular resistance in the liver. An increase in portal vein resistance leads to a decrease in portal blood flow velocity and blood flow, which leads to a reduction in the blood oxygen supply to the liver and all these further exacerbates liver hypoxia [16]. The ultimate solution for chronic hepatitis is cirrhosis of the liver (LC), a diffuse process in which the normal architecture of the liver is transformed, and abnormal nodules are formed. Portal hypertension and liver failure increase the risk of developing hepatocellular carcinoma [17].



### 2. Diagnosis of diffuse liver disease

During decompensation phase of liver cirrhosis, when various clinical-laboratory signs appear, the diagnosis of the disease is not difficult, but the differentiation of compensated cirrhosis from chronic hepatitis and fibrosis is not easy. Accurate assessment of the liver fibrosis stage and cirrhosis is a fundamental issue not only for correct diagnosis but also for conducting timely treatment and initiating a screening protocol to avoid complications and fatal outcomes [17]. Traditional methods of research, such as ultrasonography (US), computed tomography (CT) and magnetic resonance imaging (MRI) are actively used to diagnose liver fibrosis. New imaging techniques that is newly introduced in clinical practice include US telephotography and MR telephotography. Methods of diagnosing liver fibrosis such as diffusion weighted imaging (DWI), MRI with hepatobiliary contrast agents, MR and CT perfusion, dual energy CT, contrast-enhanced US, and image texture analysis are mainly used for scientific research purposes [15].

Invasive and non-invasive methods are included in the clinically applicable methods of assessing liver fibrosis. Liver biopsy (LB) is an invasive method. Non-invasive methods include serological tests and visual-instrumental methods. Elastography is considered to be a reliable technique in clinical medicine for assessing the progression of fibrosis [17].

The METAVIR score, which is a system of histopathological evaluation, is currently the most widely used for the differentiation and classification of stages of fibrosis. According to this system, there are 5 stages of fibrosis. They are: F0 – normal liver, F1 – minimal fibrosis, F2 – significant fibrosis, F3 – severe fibrosis, F4 – cirrhosis [15,17,18,19].

Based on these scores, we can determine the forecast of the disease and observe how the process develops as a result of treatment. Whether he or she should be screened for hepatocellular carcinoma. (HCC) [15].

### 2.1. Elastography

Elastography is an imaging technique based on tissue elasticity. It can assessment the mechanical properties of tissue in a non-invasive way and detect altered elasticity in soft tissues during various diseases. Information analysis obtained from this study is used for diagnostic purposes. Ultrasound telephotography (USE), as a tissue stiffness sensitive imaging technology, was first described in the 1990s and has been further developed and refined over time [18]. There are two types of US telephotography: strain telephotography (SE), which is known as real-time telephotography (Hi-RTE) and shear wave telephotography (SWE). SE is a qualitative examination technique and assesses tissue stiffness after manual compression. SWE is a technique that performs a quantitative

measurement of stiffness in kilopascals after an acoustic or mechanical pulse received from an instrument.TE (Fibroscan) of the SWE methods, is the only method without images. The other methods Acoustic Radiation Force Impulse (ARFI) (Siemens, Erlangen, Germany and Philips) and 2D-Real Time Shear Waves Elastography (2D-SWE) (Aixplorer system, Supersonic Imagine, Aix-en-Provence, France) are both imaging methods implemented in US machines [8]. In strain-based telephotography, force is transmitted using probe pressure or endogenous mechanical force (e.g., pulsation). In shear-wave based telephotography, generation of the shear wave is due to the imaging system. In both approaches the reaction of tissue caused by the mechanical stimuli determines the estimation of the mechanical properties of the tissue [20]. MR telephotography (MRE) can be divided into two types: two-dimensional (2D) MRE as a clinical standard and it is used for clinical purposes, while (3D) MRE is an evolving type and is mainly used in studies [4]. Thus, it has been determined that tissue stiffness is a biomarker of tissue pathology. Different elastographic techniques are selected and used according to priorities for the examination of various tissues and diseases [20].

#### 2.1.1. Two-Dimensional Shear Wave Elastography (2D SWE)

Shear wave elatography (SWE) was introduced in 2005 [19]. It based on the measurement of the shear wave propagation speed in soft tissue and does not require an external vibrator to generate the shear wave. 2D SWE uses ARFI to induce shear waves in liver tissue. 2D SWE induces shear waves at multiple points, producing a cone-shaped shear wave front that propagates laterally away from the ARFI axis. The propagation of the shear waves is monitored at multiple spatial and temporal points by conventional compressive ultrasound waves and is depicted as a colorized elasticity map named as an elastogram. The size of the elastogram region changes under operator control. The operator may place a circular region of interest within this elastogram at a location subjectively considered to be free of artifacts. The mean shear wave speed (m/s) is derived from multiple measurements that is obtained from tissue in the ROI and can be algebraically converted to Young's modulus (kPa) This mechanism is used to quantify tissue stiffness by this technique [4,8,19,21,22,23].



Fig. 1. Schematic image showing physical principles of ultrasonographic shear wave telephotography.

Measurements of liver stiffness (LS) using 2D-SWE are carried out through right intercostal scans, with the patient in a supine position. LS is measured with right arm abduction. LS is assessed with a short breath hold for 4 to 5 s and neutral breathing. A trapezoidal color box (3.5 cm × 2.5 cm) is positioned in the liver parenchyma and acquires the elasticity signals. When the elastogram signals in the color box are judged to reach a plateau, i.e., after about 3 s, the image is frozen. After call-back, the most homogenous areas of elastogram signals among the sequential frames are determined using a cine loop, and a round ROI is positioned in the region of the color box. The brighter the grayscale image obtained without shadowing in the scan, the more uniform the elastogram signal generated. The ROI is located in a homogenous elastogram signal in the liver parenchyma where there is no large vessel or hepatic nodule. ROIs are located 1 to 2 cm from the liver capsule to avoid reverberation artifacts. The ROI is as large as possible and up to 2 cm in diameter, but its size is reduced if necessary, measurement should preferably be at a depth of less than 6 cm from the capsule. Measured elasticity values are expressed in kilopascal (kPa) and recorded on the image as means and standard deviations [21,22,23,24].

The measurement is updated in every 1-2 seconds [25]. Up to 20,000 images are taken per second and the so-called "film" is created that shows the propagation of sear wave. An important fact is that measurements can also be made from retrospectively stored images [19].

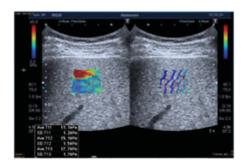


Figure 2. 2D-SWE (Two-Dimensional Shear Wave Elastography) image of F4 fibrosis in liver . liver stiffness expressed by Young modulus in kPa.

The newly introduced 2D-SWE two-dimensional telephotography can accurately estimate the stage of liver fibrosis in real time by estimating the quantitative stiffness in kilopascals. The first clinical data on liver fibrosis based on this technique were published in 2012 [9]. The LS value using 2D-SWE in healthy volunteers was found to be 4.5-5.5 kPa [24]. However, differences were detected between liver segments. The mean elasticity values for the right posterior, right anterior, left medial and left lateral segments of the liver were determined as 4 kPa±2.2 kPa (range:1-15), 3.9 kPa±2.1 (range:1-13) kPa, 3.8 kPa±2.1 (range:1-13) kPa, and 3.7 kPa±1.9 (range 1-12) kPa for each segments, respectively. It should be noted that there was no significant difference



in liver elasticity between women and men. Neither age correlated with hepatic elasticity was pointed out [23].

Elasticity in a normal liver is not affected by ethnicity either [26]. The optimal cut-off values for SWE are for the different fibrosis stages 7.1 kPa for  $F \ge 2$ ; 8.7 kPa for  $F \ge 3$  and 10.4 kPa for F = 4 respectively [19].

Samir and colleagues, carried out a study on the basis of which they concluded that estimates of the Young modulus obtained with SWE in the upper right lobe of the liver can be used to differentiate advanced fibrosis ( $\geq$ F2) from nonadvanced fibrosis, because the best correlation with the severity of liver fibrosis occurs here [27]. Meta-analysis of Li and colleagues revealed the sensitivity of SWE for staging liver fibrosis F $\geq$ 2, F $\geq$ 3, and F $\geq$ 4 was 0.85, 0.90, 0.87, the specificity was 0.81, 0.81, 0.88 and the receiver operating characteristic curve was 0.88, 0.94, 0.92 respectively [9]. This data coincides with the results of another recent meta-analysis obtained by observing 2303 patients. The study revealed that in patients with viral hepatitis the reported AUROC for detecting liver fibrosis stage  $\geq$ 2,  $\geq$ 3, and cirrhosis were 0.87 (95% CI: 0.84-0.90), 0.93 (95% CI: 0.91-0.95), and 0.94 (95% CI: 0.92-0.96), respectively. Similar diagnostic performance was reported for a subgroup of NAFLD patients in another metaanalysis. 2D SWE detects advanced fibrosis and cirrhosis with greater accuracy.

The 2D SWE method can be used to determine liver stiffness to predict complications of liver fibrosis. 2D SWE can determine the presence of clinically significant portal hypertension with summary sensitivity and specificity of 0.85 (95% CI: 0.75-0.91) and 0.85 (95% CI: 0.77-0.90), respectively. To find out more about this complication, there is still much work to be done to launch new studies for further verification [4]. Determination of splenic stiffness (SS) by 2D SWE provides useful information for predicting clinically significant portal hypertension [24,26]. As for non-alcoholic fatty liver disease (NAFLD) and 2D SWE involvement in its study, it was found that favorable data from three recent studies have not been obtained. Presumably due to the high BMI of these patients. Steatosis may be an obstructive factor in measuring tissue stiffness. In a study of patients with alcoholism, SWE had high diagnostic performance with AUCs of 0.94 and 0.95, respectively, for detecting significant fibrosis (Ishak fibrosis stage  $\geq$ 3) and cirrhosis (Ishak fibrosis stage  $\geq$ 5) [24].We must also take into account the fact that inflammatory and edematous processes in the liver, as well as venous congestion and cholestasis give us excessive indicators [15].

There is not extensive information on autoimmune liver disease. There have been 2 recent studies and due to the low prevalence of this disease, these studies included patients with autoimmune hepatitis, primary biliary cholangitis, primary sclerotic cholangitis each of which has different rates of liver damage. AUROCs in autoimmune diseases were lower than in chronic viral hepatitis. It is advisable to carry out further studies for each disease separately to identify more necessary features [24]. TE is the

most widely used elastographic method. The results of SWE were evaluated in relation to it by numerous studies and it was proven that SWE can be freely used to assess liver fibrosis and its results are even better than TE in some cases.

Osman et al. compared the results of fibroscan and SWE with biopsy responses, which showed a similar degree of agreement with no significant difference between the TE and SWE techniques when compared with the biopsy results. In this study SWE showed a higher incidence of overestimation. The agreement of fibroscan reached 90.6% compared with 87.2% of SWE. The degree of overestimation showed 5.6% in fibroscan while it was 10.6% in SWE. As well as the degree of underestimation was 3.8% and 2.2% for fibroscan and SWE respectively. SWE showed a higher incidence of mismatch between patients with F4. According to the results of this study, SWE tends to overestimate the results fibrosis score when compared to the fibroscan with the highest degree of overestimation found at F3 and F2 patients. Also, SWE shows high efficacy in all degrees of fibrosis with the lowest found at F3 and F2, while the highest efficacy found at F0 and F1.

Similar results were obtained by O'Hara et al in his study, in which they compared data from these two techniques. In addition, Ali Z and colleagues concluded a strong correlation and agreement between SWE and TE results.

The results of Osman et al. study are almost identical to Leung et al's study for SWE, in which they compared SWE results to liver biopsy with 85% and 92% SWE sensitivity and specificity respectively in the diagnosis of liver fibrosis as well as 97% and 93% sensitivity and specificity in the diagnosis of liver cirrhosis. The study by Zeng et al. revealed that SWE had a higher rate of reliability 98.1% than TE (93%). They found also a strong correlation between SWE and TE with no difference between the area under ROC curves of SWE and TE for liver fibrosis staging [11].

In addition to the fact that two-dimensional shear wave telephotography is a convenient and cost-effective analysis method, it is a simple and painless technique with good reproducibility. Results are obtained quickly and immediately. Due to the fact that SWE is integrated into conventional ultrasound imaging diagnostic apparatus, it allows morphological, detailed examination of both the right and left parts of the liver and is the best way to determine the overall distribution of fibrosis [19,28]. Other organs are also examined as needed (e.g., spleen). It is also important that the analysis is conducted in real time and allows us to easily select an area free of artifacts. We can select the size of the Q-Box and perform retrospective examination with the images stored on the device [19].

2-dimensional SWE data certainly surpassed the results of conventional ultrasonography in the case of liver fibrosis, but there was not significant difference between them in diagnosing decompensated cirrhosis [8]. According to one study, 2D-SWE can be freely used as a screening tool for early diagnosis of significant fibrosis [26]. As

mentioned, unlike TE, 2D SWE has advantage and this method is used in ascites and overweight patients [4,10]. SWE offers more accurate correlation of liver elasticity with liver fibrosis stage compared with transient telephotography, especially in identification of stage F2 or greater [26].

There are studies according to which 2D Shear Wave telephotography is more effective than FibroScan in diagnosing significant fibrosis, but make final conclusions require new studies [19]. Although 2D SWE diagnostic rate is higher than other non-invasive methods (primarily TE), it still does not reveal a significant dependence on the stages of fibrosis [22,24].

Like other methods, 2D SWE technique provides more accurate information during significant liver fibrosis than at the time of mild liver fibrosis [4].

The disadvantage of this method is that there are not enough studies yet to talk more convincingly about this technique, although the available initial results are hopeful [19].

# Conclusion

Two-dimensional SWE is actively used in the diagnosis of liver fibrosis and cirrhosis and according to our review, it gives quite convincing results. Although two-dimensional SWE data is more accurate at the stage of significant fibrosis and does not provide fully reliable information at an early stage, ultrasound telephotography is still considered to be the most perspective method. The results obtained by ultrasound telephotography and their correct interpretation are an important issue in modern radiology, therefore, studies need to be continued to test and perfect these techniques, which will improve the results and further increase the need to use this method.

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