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Non-Invasive Diagnosis of Liver Fibrosis: Modern Instrumental Methods

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Abstract: Liver fibrosis is a dynamic pathological process that develops in chronic liver diseases, the outcome of which can be cirrhosis. Biopsy remains the gold standard for diagnosing hepatic fibrosis, but non-invasive diagnostic methods are currently being actively introduced into clinical practice. Unlike liver biopsy, most noninvasive instrumental tests are simple to perform, accessible, and repeatable, making them more convenient for assessing fibrotic changes over time. The review summarizes the basic principles of methods for non-invasive instrumental assessment of the severity of liver fibrosis, studied and put into practice over recent years. The most widely used methods in clinical practice are based on the principles of elastography, which makes it possible to indirectly determine the density of organ tissue. The techniques are characterized by varying sensitivity and specificity in the diagnosis of fibrosis. The main problems arise when differentiating the stages of the disease. For some methods, restrictions on their use are ascites and excessively developed subcutaneous fat; for others, the high cost of the procedure. Meanwhile, there is every reason to believe that non-invasive techniques can take a major place in the diagnosis of liver fibrosis and replace biopsy in the near future.

Keywords: liver fibrosis, chronic liver diseases, non-invasive diagnostic methods, elastography, liver biopsy, magnetic resonance imaging, ultrasound.

Introduction Liver fibrosis (AF) is a progressive pathological condition that can lead to liver cirrhosis and its complications, such as ascites, portal hypertension, bleeding from esophageal varices, encephalopathy, and hepatocellular carcinoma. Assessing the stage of AF is fundamental to monitoring the progression of chronic liver disease (CLD), determining prognosis, optimal timing of treatment initiation, and monitoring response to therapy.

Liver biopsy is the “gold standard” for assessing the severity of AF, but this procedure is associated with numerous complications: pain, bleeding, and gallbladder perforation [1]. In addition, there is a risk of obtaining an uninformative biopsy: the liver is a large organ, its parenchyma is heterogeneous, and the volume of the biopsy taken by puncture is only 1/50,000 of the total volume of liver tissue [2]. Thus, there is a need for a reproducible, accurate and less invasive method for diagnosing AF and assessing structural changes in the organ over time in patients with CLD. Non-invasive diagnosis of AF is based on biological markers of fibrogenesis and fibrolysis or physical properties of the liver parenchyma. The most widely used instrumental methods in clinical practice are based on the principles of elastography, which makes it possible to indirectly determine the density of organ tissue [3–5]. This review aims to highlight the possibilities of non-invasive instrumental methods for diagnosing AF at the present stage. Magnetic resonance imaging Magnetic resonance imaging (MRI) is typically used to diagnose cirrhosis and its complications. MRI allows

you to detect macrostructural changes in the liver parenchyma: fibrous septa and regeneration nodes, as well as the presence of splenomegaly with calculation of organ volume, varicose veins of the portal system and ascites. The use of intravenous contrast improves the visualization of fibrosis and complications associated with cirrhosis (arterio-portal shunts, hepatocellular carcinoma) [6]. Detection and assessment of minimal/moderate fibrosis (METAVIR stages F1 and F2) is more challenging, and several new magnetic resonance techniques are being explored for this purpose.

Magnetic resonance elastography The physical basis of magnetic resonance elastography (MR elastography) is the speed and length of the wave propagating in the liver tissue: the greater the density of the tissue, the greater the speed of wave propagation. MR elastography requires special software and hardware. The drive device is positioned over the patient's right upper abdomen and generates acoustic pressure waves at a frequency of 40–120 Hz, which create shear waves in the liver. The program receives images of the propagating mechanical wave, and the algorithm generates a quantitative map of liver tissue density. Assessment of the density of the organ parenchyma correlates with the stage of AF and makes it possible to differentiate cirrhosis from fibrotic changes [6]. MR elastography has greater sensitivity in assessing liver fibrosis and cirrhosis compared to standard MRI [7]. Unlike ultrasound (ultrasound), MR elastography is independent of the operator, and the results are not affected by the presence of excess body weight or ascites in the patient. L. Huwart et al. [7] showed that MR elastography is a more accurate method for diagnosing fibrosis than transient elastography and APRI (aspartate aminotransferase to platelet ratio). In a meta-analysis of 12 studies published by S. Singh et al., MR elastography showed high sensitivity and specificity for the diagnosis of advanced fibrosis (METAVIR F3) regardless of age, sex, body mass index and etiology of liver disease. Liver biopsy data served as control [8]. The limitations of MR elastography include its high cost and long study duration. Liver density and, accordingly, the accuracy of MR elastography results can also be affected by iron overload, steatosis, cholestasis and portal hypertension [9–11]. Diffusion- weighted MRI. Diffusion-weighted MRI (DW-MRI) evaluates the ability of protons to diffuse into tissue. This method is usually used to examine patients with cancer. In the study, scientists attempted to identify the relationship between the reduced apparent diffusion coefficient that appears with fibrosis and the degree of fibrotic changes in the liver. A. Razek et al. [12] found that a reduced diffusion coefficient value correlates with the stage of AF in children and adults. Limitations of DW-MRI in the assessment of fibrosis include the fact that diffusion is influenced by hepatic steatosis, the presence of iron in the tissue, and inflammatory changes. In addition, the study is sensitive to artifacts associated with patient movement, since the confidence level of the quantitative analysis is based on the quality of the acquired images [12].

Contrast-enhanced ultrasound This technique is usually used to diagnose liver tumors. The study is performed with an intravenous bolus injection of a contrast agent (CM) and subsequent ultrasound in a special “contrast” mode with a low mechanical index [13]. However, in recent years, this technique has also begun to be used to assess AF - against the background of fibrous restructuring of the organ parenchyma, intrahepatic microcirculation changes, which can be assessed using ultrasound [14]. The liver has a dual blood supply: approximately one-third of the blood flow is from the hepatic artery and two-thirds from the portal vein. The vascular phases of contrast-enhanced liver ultrasound are similar to those obtained with computed tomography and MRI, progressing from the arterial to the portovenous phase, and ending in the late (delayed) phase. The arterial phase begins with the entry of CV into the hepatic artery. Depending on the circulatory status, this occurs 10–20 seconds after the injection of CV. The portovenous phase begins when the CV enters the main portal vein - approximately 30 to 45 seconds. The arterial and portovenous phases overlap because the latter lasts up to 45 seconds. The late phase begins after 120 seconds and lasts until microbubbles disappear from the circulation, approximately 4 to 6 minutes. An additional post-vascular phase begins 10 minutes after injection and lasts up to an hour or longer [14]. To diagnose the stage of AF, two indicators are used: the time of arrival of contrast in the hepatic veins and the intrahepatic transit time (defined as the delay between the arrival of contrast in the portal and hepatic veins). In one study [14], a hepatic vein arrival time of 17 seconds or less showed 100% sensitivity and 93% specificity for liver cirrhosis. The time of arrival of CVs in the hepatic veins is significantly shorter in patients with cirrhosis than in patients without it. Although measurement of arrival time in the

hepatic veins is a simple method, it has some limitations, for example in the presence of extrahepatic vascular shunts. F. Staub et al. [15] used a hepatic vein arrival time of 13 seconds and diagnosed advanced fibrosis (F3) with a specificity of 78.57%, sensitivity of 78.95%, positive predictive value of 78.33%, and negative predictive value. 83.33%. Elastography Fibrosis is manifested by a decrease in elasticity and an increase in the density of the liver parenchyma, and elastography is able to quantify this indicator [16–18]. There are two types of ultrasound elastography: 1) static (compression) elastography (SE) with assessment of tissue deformation; 2) dynamic elastography using: – mechanical pulse or vibration pressure, with assessment of the shear waves that arise in this case (transient elastography, TE); – acoustic radiation pressure pulses created by ultrasonic signals focused at different depths using shear wave velocity estimation (shear wave elastography, SWE); – acoustic radiation pressure (ARFI), created by a long ultrasonic signal, and assessment of the resulting longitudinal deformations.

Transient elastography. TE using the Fibroscan device (Echosens, France) was the first ultrasonic elastographic method to assess elasticity by measuring the velocity of elastic shear waves in the parenchyma generated by mechanical shock. The first clinical data obtained using this method were published in 2003 [19]. The technique is described in detail in the literature. The examination is carried out on an empty stomach. The patient moves his right arm backward as much as possible, the researcher places the ultrasound sensor over the right lobe of the liver through the intercostal space, the device produces mechanical vibration, which generates elastic transverse waves propagating through the tissue. The speed of the waves is measured and expressed in kilopascals, and it directly correlates with the elasticity of the tissue. The greater the density of the fabric, the faster the transverse wave propagates. TE is easy to perform, well tolerated by patients and gives immediate results. The technique does not depend on the operator. Liver density is calculated as the median of 10 valid (successful) measurements. A measurement with an interquartile range less than 30% of the median and a success rate greater than 60% is considered reliable. Conducted scientific studies have demonstrated good reproducibility of the method [20]. TE was initially tested to assess AF in patients with chronic hepatitis C (CHC) and then in CKD of other etiologies [21]. All these studies have shown that there is no specific threshold value, expressed in kilopascals, that allows differentiating the stages of AF. The indicator varies depending on the etiology of the liver disease. A meta-analysis published by E. Tsochatzis et al. included 40 studies of patients with CKD of various etiologies (chronic hepatitis B (CHB), CHC, alcoholic liver disease, etc.). Data concerning patients with CHC were obtained from 14 studies. The pooled sensitivity and specificity were 0.78 and 0.80, respectively, for predicting significant fibrosis (METAVIR F3). Data from patients with CHB were obtained from 4 studies, with a pooled sensitivity of 0.84 and a pooled specificity of 0.78. In this analysis, for predicting liver cirrhosis (F4 on biopsy), the sensitivity was 0.83, the specificity was 0.89, and the mean optimal cutoff value was 15.0 ± 4.1 kPa (median 14.5 kPa). The sensitivity and specificity for predicting F2 fibrosis were 0.79 and 0.78, respectively. The average optimal value for F2 was 7.3±1.4 kPa (median 7.2 kPa) [22]. The European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) has published guidelines in which values above 6.8–7.6 kPa in chronic viral hepatitis are highly likely to indicate the presence of significant AF (F≥2), while values in the range of 11.0–13.6 kPa may indicate the cirrhotic stage (F4) [23]. The European Association for the Study of the Liver Guidelines indicates that TE can be used to assess AF in patients with CHC [24]. Many studies have shown that TE is a highly sensitive method that can differentiate mild from significant fibrosis, but is not accurate enough to distinguish between the stages of minor fibrosis (F1 and F2). Limitations of TE are the high cost of equipment and the lack of standardized density values for differentiating stages of fibrosis. In addition, TE is difficult to perform when studying patients with excessively developed subcutaneous fat and ascites.

Shear wave elastography. SWE uses the force of acoustic radiation to cause microscopic tissue movements, creating a shear wave. In SWE, the deformation force of the tissue is known, and for this reason, a quantitative estimate of the tissue stiffness can be obtained, expressed as Young's modulus (kPa) or shear wave velocity (m/s) [25]. The technique is available in the Aixplorer® ultrasound system (SuperSonic Imagine, France). With the patient in the supine position with the right arm abducted as far as possible, the transducer is placed in the right intercostal space, using the

best acoustic window available to assess the liver. Registration is performed on the right lobe of the liver, and it is not recommended to move the sensor to avoid artifacts during movement. The patient must hold their breath for 3–4 seconds during the exhalation phase to obtain a stable image. The elasticity value is displayed in real time. The minimum and maximum liver density, expressed in kilopascals, is recorded. The first clinical study of the SWE technique was published by E. Bavu et al. (2011), who comparatively assessed the stages of fibrosis in 113 patients with CHC using SWE, TE and liver biopsy. The Area Under Curve (AUC) for elasticity values assessed using SWE was: 0.95 for stage F2, 0.96 for stage F3, and 0.97 for cirrhosis. In this study, AUC scores for SWE were higher than for TE for the diagnosis of F2 and F3 fibrosis and cirrhosis [26]. G. Ferraioli et al. [27] also compared SWE with TE and liver biopsy. The cutoff value was 7.4 kPa for F≥2 (AUC=0.91), 8.7 kPa for F≥3 (AUC=0.99) and 9.2 kPa for F4 (AUC=0.97). The results were similar to those obtained in the previous study. V. Leung et al. (2013) conducted a study in a group of patients with CHB, comparing TE and SWE of the liver and spleen. Liver SWE showed significantly higher accuracy than liver TE and spleen SWE at all stages of fibrosis.

The AUCs for liver SWE, liver TE, and spleen SWE were: 0.86, 0.80, and 0.81, respectively, for mild fibrosis (stage F1); 0.88, 0.78 and 0.82 - for moderate fibrosis (stage F2); 0.93, 0.83 and 0.83 - for severe fibrosis (stage F3); 0.98, 0.92 and 0.84 - for cirrhosis (stage F4). Liver SWE is most reliable in assessing the stage of fibrosis [28]. The study [29] involved 198 patients with CLD of various etiologies (CHC, CHB, autoimmune hepatitis, primary biliary cirrhosis, drug-induced liver damage); liver biopsy was used as the “gold standard”. Researchers evaluated the performance of SWE and standard ultrasound in differentiating fibrosis from cirrhosis to determine when SWE should be added to standard ultrasound. The accuracy of SWE is significantly superior to ultrasound in diagnosing AF, but when verifying decompensated cirrhosis, no significant difference was found between SWE and standard ultrasound.

Conclusion Non-invasive assessment of AF is becoming part of the standard examination of patients with CKD: diagnosis and monitoring of the stage of AF during therapy is necessary to improve long-term prognosis. Invasive diagnosis using biopsy is not always applicable. An urgent need for screening and monitoring of patients is the development and implementation of methods for non-invasive assessment of AF - informative and accessible. Currently, several liver imaging techniques are being actively studied: magnetic resonance and transient elastography, DW-MRI, contrast-enhanced ultrasound, SWE, etc. The limitations of the techniques are better understood, which allows them to be used correctly and the results interpreted. These techniques may take a major place in the diagnosis of AF stages and replace biopsy in the near future.

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