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Advances in Noninvasive Imaging Techniques for the Diagnosis of Liver Diseases: A Comprehensive Review

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Abstract

Background: The global prevalence of nonalcoholic fatty liver disease (NAFLD) is rising, currently affecting approximately 25% of the population. Accurate assessment of liver fibrosis is critical, as it significantly impacts prognosis and management strategies. While liver biopsy remains the gold standard for fibrosis evaluation, its invasive nature and associated risks have led to the development of various noninvasive imaging techniques.

Methods: This review systematically examines recent advancements in noninvasive imaging modalities for liver disease assessment, focusing on techniques such as vibration-controlled transient elastography (VCTE), magnetic resonance elastography (MRE), and shear wave elastography (SWE). The analysis includes comparative studies on diagnostic performance, accuracy, and clinical applicability of these methods in diagnosing liver fibrosis.

Results: Findings indicate that VCTE, pSWE, and MRE exhibit high diagnostic accuracy for detecting significant fibrosis and cirrhosis, with area under the receiver operating characteristic (AUROC) values ranging from 0.80 to 0.96. MRE, in particular, demonstrates superior performance in patients with obesity and advanced liver disease. Emerging techniques utilizing artificial intelligence are anticipated to further enhance diagnostic precision.

Conclusion: Noninvasive imaging biomarkers, including VCTE, SWE, and MRE, represent a promising approach to liver fibrosis assessment, potentially reducing the need for invasive biopsies. These techniques offer significant advantages in terms of patient safety and comfort while maintaining high diagnostic accuracy. Future research should focus on standardizing methodologies and integrating these imaging techniques into routine clinical practice for effective liver disease management.

Keywords: Nonalcoholic fatty liver disease, liver fibrosis, noninvasive imaging, magnetic resonance elastography, vibration-controlled transient elastography.

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1. Introduction

The incidence of nonalcoholic fatty liver disease (NAFLD) is rising globally, affecting around 25% of the world's population. The strain on the worldwide healthcare system due to the treatment of NAFLD is escalating and becoming a significant public health issue [1-3]. NAFLD encompasses a range of hepatic illnesses from isolated steatosis to nonalcoholic steatohepatitis (NASH), potentially resulting in severe outcomes such as cirrhosis, hepatocellular carcinoma (HCC), and liver-related mortality [4,5]. The advancement of liver fibrosis in patients with NAFLD is a critical determinant of prognosis, as significant and advanced liver fibrosis serves as an independent risk factor for hepatic and extrahepatic complications, as well as liver-related and overall mortality [6,7]. Consequently, the precise evaluation of hepatic fibrosis severity in patients with NAFLD is a paramount concern in contemporary medicine.

A hepatic biopsy is the definitive approach for assessing hepatic fibrosis in individuals with NAFLD; nevertheless, its widespread clinical use is limited by high costs and associated risks [8]. Furthermore, liver biopsy is restricted by its ability to sample just a minuscule fraction (1/50,000) of the complete liver. Consequently, several noninvasive tests (NITs) have been devised to address the constraints of liver biopsy, and their use in clinical practice is progressively rising [9]. Noninvasive imaging biomarkers can be categorized into ultrasound-based assessments, including vibration-controlled transient elastography (VCTE), shear wave elastography (SWE), and acoustic radiation force impulse imaging (ARFI), as well as magnetic resonance imaging (MRI)-based evaluations, such as magnetic resonance elastography (MRE) (Figure 1) [10]. Given that each test has distinct strengths and limits, understanding the attributes of each test is crucial for determining the most suitable method for evaluating the extent of liver fibrosis in patients with NAFLD.

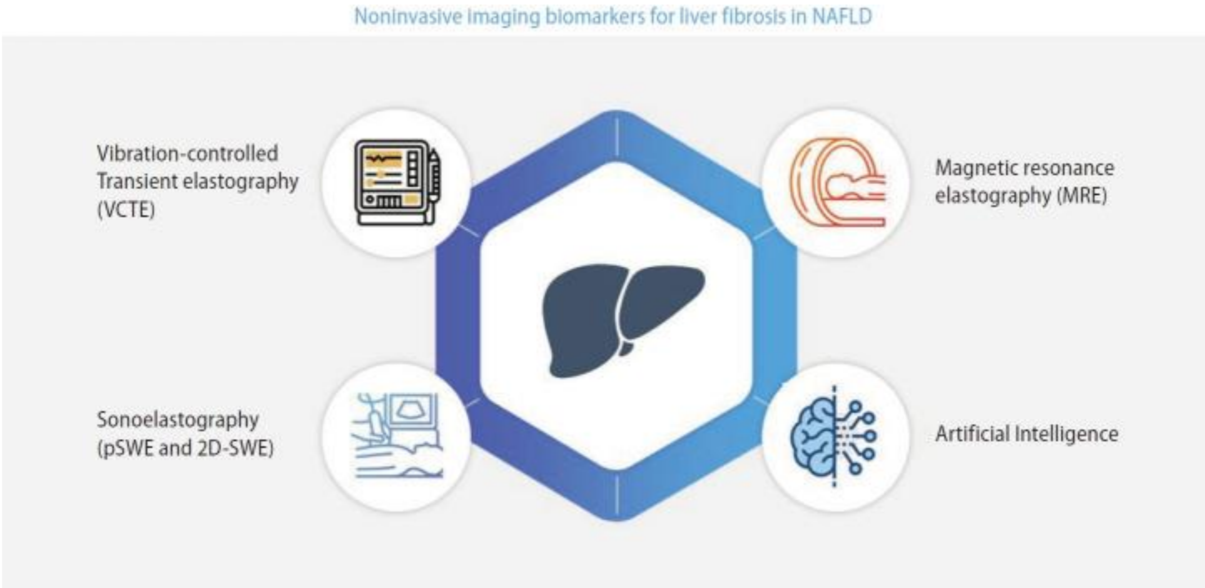

Figure 1. Noninvasive imaging biomarkers in NAFLD. NAFLD refers to nonalcoholic fatty liver disease; SWE denotes shear wave elastography.

As investigations into noninvasive imaging biomarkers progress, the development and use of more efficient testing apparatus are anticipated in the future. Methods using artificial intelligence (AI), recently highlighted, are anticipated to enhance the accuracy and optimize the efficiency of current inspection equipment [11]. Recent research on the use of AI and deep learning techniques in assessing liver fibrosis severity has shown encouraging outcomes [12,13]. This study elucidates the use and benefits of noninvasive imaging biomarkers that have been researched and employed to assess liver fibrosis in patients with NAFLD, along with the future potential of these biomarkers.

2. Elastography

Elastography approaches assess fibrosis stages by detecting shear wave velocity or tissue displacement induced by an ultrasonic or physical stimulus, reflecting liver stiffness (LS) [14]. The VCTE and MRE systems use mechanical drivers to produce shear waves and evaluate shear wave velocities by sonographic Doppler and magnetic resonance methods, respectively [15]. High-frequency sonographic impulses produce shear waves in point shear wave elastography (pSWE), acoustic radiation force impulse (ARFI), and two-dimensional shear wave elastography (2D-SWE). Due to the varying methodologies and frequencies used by various elastography techniques, their values are not uniform, necessitating care in result interpretation.

3. Elastography Utilizing Ultrasound

Transient elastography (FibroScan®; EchoSens, Paris, France) is a recognized noninvasive ultrasound elastography technology for identifying and staging liver fibrosis in patients with NAFLD [16]. VCTE comprises a 3.5-MHz ultrasound transducer positioned on the axis of a low-amplitude vibrator and employs monodimensional ultrasound to ascertain LS by measuring the velocity of low-frequency elastic shear waves traversing the liver [17]. To ensure the reliability of a VCTE result, at least 10 valid measures are necessary, and the ratio of the median valid LS measurement to the interquartile range (IQR) must be ≤0.3 [18].

A transient elastography test may be performed swiftly, often within 5 minutes, and several studies have corroborated its reliability in evaluating liver fibrosis in individuals with NAFLD [19]. Transient elastography demonstrates exceptional intraobserver and interobserver reliability [20]. Transient elastography has several limitations: the optimal cutoff point remains ambiguous; measurements may be unfeasible in obese patients; scan results may be inconsistent when conducted by inexperienced operators; and diagnostic accuracy is restricted in the initial stages of fibrosis [21].

Numerous recent studies have examined the optimal threshold value in VCTE to validate severe liver fibrosis in individuals with NAFLD [22-27]. The average body mass index (BMI) of individuals with NAFLD in those studies ranged from 27.1 to 34.8 kg/m2, with Asian research reporting a comparatively lower BMI than Western studies. The LS value assessed by VCTE, signifying substantial liver fibrosis (F2) in NAFLD patients, varied between 7.7 and 9.8 kilopascals (kPa), with the prevalence of significant liver fibrosis among patients ranging from 30.9% to 70.8% of the study cohort. The LS value indicative of advanced liver fibrosis or cirrhosis (F3 or above) ranged from 7.3 to 12.5 kPa, demonstrating appropriate area under the receiver operating characteristic curve (AUROC) values of 0.80 to 0.92.

4. Forecasting hepatic-related consequences

Recent studies indicate that baseline liver stiffness (LS) values assessed by VCTE reliably forecast hepatic decompensation, with elevated baseline LS values predicting the onset of liver-related events in individuals with NAFLD [28,29]. A multicenter cohort study examining liver-related outcomes based on LS values obtained by VCTE found that baseline LS values were independently correlated with hepatic decompensation (hazard ratio [HR]=1.03), hepatocellular carcinoma (HR=1.03), and liver-related mortality (HR=1.02) [29]. An increase beyond 20% in the LS value over an average follow-up period of 35 months was significantly correlated with the risk of liver-related events and mortality, indicating that LS values obtained by VCTE are valuable for predicting liver-related outcomes [29]. Nonetheless, because of the constraints associated with retrospective studies, the research did not adhere to a defined procedure for VCTE follow-up and was unable to precisely ascertain the consumption of alcohol and other substances.

Consequently, additional prospective and validation studies are required to elucidate the relationship between LS values obtained using VCTE and liver-related outcomes.

5. Point shear wave elastography/acoustic radiation force impulse imaging

pSWE and ARFI are ultrasonic elastography techniques that provide the quantitative evaluation of tissue rigidity [30]. LS measurement using pSWE and ARFI is conducted in the right lobe of the liver via the intercostal space. Upon choosing a region of interest (ROI), shear wave velocity is assessed within the specified area via ultrasonic tracking beams positioned laterally to a single push beam [30]. For power and ARFI data to be deemed trustworthy, the IQR/liver spasticity must be less than 30% [31-33].

Like VCTE, many meta-analyses have validated that pSWE and ARFI exhibit substantial diagnostic accuracy for severe liver fibrosis, with a mean AUROC of 0.84–0.87, and exceptional diagnostic accuracy for cirrhosis, with a mean AUROC of 0.91–0.94 [31,33]. Furthermore, we and ARFI have a strong intraobserver and interobserver agreement, shown by an intraclass correlation value ranging from 0.84 to 0.87 [34,35]. Moreover, in contrast to VCTE, the precision of pSWE and ARFI is often not limited by obesity or obstructive structures like blood arteries or the biliary system, since the ROI may be manually adjusted [30]. Nonetheless, the drawbacks of pSWE and ARFI include a lower ROI size compared to VCTE and less rigorous evaluation of quality standards.

Numerous studies have shown the clinical use of pSWE and ARFI using noninvasive imaging biomarkers, indicating that pSWE and ARFI are effective diagnostic instruments with superior accuracy for advanced liver fibrosis (F3–4) compared to low-grade fibrosis (F1–2) [36,37]. Nevertheless, research on pSWE and ARFI has mostly consisted of monocentric retrospective studies; hence, longitudinal validation in chronic liver illnesses, particularly NAFLD, is necessary to establish uniform quality standards.

6. Two-dimensional shear wave elastography

Real-time 2D-SWE is conducted in a manner akin to pSWE and ARFI. It integrates the generation of a radiation force in tissues using focussed ultrasonic beams with the real-time capture of transiently propagating resulting shear waves utilizing a high-frequency ultrasound imaging sequence [38]. In 2D-SWE, a two-dimensional parametric color map is produced by integrating several shear waves over time using fast ultrasound capture. Like pSWE and ARFI, 2D-SWE enables the operator to determine the dimensions and position of the ROI. The operator "samples" a designated region within a color map to detect shear-wave velocity, therefore acquiring a quantitative assessment of tissue elasticity using proprietary software [39].

The benefit of 2D-SWE is that it enables the operator to choose the dimensions and position of the ROI, thereby facilitating the assessment of the elasticity profile of an extensive tissue area in a single scan [40]. Moreover, 2D-SWE has benefits over pSWE and ARFI, including qualitative (color-coded) and quantitative assessment, enhanced ease of measurement, and stability of the obtained values [41,42]. Nonetheless, 2D-SWE has many drawbacks, such as the subjective character of the color scale, possible bias in ROI selection, and an absence of meta-analyses validating its therapeutic applicability.

Numerous recent studies have shown that liver stiffness (LS) assessed by 2D-SWE has a substantial correlation with the degree of liver fibrosis determined by liver biopsy in individuals with NAFLD [43]. A meta-analysis performed in Europe indicates that 2D-SWE has commendable diagnostic efficacy for considerable liver fibrosis (≥F2, AUROC=0.86), exceptional diagnostic efficacy for severe fibrosis (≥F3, AUROC=0.93), and outstanding diagnostic efficacy for cirrhosis (F4, AUROC=0.92). The ideal threshold values for identifying severe liver fibrosis and cirrhosis are 7.1 and 13.0 kPa, respectively. The AUROC for diagnosing severe liver fibrosis (P=0.001) and cirrhosis (P=0.022) with 2D-SWE surpassed that of VCTE [44]. Nevertheless, due to the absence of studies on the clinical use of 2D-SWE and comparison analyses with other noninvasive techniques, more research is required.

7. Elastography Based on Magnetic Resonance Imaging

Liver MRE may be conducted with current magnetic resonance imaging scanners. The configuration comprises an active pneumatic mechanical driver situated outside the scanning chamber and a linked passive driver positioned on the liver [45]. The active driver produces constant acoustic vibrations that are sent to the passive driver and then to the abdomen, encompassing the liver. These waves generate tiny shear displacement of tissues, which is shown using MRE sequences as propagating shear waves [46]. Subsequently, a magnitude picture depicting the architecture of the upper abdomen and a phase-contrast image illustrating shear waves at the same level are reconstructed, together with grayscale and colored stiffness maps, referred to as electrograms. Subsequently, readers delineate the ROI inside the liver's confidence map, excluding the liver margin, artifacts, fissures, fossa, and areas of wave interference [45]. The average LS value is determined by using ROIs across four slices. The LS value obtained using MRE is quantified in kPa, indicating the tissue's elasticity and viscosity.

MRE can assess the whole liver, with technical failure occurring in less than 5% of exams [47-49]. MRE measurements have great reproducibility, demonstrating strong intraobserver and interobserver agreement [50-53]. The liver stiffness (LS) value obtained using magnetic resonance elastography (MRE) is not substantially influenced by hepatic steatosis, and MRE is capable of measuring LS in obese individuals [54-57]. Moreover, hepatic inflammation does not compromise the precision of MRE in individuals with NAFLD [55].

The predominant cause of technical malfunction in MRI is iron overload [55]. The inadequate transmission of shear waves into the liver, attributed to significant ascites, increased subcutaneous fat thickness, and insufficient contact between the passive driver and the abdominal wall, resulted in measurement failure. Inconsistent breath-holding and movements throughout the procedure can result in technical failure in patients with significant ascites [45]. The variability in fibrosis advancement across various liver diseases may result in imprecise liver stiffness assessments, especially in tiny regions of interest. MRE is unable to distinguish between LS resulting from congestion and that arising from elevated vascular pressure; thus, the LS value obtained with MRE must be taken with caution [58,59]. Variations in MRI specifications and suppliers among institutions and research provide a further challenge in interpreting LS results obtained using MRE. Currently, due to its expense and restricted availability, MRE cannot be universally used in clinical practice.

Numerous studies have shown that MRE has high accuracy in diagnosing and stratifying hepatic fibrosis in individuals with NAFLD, reliably predicting substantial or advanced liver fibrosis and cirrhosis with constant AUROC values of 0.90 [60-63]. A recent meta-analysis demonstrated the high accuracy of MRE, with an AUROC of 0.96 for advanced liver fibrosis and 0.92 for cirrhosis, with LS cutoff values of 3.62–4.8 and 4.15–6.7 kPa, respectively [58]. A meta-analysis of nine trials including 232 patients with NAFLD indicated accurate LS cutoff values of 2.88, 3.54, 3.77, and 4.09 kPa for identifying fibrosis stages 1, 2, 3, and 4, respectively [55].

A recent meta-analysis involving individual data from 230 patients with biopsy-confirmed NAFLD demonstrated that MRE surpassed VCTE in identifying all stages of fibrosis (AUROC for fibrosis stage ≥1, 0.87 vs. 0.82 [P=0.04]; stage ≥2, 0.92 vs. 0.87 [P=0.03]; stage ≥3, 0.93 vs. 0.84 [P=0.001]; and stage ≥4, 0.94 vs. 0.84 [P=0.005]) [64]. Comparative research on MRE and pSWE is few; yet one study indicated that MRE had superior accuracy compared to pSWE in detecting all stages of fibrosis in individuals with NAFLD, particularly among those with obesity [56]. Recent research indicated that MRE exhibited more accuracy than 2D-SWE in identifying stages ≥1 and ≥2 fibrosis, but not in stages ≥3 or 4 fibrosis [27]. Alternative MRI methodologies, such as diffusion-weighted imaging and contrast-enhanced MRI, have also been shown to have worse accuracy compared to MRE in evaluating liver fibrosis [46-66]. Thus, the LS value obtained using MRE is regarded as the most precise noninvasive imaging biomarker for identifying all phases of fibrosis.

Recently, noninvasive liver stiffness-based models integrating two distinct biomarkers have demonstrated encouraging outcomes in detecting patients with substantial liver fibrosis, enhancing positive predictive value (PPV), and consequently decreasing screening failure rates in clinical trials while minimizing unnecessary liver biopsies [67-69]. Prior research indicated that MEFIB (MRE plus fibrosis-4 [FIB-4]) exhibited much superior diagnostic accuracy compared to both MRE and the FIB-4 index independently [67]. A recent study significantly compared MEFIB, MAST (MRI–aspartate aminotransferase), and FAST (FibroScan–aspartate aminotransferase) in identifying stage ≥2 fibrosis in patients with NAFLD, revealing MEFIB's superiority (PPV, 95%; negative predictive value, 90%) over both MAST and FAST (both P<0.001) [69].

8. Forecasting hepatic-related consequences

Numerous retrospective investigations indicate that MRE may be important in forecasting the long-term prognosis of individuals with NAFLD [70-72]. A recent meta-analysis of six cohorts, including 1,707 patients with a median follow-up of three years, examined the correlation between the LS value assessed by MRE and liver-related outcomes [67]. The hazard ratio for liver-related events in patients with a liver stiffness (LS) value of 5–8 kPa was 11.0 (P<0.001), while in patients with an LS value of ≥8 kPa, it was 15.9 (P<0.001), relative to those with an LS value of <5 kPa. The MEFIB index was established using the optimal cutoff values for LS and the FIB-4 index, which are considered positive when the LS value measured by MRE is ≥3.3 kPa and the FIB-4 index is ≥1.6. A positive MEFIB index showed a strong correlation with liver-related outcomes (HR=20.6; P<0.001), whereas a negative MEFIB exhibited a significant negative predictive value for liver-related outcomes (99.1% at 5 years).

Nevertheless, few retrospective investigations have elucidated the correlation between MRE and the clinical outcomes of individuals with NAFLD. Consequently, additional multicenter prospective studies are necessary to elucidate the relationship between liver stiffness evaluated by MRE and liver-related clinical outcomes.

9. Novel approaches based on magnetic resonance imaging

Advancements in MRE approaches, such as automated liver elasticity assessments and enhancements in shear-wave transmission, are poised to provide a more rapid and dependable examination of the liver. Three-dimensional (3D) magnetic resonance elastography (MRE) is an innovative imaging modality that evaluates shear-wave propagation over many planes to eliminate mathematical assumptions [63]. A distinct motion-sensitized, multislice, spin-echo echo-planar imaging sequence is conducted during the 3D-MRE examination to evaluate shear-wave displacements in the x-, y-, and z-directions.

While 3D-MRE demonstrates superior accuracy than 2D-MRE in forecasting severe liver fibrosis in NAFLD patients, more validation is necessary to substantiate the advantages of this approach [63]. Multiparametric MRI quantifies shear stiffness, loss modulus, and MRI-derived fat fraction in a single examination. 3D-MRE integrates a damping ratio at a reduced frequency, potentially enhancing the identification of NASH and NASH-associated fibrosis [73].

10. Conclusion

The primary use of noninvasive imaging biomarkers in NAFLD is to differentiate individuals with substantial or advanced hepatic fibrosis from those with moderate or absent fibrosis for prognostic evaluation and clinical decision-making. VCTE is the most extensively validated test; pSWE and 2D-SWE have performance equivalent to VCTE; and MRE is now regarded as the most precise noninvasive method for detecting and staging liver fibrosis. The clinical use of these tests is often contingent upon the availability of technology and the local competence within each institution.

A significant disadvantage of NITs is their inadequate accuracy in early-stage fibrosis diagnosis and their insufficient ability to differentiate between neighboring fibrosis stages. Distinguishing other processes that elevate LS values, including inflammation, biliary obstruction, cholestasis, passive congestion, and heightened portal venous pressure, from liver fibrosis presents an additional barrier. Investigations into noninvasive imaging biomarkers in NAFLD, particularly for their use in screening and risk assessment, will continue as the incidence of the illness escalates and novel therapeutic approaches are developed. Ultimately, a combination of noninvasive imaging indicators, liver biopsies, and clinical characteristics is essential for the precise evaluation of fibrosis stage and risk classification in individuals with NAFLD.

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التقدم في تقنيات التصوير غير التدخلي لتشخيص أمراض الكبد: مراجعة شاملة

الملخص

الخلفية :تزداد انتشار مرض الكبد الدهني غير الكحولي (NAFLD) على مستوى العالم، حيث يؤثر حاليًا على حوالي 25% من السكان. يعتبر التقييم الدقيق لتليف الكبد أمرًا حاسمًا، حيث يؤثر بشكل كبير على التشخيص واستراتيجيات الإدارة. على الرغم من أن خزعة الكبد تظل المعيار الذهبي لتقييم التليف، فإن طبيعتها الغازية والمخاطر المرتبطة بها أدت إلى تطوير تقنيات تصوير غير غازية متنوعة.

الطرق :تستعرض هذه المراجعة بشكل منهجي التقدمات الأخيرة في تقنيات التصوير غير الغازية لتقييم أمراض الكبد، مع التركيز على تقنيات مثل الإيلاستوجرافيا الانتقالية المعتمدة على الاهتزاز(VCTE) ، والإيلاستوجرافيا بالرنين المغناطيسي(MRE) ، وإيلاستوجرافيا الموجات القصيرة (SWE).يتضمن التحليل دراسات مقارنة حول الأداء التشخيصي، والدقة، والقابلية السريرية لهذه الطرق في تشخيص تليف الكبد.

النتائج :تشير النتائج إلى أن VCTE و pSWEو MREتظهر دقة تشخيصية عالية في الكشف عن التليف الكبير والتشمع، مع قيم منطقة تحت منحنى التشغيل (AUROC) تتراوح من 0.80 إلى 0.96. تُظهرMRE ، على وجه الخصوص، أداءً متفوقًا في المرضى الذين يعانون من السمنة وأمراض الكبد المتقدمة. من المتوقع أن تعزز التقنيات الناشئة التي تستخدم الذكاء الاصطناعي الدقة التشخيصية بشكل أكبر.

الخاتمة :تمثل المؤشرات الحيوية للتصوير غير الغازي، بما في ذلك VCTE و SWEوMRE، نهجًا واعدًا لتقييم تليف الكبد، مما قد يقلل من الحاجة إلى الخزعات الغازية. تقدم هذه التقنيات مزايا كبيرة من حيث سلامة المرضى وراحتهم مع الحفاظ على دقة تشخيصية عالية. يجب أن تركز الأبحاث المستقبلية على توحيد المناهج ودمج هذه تقنيات التصوير في الممارسة السريرية الروتينية لإدارة فعالة لأمراض الكبد.

الكلمات المفتاحية :مرض الكبد الدهني غير الكحولي، تليف الكبد، التصوير غير الغازي، الإيلاستوجرافيا بالرنين المغناطيسي، الإيلاستوجرافيا الانتقالية المعتمدة على الاهتزاز.