Review Article

# Adaptation of Clinical Practice Guideline for Assessment of Liver Fibrosis in Patients with Non Alcoholic Fatty Liver Disease in Isfahan Province

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## Abstract

Non-alcoholic fatty liver disease (NAFLD) refers to the presence of hepatic steatosis (accumulation of fat in the liver to over 5% of its weight) in the absence of secondary causes of fat accumulation in the liver such as excessive alcohol use. NAFLD is divided into two types: non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH). Therefore, in this clinical guideline, we sought to determine general and important policies for this disease and modify its managment approaches. We adapted this guideline for the management of NAFLD in Isfahan Province. This guideline was developed by clinical appraisal and review of the evidence, available clinical guidelines, and in consultation with members of the Isfahan Chamber of the Iranian Association of Gastroenterology and Hepatology. Biopsy is recommended as the most reliable method (gold standard) to diagnose steatohepatitis and fibrosis in patients with NAFLD. NAFLD fibrosis score (NFS) and fibrosis-4 (FIB-4) are recommended as the test with the highest predictive value for advanced fibrosis in patients with NAFLD compared to other serologic tests. Among the noninvasive methods used to assess liver fibrosis, transient elastography (TE) is preferable to other methods.

**Keywords:** *Clinical practice guideline, fatty liver, guideline, liver fibrosis, NAFL, NAFLD, NASH, non-alcoholic fatty liver disease, non-alcoholic fatty liver, non-alcoholic steatohepatitis*

## Introduction

Non-alcoholic fatty liver disease (NAFLD) refers to the presence of hepatic steatosis (accumulation of fat in the liver to over 5% of its weight) in the absence of secondary causes of fat accumulation in the liver such as excessive alcohol use.[1-3] NAFLD is divided into two types: non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH). Although both are considered NAFLD, they are different. In NAFL, hepatic steatosis is present without evidence of overt hepatitis, whereas in NASH, hepatic steatosis is associated with hepatitis and may not even be cytologically differentiable from alcoholic steatosis.[1,2,4,5]

NAFLD is the most common liver disease worldwide, especially in Western societies, the second leading cause of liver transplantation and the third leading cause of hepatocellular carcinoma (HCC). The prevalence of NAFLD and NASH in the United States (USA) is 30% and 5%, respectively; the prevalence of NAFLD is approximately 25% across the world and has been estimated at 27.4% in Asia.[1,2,4]

The prevalence of the disease has doubled in the last 20 years, while the prevalence of other chronic liver diseases has remained constant or even decreased. NASH is also a chronic liver disease worldwide that is closely associated with diabetes and obesity. At least 1.46 billion adults and 170 million children in the world in 2008 were overweight or obese. It is also estimated that approximately six million people in the USA have NASH and about 600,000 have NASH-related cirrhosis.[3]

Most of the patients with NAFLD are between 40 and 50 years old, and its prevalence increases with age. The prevalence of NAFLD seems to be higher in men, but the prevalence of NASH and fibrosis appears to be higher in postmenopausal women. NAFLD is more prevalent in patients with central obesity, type 2 diabetes and insulin insensitivity, dyslipidemia, and metabolic syndrome. It is independent of polycystic ovary syndrome (PCOS), hypothyroidism, obstructive sleep apnea (OSA), and hypogonadism.[1,2,4-6]

In most patients, NAFLD is asymptomatic and is only diagnosed accidentally when a



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liver blood test or abdominal ultrasound is performed for any other reason. Even then, more than 80% of patients with NAFLD have a normal liver blood test result. Blood biochemistry shows a slight increase in transaminases. Serum transaminase levels are useful for NAFLD screening, but do not indicate NAFLD severity. Noticeably, a significant number of patients with NAFLD also have normal transaminase levels.[4]

The natural history of NAFLD is almost dual so that NAFL has generally a benign course, while NASH can progress to hepatic fibrosis, liver cirrhosis and failure, and HCC.[2] The high global prevalence, dangerous complications, and associated mortality of NAFLD necessitate diagnostic methods; the development and severity of fibrosis in these patients accentuate the need to manage its complications such as cirrhosis, liver failure, and liver cancer.

Given various methods of examining fibrosis in different countries based on criteria such as test costs, diagnostic power, access to tests, and national facilities, there are several clinical strategies to examine hepatic fibrosis. However, there is no such guideline and protocol in Iran as far as we searched local and international databases. Due to geographical and economic differences and lack of access to all methods of measuring hepatic fibrosis, it is not possible to model these protocols objectively.

It seems that the codification of an appropriate clinical guideline will lead to familiarity and coordination among the professionals involved and reduces NAFLD complications. We codified a clinical guideline using a critical review of the evidence, available clinical guidelines, and consultation with members of the Isfahan Association of Gastroenterology and Hepatology. Family physicians and general practitioners, as the main users of this guideline, are the first level of exposure to patients with hepatic fibrosis. Screening and determining people who need examination, treatment, or clinical and laboratory follow-up is a necessity for family doctors and general practitioners who are in the first line of the health medical system. Besides, an appropriate clinical guideline can correct and coordinate the approach of internal medicine specialists' gastroenterologists and hepatologists to this disease.

Coordinated implementation of clinical guidelines in the health system can help implement equity in health by preventing wastage of funds by allocating facilities to critical cases. The use of clinical guidelines along with robust expertise can lead to the standardization of health services. Therefore, in this clinical guideline, we sought to determine general and important policies for this disease and modify its management approaches.

## Methods

To codify the guideline, keywords including "liver fibrosis," "fatty liver," "non-alcoholic fatty liver disease," "non-alcoholic fatty liver," "non-alcoholic steatohepatitis," "NAFLD," "NAFL," "NASH," "guideline," and "clinical practice guideline" in the search engine and databases PubMed, Trip database, Google Scholar, ClinicalKey, and the website of scientific and prestigious associations such as the American Association for the Study of Liver Diseases (AASLD), the European Association for the Study of the Liver (EASL), the National Institute for Health and Care Excellence (NICE) guideline, and the American College of Gastroenterology (AGA) were searched [Table 1].

Guidelines published in English and available in full text were collected. Simultaneously, relevant literature was searched for the best evidence. The development of this clinical strategy was conducted at the Isfahan University of Medical Sciences in 2020–2022.

The review of clinical guidelines was conducted using the Appraisal of Guidelines, Research and Evaluation (AGREE) scoring system. The 23 criteria of the scoring system are classified into six sections, each of which addresses one aspect of guideline quality.[7] In a specific schedule, the clinical recommendations and solutions of the question were generated based on different guidelines. The level of evidence for each of the recommendations was obtained using international guidelines and solutions at four levels (high, moderate, low, and very low) [Table 2].[4,8] Thirty-five eligible members of the Isfahan Association of Adult Gastroenterology and Hepatology were enrolled by a census of all available people and the people participated voluntarily for the survey.

**Table 1: Databases and associations used to codify guideline**

| No. | Guideline's indexing | Weblink |
|---|---|---|
| 1 | PubMed | https://www.ncbi.nlm.nih.gov/pubmed/ |
| 2 | NICE guidelines | https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-guidelines |
| 3 | Trip database | https://www.tripdatabase.com/ |
| 4 | Google Scholar | https://scholar.google.com/ |
| 5 | ClinicalKey | https://www.clinicalkey.com/#!/browse/guidelines |
| 6 | European Association for the Study of the Liver (ESAL) | https://easl.eu/publications/clinical-practice-guidelines/ |
| 7 | American Association for the Study of Liver Diseases (AASLD) | https://www.aasld.org/publications/practice-guidelines |
| 8 | American College of Gastroenterology (AGA) | https://gastro.org/guidelines/ |

Expert opinion on the generated recommendations was evaluated using the electronic voting method and the feedback collection form, and the level of agreement for each recommendation was calculated based on voters' percentage [Table 3]. Finally, after analysis and classification of the elicited opinions, the recommendations were reviewed and finalized in the presence of the members of the clinical strategy codification team [Table 4].

After the final approval of the clinical guideline, a meeting was held with the collaborating team every 2 years to re-search and review the resources. In this meeting, the partner team was required to provide the latest evidence and scientific information and make changes if approved by the other members [Table 5 and Figure 1].

## Who should be screened for NAFLD?

The EASL, NICE, Asia–Pacific, and the World Gastroenterology Organisation (WGO) guidelines recommend NAFLD screening in high-risk populations. The high-risk populations for screening and undergoing liver enzyme tests include those with obesity, type 2 diabetes, metabolic syndrome, abnormal liver enzymes, hypertension, sleep apnea, family history, black race, hyperlipidemia, and sedentary lifestyle.[3,6,9,10]

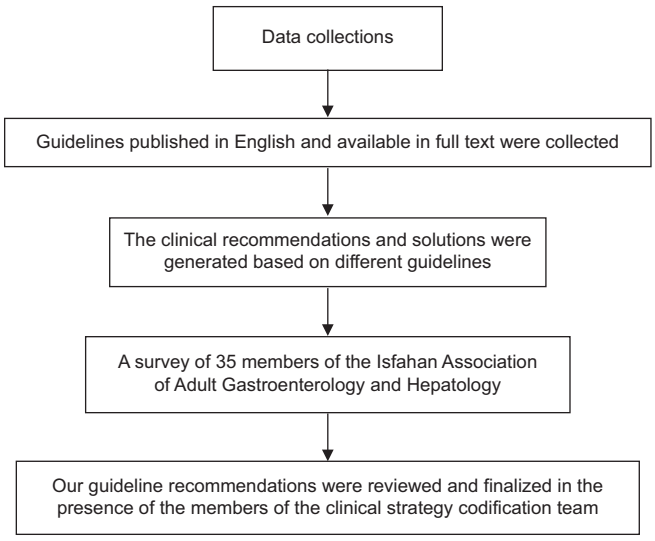


**Figure 1: Search method**

**Table 2: Level of evidence**

| Quality element | Description |
|---|---|
| High | Further research is very unlikely to change our confidence in the estimate of effect |
| Moderate | Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate |
| Low | Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate |
| Very low | Any estimate of effect is very uncertain |

**Table 3: Level of agreement**

| Leveling | Percent of agreement |
|---|---|
| Strong | >75% |
| Conditional | 66–74% |
| Weak | 50–65% |

## Which noninvasive test is used to diagnose NAFLD?

The purpose of noninvasive assessment is first to detect patients with NAFLD among individuals at high risk and then to monitor disease progression and treatment response, and identify patients with the worst prognosis.[11] The Italian Association for the Study of the Liver (AISF) guideline recommends that noninvasive NAFLD markers be used for their negative predictive value to prevent liver biopsy.[12] The two main types of noninvasive assessment methods of hepatic fibrosis are as follows:

- Serologic tests
- Imaging examinations.

## What are the types of serologic tests to diagnose NAFLD?

NAFLD fibrosis score (NFS) is based on six components: age, body mass index (BMI), hyperglycemia, albumin, platelets, and aspartate transaminase/alanine transaminase (AST/ALT) ratio, which is calculated using the published formula. This score is recommended as a prognostic marker to rule out the progression of the disease to fibrosis.[2,13]

Fibrosis-4 (FIB-4) index is an algorithmic calculation of four parameters consisting of platelet, age, AST, and ALT. The NFS and FIB-4 index are especially used in American guidelines to study advanced fibrosis.[1,2] The EASL and AASLD guidelines state that NFS and FIB-4 show the best predictive value for advanced fibrosis in patients with NAFLD compared to other scores.[2,14] The EASL guideline emphasizes that NFS and FIB-4 have stronger negative predictive value (approximately 90%) for advanced fibrosis than the respective positive predictive value.[14] Patients who are not likely to have advanced fibrosis (low risk, [FIB-4] <1.3) should undergo more frequent risk assessment with FIB-4 every 1–2 years.[15]

The AST to platelet ratio index (APRI) is calculated using AST level and platelet count. The AGA guideline states that APRI has a sensitivity of 0.78 and a specificity of 0.71.[1] Another index is AST/ALT ratio, which is usually <1 in healthy people. The AST/ALT ratio of >1 in the absence of alcohol consumption may indicate cirrhosis.[16]

The enhanced liver fibrosis (ELF) algorithm consists of three matrix turnover proteins (hyaluronic acid, tissue inhibitor of metalloproteinase 1, and N-terminal procollagen III peptide) and has 80% sensitivity and 90% specificity for diagnosing advanced fibrosis. This panel has been commercially approved in Europe but is not available for clinical use in the USA.[2,5] The NICE guideline

**Table 4: Summary of recommendations from different guidelines regarding various liver fibrosis assessment methods**

| No. | Guidelines | Serologic tests | Imaging examinations | Biopsy |
|---|---|---|---|---|
| 1 | AASLD (2) | NFS or FIB-4 | TE or MRE | Liver biopsy is the gold standard of diagnosis. |
| 2 | EASL–EASD–EASO (10) | NFS, FIB-4, (ELF), or FibroTest | TE is an acceptable noninvasive method for detecting patients at low risk of advanced fibrosis or cirrhosis. | Liver biopsy is essential for the diagnosis of NASH and is the only method that significantly differentiates NAFL from NASH, despite limitations due to sample diversity. |
| 3 | EASL (14) | • AST, ALT, and platelet count should be part of the routine initial testing.<br>• APRI, FIB-4, NFS, and ELF | • Ultrasound is recommended as a first-line tool for the diagnosis of steatosis in clinical practice.<br>• MRE is the most accurate noninvasive method for staging liver fibrosis. However, it is only slightly better for F3–F4 fibrosis than other noninvasive methods and is not recommended as the first line of diagnosis due to its cost and limitations.<br>• TE should be used to rule out and diagnose advanced chronic liver disease. | Liver biopsy is the standard reference for NASH diagnosis. |
| 4 | Japanese (4) | NFS and ELF | • CT scan and MRI are more objective and sensitive techniques for determining steatosis, but MRI remains to be widely available and is much more expensive.<br>• TE shows promising results for assessing the severity of liver stiffness. | Liver biopsy is a definitive diagnostic method for NFLD, but it is expensive, invasive, and sampling error, and varied interpretations are likely. Liver biopsy is recommended only for those patients with NAFLD who are at increased risk of NASH or have suspected chronic liver disease due to advanced fibrosis. |
| 5 | NICE (6) | ELF | Radiographic tests<br>Magnetic resonance-based techniques | Liver biopsy is the gold standard of diagnosis but is impractical and very expensive for large-scale use. |
| 6 | WGO (16) | AST/ALT | • MRI has quantitative value, but cannot differentiate between NASH and alcoholic steatohepatitis.<br>• Ultrasound is a routine screening test for fatty liver.<br>• TE is currently not recommended for general use due to limited access, high cost, and lack of controlled data. | Although liver biopsy is invasive and has the potential for sampling error and varied histological interpretations, it is essential for NASH diagnosis and staging. |
| 7 | WFUMB (27) | Blood markers such as platelets, hyaluronic acid, collagen IV, AST/ALT ratio, and serologic tests such as Fibro index, FIB-4, and FibroTest | • TE is useful for assessing diffuse liver disease and is able to distinguish significant fibrosis (F2 or greater) from insignificant fibrosis (F0–F1). But obesity and ascites limit the use of this method.<br>• Acoustic radiation force impulse imaging (PQSWE and SWE) | Liver biopsy is the gold standard of diagnosis. |
| 8 | AGA (1) | Use of direct and indirect serum markers such as FIB-4 and AST/ALT ratio | • TE (one of the most common methods of assessment)<br>• MRE<br>• Acoustic radiation force impulse imaging (PQSWE and SWE) | Liver biopsy is the gold standard of diagnosis. |
| 9 | EFSUMB (24) | Not mention | • TE<br>• Acoustic radiation force impulse imaging (PQSWE and SWE) | Liver biopsy is the gold standard of diagnosis. |

**Table 5: Recommendations of liver fibrosis assessment guideline in Isfahan Province**

| No | Recommendations | Level of evidence | Level of recommendation |
|---|---|---|---|
| 1 | Biopsy is recommended as the most reliable method (gold standard) to diagnose steatohepatitis and fibrosis in patients with NAFLD. | High | Strong |
| 2 | NFS is recommended as the test with the highest predictive value for advanced fibrosis in patients with NAFLD compared to other serologic tests. | High | Strong |
| 3 | FIB-4 is recommended as the test with the highest predictive value for advanced fibrosis in patients with NAFLD compared to other serologic tests. | High | Conditional |
| 4 | Noninvasive serum markers are recommended to predict the presence or absence of fibrosis. | Moderate | Conditional |
| 5 | Noninvasive serum markers are recommended to differentiate between intermediate stages of fibrosis. | Moderate | Strong |
| 6 | Noninvasive serum markers are recommended for significant cirrhosis. | Moderate | Conditional |
| 7 | If serum markers are negative, it is recommended to repeat the test every 2 years and, in case of fibrosis or abnormal liver enzymes, every year. | Very low | Conditional |
| 8 | For the diagnosis of overt cirrhosis, simple laboratory tests and then, if necessary, ultrasound are recommended. | High | Strong |
| 9 | Among the noninvasive methods used to assess liver fibrosis, TE is preferable to other methods. | High | Strong |
| 10 | TE is recommended to distinguish significant fibrosis (F2 or greater) from insignificant fibrosis (F0–F1). | low | Conditional |
| 11 | TE is not recommended for the diagnosis of patients without fibrosis or with minimal fibrosis (F0 and F1) and patients with severe fibrosis and cirrhosis (F3 and F4). | low | Weak |
| 12 | TE is recommended for patients with NAFLD to be screened for fibrosis. | High | Strong |
| 13 | TE is recommended for stage fibrosis 1–4 in patients with NAFLD. | High | Strong |
| 14 | TE is recommended to follow up on the changes in the fibrosis stage (exacerbation/ mitigation) in patients with NAFLD. | High | Strong |
| 15 | In case of limitations such as obesity, ascites, hepatitis, inflammation or congestion of the liver, cholestasis, and liver tumor; TE is not recommended as a suitable and available noninvasive tool to assess fibrosis and fatty liver severity. | Moderate | Strong |
| 16 | For re-screening for fibrosis/advanced fibrosis/cirrhosis, repeat TE is recommended every 5 years, except in patients with type 2 diabetes mellitus and increased BMI and ALT above normal, for whom the imaging examination is recommended to be repeated every 3 years. | Very low | Conditional |
| 17 | MRE is the most accurate alternative biopsy imaging examination that is not recommended for staging liver fibrosis as the first line of diagnosis. | low | Weak |
| 18 | In patients with ascites and obesity, SWE is recommended as a better method than TE for the diagnosis of fibrosis/advanced fibrosis/altered fatty liver fibrosis. | low | Strong |
| 19 | SWE, as with TE, is not recommended to distinguish between F2–F3 fibrosis stages. | low | Strong |
| 20 | A combination of serology tests and ultrasound is recommended to improve the ability to correctly assess the degree of fibrosis in patients. | High | Strong |
| 21 | The optimal approach to assess fibrosis is to use a noninvasive serum test (NFS or FIB-4) along with TE. If TE is not available, two different noninvasive serum tests should be used. | High | Strong |

recommends that advanced hepatic fibrosis be ruled out if the ELF score is less than 10.51. Reassessment of advanced hepatic fibrosis should be performed every 3 years for adults and every 2 years for children.[6]

FibroTest is a combination of quantitative results of five serum biomarkers including alpha-two macroglobulin, haptoglobin, apolipoprotein A1, total bilirubin, gamma-glutamyl transferase (GGT), age, and gender.[17,18] Fibrometer is a combination of platelet count, prothrombin, AST, alpha-2-macroglobulin, hyaluronic acid, blood urea nitrogen, and age. This test has been effective in predicting severe liver fibrosis in patients with chronic viral hepatitis.[19]

Hepascore contains a combination of bilirubin, GGT, hyaluronic acid, alpha-2-macroglobulin, age, and sex. Hepascore provides useful information about the different stages of fibrosis among hepatitis C patients as well as for the differentiation of advanced fibrosis in patients with alcoholic liver disease (ALD).[20,21] Hepascore has a sensitivity of 82%, a specificity of 65%, a positive predictive value of 70%, and a negative predictive value of 78% for predicting fibrosis.[21]

The Asia–Pacific guideline states that serum aminotransferase levels are not useful for NAFLD screening, and may be normal in patients with NAFLD and may increase in some patients with simple steatosis alone.[9]

The WGO guideline recommends clinical, laboratory, and instrumental follow-up for noninvasive monitoring of fibrosis every 2 years in NAFLD patients with normal liver enzymes and a low risk of advanced fibrosis.[11] The EASL and AISF guidelines recommend repeating the test every 2 years if serum markers are negative, repeating the test every year in case of fibrosis or abnormal liver enzymes, and repeating the test every 6 months in case of cirrhosis.[11,12,14]

## What are the types of imaging tests for NAFLD diagnosis?

Abdominal ultrasound is currently the most common and first-line method for diagnosing hepatic steatosis in patients with elevated liver blood tests or suspected NAFLD.[4,11] Ultrasound has a sensitivity of 92% and a specificity of 100% for the diagnosis of NAFLD. Its advantages include availability and low cost. However, its sensitivity is low in obese patients (BMI >40 kg/m$^2$) and may not diagnose NAFLD when the liver fat content is less than 20%. Despite these limitations, ultrasound can assess moderate to severe steatosis very well.[9,11,22,23] The NICE guideline recommends that liver ultrasound be used to diagnose hepatic steatosis in children with metabolic syndrome and type 2 diabetes, and if it is negative, be repeated every 3 years.[6]

Magnetic resonance imaging (MRI) is the gold standard to assess and quantify hepatic steatosis and detects liver fat as high as 5–10%. Despite high accuracy, restricted access, stupendous cost, and long implementation time make this method not recommended in common clinical settings.[11] Computed tomography (CT) scan and MRI seem to be more objective and sensitive techniques for quantifying steatosis, but MRI is still less available and much more expensive. CT scan also exposes patients to ionizing radiation, so its use is not recommended, especially for children.[4,23]

The American Radiological Association and European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) offer several major noninvasive imaging modalities including transient elastography (TE), magnetic resonance elastography (MRE), and shear wave elastography (SWE) [point quantification SWE (PQSWE) and two-dimensional (2D) SWE] for the assessment of hepatic fibrosis.[24,25]

TE or FibroScan easily and noninvasively measures the amount of stiffness in the liver tissue. Its cut-off value is 9.9 KpA for advanced fibrosis in adults with NAFLD with 95% sensitivity and 77% specificity.[11] TE indications for patients with NAFLD include screening and staging of fibrosis and follow-up of diagnosed fibrosis.[25,26] Suspected advanced fibrosis (F3/F4) can also be primarily clarified by elastography.[26] The use of TE in patients with chronic hepatitis B is also useful for the diagnosis of liver cirrhosis.[4,24] In the absence of limitations such as obesity, ascites, hepatitis, inflammation or congestion of the liver, cholestasis, and liver tumor, TE is a suitable and available noninvasive tool to assess fibrosis and estimate the severity of fatty liver.[14,27] Repeat TE is recommended every 5 years, except for patients with type 2 diabetes mellitus and increased BMI and ALT above normal level for whom the procedure is recommended every 3 years.[24,27,28]

MR imaging systems for MRE are equipped with a device for generating shear waves in the body that implements mechanical waves and processing software to produce quantitative color-coded images (elastograms) that measure tissue hardness in kPa. This procedure is conducted by holding the breath with a full exhalation and takes 12–15 seconds. This procedure is usually repeated four times and takes less than a minute. The area of the liver that is routinely evaluated by MR is the right lobe and therefore shows a much larger volume of liver tissue than that performed with ultrasound elastography.[25]

MRE is the most accurate noninvasive method for staging hepatic fibrosis and is more widely used than TE in patients with ascites and obese patients. However, it is only slightly better for F3–F4 fibrosis than other noninvasive tests. Due to its cost and limitations, MRE is not recommended as the first-line noninvasive test.[14] Some evidence suggests that to identify different fibrosis stages in patients with NAFLD, it is better to use MRE than TE to diagnose intermediate fibrosis stages but for advanced stages of fibrosis, MRE and TE have the same prediction.[11] The AASLD guideline recommends that MRE and TE are both useful tools to detect NAFLD patients with advanced hepatic fibrosis.[2]

In acoustic radiation force impulse (ARFI) imaging, tissue mechanical stimulation with short-lived sound pulses is used that propagates shear waves away and causes local displacement in the tissue. Its sensitivity and specificity for cirrhosis are higher than 90%, but for stages F2 to F4, it is approximately 85%. The advantage of this imaging method is that it can be used with a standard ultrasound device and overcomes the limitations of ascites and obesity seen with TE.[17] Besides this, SWE, as with TE, seems to be unsuitable for distinguishing intermediate fibrosis stages.[11]

## What are the best diagnostic algorithms and follow-up strategies?

In general, the use of several serologic tests or a combination of serologic tests with imaging examinations increases the possibility of accurately assessing the stage of fibrosis.[10,24,26] The EASL guideline recommends that a sequential combination of NFS and FIB-4, as the first test, followed by TE (better than any other test used alone) be used to identify patients at moderate or high risk of advanced liver disease (with an accuracy of 75–80% and reduction of uncertainty to less than 10%).[14] The AASLD guideline recommends NFS or FIB-4 and TE or MRE as the first line of examination to detect patients with advanced fibrosis.[2]

## Who needs a liver biopsy?

Liver biopsy is currently the most reliable method (gold standard) to diagnose steatohepatitis and fibrosis in patients with NAFLD. Biopsy has limitations such as sampling error, variation in the interpretation of results by pathologists, high costs, and patient discomfort. Therefore, biopsy should be performed in patients who benefit most from diagnosis, treatment, and prognostic information.[1,2,5,6,17,24]

The NICE guideline states that it is essential to use a simple noninvasive biopsy method to determine the NASH because 20–30% of the population has NAFLD.[6] Except for the NICE guideline, which does not provide specific indications for patients who should undergo liver biopsy, other guidelines basically agree that liver biopsy should not be conducted in all patients with NAFLD. Liver biopsy is recommended only in patients with an unspecific diagnosis or suspected NAFLD-related advanced liver disease.[2,3,9,11]

The AASLD recommends liver biopsy in patients with metabolic syndrome who are at increased risk of hepatitis, or when NFS, FIB-4, or liver stiffness measured by TE or MRE suggests advanced hepatic fibrosis.[2] The Asia–Pacific guideline recommends that liver biopsy be used in patients with NAFLD who are suspected of having chronic liver disease or when NASH needs to be differentiated from other chronic liver diseases (especially autoimmune hepatitis).[9]

The EASL and AISF guidelines also recommend that liver biopsy be performed to confirm the presence of advanced fibrosis when both serologic tests and noninvasive imaging examination show a moderate or high risk of advanced liver disease. In addition, they emphasize that in patients with NAFLD at high risk of disease progression, repeat liver biopsy should be considered on a case-by-case basis every 5 years.[5,12]

## What are the types of liver biopsy procedures?

### A) Percutaneous liver biopsy:

In this method, the patient lies on his back with his right hand up and his head on the bed. The clinician then makes a small incision under the last right rib and inserts the needle. Liver biopsy takes only a few seconds. As the needle enters and leaves the liver quickly, the patient is asked to hold his or her breath. Contraindications to percutaneous biopsy include patient non-cooperation, coagulation disorders, hepatitis, extrahepatic biliary tract obstruction, ascites, obesity, possible vascular lesions, amyloidosis, and hydatid disease.[29]

### B) Transjugular liver biopsy:

Coagulation disorders or ascites are common in liver disease patients. Under these conditions, percutaneous liver biopsy is prohibited due to the increased risk of bleeding. For this reason, Transjugular liver biopsy (TJLB) or transfemoral transcaval liver biopsies (TFTC) are good alternatives. In TJLB, a very thin tube is traveled through the jugular (cervical) vein to the hepatic vein and then to

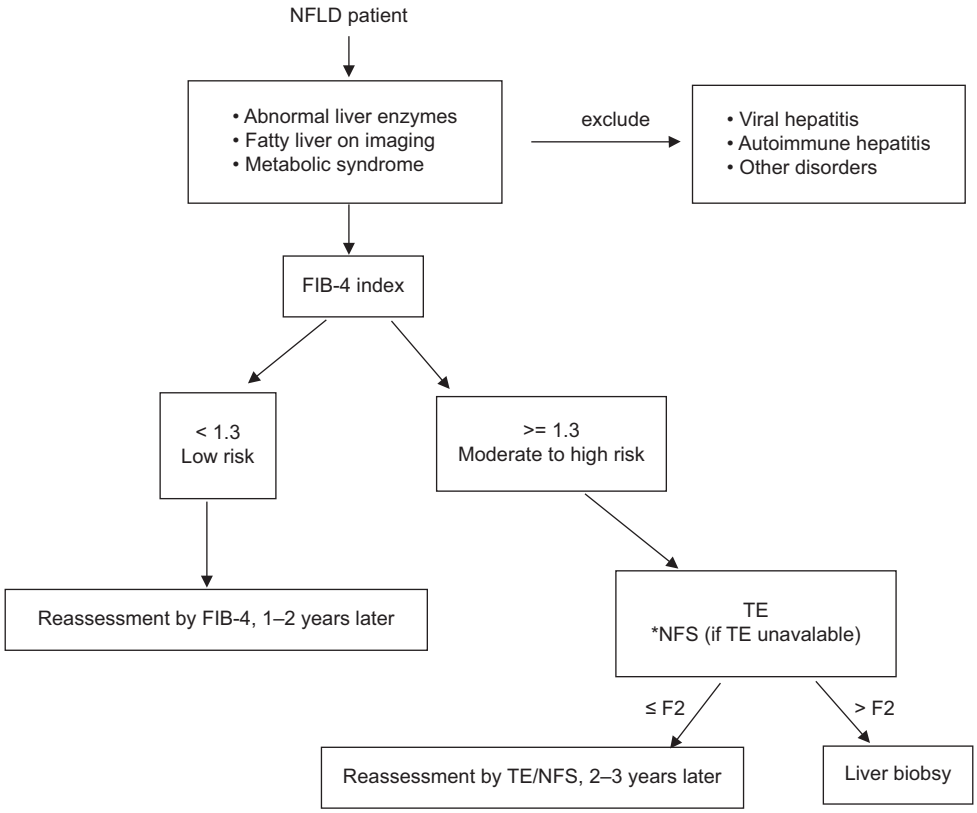


**Figure 2: Algorithm for assessment of liver fibrosis in patients with non alcoholic fatty liver disease**

the liver itself. Then, a contrasting color is injected into the tube and some pictures are taken using X-rays. The color marked in the pictures allows the clinician to see the hepatic vein. Then, a needle is inserted into the liver through the tube to remove a small piece of the tissue. After removal of the tube, the neck slit is bandaged. Sometimes when TJLB has been unsuccessful or is not technically practical (such as in patients with internal jugular vein thrombosis), the TFTC may be used.[30]

**C) Laparoscopic liver biopsy:**

Laparoscopic biopsy is used for patients with coagulation disorders for whom TJLB is not practical or has been unsuccessful. In this method, a tube, which carries a camera, is inserted through the skin into the abdomen. The sampling needle is passed through the tube to the liver, and a sample of the liver tissue is removed. This method is more invasive than previous methods, and its diagnostic performance is high [Figure 2].[29,30]

Image-guided biopsy is recommended in patients with known liver lesions, people with history of intra-abdominal surgery, patients with small liver that is difficult to puncture, obese patients, and patients with ascites.

For most patients, percutaneous liver biopsy is the preferred approach because it is less invasive and less expensive than other methods. TJLB is generally recommended in patients with clinically obvious ascites who require liver biopsy, although percutaneous biopsy (after ascites evacuation) or laparoscopic biopsy is also acceptable.[29]

### If there is fibrosis, which scoring system is used?

There are several histological scoring systems for chronic liver disease. Many use the meta-analysis of histological data in viral hepatitis (METAVIR) scoring system. The METAVIR score rates fibrosis on a 5-point scale from 0 to 4. A score higher than F2 indicates significant fibrosis.[31]

F0 = no fibrosis.

F1 = portal septal fibrosis without septum.

F2 = portal fibrosis with multiple septa.

F3 = large number of septa without cirrhosis.

F4 = cirrhosis.

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### Conflicts of interest

There are no conflicts of interest.

### Authors Contributions

All author contributed to the design, collected data, interpretation of result, editing and review this article.

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