REPLACEMENT OF LIVER BIOPSY BY NON-INVASIVE TEST IN CHRONIC LIVER DISEASE: A SYSTEMATIC REVIEW

BY
MICHAEL HAMAOUI
COURSE VI
GROUP 30

Supervisor: Dr Mitraite
Department of Radiology
Medical academy
Lithuanian University of Health Sciences
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ABSTRACT

Background: Among the available approaches, in order to diagnose and for the management of parenchymal liver disease, liver biopsy remains the choice, which possibly provides the most direct and reliable information regarding fibrosis patterns and changes in the parenchyma at different clinical stages and with different etiology. Liver biopsy may be used in patients with suspected liver cirrhosis to confirm the diagnosis, or exclude other liver pathologies. It provides accurate staging of the degree of liver injury in order to enable the prediction of prognosis and manage treatment decisions. However, it is an invasive procedure that carries the risk of morbidity, mortality and sampling error is very frequent since a large sample is required for an ideal assessment. In recent years, different approaches have been developed and improved, as non-invasive procedures to diagnose chronic liver disease. These non-invasive tests represents a lower cost, an easy and routinely procedure and can be suitable for liver biopsy replacement. It is expected to reduce, but not completely eliminate the need of liver biopsy.

Objectives: This work aims to compare and review recent literature about the non-invasive tests used in the diagnosis of chronic liver disease, considering its limitations and advantages in order to identify if liver biopsy could be replaced.

Methods: A systematic literature review was performed to ascertain the performance and prognosis accuracy of laboratory tests (direct and indirect markers), Fibroscan, ultrasonography, Ultrasound elastography, CT scan and MRI for the detection of liver fibrosis and cirrhosis.

Results: The combination of direct and indirect markers has reported an accuracy of 95.3% in chronic liver disease. The performance of Fibroscan has shown an accuracy of 92%, it correlates with liver biopsy examination for significant fibrosis. The accuracy of Fibroscan remains very high, nevermind the cause of fibrosis and cirrhosis, Contrast enhanced CT imaging is been considered to be the most potential technique in the evaluation of liver fibrosis. The MR elastography in the detection of liver fibrosis and cirrhosis demonstrate an excellent outcome with a predictive sensitivity of 98% and specificity of 99%.

Conclusion: Non-invasive markers are improving day after day, becoming less expensive and more accurate, however they cannot replace liver biopsy. All those non invasive tests have shown a reduction in the need of liver biopsy, based on these findings, it is conceivable to anticipate and predict the outcome of liver disease, therefore it is expected to reduce but not completely abolish the use of liver biopsy.
ALT: Alanine transaminase
AST: Aspartate transaminase
ALD: Alcohol liver disease
AUC: Area under the curve
ARFI: Acoustic radiation force impulse
AFLD: Alcohol fatty liver disease
APRI: AST to platelet ratio index
CT: Computer tomography
CHC: Chronic hepatitis C
DWI: Diffuse weight imaging
HCV: Hepatitis C virus
HBV: Hepatitis B virus
HA: Hyaluronic acid
LB: Liver biopsy
MRI: Magnetic resonance imaging
MELD score: Model for end stage liver disease
MRE: Magnetic resonance elastography
NAFLD: Non-alcoholic fatty liver disease
NASH: Nonalcoholic Steatoathitis
PIIIP: Procollagen III peptide
TE: Transient elastography
US: Ultrasound
YKL-40: Human cartilage glycoprotein-39
Liver cirrhosis represents the end stage of many forms of chronic hepatitis of different etiology and with quite variable courses.

Alcohol has long been identified as the strongest risk factor for liver cirrhosis. In fact, cirrhosis mortality has traditionally been used as a valid indicator for tracing the health consequences of alcohol abuse. However, viral infections such as hepatitis B and C viruses (HBV and HCV) are also important determinants of cirrhosis, and their possible contribution to temporal trends should be taken into account.

Cirrhosis is defined as the histological development of regenerative nodules surrounded by fibrous bands in response to chronic liver injury. The process involves the whole liver and is essentially irreversible.

The accumulation of collagen fibers and non-collagenous components in the extracellular matrix determines a progressive distortion of liver structure wall until a clear picture of a diffuse process characterized by fibrosis and the conversion of a normal liver architecture into structurally abnormal nodules surrounded by annular fibrosis.

It is a process that is influenced by many risk factors in many ways (sex, genetics, environment, lifestyle, obesity, immunosuppression, treatment).

Although cirrhosis diagnosis is based on histological features, it can be clinically classified as compensated and decompensated which is defined by the presence of clinical and laboratory signs (ascites, encephalopathy, esophageal varices, thrombocytopenia, hypoalbuminemia) and the presence of portal hypertension.

Liver biopsy remains the gold standard to confirm liver cirrhosis; it provides an accurate staging and degree of liver injury. However, it implies risks of morbidity, mortality and sampling error is very frequent. LB was primarily used with the purpose of helping find the etiology of liver dysfunction. It is now as well performed to assess the degree of necroinflammatory and fibrotic changes, which will provide information to base therapeutic decisions.

For the last decades, non-invasive methods have been used to detect and follow up liver cirrhosis with the aim of providing a more accurate assessment of liver injury and progression to liver cirrhosis.
Aim and objectives:
Non-invasive tests in the detection of chronic liver disease have been analyzed and compared from previous literature in order to detect if liver biopsy could be replaced or abolished. The research process is established in order (1) to report the non-invasive tests in chronic liver disease diagnosis, (2) the role of the tests and managements in chronic liver disease, (3) the advantages, accuracy and limitations of the tests.

Methods:
A systematic literature review was conduct to ascertain the performance and prognosis accuracy of laboratory tests (direct and indirect markers), Fibroscan, ultrasonography, ultrasound elastography, CT and MRI for the detection of liver fibrosis and cirrhosis. The search encompassed articles published throughout the last 10 years in English language. Studies were included if: (1) they included epidemiology data; (2) they were published or accepted for publication as full-length articles. Studies were excluded if: (1) they were published before 20 years; (2) they were published only in abstract form so that the methodological quality could not be assessed.
All result of studies has been review, studied and compare in order to explain the advantages, accuracy and limitations of the tests.

Conflict of interest: the author reports no conflicts of interest.
1. Laboratory tests:
Serum markers have been reported to reflect liver injury and offer a sampling of all liver. Some of them are more informative than others. Far less invasive than liver biopsy, it is based on routine laboratory test results and it is therefore readily available in the clinical practice. It determines the severity of hepatic fibrosis. On the following will review and analyze the different markers that detect liver cirrhosis.

1.1 Indirect markers of fibrosis and cirrhosis: Indirect markers are routinely done and reflect alteration in hepatic function. The first indirect markers were transaminases, ALT level can provide information of liver injury, however it doesn’t correlate always with liver damage, it can be found that the level of transaminase remains normal in cirrhosis because of the decrease function and production of the liver (figure 1). Although AST/ALT ratio provides useful clinical information regarding both cause and severity of liver disease. The increased ALT level is related to mitochondrial dysfunction and reduces clearance of AST by hepatic sinusoidal cell. Therefore AST/ALT ratio has been showed to be an indicator in the progression of chronic hepatitis to liver cirrhosis. In variant studies, there is a good correlation between AST/ALT ratio, child-Pugh’s score, MELD score and monoethylglycineexylidide. An AST/ALT ratio more than 1 suggest severe liver injury, In chronic hepatitis B patients without clinical signs of cirrhosis, AST/ALT ratio more than 1.0 may predict the progression of fibrotic change. However the ratio does not go above 2.0. In chronic hepatitis C patients the elevation of AST/ALT ratio correlates as well with the fibrotic change [1]. An AST/ALT ratio over 2.0 is common in alcoholic cirrhosis, but it could be associated because of recent alcohol exposure rather than cirrhosis. Thrombocytopenia is a common complication in cirrhosis, it is explained by the sequestration of thrombocytes in the spleen and decreased production of thrombopoietin in the liver. The Aspartate aminotransferase (AST) to platelet ratio has shown correlation identifying the presence of significant fibrosis and cirrhosis. In a retrospective study, the increase APRI and the decrease of platelet count were significant factors associated with advanced liver fibrosis and cirrhosis compared to the absence of a significant fibrosis, only APRI presented a more accurately than the other serum makers in chronic hepatitis B and C patients and significantly differentiated between the F3 stage and F4 (METAVIR score, figure 2) [2].
Fibrotest remains one of the most widely investigated combination set of non-invasive markers of liver fibrosis. It is a combination of five-blood test including gamaGT, bilirubin, haptoglobin, apoliproprotein A1 and a2 macroglobulin. It is related to the gender and the age of the patient. Fibrotest has shown an accuracy of predicting the presence of severe fibrosis and cirrhosis with an AUC of 0.85 it has been extensively tested in-patient with chronic hepatitis C. A recent Meta analysis of 14 studies was conducted to assess the performance of panels of serum markers of hepatic fibrosis, it has shown a possible difference between cirrhosis and no cirrhosis with a median AUC of 0.87, but has difficulties providing information on fibrosis staging [3].

**Figure 1**: Serum aminotransferase levels in various liver diseases. Both chronic hepatitis and cirrhotic patients may have aminotransferase levels within the reference range. The red line indicates the upper limit of the reference range

**Figure 2**:

The METAVIR System

Algorithm for Evaluation of Histological Activity:

<table>
<thead>
<tr>
<th>Piecemeal Necrosis</th>
<th>Lobular Necrosis</th>
<th>Histological Activity Score</th>
</tr>
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<tbody>
<tr>
<td>0 (none)</td>
<td>0 (none or mild)</td>
<td>0 (none)</td>
</tr>
<tr>
<td>0</td>
<td>1 (moderate)</td>
<td>1 (mild)</td>
</tr>
<tr>
<td>1 (mild)</td>
<td>2 (severe)</td>
<td>2 (moderate)</td>
</tr>
<tr>
<td>2</td>
<td>0, 1</td>
<td>1</td>
</tr>
<tr>
<td>3 (severe)</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>0, 1, 2</td>
<td>3 (severe)</td>
</tr>
</tbody>
</table>

Fibrosis Scoring:

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No fibrosis</td>
</tr>
<tr>
<td>1</td>
<td>Stellate enlargement of portal tract but without septa formation</td>
</tr>
<tr>
<td>2</td>
<td>Enlargement of portal tract with rare septa formation</td>
</tr>
<tr>
<td>3</td>
<td>Numerous septa without cirrhosis</td>
</tr>
<tr>
<td>4</td>
<td>Cirrhosis</td>
</tr>
</tbody>
</table>
The Forns Index uses simply obtained parameters: Age, gamma-glutamyltransferase (GGT), cholesterol, and platelet count but it requires a relatively complicated calculation (figure 3). A cutoff score of less than 4.25 had a negative predictive value of 96% for excluding significant fibrosis (F2, F3, or F4). At a cutoff of greater than 6.9, the positive predictive value was 66% for significant fibrosis (F2, F3, or F4). This tool is useful and has good predictive value in selecting those with low risk of significant fibrosis, but does not reliably predict more advanced fibrosis or cirrhosis.

<table>
<thead>
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<th>Forns Index =</th>
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<tbody>
<tr>
<td>7.811 - 3.131 \times \ln(\text{platelet count [10^9/L]}) + 0.781 \times \ln(\text{GGT [IU/L]}) + 3.467 \times \ln(\text{age}) - 0.014 \times \text{cholesterol [mg/dL]}</td>
</tr>
</tbody>
</table>

*Figure 3:* Forns Index equation

1.2 Direct markers:
The direct or class I markers are the true markers that measure biochemical parameters in the peripheral blood; it will help to detect significant fibrosis and cirrhosis. Serum hyaluronic acid (HA) has been identified as a potential marker of fibrosis. The synthesis and the deposition of (HA) increases during fibrogenesis and a small parts or their split products is released into the systematic circulation, leading to an increase in their serum concentration. The HA level is higher for stage F4 and F3 (METAVIR score) than in F1 and F2. There is no significance in (HA) level for stages F0, F1, F2 and F3. In a prospective cohort of 140 patients, hyaluronic acid has been establish to be an excellent value for diagnosis of cirrhosis (Figure 4), The AUROC was .93 +/- 0.2 for the detection of cirrhosis. [4]. In a study conducted with 79 patients with NAFLD, they reveal the accuracy of (HA) in detecting severe fibrosis and cirrhosis, with 0.92 AUC value for cirrhosis. [5].
Laminin is a noncollagenous glycoprotein component of the ECM that is produced by hepatic stellate cells. It is deposited in the basement membrane of the liver. Serum levels of laminin are elevated above the upper limits of normal range (0.59–1.4 U/mL) or (9.74–2.46) as defined by different authors. Furthermore Kropf et al. had proposed a cutoff value of 1.45 for laminin for the detection of both liver fibrosis and cirrhosis in patients with chronic liver disease, and they correlate with the degree of perisinusoidal fibrosis. It showed an accuracy of 77% in the detection of significant fibrosis in CHC.

A relatively new marker recently has been described for the evaluation of hepatic fibrosis in chronic liver disease, YKL-40 is a glycoprotein strongly expressed in human cartilage and liver.

It is secreted by hepatic stellate cells, a principle effector in liver fibrogenesis.

In a cohort of 129 patients, serum YKL-40 was high in patient with alcoholic liver cirrhosis and non cirrhotic fibrosis, however the elevated serum was higher in alcohol cirrhosis than alcoholic hepatitis with a median level of YKL-40 3 to 5- fold higher than the upper normal level [6]. It is closely related to the degree of fibrosis. In a 10 years cohort with patient infected with hepatitis C virus, the sensitivity and specificity of YKL-40 for predicting disease progression in rapid fibrosing patients was greater than 95 %. [7].

Figure 4: Significant elevation of Hyaluronic Acid in fibrosis stage 4.
The serum type IV Collagen (Type IV collagen 7s domain) is recently an aid used in diagnosis in liver fibrosis and cirrhosis. It is composed of a major triple-helix, an amino-terminal triple-helix (7s domain) and a carboxy-terminal globular domain. The first two forms have been used in clinical studies. The serum 7-S domain level of patients with liver disease mainly reflects the degradation of type –IV collagen. In addition, the synthesis of type-IV collagen in the liver is increased in hepatic fibrosis. Therefore it is estimated that the deposition of serum type-IV collagen level may be increased in patients with liver cirrhosis in hepatitis C and NAFLD [8]. In a prospective study of 72 patients, it has been demonstrated that serum concentration of 7s collagen were markedly elevated in Nonalcoholic Steatohepatitis (NASH) patients with advanced hepatic fibrosis compared with patients with mild hepatic fibrosis. [9]. In comparison, type IV collagen is more used when focusing particularly on the diagnosis of advanced hepatic fibrosis.

In hepatitis C, procollagen III has been used as well to evaluate the stage of hepatic fibrosis, however, it is less accurate than collagen IV and (HA). Therefore it is not used as non-invasive markers for hepatic fibrosis. Type III collagen (PIIIP), correlates with the histological inflammation than fibrosis, therefore it reflects primarily active hepatic fibrogenesis in chronic liver disease. [10]. In a limited number of studies, cytokines have been tested for the prediction of liver fibrosis and cirrhosis, in which it has been found to have less value than ECM tests.

Direct markers may improve the diagnosis of the severity of hepatic fibrosis. To obtain a better accuracy, some authors have tried to combine different direct markers. In a recent study, the combination of laminin, (HA) and type IV collagen could predict the diagnosis of a significant fibrosis with 100% positive predictive value and specificity in Non alcoholic fatty liver disease. (11).
**Figure 5:** Diagnosis performance of non invasive markers of liver fibrosis in discriminating between no mild fibrosis (F0-F1 by METAVIR) and moderate advance fibrosis (F > 2 by METAVIR).

<table>
<thead>
<tr>
<th>Direct markers</th>
<th>Disease:</th>
<th>Sensitivity:</th>
<th>Specificity:</th>
<th>AUC:</th>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyaluronic acid</td>
<td>HCV</td>
<td>75-79</td>
<td>80-100</td>
<td>0.82-0.92</td>
</tr>
<tr>
<td></td>
<td>HBV</td>
<td>91</td>
<td>98.1</td>
<td>0.98</td>
</tr>
<tr>
<td></td>
<td>AFLD</td>
<td>87</td>
<td>93</td>
<td>0.79-0.87</td>
</tr>
<tr>
<td></td>
<td>NAFLD</td>
<td>66-85</td>
<td>68-91</td>
<td>0.78-0.87</td>
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<tr>
<td>Laminin</td>
<td>HCV</td>
<td>80</td>
<td>83</td>
<td>0.82</td>
</tr>
<tr>
<td></td>
<td>NAFLD</td>
<td>82</td>
<td>89</td>
<td>n.a.</td>
</tr>
<tr>
<td>YKL-40</td>
<td>AFLD</td>
<td>88.5</td>
<td>50.8</td>
<td>n.a.</td>
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<tr>
<td>Type IV</td>
<td>HCV</td>
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<td>75-88</td>
<td>n.a.</td>
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<tr>
<td>Collagen-7s</td>
<td>NAFLD</td>
<td>70</td>
<td>81</td>
<td>0.83</td>
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<tr>
<td>Procollagen</td>
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<td>60-78</td>
<td>74-75</td>
<td>0.69</td>
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<tr>
<td>III</td>
<td>AFLD</td>
<td>80</td>
<td>87</td>
<td>0.87</td>
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<table>
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<td>59-80.6</td>
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<tr>
<td></td>
<td>HBV</td>
<td>34</td>
<td>93</td>
<td>0.78</td>
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1.3: direct and indirect markers combined: Direct and indirect non invasive markers may be used to diagnose significant fibrosis or cirrhosis. In some studies, the panels called fibrometer combining platelets, prothrombine time, AST, alphaM, age, urea and (HA) with two main diagnosis targets (fibrosis stage and area of fibrosis) are applied in different causes of chronic liver disease: Chronic viral hepatitis, alcoholic liver disease and non-alcoholic fatty liver disease. In a study of Cales, it has been reported that a combination of fibrometer and fibrotest may save 44.8 % liver biopsies with an overall accuracy of 95.3 %.
3. Ultrasound and colour-Doppler ultrasound.

In the Diagnosis and fallow up of hepatic disease, Ultrasonography (US) is a non-invasive and inexpensive technique used as first line examination. (US) can identify causes of portal hypertension different than cirrhosis and therefore is performed routinely at the beginning of the diagnostic work-up of cirrhosis and portal hypertension. Findings of cirrhosis on conventional (US) include changes in liver morphology and portal hypertension.

Signs of cirrhosis:

- Surface nodularity 88% sensitive, 82-95% specificity
- Overall coarse and heterogeneous echo texture
- Segmental hypertrophy/atrophy
  - Caudate width: right lobe width >0.65 (43-84% sensitive, 100% specific)
  - Reduction of the transverse diameter (>30mm) of the medial segment of the left lobe (segment IV)

Signs of portal hypertension:

- Doppler flow changes
  - Portal venous system
    - Enlarged portal vein: >13mm (42% sensitive, 95-100% specific)
    - Slow portal venous flow <15 cm/sec
    - Portal vein thrombosis +/- cavernous transformation
    - Enlarged SMV and splenic vein: >10mm
  - Hepatic veins
    - Portalization of hepatic vein waveform
  - Hepatic arteries
    - “Corkscrew “appearance
    - Increase velocity
- Splenomegaly
- Ascites
- Fatty change
Figure 6: Sonography of diffuse liver in-patient with cirrhosis, the surface nodularity is shown clearly with evidence of irregular surface, facilitated by the presence of ascites.

In a study of 300 patients, liver surface nodularity had the highest diagnostic accuracy, with specificity of 95% (Figure 6), (Figure 7). When surface nodularity was considered alone, post-test probability of severe fibrosis or cirrhosis increased from 35% to 86%. As caudate lobe hypertrophy and hepatic venous blood flow were also taken into account, post-test probability increased only by 2% (13).

Figure 8:
A systematic review was performing to identify studies (21 selected studies) investigating the diagnosis accuracy of US imaging for CLD [14]. The assessment of the diagnosis was based on liver echogenicity, caudate lobe to right lobe ratio, portal vein maximum velocity, hepatic vein pulstility, liver parenchyma echo-pattern, spleen size and liver surface. Poor result was demonstrated in measurement of liver echogenicity, because it is associated in steatosis and not with fibrosis. Diagnosis accuracy for the caudate lobe to right lobe ratio has high specificity >90% and low sensitivity about 40 %. The most reported technique was the liver surface with high specificity (78%- 95%) and moderate sensitive (51%-73%). It has shown that assessment of liver surface demonstrate a useful screen for patient at risk CLD to assist in determining who should undergo a liver biopsy. Ultrasound diagnosis of severe fibrosis and cirrhosis is very accurate in HBV with sensitivity of 77% and specificity of 92.5% versus HCV-related cirrhosis providing sensitivity of 82.4%, specificity of 70.7% established by a score system consisting of liver surface, parenchymal echogenicity, vessel pattern and splenic size [15].

2. Transient Elastography (fibroscan)
It is well known that liver stiffness is related to degree of hepatic fibrosis. Liver elasticity is closely related with the fibrosis severity determined by histologic analysis. A recent Technique has been developed to quantitatively and non-invasively measures of liver stiffness. Transient elastography (TE) is now the most widely used non-invasive method for assessing the degree of liver fibrosis. It is explained by low frequency transient vibration that are transmitted, the elastic shear waves are generated and propagate through the underlying tissues. A pulse-echo is performed to measure the velocity of propagation of the wave directly related to the tissue stiffness. The result of fibroscan is given according the cut-off values expressed in Kpa. Significant fibrosis is present with value of 7.1 to 8.1 and cirrhosis by a cut-off value of 12.5 to 14.5. Performed rapidly, painless, and has high patient acceptance, TE is now assessing in routine practice. It has been shown to correlate in-patient with hepatitis C and other chronic liver disease. The results correlate with those of liver biopsy examination for significant fibrosis in 84% of the case and therefore can be used reliably for first line pretherapeutic evaluation of fibrosis in HCV infected patient [11a]. In a prospective study of 1,257 patient with chronic liver disease, positive and negative value for predictive of cirrhosis were 74% and 96%, and the performance accuracy rate was optimal of 92% (Figure 8), the result also suggest that the cut off values could be optimized if specifically defined for each cause. [12].
Significant increase in diagnosis of severe fibrosis accuracy has been reported when Transient elastography was combined with APRI in HCV infected patient [29]. Combined liver stiffness measurement by Fibroscan and US score has shown equal but not superior prediction of liver fibrosis and cirrhosis in-patient with chronic viral hepatitis; therefore it doesn’t improve the accuracy assessing hepatic fibrosis [16].

**Figure 8**: Diagnostic value (ROC curves) of Liver stiffness measurement for the diagnosis of cirrhosis in 775 patients, in 298 with HCV, in 122 with HBV, and in 122 with either alcoholic or nonalcoholic steatohepatitis.

3. **Second generation elastography.**

Transient elastography is first generation ultrasound elastography; new methods and techniques have been developed for second generation as acoustic radiation force impulse imaging (ARFI). It is not based only using shears wave speed but as well an acoustic pulse that generate shear waves and propagate into the tissue. The propagation speed of those shears waves increase with fibrosis severity and it is measured in meters. ARFI has different advantages over transient elastography; elastograms can be obtained in patients with ascites because the ultrasound beams penetrate trough liquids. Deeper region of the liver can also be assessed compare to Fibroscan. In early and rapid detection of significant fibrosis ARFI has proved to be a better predictor in chronic liver disease. In a study of 74 patients that underwent ARFI elastography, APRI index, FibroMax and successful liver biopsy, ARFI shows very good accuracy in prediction of F3 or F4 liver fibrosis with an AUC= 99.3% (21). However, ARFI does not show good result correlation in obese patient with chronic liver disease and non-alcoholic fatty liver disease [28]. ARFI appear to shown a better prediction for severe fibrosis and cirrhosis than APRI in patients with ALD.
It correlates strongly with necroinflammatory activity [22]. ARFI is a powerful tool, in prediction of fibrosis in-patient with HCV. In a large cohort of patient with chronic hepatitis C, ARFI correlated with liver fibrosis and the value increased in parallel with the stage of fibrosis with a P value < 0.0001. It integrates good value in differentiation in moderate to severe fibrosis but is not enough accurate between F1 and F2 METAVIR score [23].

4. CT and MRI
Second line imagining is important in the detection of intra and extrahepatic features in the diagnosis of liver fibrosis and cirrhosis. Alterations are seen in liver morphology such as surface and parenchymal nodularity with regenerative nodules, fatty changes, segmental hypertrophy and atrophy. Furthermore, blunt liver edges; collateral circulation, splenomegaly and signs of portal hypertension have been described as important findings in liver cirrhosis. Studies have demonstrated that liver parenchymal abnormalities, manifestation of portal hypertension and morphological changes in liver are the best predictive signs on MRI and CT [17]. CT findings may result into clinical evaluation of patients with chronic liver disease for a variety of reasons. Liver fibrosis or cirrhosis despite the stages can be found in a routine screening of patients undergoing abdominopelvic CT imaging, in different indications in the Emergency Department. A CT fibrosis score combining a reduced hepatic vein diameter and an elevated caudate to right lobe ratio are two variables that has been the most accurate measure for predicting cirrhosis. The CT fibrosis score has been evaluate in systemic literature review and reveal a sensitivity of 83% and a specificity of 76% for pre-cirrhotic liver fibrosis and a sensitivity of 88% and a specificity of 76% for liver cirrhosis [24] (Figure 9). (A variety of technique in CT can be applied for the evaluation of hepatic fibrosis. Contrast enhanced CT imaging is been considered to be the most potential technique in the evaluation of liver fibrosis. Liver perfusion reveals to be an important alteration in liver cirrhosis. Perfusion imaging provides the ability to detect regional and global alterations in liver blood flow. As portal venous flow decrease, hepatic arterial flow in contrast increases, a process known as hepatic arterial buffer [25], [26]. Hepatic micro vascularity parameters: mean transit time and permeability surface area product of contrast material are significant altered in liver cirrhosis, the main function is to image blood capillary time and it has been possible to use those parameters in chronic liver disease [27], it correlate with the degree of hepatic dysfunction and therefore perfusion CT can be used to evaluate the hemodynamic changes in patient with liver cirrhosis.
**Figure 9:** Pathologic caudate-right lobe ratio (CRL) in a patient with pre-cirrhotic liver fibrosis. Hypertrophy of the left and atrophy of the right liver. In axial planes a line parallel to the midsagittal plane was drawn through the right lateral wall of the first bifurcation of the right portal vein. Distances perpendicular to the drawn line to the most medial margin of the caudate lobe and the lateral margin of the right lobe midway between the main portal vein and the inferior caval vein were measured. The two distances were divided (caudate lobe/right lobe) and defined as the caudate-right-lobe ratio (CRL). The sum of liver vein diameters (LD) equals 7.8 mm. LD divided by CRL equals the CT fibrosis score, which is below 20 and therefore compatible with liver cirrhosis.

MRI is becoming more important in the liver imaging, with the advantage of lacking the ionizing radiation compare to the CT and the possibility of performing multiparametric imaging. With advances in technology, different methods have been developed such as diffusion-perfusion weighted MRI (DWI), MR elastography and MR spectroscopy. One of the first imaging biomarkers for diagnosing cirrhosis was the evaluation of caudate lobe hyperplasia with the caudate right lobe ratio [18]. Conventional MRI cannot observe early fibrosis but these images are sensitive for detecting moderate and advance fibrosis. In-patient with cirrhosis, microscopic water diffusion is decrease. The reduced liver diffusion can be qualitatively observed on the DW images. DWI, which is widely used in brain imaging, has become possible in the abdomen. It is based on water diffusion and microcapillary/blood perfusion (Figure 10). It does not require gadolinium contrast, which is an advantage for patients with renal dysfunction at risk for nephrogenic systematic fibrosis. In a study, the role of DWI in HCV patients demonstrates an excellent performance for the prediction of moderate and severe fibrosis and severe fibrosis and cirrhosis compare to Fibroscan and serum markers [19]. DWI could potentially used to fallow treated liver fibrosis and perform conventional MRI at the same time to detect not only fibrosis nut also hepatocellular carcinoma and signs of hypertension.
Figure 10: Transverse signal video inversion of the DWI shows decrease water diffusion in a patient with liver cirrhosis.

As explained above, the properties of the liver tissue in cirrhosis are becoming very firm. Based on these considerations, MR Elastography (MRE) has been developed for the evaluation of the liver and diagnosis in hepatic fibrosis and cirrhosis. It involves a three step process: (i) generating mechanical waves within the tissues of interest, (ii) imaging the micron-level displacement caused by propagating waves using a special MRI technique with oscillating motion-sensitizing gradients, and (iii) processing the wave images using an inversion” algorithm to generate quantitative maps of mechanical properties. MRE measured hepatic stiffness increase systematically with fibrosis stage. The predicted sensitivity and specificity for detecting liver fibrosis is 98% and 99% (Figure 11), [20].

Figure 11: MR elastography of the liver in a normal volunteer and a patient with cirrhosis. In the far right column, the wave image show that the shear wavelength was higher in the fibrotic liver than in the normal and the elastograms show that the mean shear stiffness of the fibrotic liver was much higher than the one with normal liver (12.1 +/- 1.2 kPa vs 1.8 +/- 0.3 kPa, respectively)
RESULTS

Study review has been used to describe non-invasive tests that could be perform to detect chronic liver disease. The data has shown accuracy of the tests depending on the etiology.

Direct and indirect markers: Serology markers are separate into two groups: Indirect and direct markers in each of the markers are reliable and have a better accuracy on the diagnosis of chronic liver disease depending on the etiology.

In indirect markers, AST/ALT has shown a good correlation as an indicator for progression of fibrosis, it s not accurate if it is taken as a single marker and cannot differentiate the stage of fibrosis. The ratio between AST/ALT has more specificity for the diagnosis of cirrhosis in chronic hepatitis patients. APRI has been well observed to detect specifically advanced liver fibrosis and cirrhosis in-patient with hepatitis B and C with a good sensitivity (41-91%) and specificity (47-975%). Between all indirect markers, Fibrotest remain the most accurate for predicting the presence of severe cirrhosis in hepatitis C infected patients and shows an AUC of 0.85. Regarding HBV it has a sensitivity of 34% and specificity of 93%. One of the advantages remains the possibility to observe the difference between cirrhosis and no cirrhosis with an AUC of 0.87%. Forns test is a useful tool as a predictive value but has not been able to predict advanced fibrosis or cirrhosis.

Regarding the direct markers HA has shown great value in diagnosis of cirrhosis with an AUC value of 0.93 for patient with alcohol liver disease. Nevertheless it is not well establish in lower stage of fibrosis and doesn’t t show significant result. In recent studies, YKL-40 described as new markers in hepatitis C and show sensitivity and specificity greater than 95%, it also has a better prediction of cirrhosis in alcohol liver disease than non-alcohol liver disease. In hepatitis C, collagen IV has shown better accuracy than procollagen III in advance liver disease than primarily. A new combination of direct markers has established a positive predictive value and specificity of 100%, it is the combination of laminin, HA, and type IV collagen. The combination of direct and indirect markers has reported an accuracy of 95.3% in chronic liver disease.
The performance of Fibroscan has shown an accuracy of 92%, it correlate with liver biopsy examination for significant fibrosis. The accuracy of Fibroscan remains very high no matter the cause of fibrosis and cirrhosis. However it does not show good value in obese patient.

In ultrasonography, diagnosis of cirrhosis remain used widely due to the great accuracy it doesn’t depend on the etiology, it has been reported that surface nodularity has shown the best accuracy for diagnosis in patients with cirrhosis with specificity of 95%, Transient elastography is usually used in association with conventional Ultrasonography. TE remains a good diagnostic tools in HCV infected patient ALD, however it is difficult to estimate moderate fibrosis, due to the lack in sensitivity.

CT scan is a very powerful tool, and a variety of technique can be applied in the evaluation of liver fibrosis and cirrhosis. Contrast enhanced CT imaging is been considered to be the most potential technique in the evaluation of liver fibrosis. Liver perfusion reveals to be an important alteration in liver cirrhosis. Conventional MRI cannot observe early fibrosis but it is more sensitive for moderate to late fibrosis. In HCV patient, DWI has shown better prediction of severe fibrosis and diagnosis than fibroscan and serum markers level. The MR elastography in the detection of liver fibrosis and cirrhosis demonstrate an excellent outcome with a predictive sensitivity of 98% and specificity of 99%.
Liver biopsy remains the gold standard to confirm liver cirrhosis, it provides an accurate staging and degree of liver injury. However, it remains vastly controversial and a debated subject because it implies risks of morbidity, mortality and sampling error is very frequent since a large sample is require for an ideal assessment.

The development of non-invasive markers and procedure for diagnosis liver damage has been evolved demonstrate with impressive diagnostic accuracy, reliability that can be used as an alternative of liver biopsy.

There is an urgent need for non-invasive surrogate markers for a more practical and rapid initial screening for disease stage and risk of progression.

Serology markers can be divided into direct and indirect markers.

The indirect markers of fibrosis are still insufficient to monitor the evolution of chronic liver disease. The accuracy may be reduced by multiple factors such as comorbidity and on going drugs therapies.

APRI has to be taken in caution because of their sensitivity in predicting fibrosis that can be influenced by the etiology of fibrosis. However the most reliable tests in serology is the combination of the direct and indirect markers due to the possibility of applying the test to different cause of chronic liver disease and can therefore explain the cause and predict the stage in chronic liver disease. The combination of fibrometer and fibrotest may save 44.8 % liver biopsies with an overall accuracy of 95.3 %.

Imaging techniques in associations with serology markers remains reliable in prediction or staging of liver fibrosis

Now a day, Ultrasound technique is repeatedly used in liver damage detection. It is easy to perform and has become a standard diagnosis test. It gives a relatively high accuracy on the diagnosis and it is based on clinical finding and liver morphology. The most reported technique is the liver surface nodularity with high specificity more than 90%. In some specific case, Ultrasound will determine if liver biopsy is indicated or not.

Fibroscan has shown great value in diagnosis of chronic liver disease, it shows a very good sensitivity in patient with HCV and alcohol liver disease, but has its limit too, it doesn’t predict fibrosis with patient with mild fibrosis, and therefore it is always clinically associated with the use of serology markers and ultrasonography. The advantage of those tests can be explain by the routinely use and easy interpretation.
Improvement methods and technique in radiology imagery as called second generation elastography will offer accurate prediction cirrhosis in chronic liver disease; ARFI is a powerful non-invasive tool with a very high accurate diagnosis of moderate to severe fibrosis in-patient with ALD, HCV and other chronic liver disease. It is becoming part as a routine test with many advantages. In order it can be integrate into a conventional ultrasound system and allow a very exact liver stiffness measurement. It can also be used in-patient with ascites and narrow intercostal spaces or in whom Fibroscan has not been obtained.

CT scan is a potential accurate tool for diagnosis of liver fibrosis and cirrhosis, but until now the measurement of liver stiffness by CT has limitation because of the potential harmful dose of radiation. However MR elastography and diffuse-weighted MRI are able to detect liver fibrosis in a pre-cirrhotic stage with great accuracy. MR elastography appears to be the most reliable MRI based methods. It has shown a greater sensitivity and specificity than DWI for staging fibrosis. Other advantages of MR imaging techniques are the ability to assess the entire liver.

The non-invasive markers are improving day after day. For instance, serum panels are useful in measuring liver damage over time; they are rapidly and routinely performed. However they are unsuitable for staging the hepatic fibrosis, because of the inability to quantify the extend or area distribution of liver fibrosis. Radiology imagery as CT scan is emerging with greater accuracy and has the possibility to quantify and qualified the stage of the damage liver. However it is not without consequences and involved a great dose of radiation. In the near future, MRI may represent an alternative to liver biopsy. It appears to be the best choice to detect the pre-cirrhotic stage. The advantages are also based on the diagnosis and could prevent cirrhosis.

**Conclusion:**
Those entire non-invasive tests have shown a reduction of the need of liver biopsy, based on these findings, it is conceivable to anticipate and predict the outcome of liver disease and prevent complication. Therefore it is expecting to reduce but not completely abolish the use of liver biopsy. Further studies have to be made to explore the real potential of all those tests.
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