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THE ENHANCED LIVER CIRRHOSIS TEST (ELF) ACCURATELY IDENTIFIES CIRRHOSIS IN PATIENTS WITH CHRONIC LIVER DISEASE

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Abstract

Chronic liver disease (CLD) is the leading cause of death worldwide. That caused by Viral Hepatitis B and C (HBV, HCV), Alcoholic Liver Disease (ALD) and Non-Alcoholic Fatty Liver Disease (NAFLD). The present article provides an overview of the literature reporting some relevant biomarkers (ELF test) that have been found to be associated with liver fibrosis and that potentially may be used to predict the onset and/or monitor the progression of liver cirrhosis alternative the liver biopsy. This article provides an overview of the current published evidence on the clinical utility of the ELF test. This review collects the main evidence on the emerging role of Enhanced Liver Fibrosis (ELF) score as a prognostic marker of hepatitis, cirrhosis, and other liver diseases as the marker in cases of intoxication with organ phosphorus compounds and myocardial infarction or acute infections, and evidence that proves to use the Enhanced Liver Fibrosis as clinical practice presents an attractive alternative to both biopsy and imaging modalities that require significant high costs, also trained clinician.The most recent study proves that enhanced liver fibrosis score can be used instead of liver biopsy test and Transient Elastography for diagnosing liver fibrosis.

Keywords: Enhanced Liver Fibrosis Score, Transient Elastography, Liver, Liver Biopsy, Liver Diseases Alcoholic Liver Disease (ALD) and Non-Alcoholic Fatty Liver Disease (NAFLD).

Introduction

The stage of fibrosis is the most important one indicator of morbidity and mortality in chronic liver disease(1). Significant contributors include Viral Hepatitis B and C (HBV, HCV), Alcoholic Liver Disease (ALD) and Non-Alcoholic Fatty Liver Disease (NAFLD), although several other aetiologies exist and some of these causes may co-exist. Managing patients with CAD requires evaluation and accurate diagnosis of fibrosis to identify those who are most at risk and who need treatment or lifestyle modification. Suppression or reversal of fibrosis and possibly even early cirrhosis can restore liver functionality and minimize complications such as the development of Portal Hypertension or Hepatocellular Carcinoma. Liver biopsy remains the gold standard to evaluate liver fibrosis. Not least, one has to keep in mind that liver biopsy provides additional information like histological grading and etiology that may be overlooked when surrogate markers are used (2-5). But in recent years, large restrictions have been recognized that undermine the sensitivity and accuracy of diagnosis. But in recent years, large restrictions have been recognized that undermine the sensitivity and accuracy of diagnosis.

Although detailed vision in the cellular mechanisms that lead to liver fibrosis and cirrhosis, the current availability of non-invasive tests to monitor fibrosis is limited to date. Ideally, those tests should answer two questions. First, what is the stage of fibrotic organ damage (i.e. the amount of deposited ECM and the disturbed balance of hepatic microarchitecture)? Secondly, what is the net balance between ECM

deposition and degradation (i.e. the dynamics of ECM turnover)? The former serves to evaluate the prognosis and indicate therapy, while the latter might be used to control the efficacy of treatment with regard to disease progression.

The alternatives to biopsy have recently become available, including both imaging modalities and blood tests. Enhanced Liver Fibrosis (ELF) requires a blood sample only to assess the levels of three direct markers [Hyaluronic Acid (HA), Amino-terminal Propeptide of Type III collagen (PIIINP) and Tissue Inhibitor of Matrix Metalloproteinase 1 (TIMP-1)] of fibrosis and utilizes an algorithm to calculate a numeric score(6).

When using this test for patients with Chronic Liver Disease allows physicians to better evaluate in the progression of liver fibrosis. It can significantly reduce the number of patients requiring Biopsy.

Disadvantages of biopsy

Fibrosis is not always homogeneous within the Biopsy sample. Different results with different of Biopsy size. The longer the sample size, the greater the accuracy of the diagnosis. The different conclusions that can be reached depending on the length of the biopsy sample and the placement of the collection needle.

Simple complications are relatively common in patients with postoperative pain such as severe bleeding which requires transfusion.

Biopsy is inherently invasive and contraindicated in some (such as patients who are undergoing anticoagulant treatment and those with advanced cirrhosis)

Patients are often reluctant to undergo repeat biopsy, limiting their use in monitoring fibrotic changes and treatment effectiveness.

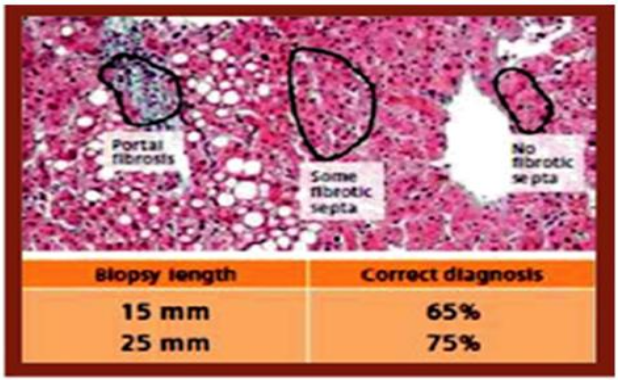

Figure 1: Size of biopsy sample and diagnostic accuracy(7)

Table 1: ELF score guidance

ELF Test Score	Interpretation	Action plan
>9.8	Likely severe fibrosis	Biopsy may not be required for liver fibrosis assessment
7.7-9.8	Uncertain may be moderate fibrosis	Biopsy may be recommended
<7.7	Likely no or mild fibrosis	Biopsy may not be required for fibrosis assessment

The ELF score provides a valuable enhancement over biopsy staging, in that, it is a continuous rather than categorical variable and is thus more sensitive to disease status and change. ELF score thresholds have been identified in populations of patients with known Chronic Liver Disease to identify these commonly used categories of fibrosis(8).

The low value of 7.7 was optimized for sensitivity, meaning any patient at or below that value has a low probability of any biopsy-proven significant fibrosis (none to mild). When used in a CLD population, a low ELF score can identify patients who are likely to avoid Biopsy safely (at least at the time of the ELF testing). Studies have suggested that as many as 43% of CLD patients could be safely ruled out for Biopsy using the ELF cut-off of 7.7 or less. Patients could then be monitored for any change, as fibrosis is a dynamic process and can change with time.

The high cut-point of 9.8 was optimized for specificity and is associated with biopsy-proven significant fibrosis. This means patients presenting with values greater than 9.8 are likely to have advanced fibrosis (to include cirrhosis) if they underwent Biopsy. Although a liver Biopsy is likely to be required for full assessment of the disease etiology and status, patients with high ELF scores could also likely avoid biopsy because the score indicates rule-in for significant fibrosis and instead be managed according to the specific cause of their CLD (e.g., antiviral therapy for HBV or HCV, alcohol abstinence for ALD and treatment of Non-Alcoholic Steatohepatitis [NASH])(9, 10).

ELF score values in chronic hepatitis C (CHC)

Study done by Ralf L et al. that study ELF scores in chronic hepatitis c. included 79 patients with CHC. The relation between ELF scores and histological staging. They found increasing levels of ELF score ranges from normal controls over moderate fibrosis

to end-stage cirrhosis. They conclusion, the ELF score appears to be a valuable tool for fibrosis staging in chronic liver disease. They recommended that factors of influence such as gender and age need to be taken into account. This is of particular relevance in the evaluation of low level fibrosis(8).

J.Parkes, et al. Studied the Enhanced Liver Fibrosis (ELF) test accurately identifies liver fibrosis in patients with chronic hepatitis C. That paper reported the simplification of the ELF test and its ability to identity severity of liver fibrosis in external validation studies in patients with chronic hepatitis C (CHC). In this study were analysed 347 biopsy and serum samples from patients with CHC in three independent. In this study were analysed 347 biopsy and serum samples from patients with CHC. In three independent. The simplified ELF test was able to predict severe fibrosis and using clinical utility modelling to predict severe fibrosis. Concluded that in chronic hepatitis C a simplified ELF test can detect severe liver fibrosis with good accuracy(11).

Primary Biliary Cirrhosis

Primary biliary cirrhosis (PBC) is a chronic cholestatic liver disease predominantly affecting middle-aged women. It is hypothesized that PBC begins with loss of immune self-tolerance, leading to damage of the biliary epithelial cells of small bile ducts. Recent evidence has suggested that environmental factors, including infectious agents and chemicals, might play a role in inducing PBC in genetically predisposed patients.The diagnosis of PBC is based on a combination of findings, including cholestatic liver enzyme levels, positive antimitochondrial antibody (AMA), and characteristic liver biopsy findings. AMA is positive only in 95% of patients. Liver biopsy reveals portal hepatitis and granulomatous destruction of bile ducts (12).

Recent evidence suggests that the ability of this algorithm of enhanced liver fibrosis score to predict clinical outcomes is as good as or better than traditional prognostic tests for PBC, particularly in early stages of the disease. In a study conducted by MJ Mayo et. al in 161 patients with PBC were prospectively followed between 1993 and 2003 they collected all the result of serum blood test at entry and every 3 months. At entry and at 2-year intervals, they also underwent liver biopsy test to assess histological changes, endoscopy to look for new varices, and abdominal ultrasound to look for new ascites. On the same day, a serum sample was stored over the long term, frozen, and later used for the serum fibrosis marker assay. Thus, all biochemical, serological, and histological data were precisely synchronized. Calculated the Enhanced liver fibrosis (ELF) test scores, were determined on frozen sera after the close of the study. This study concluded, the ELF algorithm is a highly accurate noninvasive measure of PBC disease severity that provides accurate prognostic information. The ability of this algorithm to predict clinical outcomes is as good as or better than traditional prognostic tests for PBC, particularly in early stages of the disease. It is a simple, noninvasive technique with long-range predictive ability that should be very useful in the clinical assessment of PBC.(13)

Nonalcoholic Fatty Liver Disease

Non-alcoholic fatty liver disease (NAFLD) is the buildup of extra fat in liver cells that is not caused by alcohol. It is normal for the liver to contain some fat. However, if more than 5% - 10% percent of the liver's weight is fat, then it is called a fatty liver (steatosis).(14)

Nonalcoholic fatty liver disease occurs in every age group but especially in people in their 40s and 50s who are at high risk of heart disease because of such risk factors as obesity and type 2 diabetes. The condition is also closely linked to metabolic syndrome, which is a cluster of abnormalities including increased abdominal fat, poor ability to use the hormone insulin, high blood pressure and high blood levels of triglycerides(15, 16).

NAFLD is initially suspected if blood tests show high levels of liver enzymes. The ultrasound is used to confirm the NAFLD diagnosis. Recently the enhanced liver fibrosis score can be used to identify patients who have early fibrosis in NAFLD.

In the study done in all of the United Kingdom, Nottingham and Newcastle-upon-Tyne, which studied Noninvasive Markers of Fibrosis in Nonalcoholic Fatty Liver Disease(17). That reported that enhanced liver fibrosis score can be used to identify patients who have early fibrosis in NAFLD, making them suitable tests for screening the increasing number of patients presenting with abnormal liver function tests, obesity, and metabolic syndrome. Also resulted, in that study, the ELF panel had excellent performance in distinguishing severe fibrosis (stage 3/4) with an AUC of 0.90 [confidence interval, 0.84-0.96]. Athreshold of 0.3576 was

associated with a sensitivity of 80%, a specificity of 90%, a positive predictive value of 71%, and a negative predictive value of 94%. In distinguishing moderate fibrosis, the overall AUC was 0.82 (confidence interval, 0.75-0.88). A threshold of _0.1068 was associated with a sensitivity of 70%, a specificity of 80%, a positive predictive value of 70%, and a negative predictive value of 80%. In distinguishing no fibrosis, the overall AUC was 0.76 (confidence interval, 0.69-0.83). A threshold of _0.2070 was associated with a sensitivity of 61%, a specificity of 80%, a positive predictive value of 81%, and a negative predictive value of 79%.

Conclusion

Accurate diagnosis of liver cirrhosis is critical to optimal management of chronic liver diseases. The distinction of patients with severe cirrhosis of those with benign diseases required an invasive biopsy, which is still unable to accurately assess the damage. In addition, biopsy is associated with pain, risk and large cost. The number of CLD patients is expected to increase significantly in the coming years. For this reason, a repeatable direct blood test for fibrosis offers great clinical attractiveness. The ELF test has been clinically validated in a range of Chronic Liver Disease.

ELF results in the previous studies allow the classification of fibrosis with a good probability that it is mild, moderate or severe and helps patients to reach the appropriate clinical pathway.

The routine accreditation of the ELF test in clinical practice provides an attractive alternative to both forms of biopsy and imaging that require substantial capital investment, trained physician, and limited patient access. As with all other current alternatives to biopsy, ELF can facilitate, but not completely replace the need for biopsy referral.

The most recent study proves that enhanced liver fibrosis score can be used instead of liver biopsy test and Transient Elastography for diagnosing liver fibrosis.

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