THE ELF TEST: A SIMPLER WAY TO DIAGNOSE AND MANAGE LIVER FIBROSIS

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ABSTRACT

Liver disease is a major cause of mortality both globally and in the United Kingdom. The earlier liver fibrosis is detected, the sooner interventions can be implemented, including lifestyle changes and medications. Non-invasive tests (NITs) for liver fibrosis are beginning to augment and replace liver biopsy in liver fibrosis assessment due to their ease of use, lack of complications and reproducibility. The enhanced liver fibrosis (ELF) test is a blood test that measures three molecules involved in liver matrix metabolism to give a score reflecting the severity of liver fibrosis. We will review the evidence supporting ELF as a diagnostic test, a prognostic marker and its use in disease monitoring. In doing so we will highlight the important role ELF plays in the early recognition of liver fibrosis facilitating timely referral to a liver specialist. The ELF test is useful in primary, secondary and tertiary care; not only allowing earlier diagnosis and more accurate prognosis, but also providing the opportunity to personalize treatment based on the patient's response.

KEY POINTS

• **Opportunity to use innovative NITs for diagnosis, prognostication and monitoring liver fibrosis.**
• **NITs can be used as well as or in place of liver biopsy**
• **ELF is an accurate diagnostic test to determine the severity of liver fibrosis.**
• **The ELF test is recommended in the National Institute for Health and Care Excellence guidelines on the management of non-alcoholic fatty liver disease (NAFLD).**
• **The ELF test has been validated in all common chronic liver diseases**
• **The ELF test also provides valuable prognostic information at least as accurate as liver biopsy.**
• **ELF can be used to monitor disease progression and response to treatment.**

KEY WORDS
• **Enhanced liver fibrosis (ELF) test**
• **Liver fibrosis**
• **Cirrhosis**
• **Non-invasive test (NIT)**
• **Liver disease**

INTRODUCTION

One of the most rapidly moving fields in hepatology is the discovery of NITs which aim to detect and quantify liver fibrosis at an early stage when interventions can alter progression to cirrhosis and with out the need for biopsy. Here we will review the growing impact the ELF test has had on this field in the last 10 years.

Chronic liver disease is placing an ever-increasing burden on the NHS in the United Kingdom currently estimated to cost £90bn per annum. Undetected, chronic liver disease may progress to fibrosis and eventually cirrhosis as collagenous scar tissue accumulates and the hepatic vasculature is distorted. Globally, decompensated cirrhosis is the eleventh leading cause of mortality (WHO 2016) and this rises to fifth for middle aged men in the United Kingdom. Furthermore, progression of liver disease to advanced fibrosis and cirrhosis puts patients at a much greater risk of developing hepatocellular carcinoma (HCC), which is now the third commonest cause of cancer related death in the world (McGlynn et al 2015). Looking towards the future, whilst chronic liver disease caused by viral hepatitis is certainly going to decrease due to effective antiviral agents, the incidence of liver disease caused by obesity related non-alcoholic fatty liver disease (NAFLD) is likely to continue to rise.

In order to reduce the morbidity and mortality associated with chronic liver disease it is important that detection of fibrosis takes place before decompensation or end stage liver disease. By intervening at an early stage the incidence of oesophageal varices, encephalopathy and ascites will hopefully be reduced (Tsochatzis et al 2012; Williams et al 2015) and early detection of HCC can permit curative interventions. In NAFLD early interventions include lifestyle changes such as alterations in diet and exercise. Furthermore a range of new drugs are in late stages of development to prevent or reverse liver fibrosis.

For other causes of chronic liver disease (CLD) early detection of liver fibrosis can indicate the need for disease-specific treatments such as antiviral therapy, immunomodulators in autoimmune disease and abstinence from alcohol. Furthermore once cirrhosis has developed randomized controlled trials have demonstrated improvements in morbidity and mortality for treatments aimed at reducing portal pressure and reducing the bacterial burden and ammonia production in the gut. Early instigation of screening for liver cancers, which arises from earlier diagnosis of liver cirrhosis, offers the hope of the detection of smaller tumours that may be amenable to cure or more successful control. Later interventions include procedures such as transjugular intrahepatic portosystemic shunting (TIPSS), variceal banding, and eventually the only definitive treatment for advanced cirrhosis – liver transplantation.

Historically the gold standard and most specific test for the assessment of liver fibrosis has been liver biopsy. Biopsies are staged using a numerical system that assigns numbers (0-6 or 0-4) correlating to mild, moderate or severe fibrosis, and cirrhosis. In the Ishak scoring system a score of 0 corresponds to no fibrosis; stages 1-3 describe increasing fibrotic changes; stage 4 describes marked portal bridging; stage 5 describes nodule formation; and finally stage 6 describes cirrhosis. However, there are a number of drawbacks associated with liver biopsy. For example, it is not appropriate as a screening

test in a general practice setting or on a hospital ward, due to the invasive nature of the test and the expertise and cost required for both the procedure and analysis. Biopsies cannot be performed frequently in order to monitor disease progression. Despite the undoubted diagnostic value of liver biopsy in assessing disease aetiology and pathology the hazards associated with biopsy and the variability of the results due to sampling error associated with the size of the biopsy and inter-observer variability have led to the search for alternative approaches to fibrosis measurement.

Over recent years a number of non-invasive tests (NITs) have been discovered and validated, with the aim of detecting liver fibrosis before cirrhosis develops and becomes symptomatic and without the need for liver biopsy. Due to their ease of use, reliability and reproducibility they can also be used to monitor disease progression and response to treatment. Imaging and liver stiffness measurement (LSM) have played a large role in this, with fibroscan as the leading modality and many more techniques being developed in its wake such as acoustic radiation force impulse (ARFI) and supersonic shear imaging (SSI). Fibroscan has been widely evaluated and has been shown in multiple studies to be an accurate method for the detection of advanced fibrosis and cirrhosis (Castera et al 2008; Fernandez et al 2015). It is relatively easy to perform and is very well accepted by patients, providing prognostic as well as diagnostic value. Fibroscan now forms part of NICE guidance for the Non-invasive testing of liver cirrhosis (National Institute for Health and Care Excellence (NICE) 2017). However, fibroscan has been reported as performing less well in the detection of lesser degrees of fibrosis. With all NITs this may be because liver biopsy, as a reference standard, performs poorly in differentiating minor degrees of fibrosis, thus limiting the perceived performance of the comparator NIT.

A major consideration is that, similar to biopsy and other methods of LSM, fibroscan requires specialist expertise and instrumentation in order to achieve the levels of performance reported in the literature. Thus its use is limited by access to expertise and equipment. Furthermore, even in the most expert hands and optimal settings, Fibroscan fails to produce a usable result in up to 15% of measurements, particularly in the obese population (Cassinotto et al 2016). The XL probe has been developed for use in the obese population in order to improve accuracy.

Blood tests have the advantage that they can be obtained more easily, more quickly and are can be automated so that test performance is very reproducible. Furthermore, the continuous variable scores can offer more information than biopsy on minor changes in fibrosis severity, and more accurately reflect the biological process of fibrosis than categorical stages used in histological staging systems. Non-invasive blood tests used in the assessment of fibrosis include simple panels combining routine biochemical and haematological markers such as Fibrosis-4 index, aminospartate:platelet ratio index and the Forn's index (Wai et al 2003; Ucar et al 2013). These tests have the advantage of being cheaper and more readily available. However, more complex panels that measure matrix breakdown constituents such as Hepascore (Adams et al 2005) and Fibrometer (Cales et al 2005) tend to perform better at distinguishing between severe and mild fibrosis. The first direct biomarker NIT of this kind, the Enhanced Liver Fibrosis Test (ELF) has been validated in a wide range of liver disease etiologies.

The ELF test combines the measurement of three molecules involved in the metabolism of liver matrix; hyaluronic acid (HA), procollagen III amino acid terminal peptide (PIIINP) and tissue inhibitor of metalloproteinase 1 (TIMP-1). It was first derived and validated in a study by Rosenberg et al in 2004 (2004) using a cohort of over 1,000 patients. It has since proven to be a very effective and robust NIT in diagnosis, prognosis and disease monitoring of liver fibrosis. Subsequent studies have confirmed good accuracy, precision, analytical performance, linearity and robustness.

DIAGNOSIS

In order to replace biopsy for the assessment of liver fibrosis in suspected chronic liver disease, the ELF test must first be compared to the gold standard for diagnosis, the liver biopsy. In the original derivation and validation study (Rosenberg et al 2004) the ELF algorithm was able to detect fibrosis with 90% sensitivity and rule out significant fibrosis with a negative predictive value of 92% in a cohort containing a wide range of liver aetiologies. This initial study showed huge promise for the ELF test as an effective NIT in the diagnosis of liver fibrosis in patients with known chronic liver disease. Since then it has been validated as a diagnostic measure of liver fibrosis in patients with NAFLD (Guha et al 2008), hepatitis C (Parkes et al 2011; Fernandes et al 2015), HIV/hepatitis C virus co-infection (Swanson et al 2016), hepatitis B (Trembling et al 2014), primary biliary cirrhosis (Mayo et al. 2008), primary sclerosing cholangitis (De Vries et al. 2017), methotrexate-induced liver injury (Martyn-Simmons et al 2014) and alcoholic liver disease (Thiele et al 2018). Whilst the ELF test has been validated in all of these specialties it is not yet widely used in practice in all of them outside of hepatology.

The ELF test has also shown promising results in the paediatric population. Liver biopsies can often prove more difficult in the younger population, which along with issues around compliance and parental concerns, make establishing an effective NIT high priority. In NAFLD the ELF test has been shown to be an accurate measurement of liver fibrosis in paediatric population, both in isolation (Nobili et al 2009) and in combination with the paediatric NAFLD fibrosis index (PNFI) (Alkhouri et al 2011).

Leading on from this, the ELF test has also been shown to be an effective diagnostic test when used in combination with other NITs, such as the aminospartate:platelet ratio index in the assessment of liver fibrosis in hepatitis C (Petersen et al 2014). This suggests that ELF is a valuable diagnostic test both in isolation and in combination with other tests, and future work is likely to explore which are the optimal combinations of NITs that produce the best diagnostic yield.

Several studies have also looked in to the accuracy of the ELF test at different diagnostic thresholds, and how these perform despite confounding factors such as age and the presence of steatosis (Fagan et al 2015; Lichtinghagen et al 2013). There has been much work undertaken in conjunction with the test manufacturer, Siemens Healthineers, into

what are the optimal cut-off values. The values now agreed upon with the manufacturer are as follows; <7.7 for exclusion of significant fibrosis, ≥7.7 to <9.8 for moderate fibrosis, ≥9.8 to <11.3 for severe fibrosis, and ≥11.3 for cirrhosis (Day et al 2018). These cut-offs can be used by clinicians when analysing the results of the ELF test, and should aid the relaying of preliminary information obtained from the results of the test to patients.

In patients with NAFLD, NICE guidelines now recommend screening for advanced fibrosis using the ELF test (Glen et al 2016). The cut-off recommended for the diagnosis of advanced fibrosis is 10.51. These patients should then be referred to a hepatologist for further assessment. By identifying the patients with advanced fibrosis, these patients can undergo closer monitoring for the associated complications and considered for commencement of pharmacotherapy. Patients below this cut-off should be re-assessed every three years for adults and 2 years for children.. This is extremely useful for secondary care physicians who suspect their patient may have signs of advanced liver disease. As the ELF test is continuing to be validated in more and more disease aetiologies it is very possible it will be recommended in many more diseases for the assessment of fibrosis in years to come. The same threshold of 10.51 has been used in stratifying referrals from primary care with alcohol related liver disease (Thiele et al 2018) with good effect, illustrating the broad applicability of the ELF test in different aetiologies of CLD.

PROGNOSIS

As well as being useful for the diagnosis of liver fibrosis, the ELF test is also a useful prognostic marker in patients with liver disease. In a study by Parkes et al (2010) the prognostic ability of the ELF test was compared to liver biopsy in the original ELF cohort. This study showed that the ELF score performed at least as well as biopsy in predicting which patients would have a liver-related outcome (including any episode of decompensated cirrhosis, HCC, liver transplantation or liver-related death). The survival curves for different ELF cut-off values are displayed in Figure 1. The ELF cut-off scores of ≥9.8 to <11.3 and ≥11.3 correspond to severe fibrosis and cirrhosis respectively and the prognosis for these patients is displayed in Figure 1.

Individual studies have shown the ELF test to be a highly accurate prognostic marker in primary biliary cirrhosis (Mayo et al 2008), alpha1-antitrypsin deficiency (Janciauskiene et al 2011) and primary sclerosing cholangitis (de Vries et al 2017). A unit change in ELF score has been associated with a doubling in the risk of a liver-related outcome (Parkes et al 2011), and in some studies this has been shown to be as high as a four-fold increase (Irvine et al 2016). The ability of the ELF test to provide such accurate prognostic data is crucial when evaluating which patients need closer disease monitoring for complications such as varices, and when conveying information to patients about their disease and associated prognosis.

DISEASE MONITORING

As well as being highly valuable as a diagnostic test and prognostic indicator, the ELF test has also been shown to be very effective in monitoring progression of disease and response to treatment. This reduces the need for frequent liver biopsies in patients with established liver disease. In PSC the ELF test has been used to monitor fibrosis progression in a randomized-controlled trial of obetacholic acid (Nevens et al 2016). It has also been used alongside liver biopsy to monitor response to Liraglutide in non-alcoholic steatohepatitis (Armstrong et al 2016). In a study in 2017, Tanwar et al looked the ability of the ELF test to predict changes in liver fibrosis over a longer period in hepatitis C patients who had failed initial therapy and were now being trialed with pegylated interferon +/- Silymarin (Tanwar et al 2017). Their model, which combined histology and ELF score at baseline along with the ELF score at 12 months, was able to predict histology at 24 months. Using ELF in this way can allow earlier selection of patients who are likely to benefit from longer-term treatment, allowing a response-guided approach to treatment.

More recently the ELF test has been incorporated in a number of studies of drugs being investigated in the treatment of liver fibrosis in NAFLD and alcoholic liver disease. Comparison with liver biopsies has shown that ELF is an accurate monitoring test capable of detecting both fibrosis progression and regression. A retrospective analysis of NIT in a cohort of patients treated with hepatitis B virus polymerase inhibitors revealed that changes in ELF accurately monitored changes in histological fibrosis in hepatitis B.

In patients with established portal hypertension the ELF test has been shown to track hepatic venous pressure gradient accurately and so may be used to monitor patients at risk of, or with established portal hypertension without the necessity to perform invasive monitoring.

As the ELF score is a continuous variable it allows potential for closer monitoring of disease than biopsy alone. Analysis has shown that a change in ELF of 0.5 correlates with a single stage change in the Ishak staging system (Day et al 2018). However a small progression in fibrosis severity may not change the categorical stage as reported by a pathologist. The ELF test may well be a more accurate way of detecting these minor changes and while it may not push the score in to a new cut-off range, it would help clinicians in predicting the rate of disease progression. As previously mentioned this is supported by earlier work from Parkes et al showing that as little a 1 unit change in the score can actually double the likelihood of a liver-related event at seven years (Parkes et al 2010).

CONCLUSION

The Elf test has been shown to be an accurate diagnostic test as well as a prognostic and disease-monitoring marker in liver fibrosis. The extensive literature supports its use in replacing invasive tests such as liver biopsy when staging fibrosis. It is now being used alongside other non-invasive tests such as elastography in order to diagnose liver fibrosis,

monitor response to treatment and provide invaluable prognostic information. The ELF test is far more readily available than biopsy to both primary care practice and hospital clinicians and can quickly identify which patients require further investigation and management. The fact that it now forms a key part of the NICE guidelines in the management of NAFLD reflects this. The ability of the ELF test to provide detailed prognostic information reflects how closely it represents the biological process of fibrosis and allows clinicians to provide patients with accurate information early on. The minor changes in fibrosis detected by ELF and the ease of its use also enables it to be a very useful monitoring test and marker of response to treatment.

Further work may be warranted in to the combination of the ELF test with other NITs, including imaging-based tests, although it has proven to be accurate in isolation. Future work is also likely to focus on the applicability of ELF in even more aetiologies of liver disease. It is therefore very possible that the ELF test will spread across more guidelines in to the management of liver disease over the next few years.

This article aims to provide clinicians with the basic information required to understand the potential and the application of the ELF test in a range of clinical settings. While introducing and explaining the ELF test has been a major focus of this article it is important to recognize that there are a variety of NITs available but few with the robustness, wide applicability and evidence base of the ELF test. As it progressively becomes more widely used we expect fibrosis to be identified at an earlier stage, allowing earlier intervention and most importantly a decrease in the substantial morbidity and mortality associated with liver disease.
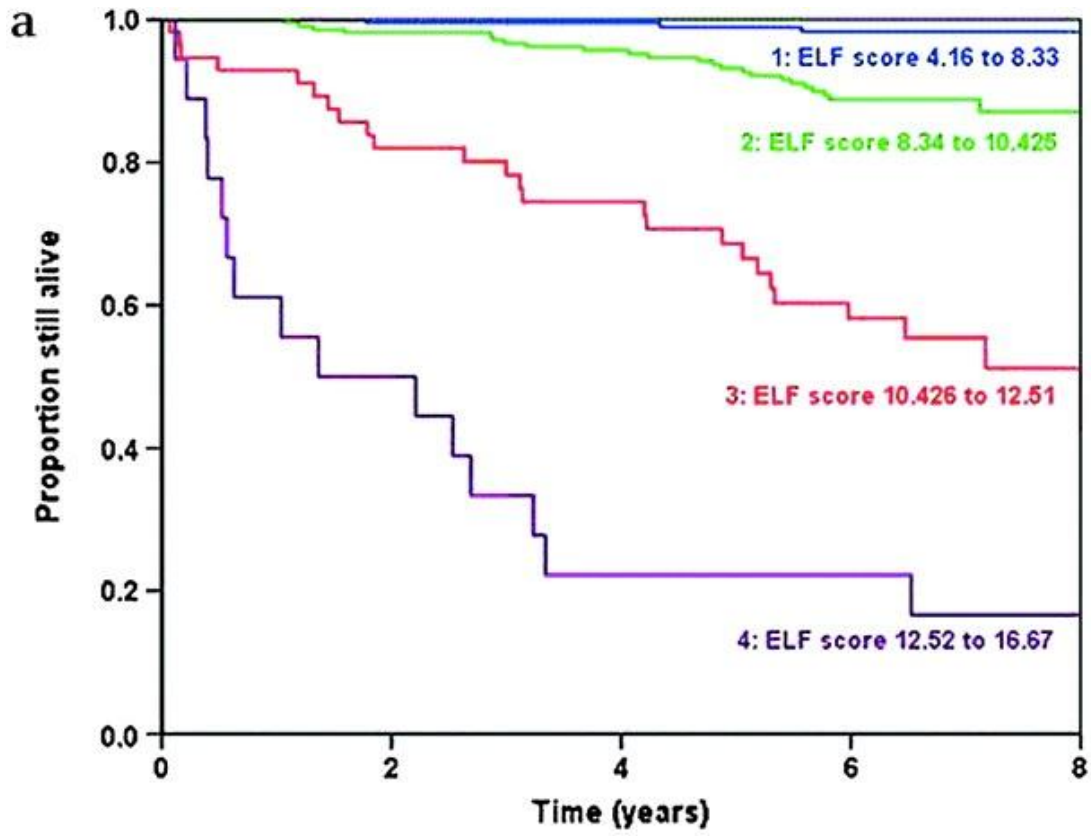
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FIGURE 1

The figure shows a Kaplan-Meier survival curve with "Proportion still alive" (0.0 to 1.0) on the y-axis and "Time (years)" (0 to 8) on the x-axis. Four curves are labeled:
- 1: ELF score 4.16 to 8.33 (blue)
- 2: ELF score 8.34 to 10.425 (green)
- 3: ELF score 10.426 to 12.51 (red)
- 4: ELF score 12.52 to 16.67 (purple)

- Parkes et al 2010. Kaplan-Meier survival curve to 8 years from liver-related outcomes for enhanced liver fibrosis (ELF) test.