The enhanced liver fibrosis (ELF) test in diagnosis and management of liver fibrosis

ABSTRACT

Liver disease is a major cause of mortality both globally and in the UK. The earlier liver fibrosis is detected, the sooner interventions can be implemented, including lifestyle changes and medications. Non-invasive tests for liver fibrosis are beginning to augment and replace liver biopsy in assessment of liver fibrosis because of 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. This article reviews the evidence supporting ELF as a diagnostic test, a prognostic marker and its use in disease monitoring. In doing so it highlights 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.

One of the most rapidly moving fields in hepatology is the discovery of non-invasive tests which can detect and quantify liver fibrosis at an early stage when interventions can alter progression to cirrhosis and without the need for biopsy. This article reviews the growing impact that the enhanced liver fibrosis (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 UK, currently estimated to cost £90 billion 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 (World Health Organization, 2018) and this rises to fifth for middle-aged men in the UK. Furthermore, progression of liver disease to advanced fibrosis and cirrhosis puts patients at a much greater risk of developing hepatocellular carcinoma, which is now the third commonest cause of cancer-related death in the world (McGlynn et al, 2015). Looking towards the future, while the incidence of chronic liver disease caused by viral hepatitis is going to decrease because of the use of effective antiviral agents, the incidence of liver disease caused by obesity-related non-alcoholic fatty liver disease is likely to continue to rise.

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In order to reduce the morbidity and mortality associated with chronic liver disease it is important that fibrosis is detected 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 hepatocellular carcinoma can permit curative interventions. In non-alcoholic fatty liver disease early interventions include lifestyle changes such as alterations in diet and exercise. Furthermore there is a range of new drugs in late stages of development to prevent or reverse liver fibrosis.

For other causes of chronic liver disease 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 detecting smaller tumours that may be amenable to cure or more successful control. Later interventions include procedures such as transjugular intrahepatic portosystemic shunting, 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 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, because of the invasive nature of the test and the expertise and cost required for both the procedure and analysis. Biopsies cannot be performed frequently to monitor disease progression. Despite the undoubted diagnostic value of liver biopsy in assessing disease aetiology and pathology,

> Liver biopsies can often prove more difficult in the younger population which, along with issues around compliance and parental concerns, make establishing an effective non-invasive test high priority.

the hazards associated with biopsy and the variability of the results as a result of 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 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. Owing 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 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 and supersonic shear imaging. FibroScan has been widely evaluated and shown 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 National Institute for Health and Care Excellence (2017) guidance for the non-invasive testing of liver cirrhosis. However, FibroScan performs less well in detecting lesser degrees of fibrosis. With all non-invasive tests 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 non-invasive test.

A major consideration is that, similar to biopsy and other methods of liver stiffness measurement, FibroScan requires specialist expertise and instrumentation 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 the 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 (Calès et al, 2005) tend to perform better at distinguishing between severe and mild fibrosis. The first direct biomarker non-invasive test of this kind, the ELF test, has been validated in a wide range of liver disease aetiologies.

The ELF test combines the measurement of three molecules involved in the metabolism of liver matrix: hyaluronic acid, 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 (2004) using a cohort of over 1000 patients. It has since proven to be a very effective and robust non-invasive test 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 non-invasive test 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 non-alcoholic fatty liver disease (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). While the ELF test has been validated in all of these conditions 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 non-invasive test high priority. In non-alcoholic fatty liver disease the ELF test has been shown to be an accurate measurement of liver fibrosis in children, both in isolation (Nobili et al, 2009) and in combination with the paediatric non-alcoholic fatty liver disease fibrosis index (Alkhouri et al, 2011).

Leading on from this, the ELF test is an effective diagnostic test when used in combination with other non-invasive tests, 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 non-invasive tests that produce the best diagnostic yield.

Several studies have also looked into 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 (Lichtinghagen et al, 2013; Fagan et al, 2015). Much work has been undertaken in conjunction with the test manufacturer, Siemens Healthineers, into the optimal cut-off values. The values now agreed upon with the manufacturer are: <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 non-alcoholic fatty liver disease, National Institute for Health and Care Excellence 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 patients with advanced fibrosis, these patients can undergo closer monitoring for the associated complications and considered for starting pharmacotherapy. Patients below this cut off should be re-assessed every 3 years for adults and 2 years for children. This is extremely useful for secondary care physicians who suspect that 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 that 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 chronic liver disease.

Prognosis

As well as being useful for the diagnosis of liver fibrosis, the ELF test is 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. 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, hepatocellular carcinoma, 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*.

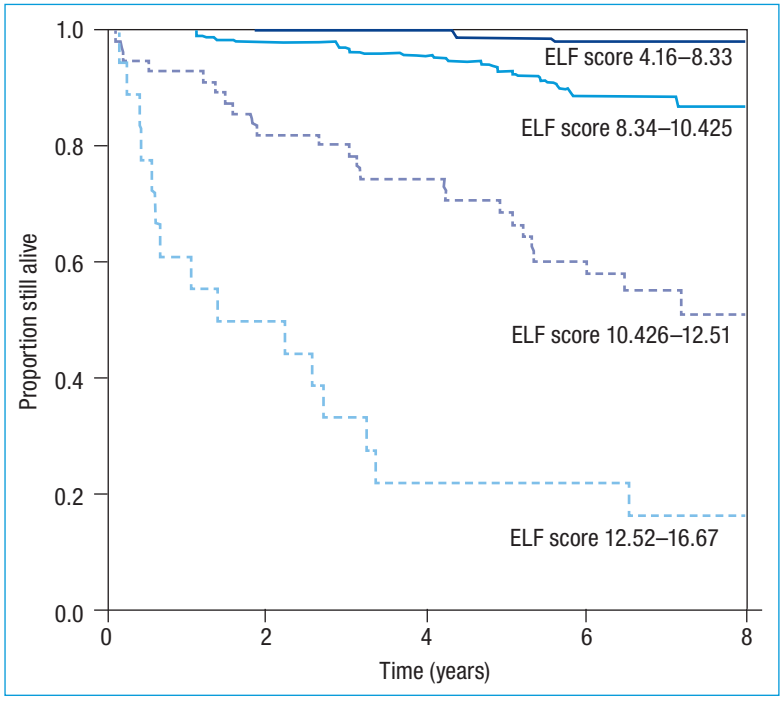

Figure 1. Kaplan–Meier survival curve to 8 years from liver-related outcomes for enhanced liver fibrosis (ELF) test. From Parkes et al (2010).

Individual studies have shown the ELF test to be a highly accurate prognostic marker in patients with 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 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 is also 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 patients with primary sclerosing cholangitis 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). Tanwar et al (2017) 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 trialled with pegylated interferon +/- silymarin. 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

KEY POINTS

- Innovative non-invasive tests can be used for diagnosis, prognostication and monitoring liver fibrosis.
- Non-invasive tests can be used as well as or in place of liver biopsy.
- The enhanced liver fibrosis (ELF) test 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.
- 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.

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 non-alcoholic fatty liver disease 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 non-invasive tests in a cohort of patients treated with hepatitis B virus polymerase inhibitors revealed that changes in ELF accurately monitored changes in histological fibrosis in patients with hepatitis B.

In patients with established portal hypertension the ELF test tracks 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 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 be a more accurate way of detecting these minor changes and while it may not push the score into a new cut-off range, it would help clinicians predict the rate of disease progression. As previously mentioned this is supported by earlier work from Parkes et al (2010) showing that as little as a one unit change in the score can actually double the likelihood of a liver-related event at 7 years.

Conclusions

The ELF test is 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 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 National Institute for Health and Care Excellence guidelines in the management of non-alcoholic fatty liver disease 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 into the combination of the ELF test with other non-invasive tests, 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 into the management of liver disease over the next few years.

This article provides 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 non-invasive tests available but few with the robustness, wide applicability and evidence base of the ELF test. As it progressively becomes more widely used the authors expect fibrosis to be identified at an earlier stage, allowing earlier intervention and most importantly leading to a decrease in the substantial morbidity and mortality associated with liver disease. **BJHM**

Figure 1 *is reproduced from Parkes et al (2010) with permission of BMJ Publishing Group Ltd.*

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