Non-invasive fibrosis markers

Professor Andrew K Burroughs and Dr Emmanuel Tsochatzis are taking a modelling approach to analyse cost-effectiveness and quality adjusted life years of non-invasive testing strategies for liver fibrosis.

Could you outline the most important findings from this?

AB&ET: An important finding from the meta-analysis was that the vast majority of included studies carried a high risk of methodological bias, which is very significant when interpreting results. For instance, diagnostic cut-offs of non-invasive tests (NITs) were not always predetermined, which might lead to over-interpretation of their diagnostic accuracy. In other studies, NITs were not always performed according to the recommendations of the manufacturer, or the liver biopsy was of inadequate length to reliably assess fibrosis.

Bias aside, NITs perform better at the extremes of fibrosis, ie. in distinguishing cirrhosis from no cirrhosis and any fibrosis from absence of fibrosis. They do not perform very well at accurately staging fibrosis. In broad terms, direct serum tests and imaging modalities, such as transient elastography (Fibroscan®) and acoustic radiation force impulse (ARFI), perform better than indirect serum tests. Specific choices should take into account cost and local availability.

Quality-adjusted life years (QALYs) were used to measure health outcomes. Why was this metric chosen and what advantages and disadvantages does it have over other measures?

ET: The QALY metric was chosen as this is part of the current methodology for cost-effectiveness, and is also the metric used for national bodies such as the National Institute for Health and Care Excellence (NICE) here in the UK. It enables us to make comparisons across different therapies and management algorithms in the same and different fields of medicine. QALY combines data on life expectancy with data reflecting quality of life (sometimes referred to as ‘utility’ data).

Can you explain your method for generating a quantitative description of the cost-effectiveness of the various NIT methods?

ET: Cost-effectiveness of testing strategies is presented as an incremental cost-effectiveness ratio (ICER) using the formula: ICER = (C1-C0) / (E1-E0), where C1 = lifetime cost of strategy 1, C0 = lifetime cost of (the next best) strategy 0, E1 = QALYS from strategy 1 and E0 = QALYS from (the next best) strategy 0.

How will you analyse parameter uncertainty?

AB&ET: Parameter uncertainty is assessed with sensitivity analyses, eg at different thresholds of the QALYs, of disease prevalence and of the accuracy of the tests. This results in a range of ICERS for specific testing strategies, which can be evaluated with best- and worse-case scenarios in mind.

What are your hopes for the future of the field, and specifically for your own research?

AB&ET: The hope is to further refine the tests to improve accuracy by using quantitative evaluations of the amount of collagen in liver biopsy material. The comparator for indirect NITs has been, at best, a correlation with a histological staging system that does not quantify fibrosis but uses classification into categories. These are not arithmetically related and are not a continuous measure of fibrosis. NITs need to be compared with a continuous histological measure of fibrosis such as collagen proportionate area (CPA). We have been working on this as well.
FIBROSIS OCCURS IN response to cell and tissue injury, whereby excess fibrous scar tissue accumulates, disrupting the physical architecture and function of the underlying organ and tissue. This commonly occurs in the liver when healthy tissue becomes damaged by, for example, excessive alcohol consumption, viral hepatitis, or in association in some cases with obesity and diabetes. When fibrotic tissue accumulates over a long period of time, the scarring generated is known as cirrhosis. As the condition progresses the liver slowly loses its ability to function, resulting in chronic liver disease. If cirrhosis is not diagnosed and treated, the liver can fail. Each year in the UK, 4,000 people die from cirrhosis – making it the fifth highest cause of death – and 700 people with the condition each year need a lifesaving liver transplant.

LIVER BIOPSY

In the early stages of cirrhosis there are very few symptoms, but as more of the organ tissue becomes dysfunctional, patients can experience loss of appetite, fatigue, nausea and itchy skin. As the organ begins to fail, symptoms can include jaundice, vomiting of blood and the build-up of fluid in the abdomen and sometimes the lungs. A significant problem for patients with liver disease is that it cannot be cured – liver tissue cannot be repaired once it has lost its function. Therefore, it is important to diagnose cirrhosis as early as possible so that the symptoms can be managed and its progression can be monitored and slowed.

Currently, the standard method for detecting the presence of liver disease and monitoring its progression and response to treatment is a liver biopsy. It is an invasive procedure, comes with an element of risk and is only able to monitor a small area of liver tissue at any point in time. Consequently, a group of researchers from University College London in the UK led by Professor Andrew K Burroughs is investigating the cost-effectiveness of alternative, non-invasive methods for the assessment and monitoring of liver fibrosis and cirrhosis. Advantages of non-invasive tests (NITs) for fibrosis – where the skin is not broken and there is no contact with mucosa beyond a natural body orifice – over liver biopsies include that they are easier to perform, involve less risk to the patient, can be more easily repeated on a regular basis on the same patient and have a lower associated cost.

THE NON-INVASIVE APPROACH

The tests that the researchers are considering for their analysis can be divided into two categories – imaging and blood tests. Some of the imaging strategies are widely available in health centres. For example, ultrasound has no known harmful effects and is able to measure the ability of tissue to echo high frequency sound waves in order to determine its integrity; computed tomography (CT scanning) is effective but exposes the patient to X-rays, elevating their lifetime risk of developing cancer; and magnetic resonance imaging (MRI) can also be used but is unsuitable for patients with metallic implants or cardiac pacemakers, and carries the rare risk of an allergic reaction or renal damage from the intravenous contrast agent.

Less widely available imaging tests include transient elastography, which uses sound waves to assess the elasticity of the liver, and magnetic resonance elastography, which measures elasticity using complex algorithms. In addition to these methods, there are various blood tests that measure the level of liver damage. These include measuring platelet count, detecting extracellular matrix turnover, monitoring the occurrence of fibrogenic cell changes and tests for enzyme markers of liver injury, such as alanine transferase and aspartate transferase, which can be used to screen particular at-risk patient groups, such as the elderly, those with diabetes or alcohol abusers.

CONSIDERING COST

In the current economic climate, cost-effectiveness is an important factor to take into account when considering changing the standard medical diagnostic and monitoring procedures for a particular disease. Burroughs explains: “In order to see how much increased benefit there may be, one has to evaluate a diagnostic taking cost into consideration, including the impact of false-positive and false-negative diagnosis”. To do so, the team uses quality-adjusted life years (QALYs), a method which combines factors such as cost over the lifetime of current and alternative strategies, and how length and quality of life are affected by the different options.

The research has been primarily carried out by performing meta-analyses on previously published studies to determine the diagnostic accuracy of the different NITs that have been used...
**INTELLIGENCE**

**COST-EFFECTIVENESS OF NON-INVASIVE METHODS FOR ASSESSMENT AND MONITORING OF LIVER FIBROSIS AND CIRRHOSIS IN PATIENTS WITH CHRONIC LIVER DISEASE**

**OBJECTIVES**

- To compare the diagnostic accuracy of different non-invasive tests in the diagnosis and monitoring of liver fibrosis and cirrhosis.
- To compare the incremental cost per quality-adjusted life years of different non-invasive fibrosis assessment strategies in patients with various aetiologies of chronic liver disease.

**KEY COLLABORATORS**

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**PROFESSOR ANDREW K BURROUGHS** qualified at Liverpool University in 1976, and trained in Hepatology under Professor Dame Sheila Sherlock at the Royal Free Hospital where he has been a consultant hepatologist since 1983. He was awarded a personal Chair as Professor of Hepatology at University College London in 2002 and was elected to the UK Academy of Medical Sciences (FMedSci) in 2010.

**DR EMMANUEL TSOCATLIS** finished his training and PhD at Hippokration General Hospital, Greece. For the past five years, he has been combining clinical duties and postdoctoral research in the Sheila Sherlock Liver Transplantation Unit of the Royal Free Hospital in London under the supervision of Professor Burroughs.

Advantages of non-invasive fibrosis tests over liver biopsies include that they are easier to perform, involve less risk to the patient, can be more easily repeated on a regular basis on the same patient and have a lower associated cost.

In comparison to liver biopsy. This information has been considered in the context of how much NITs cost to perform, how they affect the patient’s prognosis and how effective they are for treating different liver disease aetiologies. Meta-analysis provides comprehensive results compared to carrying out single individual studies of liver disease patients, and thus includes many more subjects in the analysis than an individual experimental approach feasibly could, increasing the robustness and statistical significance of the results.

**FEASIBLE ALTERNATIVES**

The meta-analyses carried out by Burroughs and his team have identified some feasible alternative diagnosis and monitoring strategies to the standard liver biopsy approach, but the exact NIT strategy is dependent on the cause of the liver disease, as the condition has different rates of progression and responds to treatments in different ways depending on the cause. For example, liver diseases caused by different forms of the hepatitis B virus have been shown to require different NIT strategies – hepatitis B e antigen (HBeAg)-positive patients would benefit from sequential testing with two NITs, whereas for HBeAg-negative people, a treat-all strategy without prior testing is more cost-effective.

Not only do the specific causes of the diseases need to be taken into account, but progression of the symptoms also affects the cost-effectiveness of NITs, as Burroughs elaborates: “Elastography could be used as a good screening test for cirrhosis, with a 90 per cent disease probability following a ‘positive’ measurement, but not for lesser fibrosis degrees. In this situation, a ‘negative’ measurement is less accurate and informative, with disease only being present in 15 per cent of patients”. As a consequence of this, and the fact that the different stages of fibrosis development are not well understood in the context of how they affect the reliability of transient elastography, the researchers are not recommending that decisions on patients’ disease management are made using this NIT unless the disease has reached the cirrhosis stage and thus the results of the test can be more surely relied upon.

Burroughs and colleagues recognise the need for further clarification on the cost-effectiveness of the alternative NIT approaches and that, going forward, new strategies need to be properly assessed for their efficacy and reliability. However, he is optimistic for the future: “I hope that the project will establish an evidence-based platform for the use of these NITs in clinical practice”.