Detecting chronic liver disease: are liver function tests the solution?

Abstract

By 2020, chronic liver disease will have eclipsed ischaemic heart disease as the leading cause of working life years lost in the UK. As mortality from chronic liver disease continues to rise, the landscape of aetiology has shifted from infectious to non-communicable causes. In parallel with the growing prevalence of obesity and type 2 diabetes, non-alcoholic fatty liver disease is estimated to affect 25% of the UK adult population. Simultaneously, escalating alcohol consumption has fuelled public health and economic concerns regarding its widespread impact on working-age adults. Given that chronic liver disease remains clinically silent until its advanced stages, there is an urgent unmet need to identify affected individuals earlier in the disease process, enabling targeted intervention strategies which may improve prognosis. Robust epidemiological data have shown that liver fibrosis is the strongest predictor of clinically meaningful outcomes, including decompensation, liver cancer and overall mortality. Detecting fibrosis among at-risk individuals, in a manner that is reproducible, non-invasive, safe and cost effective, has become a major challenge of our time. This article addresses the pitfalls of the standard panel of liver function tests, discusses other non-invasive biomarkers and reviews imaging technologies which may revolutionise community-based diagnosis and stratification of chronic liver disease.

Key words: Biomarkers; Chronic liver disease; Commissioned pathway; Fibrosis detection; Primary care

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Landscape of chronic liver disease in the UK

In recent decades, industrialised economies have witnessed declining trends in mortality from chronic diseases. The major exception to this in the UK is chronic liver disease. As the third leading cause of premature death, standardised mortality rates from chronic liver disease in the UK have risen by 400% since 1970, surpassing those of other western European countries (Williams et al, 2014). This rising burden of liver disease disproportionately affects individuals of working age and chronic liver disease is expected to overtake ischaemic heart disease as the leading cause of working life years lost by 2020 (Hudson et al, 2017; Williams et al, 2018). The landscape of chronic liver disease aetiology has also changed in this period. Major developments in antiviral treatment have reduced the proportion of patients with end-stage liver disease attributable to chronic hepatitis B or C, moving the clinical focus towards alcohol and obesity-related liver diseases.

In parallel with the growing burden of obesity and type 2 diabetes, non-alcoholic fatty liver disease is estimated to affect 1 in 4 adults, has become a leading cause of chronic liver disease and liver cancer in the UK, and is now a major indication for liver transplantation. Simultaneously, changes in availability, pricing and patterns of alcohol consumption have led to a sharp rise in alcohol-related liver disease and associated mortality in the last 30 years. The frequent overlap and synergistic relationship between alcohol and obesity further compounds this problem, with obesity shown to be an independent predictor of cirrhosis among people who consume moderate amounts of alcohol (Liu et al, 2010), and of mortality in patients with alcoholic hepatitis (Parker et al, 2019). Together, alcohol-related liver disease and non-alcoholic fatty liver disease account for the striking rise in liver disease burden in the UK, with alcohol-related liver disease contributing to 70% of liver-related deaths (Williams et al, 2014).

Taken together, these observations highlight two points. First, the dominant causes of chronic liver disease in the UK, while requiring significant clinical and economic resource,

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are largely preventable. Second, broadly applicable, robust and cost-effective tools are urgently needed to detect, monitor and intervene in chronic liver disease at a population level.

Detection of chronic liver disease

What do we do now?

Abnormal results from liver function tests are often indicative of liver injury – whether acute or chronic – and detection of abnormal liver chemistry should prompt further investigation for potential aetiologies and staging of disease (Newsome et al, 2018). Further investigation of newly deranged liver function tests has a low diagnostic yield for parenchymal disease (<3%) but remains an important first step in identifying those in need of treatment and follow up (Lilford et al, 2013). In addition, the presence of specific risk factors will increase the pre-test probability of positive diagnostic serology (eg intravenous drug use and risk of viral hepatitis, history of autoimmune diseases and risk of autoimmune hepatitis).

In primary care, a large proportion of requests for liver function tests are related to chronic disease management: 25% of the population have their liver function tests measured at least once in 10 years, of which only 1 in 3 are abnormal (Donnan et al, 2009). In a Tayside population-based cohort study, 2-year follow up of patients with abnormal liver chemistry led to significant liver-related diagnoses in only 481 of the 95 977 sampled (0.5%) (McLernon et al, 2014). In another study, patients with abnormal liver chemistry (n=354) and negative non-invasive diagnostic serology underwent liver biopsy to determine the nature and extent of liver disease. In this population, diagnostic yield for advanced fibrosis was low (14.4%) (Skelly et al, 2001). This means that liver function tests are commonly requested, usually for the management of chronic diseases (which are linked to risk factors such as obesity and diabetes), and the yield for finding significant disease is low. The clinician must also consider the burden of disease that goes undetected when liver function test results are normal (Mofrad et al, 2003). As such, focus has shifted from the use of liver function tests to diagnose and stage disease to alternative non-invasive methods for screening and stratification of disease.

Robust epidemiological data show a clear correlation between progression of liver fibrosis and 'hard' outcomes such as development of cirrhosis, decompensation (development of jaundice, ascites, variceal bleeding or encephalopathy) and mortality (Hagström et al, 2017). Screening and diagnostic tests must therefore focus on the detection of individuals at greatest risk of adverse outcomes; in practice this means identifying asymptomatic patients with possible advanced fibrosis. The estimated prevalence of advanced liver fibrosis in the general population is 0.9–2% and of cirrhosis is 0.1–1.7% (Harris et al, 2017). However, screening the general population remains a controversial issue, fuelled by concerns regarding short-term financial costs, lack of evidence, diagnostic inaccuracy with current screening technologies, opportunity costs and inadequate workforce and resource allocation to handle the inevitable increase in volume of patients being referred to hepatology services (Hudson et al, 2017; Jarvis and Hanratty, 2017).

A targeted approach, in which individuals with risk factors for alcohol-related or metabolic liver disease are offered screening to exclude advanced liver fibrosis, may be a more pragmatic and efficient use of resource (**Figure 1**). This strategy has been advocated by the European Association for the Study of the Liver (2016) for patients with metabolic risk factors to optimise detection of non-alcoholic fatty liver disease, including steatohepatitis and fibrosis. **Figure 1** depicts two clinical scenarios to demonstrate how risk factor-based disease stratification may facilitate detection of chronic liver disease in practice.

Figure 1a demonstrates the work-up for a young patient with incidentally abnormal liver chemistry and without lifestyle-associated risk factors. Thorough history revealed recent use of a potentially hepatotoxic medication. Abdominal ultrasound revealed no structural parenchymal abnormalities and a non-invasive liver screen excluded viral and autoimmune causes of liver disease. In this context and with the trend of improving transaminase levels, the likely diagnosis is idiosyncratic drug-induced liver injury secondary to ibuprofen and does not require disease stratification.

In contrast, **Figure 1b** highlights use of a recommended pathway for investigating patients with risk factors for lifestyle-associated liver disease. Although liver enzymes were normal, hypoalbuminaemia, coagulopathy and low levels of platelets together with

RB, 33-year-old man, elective admission under orthopaedic team for arthroscopic knee surgery.

Recent ibuprofen 800 mg three times daily for knee pain. This was stopped 2 days before admission.
Past medical history: Nil known. Alcohol intake: 10 units/week

	Day 1	Day 3	Day 5
Alanine aminotransferase (units/litre)	91	64	32
Aspartate aminotransferase (units/litre)	130	87	45
Billirubin (µmol/litre)	35	22	17
Alkaline phosphatase (units/litre)	84	96	92
Albumin (g/litre)	45	46	43

Ultrasound: Normal
Non-invasive liver screen: normal
Risk factors for chronic liver disease: None

Diagnosis: Drug-induced liver injury

Outcome: Spontaneous resolution
Discharged without hepatology follow up

JH, 67-year-old man, admission to the acute take with dyspnoea and a productive cough. Diagnosed with lower respiratory tract infection. Treated with amoxicillin and discharged home.

Past medical history: type 2 diabetes mellitus, hypertension, hypercholesterolaemia.
Obesity (body mass index 32 kg/m^2).
Alcohol intake: 20 units/week.
Liver function tests requested as part of routine admission work up

Alanine aminotransferase	32	Haemoglobin (g/litre)	129
Aspartate aminotransferase (units/litre)	48	White blood cell count (10^9/litre)	13.2
Billirubin (µmol/litre)	9	Platelets (10^9/litre)	109
Alkaline phosphatase (units/litre)	105	Prothrombin time (seconds)	14.4
Albumin (g/litre)	32		

Risk factor-based approach in primary care:
Fibrosis-4 score: 5.6 (cut-off: <1.3)
Non-alcoholic fatty liver disease fibrosis score: 2 (cut-off: <-1.455)

Referred to hepatology clinic:
Fibroscan: Transient elastography 15.7 kPa

Liver biopsy

Diagnosis: Established cirrhosis secondary to non-alcoholic fatty liver disease

Outcome: Hepatology clinic follow up

Figure 1. a. Flow chart of a young patient with incidentally abnormal liver chemistry and without lifestyle-associated risk factors. b. Flow chart of a recommended pathway for investigating patients with risk factors for lifestyle-associated liver disease. Note the presence of advanced liver disease on biopsy despite normal liver chemistry.

the metabolic syndrome suggest that this patient is at high risk of advanced chronic liver disease. A Fibrosis-4 (FIB-4) score of 5.6 is suggestive of advanced fibrosis. The authors would then recommend a more discriminating test such as an extended liver fibrosis test or transient elastography. In this case, the patient was referred to a hepatology clinic, where transient elastography revealed a liver stiffness measurement of 15.7 KpA, again suggesting advanced liver disease. A liver biopsy was organised that confirmed established cirrhosis, likely secondary to non-alcoholic fatty liver disease.

Where: primary or secondary care?

It is clear that by the time chronic liver disease becomes clinically manifest, opportunities for effective intervention are limited and transplant-free survival is poor (D'Amico et al, 2006). Given the prevalence of risk factors, and the fact that disease progression remains clinically silent until its advanced stages, the burden of undiagnosed chronic liver disease in the general population is potentially enormous. This underscores the need to diagnose chronic liver disease at an earlier stage, enabling education, intervention and monitoring which may improve prognosis. It is therefore logical to aim for early diagnostic strategies to be focused in primary care settings, as this will considerably broaden access for at-risk asymptomatic individuals.

Screening for clinically significant disease in primary care has become the emphasis of numerous studies, with population-level screening identifying potentially significant disease in around 6% of an unselected population cohort in one study (Caballeria et al, 2018). Higher rates of fibrosis have been detected in community populations screened in the context of risk factors, including alcohol (51%) (Sheron et al, 2013), diabetes (34%) (Harman et al, 2015) or obesity (31%) (Harris et al, 2019). As well as detecting more disease, this targeted approach is cost effective to the NHS (Tanajewski et al, 2017).

In Nottingham, a risk factor-based approach is combined with transient elastography to identify patients with asymptomatic chronic liver disease (The Scarred Liver Project, Figure 2). Data now show that using a combination of traditional elevated levels of liver enzymes in conjunction with targeting of risk factors detects more disease than pathways that use the presence of abnormal liver function test results as an initial screening tool (Chalmers et al, 2019).

How: what tools should we use?

The reference standard for diagnosis, fibrosis assessment and prognostication is liver biopsy, but its invasive nature, vulnerability to sampling error and low acceptability render biopsy unsuitable as a screening tool in the general population. Non-invasive diagnostic tools should ideally be accurate, reproducible and cost effective, and based in primary care. As of 2019, there are no universally adopted diagnostic algorithms to optimise detection of chronic liver disease at a population level.

Liver function tests therefore detect the 'tip of the iceberg' when it comes to diagnosing chronic liver disease and are clearly insufficient to enhance community-based diagnosis. In recent years, a number of blood-based biomarkers, clinical prediction tools and imaging modalities have been proposed to meet this challenge (Table 1).

Blood-based biomarkers

There are now a number of well-validated, non-invasive clinical prediction tools and biomarkers to aid screening and identification of significant fibrosis in those at risk of liver disease (whether in the presence of abnormal liver function test results or just based on risk factors alone). The BARD score (weighted sum of body mass index, aspartate aminotransferase:alanine aminotransferase ratio and presence of diabetes), non-alcoholic

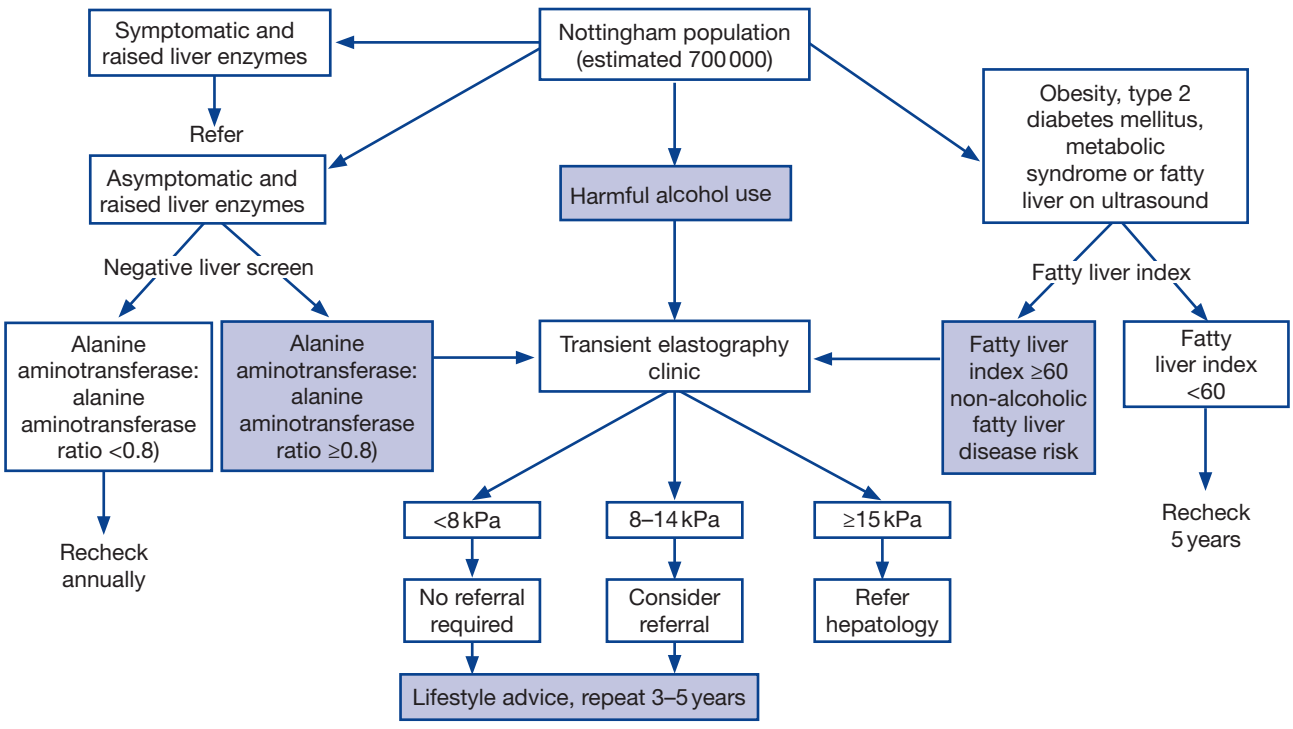

Figure 2. Scarred Liver Project algorithm used by primary care services in Nottinghamshire to detect chronic liver disease.

Table 1. Proposed measures to optimise detection of chronic liver disease in primary care

Who	Target specific high-risk populations: hazardous alcohol use, obesity, metabolic syndrome, type 2 diabetes mellitus, abnormal liver function test results		
Where?	Primary care		
How?	Algorithms	Non-alcoholic fatty liver disease	Fatty liver index, BARD, non-alcoholic fatty liver disease fibrosis score
		Generic	APRI, fibrosis-4 score, aspartate aminotransferase:alanine aminotransferase ratio
	Specific tests	Extended liver fibrosis (ELF) panel	
		Transient elastography	
When?	On identification of risk factors		
	If baseline investigations exclude advanced fibrosis, repeat every 3 years*		

**Based on National Institute for Health and Care Excellence (2016b) guidelines, evidence base unclear. APRI = aspartate aminotransferase:platelet ratio index; BARD = body mass index, aspartate aminotransferase:alanine aminotransferase ratio, diabetes*

fatty liver disease fibrosis score (age, body mass index, diabetes, aspartate aminotransferase, alanine aminotransferase, platelet count, albumin), aspartate aminotransferase:platelet ratio index and the FIB-4 index (age, alanine aminotransferase, aspartate aminotransferase, platelet count) are simple scoring systems, based on commonly used biochemical variables and metabolic measures, have been well validated in non-alcoholic fatty liver disease populations and can reproducibly exclude advanced fibrosis (McPherson et al, 2010).

In people with alcohol-related liver disease, the aspartate aminotransferase:alanine aminotransferase ratio is currently the most widely used simple prediction tool, with a ratio >1 suggesting advanced fibrosis (Nyblom et al, 2004). A study comparing the FIB-4 index with transient elastography and liver biopsy reported good diagnostic performance in the detection of advanced fibrosis in alcohol-related liver disease (area under the receiver operating characteristics curve 0.85, 95% confidence interval 0.80–0.90) (Thiele et al, 2018). Likewise, the aspartate aminotransferase:platelet ratio index demonstrated reasonable diagnostic accuracy (area under the receiver operating characteristics curve 0.80, 95% confidence interval 0.74–0.86).

A growing number of direct biomarkers, quantifying by-products of the fibrogenic process, are commercially available. Of these, the extended liver fibrosis panel has gained most traction and has been recommended in National Institute of Health and Care Excellence (2016a) guidelines as the tool of choice to detect advanced fibrosis in patients with non-alcoholic fatty liver disease. Other blood-based biomarkers of liver fibrosis include Fibrometer, Pro-C3 and Fibrospect, all of which have demonstrated high diagnostic accuracy in non-alcoholic fatty liver disease cohorts, as well as robust results in other aetiologies including alcohol-related liver disease and hepatitis C (Vilar-Gomez and Chalasani, 2018).

Imaging modalities

In addition to blood-based biomarkers, a range of quantitative imaging-based tools has been developed in response to a growing unmet need to evaluate fibrosis burden in patients with chronic liver disease. By far the most popular and broadly applicable imaging tool in community-based settings is transient elastography (Fibroscan, Echosens, France). A point-of-care device, the Fibroscan consists of an ultrasonographic transducer attached to a low-frequency vibrator (50 MHz), measuring shear wave velocity through the liver substance and displaying results as 'liver stiffness', thereby providing a surrogate marker of fibrosis. Fibroscan has been well validated across major liver disease aetiologies, providing a robust, reproducible diagnostic tool with which to distinguish patients at risk of advanced fibrosis (Voican et al, 2017; Jiang et al, 2018). The Fibroscan technique is quick to learn and has been used in nurse-led pathways (McCorry et al, 2012). Its ability to give a result in real

time enables delivery of prompt intervention through lifestyle advice and signposting to appropriate services at the time of assessment.

Other elastographic techniques include supersonic shear wave elastography and acoustic radiation force impulse. Both have impressive diagnostic accuracy and, in some cases, have exceeded transient elastography in terms of diagnostic sensitivity in non-alcoholic fatty liver disease (0.91 for acoustic radiation force impulse) (Friedrich-Rust et al, 2012).

Growing evidence suggests that the diagnostic performance of non-invasive tools may be enhanced by combining imaging and blood-based biomarkers. For example, the combination of transient elastography and extended liver fibrosis increases the diagnostic sensitivity compared to each test in isolation (Patel et al, 2018). This process of using an initial screening test with a blood biomarker followed by further assessment of fibrosis stage (often in secondary care) is used in a number of current clinical guidelines (European Association for the Study of the Liver, 2016; Newsome et al, 2018).

Further to elastography techniques, advances in magnetic resonance technologies have enabled the incorporation of magnetic resonance imaging and magnetic resonance elastography methods in the evaluation of liver disease. Magnetic resonance imaging with proton density fat fraction has shown superiority over transient elastography with controlled attenuation parameters in the quantification of liver steatosis and is now considered the non-invasive gold standard technique for detection of liver fat (Park et al, 2017).

Ultrasound-based elastographic techniques may be restricted by anatomical variations, including narrow rib spaces and chest wall adiposity, so magnetic resonance imaging and magnetic resonance elastography overcome these barriers to enable accurate quantification of liver steatosis and fibrosis respectively. A further advantage of magnetic resonance elastography is its ability to evaluate the global liver fibrosis burden, making it less vulnerable to sampling error.

While magnetic resonance-based techniques undoubtedly provide the most accurate method for detection of steatosis and advanced fibrosis in non-alcoholic fatty liver disease, in practice they are not feasible for use as a point of care tool at a population level.

Conclusions

Reducing the burden of liver disease in the UK is paramount if better long-term health outcomes are to be achieved. A multi-pronged strategy is needed to deliver this, focusing on prevention, detection and intervention for at-risk individuals. Given the high population prevalence of alcohol-related liver disease and non-alcoholic fatty liver disease, and the asymptomatic nature of both diseases until their advanced stages, this article outlines strategies for a risk factor-based approach to optimise detection of chronic liver disease at a population level. Liver function tests detect ‘the tip of the iceberg’ and are insufficient to enable comprehensive community-based diagnosis of chronic liver disease. Promising blood-based and imaging biomarkers have revolutionised the scope for screening and diagnosis across primary and secondary care, and can enable more efficient resource allocation, reducing the need for liver biopsy and enhancing detection of individuals at high risk of adverse health outcomes for referral to hepatologists. The success of the Scarred Liver Project in detecting such individuals provides a blueprint for risk stratification pathways which could prove cost effective and deliver long-term health benefits at a population level.

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Conflicts of interest

The authors declare no conflicts of interest.

Key points

- Chronic liver disease is the third leading cause of premature death in the UK, with mortality rates increasing by 400% since 1970.
- Alcohol-related and non-alcoholic fatty liver disease are the dominant causes, both of which are a huge economic burden and are potentially preventable.
- In practice, detection of liver disease frequently relies on the presence of abnormal liver enzyme levels, despite it being well recognised that significant disease can exist in the presence of normal liver function test results.
- Targeting those with risk factors for liver disease can enhance detection of affected individuals and enable prompt intervention.

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