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Title:

Biomarkers of liver fibrosis

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Currently the only accepted method (gold standard) for the diagnosis of the fibrotic stages of chronic liver disease (CLD) is liver biopsy, to allow histological assessment. Liver biopsy is an invasive investigation associated with a range adverse events (e.g. pain, haemorrhage)(1,2) limiting its serial usage in clinical practice. Additionally, its use is further reduced by sampling error(3) and because histology is in effect a surrogate for clinical outcomes.

Over recent years, alternative non-invasive biomarkers for the diagnosis of liver fibrosis have been developed. Initially developed in chronic viral hepatitis these have since seen their use expanded to include all aetiologies of CLD. Such markers can be divided into indirect 'simple' markers (e.g. transaminases, gamma-glutamyl transferase, platelet count), direct 'complex' markers (e.g. procollagen peptides I/III, Type IV collagen), cytokines (e.g. interleukin-10, transforming growth factor alpha) and imaging. Here, we discuss the clinical utility, limitations and development of non-invasive biomarkers in their use as diagnostic and prognostic tests.

Clinical utility of current biomarkers in assessing liver fibrosis

Indirect 'simple' markers

Indirect markers measure components not directly involved in the fibrosis process. Whilst having the advantage of being relatively cheap and easy to perform, they lack diagnostic accuracy for the detection of hepatic fibrosis. For example, Kayadibi et al(4) found for the diagnosis of any fibrosis, the sensitivity and specificity of alanine aminotransferase to be 68% and for aspartate aminotransferase to be 81% and 48% and 83%, respectively,. These correspond to a positive predictive value in a low prevalence population (5%) of only 10% and 9%.

Direct 'complex' markers and cytokines

Direct 'complex' markers measure components of the fibrosis pathway and are frequently combined as panel markers with perceived improved diagnostic accuracy of individual markers. Currently, cross-sectional data suggest that such biomarkers could be used as an alternative to liver biopsy in some patients. For example, Guha et al present a clinical utility model showing that the Enhanced Liver Fibrosis panel can used to avoid liver biopsy in the diagnosis of advanced liver fibrosis in 88% of cases with only 14% of these incorrectly avoiding biopsy. However, these figures drop to 48% and 21% respectively for the diagnosis of any fibrosis(5). Comparable accuracy is seen when complex markers are tested are tested in viral hepataitis(6) A second use of cross-sectional data is for the prediction of liver disease development and prognosis. Kim et al found patients with non-alcoholic fatty liver disease (NAFLD) fibrosis (determined by the NAFLD fibrosis score, NFS) had a higher probability of all-cause and cardiovascular death (adjusted hazard ratio (aHR) 1.69 and aHR 3.46 respectively) compared to those with a low NFS(7). These results were partially replicated for the simpler biomarkers, aspartate to platelet ratio index (APRI) and the Fibrosis-4 index (FIB4), with both associated with increased cardiovascular death and APRI additionally associated with all-cause and diabetes related death. Angulo et al had similar findings with NFS, APRI and FIB4 (but not BARD) associated with all-cause death and all four markers associated with future clinical liver events(8).

Similarly to direct markers cytokines have been identified as potential markers of fibrosis as they are involved in the regulation of the inflammatory response to liver cell injury and fibrogenesis . A

number of studies have noted raised levels of cytokines in patients with hepatic fibrosis but few have evaluated their diagnostic accuracy.

Imaging

The future of non-invasive biomarkers is likely to lie in imaging, allowing the assessment of the whole liver, avoiding sampling error and the need for surrogate markers. Whilst transient ultrasound elastography (TE) is an easily accessible technology it is subject to operator(9) and subject limitations(10). For example, in NAFLD, accuracy in high prevalence (30%) populations is good (PPV 67%, NPV 93%), but again there is a notable fall in PPV in low prevalence (5%) populations (PPV 18%, NPV 99%)(11). It has also been noted that whilst accuracy is maintained the optimal cut-off values of TE vary by underlying aetiology(12). However Magnetic resonance (MR) elastography has excellent accuracy for advanced liver fibrosis(13,14) with the main limitation of requiring additional hardware. Furthermore, novel MR imaging protocols not requiring contrast or additional hardware are now beginning to emerge (15,16).

Diagnostic limitations of current biomarkers of fibrosis

As noted above, large numbers of cross-studies have been undertaken attempting to validate the use of non-invasive biomarkers in the diagnosis of liver fibrosis resulting in acceptable diagnostic accuracy for advanced fibrosis and cirrhosis (Metavir F3/4). However, their findings have found very limited use in early and intermediate CLD.

Further methodological concerns with these studies exist; few used a development and a validation cohort with the majority not replicated, they were often small (n<100) and spectrum bias limits applicability with the choice of study population typically tertiary care focused. A heavy reliance on area under the receiver operating curves (AUROC) misses the clinical context – with the definition of a good AUROC being relative and not absolute. The optimal diagnostic test accuracy metric is are determined by the clinical question.

There have been few longitudinal investigations of serial markers and studies focussed on clinical outcomes (as opposed to histology) are challenging but are now starting to emerge.

Development of biomarkers of NAFLD fibrosis

Of significant interest now is the ability to detect CLD in a practical manner in the community. For this reason we need to be clear on the question we want to answer, for example, do we want to detect people with fibrosis or those at risk of fibrosis? Pragmatic population based screening strategies need to be employed, focused on risk factors rather than liver enzymes(17), and using methods that are easily administered in community settings such as transient elastography(18).

In the future, researchers need to consider how changes in biomarkers over time are related to CLD and clinical outcomes. These have the potential to be powerful tools, transferable to many different populations. To date, there are no NAFLD studies considering delta change, however techniques are being investigated in hepatitis C virus using both serial serum markers(6) and serial transient elastography(19).

Summary

The optimal use of non-invasive fibrosis biomarkers in NAFLD depends on the setting and question under consideration (Table 1). At present, in secondary care settings there is evidence that some non-invasive biomarkers can be used in the diagnosis of advanced liver fibrosis, avoiding the need for invasive liver biopsy. However, these same markers and cut-offs may not be similarly suited to the identification of CLD and prediction of clinical outcomes in community populations. Furthermore further study of imaging techniques and serial measures is needed to fully understand the relationship between non-invasive biomarkers and the progression/regression of liver fibrosis in the context of hard clinical outcomes.

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Table 1. Comparison of existing and emerging non-invasive markers of hepatic fibrosis

	Liver biopsy	Indirect 'simple markers	Direct 'complex' markers and cytokines	Transient ultrasound elastography	Magnetic resonance elastography
Utility in defining stage of fibrosis	Useful for full spectrum	Most useful for advanced fibrosis	Most useful for advanced fibrosis	Most useful for advanced fibrosis	Most useful for advanced fibrosis
Prediction of clinical outcomes	Hepatocellular carcinoma, varices	Hepatocellular carcinoma	Hepatocellular carcinoma, varices	Hepatocellular carcinoma, varices	No data presently
Access to and utility of serial assessment	Not practical due to invasive nature	Easily accessible Emerging data for utility	Easily accessible Emerging data for utility	Relatively easy access (equipment and experienced operator required) Emerging data for utility	Limited access. No data presently for utility
Financial costs*	$1,500 per procedure	Various, $1-$10 per measure	Various, $70-$200 per measure/panel	Capital costs for machine $60,000 Operational cost $70 per procedure	Capital costs >$250,000 Operational cost $300 per procedure
Reliability	Sampling error (1/50,000th of liver sampled)	Laboratory variability	Typically measured at a central laboratory	Operator variability Reliability reduced in obesity, ascites, liver masses, cholestasis	Limited data available
Performance location	Hospital	Community or hospital	Community or hospital	Community or hospital	Hospital

*costs obtained from Appendix 9 in Crossan C, Tsochatzis EA, Longworth L, Gurusamy K, Davidson B, Rodríguez-Perálvarez M, et al. Cost-effectiveness of non-invasive methods for assessment and monitoring of liver fibrosis and cirrhosis in patients with chronic liver disease: systematic review and economic evaluation. Health Technol Assess 2015;19(9).