Review Article

Assessing Liver Fibrosis with Serum Marker Models

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Abstract

Chronic liver disease is characterised by liver fibrosis, which may lead to cirrhosis. Conventional serum-based liver function tests do not give information on either the presence or the rate of progress of liver fibrosis. The reference diagnostic test to detect fibrosis is liver biopsy, a procedure subject to various limitations, including risk of patient injury and sampling error.

Serum markers have been evaluated for the determination of fibrosis either singly or combined as a panel of markers, however diagnostic accuracy is greatest in studies using a panel together with an algorithm, which generates a predictive score. Serum marker models, especially those targeted at hepatitis C, have multiplied in spectacular fashion over the last five years, with most models regularly achieving a median area under the receiver operating characteristic curve (ROCC) of 0.80 versus liver biopsy. Five years after publication of the first major serum marker model, the first study to document clinical outcomes reported that applying the model to hepatitis C patients improved prediction of decompensated cirrhosis and survival compared to liver biopsy.

An obstacle to widespread adoption of serum marker models has been the lack of uniform performance indicators, such as diagnostic odds ratios and likelihood ratios. At present, serum marker models are not considered sufficiently reliable to replace liver biopsy in patients with chronic liver disease. However with continued evaluation in parallel with liver biopsy rapid advances are being made.

Liver Fibrosis

Liver fibrosis can accompany almost any chronic liver disease characterised by the presence of inflammation or hepatobiliary distortion. Fibrosis or scarring arises as a result of wound repair and is the net result of the balance between fibrinogenesis (production of extracellular matrix) and fibrolysis (degradation of extracellular matrix). Scar formation alters liver structure and the liver responds with regeneration. A review of liver fibrosis was recently published by Friedman.[1]

Progressive fibrosis of the hepatic parenchyma leads to cirrhosis, nodule formation, altered hepatic function and risk of liver-related morbidity and mortality. The commonest liver diseases causing fibrosis and possible cirrhosis are chronic viral hepatitis or steatohepatitis associated with either alcohol or obesity. Other aetiologies include autoimmune attack on hepatocytes (autoimmune hepatitis) or biliary epithelium (primary biliary cirrhosis, primary sclerosing cholangitis), inherited metabolic conditions such as haemochromatosis, neonatal liver disease, parasitic liver disease such as

schistosomiasis, chronic inflammatory conditions such as sarcoidosis, drug toxicity and vascular derangements. Cirrhosis typically develops over many years or decades, although occasionally it occurs rapidly, for example in neonatal liver disease. Once considered irreversible, ample evidence now exists that reversal of cirrhosis is possible when the underlying pathogenic insult is eliminated, for example the causative virus.[1]

Liver Fibrosis in Hepatitis C

Serum models were initially developed to predict fibrosis in patients chronically infected with the hepatitis C virus and most published data on serum marker model systems has been obtained in these patients. In addition, the natural history of liver fibrosis is best understood for this condition, where the course of liver fibrosis is very variable, ranging from decades of viraemia with little fibrosis to rapid onset of cirrhosis in 10-15 years. The available evidence shows that host factors rather than viral factors correlate with fibrosis progression. The main risk factors for more rapid progression include:

older age at infection; concurrent liver disease due to hepatitis B virus or alcohol (>50g per day); male gender; hepatic steatosis; infection with human immunodeficiency virus; immunosuppression and iron overload.[2]

Standard clinical indices cannot distinguish between degrees of fibrosis and clinical management requires identification of risk factors for progressive fibrosis and determining the duration of infection, even if the latter is an estimate. Although information on progression of fibrosis is extremely valuable, estimates of progression are tempered by the observation that fibrosis progression is not entirely linear and more advanced stages are probably associated with accelerating progression. However, an estimate of the current degree of fibrosis is valuable for the following reasons:

1. The actual stage of fibrosis will indicate the likelihood of response to treatment, with advanced stages generally having an inferior response rate;
2. If progression is slow, treatment with antiviral therapy may be less urgent;
3. The approximate time to the development of cirrhosis can be estimated.

Liver Biopsy

Liver biopsy assessed histopathologically has long been the 'gold standard' for describing liver histology, disease activity and liver fibrosis. Biopsy also provides a unique additional source of additional information such as steatosis and iron status of the liver. Factors which improve the diagnostic accuracy of liver biopsy include the use of a semi-quantitative technique for assessing fibrosis, the presence of uniform disease throughout the liver, multiple passes of a trucut needle and a biopsy of 2 cm or greater in length.[3]

The most widely used systems for grading activity and staging fibrosis are the semi-quantitative Ishak[4] and METAVIR systems.[5] Most serum marker models used to predict fibrosis in hepatitis C patients are compared to biopsy results obtained with the five point scale METAVIR system, where fibrosis is described as follows: chronic hepatitis without fibrosis (F0); portal fibrosis without septae (F1); portal fibrosis with a few septae (F2); septal fibrosis without cirrhosis (F3) and complete cirrhosis (F4). A separate scale, the Brunt system, has been developed to describe the morphological changes of non-alcoholic fatty liver disease.[6]

Limitations of Liver Biopsy

There are several issues impacting on the use of liver biopsy that prevent its routine use as a clinical tool. Some are beyond the scope of this review, for example lack of manpower to undertake biopsies on all patients who require it, associated cost and risk of patient injury. However, three limitations especially relevant to the application of serum marker models, should be briefly discussed.

Fibrosis Staging Systems

Although histologic staging of fibrosis is widely used, it is based on two flawed assumptions: firstly, it is not appropriate to describe a continuous variable such as the amount of fibrosis with categorical values such as fibrosis stages. Secondly, the staging systems assume a linear increase in the severity of fibrosis between stages, although it is recognised that this is not true.[7] A serum-based model giving an algorithm-based score is a continuous variable and may be a more valid parameter.[7]

Sampling Error

Sampling error is an intrinsic problem of biopsy. A 10-15 mg sample of tissue represents a tiny fraction of an organ weighing 1500 g. Even a disease like hepatitis C that affects the liver relatively uniformly will vary from lobule to lobule, although the error is typically not greater than one fibrosis stage. In one study, simultaneous biopsies were taken laparoscopically from right and left hepatic lobes from 124 patients with hepatitis C.[8] A difference of at least one stage between right and left lobes was documented in 33% of patients, which could not be attributed to intra-observer variation, which was low. Only two patients had a difference of two fibrosis stages. Sampling error is especially evident in small biopsies.

Inter-observer Variation

The third limitation is inter-observer variability amongst pathologists in categorising the degree of fibrosis, which is considered to be up to 20%.[9] Assessment of fibrosis remains subjective and it is difficult to compare results of different studies using different scoring systems, for example Ishak and METAVIR.

The Case for Serum Marker Models

Aside from the limitations of liver biopsy, there is an urgent need to develop non-invasive serum markers for the following reasons:

1. There is increasing evidence that even advanced fibrosis is reversible. Having shown that severe disease is amenable to therapy, a requirement arises for more frequent testing than allowed by liver biopsy.[1]
2. It is expected that antifibrotic therapies will be developed which will require early and regular monitoring of response to establish effectiveness and optimise dosing. As noted above, the need for regular monitoring will greatly exceed what is appropriate for liver biopsy.[1]

Several non-invasive diagnostic imaging tests for fibrosis and cirrhosis, which do not involve testing serum, have been

evaluated. Although beyond the scope of this review, they are mentioned for completeness. These include positron emission tomography, transient elastography and magnetic resonance imaging.

Conventional Liver Function Tests

Conventional liver function tests reflect hepatocyte damage (e.g. alanine aminotransferase (ALT) and aspartate aminotransferase (AST)), biliary obstruction (e.g. bilirubin (Bil) and alkaline phosphatase or biosynthetic function (e.g. albumin and prothrombin time (PT)). These tests have been available since at least the early 1970s and although they provide information about important aspects of liver function, they do not assess liver fibrosis or cirrhosis, critical end-points of a variety of chronic liver diseases. Conventional liver function tests can yield results within the reference range in the presence of the full range of liver biopsy METAVIR fibrosis staging from mild (F1) to significant (F2) fibrosis and even advanced fibrosis or cirrhosis (F3 or F4).

Algorithm-Based Serum Marker Models

Combinations of serum markers for fibrosis calculated by algorithms, which give a discriminant score for fibrosis, represent a new group of liver function tests, which provide an alternative to an invasive liver biopsy. Providing they are properly validated, scores generated from combinations of serum tests represent a method for medical laboratory science to add value to laboratory reports. Clinicians must interpret conventional liver function tests carefully with only the individual reference ranges customarily provided by the laboratory for guidance. Experienced clinicians learn to make judgements and interpretations of conventional liver function tests, which are well beyond the scope of the reference ranges, and often difficult for less experienced clinicians. An advantage of algorithm-based scores is that a properly validated score represents evidence-based medicine as it incorporates clinical experience in the presentation of the result. For example, a result may be presented as follows: A score of >0.50 in a hepatitis C patient detects significant fibrosis (METAVIR fibrosis stages F2, F3 or F4) with a positive predictive value of 88%. The clinician can then make a judgement knowing that the chance of an incorrect result will be 12% or one in eight hepatitis C patients. An important proviso is that the prevalence of significant fibrosis in the population being tested and that of the population used to validate the positive predictive value of the score is similar.

Panels of serum markers combined as a score are also making inroads in other areas of medicine. For example, one study identified four serum markers which was combined into a score with high correlation with stroke.[10]

Current Clinical Practice

The ultimate aim of models based on serum markers is to replace liver biopsy in as many patients as possible. It is probably not realistic to expect that serum models will ever completely replace liver biopsy. In general, serum models are still positioned in the research and development arena and clinical information is being rapidly gathered, albeit mainly in patients who have already undergone liver biopsy. However editorials have begun to consider the question of whether any of the serum models are in a position to replace biopsy, especially considering its acknowledged limitations.

The major objections to implementing serum models in clinical practice are as follows: None of the models comprise entirely liver fibrosis-specific markers, they also reflect hepatocyte injury or necro-inflammatory activity rather than measuring only fibrosis.[11] There is also a lack of published data on the use of serum models to monitor response to treatment or their ability to monitor changes in fibrosis stage over time, although this shortcoming is progressively being addressed.[11]

A further objection especially relevant to the practice of medical laboratory science is that published cut-off values of serum model scores are almost certainly affected by differences in assays and/or lack of agreement on standardisation for the individual markers used to calculate the score.[11] At present, the recommendation is that analytical methods used to measure the component markers should be identical to those reported in the original publication.

A more serious problem is that serum models achieve their best results principally for identifying two groups of patients, those with minimal or no fibrosis and those with advanced fibrosis or cirrhosis. However, the accuracy for intermediate fibrosis is relatively poor.[12] Finally, the question of validating the serum models in a variety of practice settings is important but often ignored. The clinical utility of serum models is critically dependent on the prevalence of liver fibrosis in the population being investigated and almost all studies have validated models only in a tertiary clinic or hospital environment.

In the light of these objections most authorities do not advocate widespread replacement of liver biopsy, but recommend a targeted approach. Very low values of the indices used to score serum models usually have very high negative predictive values, and it has been suggested that liver biopsy could be spared in these patients as they have a very low probability of significant fibrosis.[12]

The Ideal Liver Fibrosis Marker

Although no such molecule has yet been identified or is likely

to be identified, it is useful to consider the properties of an ideal marker:

1.   Specific for liver;
2.   Readily available and standardised between all laboratories performing diagnostic biochemistry/ haematology;
3.   Not subject to false positive results, for example due to inflammation;
4.   Identifies the stage of fibrosis.

Most current serum markers are not liver specific, or may represent impaired hepatic clearance or are affected by inflammation. In addition, coexisting pathologies such as haemolysis (causing a decrease in haptoglobin (Hap) levels and/or increase in Bil levels) or rheumatoid arthritis (increase in hyaluronic acid (HA) levels) are associated with changes in levels of serum markers.

Although no ideal marker exists, several have been identified as possible useful indicators of fibrosis. Single markers often correlate with fibrosis in large groups of patients but are not sufficiently predictive in the individual patient, especially when used longitudinally over time. A systematic review compared single and multiple markers versus liver biopsy up to 2002 and noted diagnostic accuracy was greatest in studies using multiple markers.[13]

In practice serum markers are therefore used in combination where they have achieved a greater likelihood for success in discriminating minimal from significant fibrosis. Usually, three or more markers are used in combination in an algorithm to generate a score, which is then used to give a fibrosis prediction. The serum markers listed below have been chosen because they are common components of published serum models used to make fibrosis predictions. The list is not intended to be complete. A brief rationale is given for the use of each marker followed by comments on the available methods for analysis. Newer approaches such as proteomics, metabolomics and clinical glycomics are expected to yield more novel biomarkers.[14]

Major Serum Fibrosis Markers
HA
This mucopolysaccharide is a glycosaminoglycan, a high molecular weight polymer present in joints and in some tissues such as liver. It is found in synovial fluid and serum levels are elevated in various chronic liver diseases due to HA production by hepatic stellate cells and decreased clearance by sinusoidal endothelial cells. Serum levels are normally <50 μg/L and elevated levels correlate reasonably well with the degree of liver fibrosis in alcoholic liver disease[15] and hepatitis C.[16] HA has been used on its own to exclude significant fibrosis[15,16] or

more recently in combination with other markers.

Testing for serum HA is currently not widely available. It is available commercially as a self contained kit in the 96-well ELISA format (Corgenix, Colorado, US) the most efficient use requires a plate washer to perform the multiple rinses and washes as well as a plate reader to read the final absorbance. If demand increases, it is anticipated that serum HA will become available on commercial automated platforms.

α-2-Macroglobulin (α-2-M)
This is a high molecular weight protein synthesised in hepatocytes and stellate cells which is reasonably abundant in human serum, where normal levels are typically from 0.66 to 2.65 g/L. The functions of α-2-M are not well understood but it does inhibit the catabolism of matrix proteins by acting as a broad-spectrum inhibitor of nearly all enzymes that split proteins internally (endoproteases). Serum levels increase with the degree of liver fibrosis.[17]

The preferred methods for analysis are immunonephelometry and immunoturbidimetry and reagents are available as commercial kits from manufacturers of immunonephelometry platforms such as the Beckman Coulter IMMAGE and Dade-Behring BNII.

Collagen Markers
This diverse group of markers includes pro-collagen peptides, proteins such as type I, type III and type IV collagen and collagen metabolites such as laminin. For example, the N-terminal propeptide of type III collagen (PIIINP) is a valuable fibrosis marker that has been validated in alcoholic liver disease,[18] hepatitis C,[7] and non-alcoholic fatty liver disease.[7] Serum levels increase with the degree of liver fibrosis. A typical analysis method for PIIINP is by heterogeneous immunoassay using magnetic particle separation techniques on an automated analyser (Bayer Healthcare AG, Leverkusen, Germany).

Apolipoprotein A1 (Apo A1)
This is the major protein component found in high-density lipoprotein. Serum concentrations are negatively associated with liver fibrosis, i.e. levels decrease as the extent of fibrosis increases.[19] Decreased levels are also seen in uncontrolled diabetes, nephrotic syndrome, some diets and smoking. As for α-2-M, the preferred method for analysis of Apo A1 is an immunonephelometry platform such as the Beckman Coulter IMMAGE or Dade-Behring BNII.

Haptoglobin
This serum protein binds any free haemoglobin present in the circulation. Hap is an acute phase protein whose concentrations

increase in a wide variety of inflammatory conditions and in nephrotic syndrome. Concentrations decrease in in vivo haemolysis whether caused by autoimmune, iso-immune or mechanical reasons. Hap levels also decrease with increasing stages of fibrosis.[20] The preferred method for analysis is immunonephelometry.

Matrix Metalloproteinases (MMPs)

MMPs and their tissue inhibitors (TIMPs) have been shown to correlate with the development of liver fibrosis, for example circulating MMP 1 concentrations are significantly reduced as fibrosis grades increase in hepatitis C,[21] whereas TIMP 1 levels increase.

The excess collagen deposition in liver, which is characteristic of fibrosis, is the result of both decreased collagen degradation mediated by increased TIMPs and increased collagen synthesis.

Testing for MMPs and their tissue inhibitors is not currently widely available in laboratories performing diagnostic biochemistry. Commercial kits are in the 96-well ELISA format, however if demand increases it is anticipated that these analytes will become available on commercial automated platforms.

Constructing an Algorithm-Based Serum Model

Prerequisites

A set of minimum prerequisites for constructing a serum model to predict liver fibrosis can be identified. The first requirement is for a relatively homogeneous set of patients, usually with a single liver disease who are usually treatment naive with respect to antiviral therapy. For example in chronic hepatitis C, those patients with regular high alcohol intakes or co-infection with hepatitis B or human immunodeficiency viruses would typically be excluded.

A second requirement is for a pre-treatment liver biopsy and histologic staging which achieves certain minimum standards, usually for length and number of portal tracts. Further conditions may include biopsy staging conducted by the same pathologist who is blinded to the clinical data.

The third requirement concerns the serum samples, usually obtained at the same time as the liver biopsy. Constructing a serum model implies prior identification of a candidate group of potential serum markers of fibrosis from which the final panel of markers will be selected. For example in the first report describing serum markers used in combination to generate a score which could predict liver fibrosis in hepatitis C patients, a total of 11 candidate markers were assessed, whereas only five markers were used in the final model.[20]

Statistical Analyses

Most models have been developed by following these general rules. Two groups of patients are required, a training set in which all candidate serum markers are measured and a validation set in which the performance of the final model is assessed. Sometimes the two sets are created by random selection from one pool of patients or alternatively the validation set can be entirely separate, for example from another centre.

An essential requirement is to establish the desired fibrosis stage endpoints, normally there is no attempt made to predict individual fibrosis stages, instead a binary 'presence' or 'absence' is used. For example the simplest variant would be a single endpoint of significant fibrosis defined using the METAVIR system as a grade of F2, F3 or F4. Examples of other common endpoints are the presence of METAVIR grade of F3 or F4 for defining advanced fibrosis and METAVIR grade F4 for cirrhosis.

The predictive model itself is commonly formulated by performing univariate analysis on the candidate serum markers in patients with and without the desired endpoints in the training set. Those markers from the univariate analysis, together with other desired variables such as age at biopsy or gender found to be significant predictors ($p<0.05$), are then subjected to multivariate analysis by forward logistic regression to identify independent factors associated with either the presence or absence of the desired endpoint. Equations giving a score that could best predict the desired endpoints are constructed by entering different sets of independent variables into the regression model. The diagnostic value of each equation can be assessed by comparing the areas under the ROCC. An ideal equation would have an area under the curve of 1.0, whereas 0.5 indicates an equation of no diagnostic value. The equations are typically simplified by constructing a score system, for example from 0.0 to 1.0, and the best cut-off points within that range are selected from the ROCC by calculating sensitivity, specificity and positive and negative predictive values.

Performance Depends on Disease Prevalence

The utility of serum models for detecting fibrosis is critically dependent on the prevalence of liver fibrosis in the population being investigated. Thus if positive and negative predictive values are quoted for the detection of significant fibrosis using a serum model, these are only applicable at the quoted prevalence of significant fibrosis in that particular population. In addition the particular characteristics of a serum model could make it suitable for a population. Thus if a serum model is being applied to patients where the prevalence of significant fibrosis is expected to be low, for example non-alcoholic fatty liver disease, it is preferable for the model to deliver a high

negative predictive value to allow the maximum number of patients to avoid liver biopsy. An advantage of the European Liver Fibrosis Group (ELFG) model is that the adoption of different score thresholds delivered changes favouring either negative or positive predictive values, depending on the population being studied.[7]

Rapid Proliferation of Serum Models

The first report describing serum markers used in combination to generate a score, which could predict liver fibrosis in hepatitis C patients, appeared in *Lancet* in 2001 and has been widely quoted.[20] In the intervening time, there has been an explosion of interest in the area such that it is unusual to read an issue of any specialist hepatology journal, which does not describe a new serum model. However what is lacking is good data comparing serum models with each other. The problem is compounded by the commercialisation of some of the models, with the result that if the all-important algorithm used to calculate the score is not published, comparative studies are not possible.

FibroTest

FibroTest was first described for hepatitis C patients in 2001,[20] and is licensed to BioPredictive (www.biopredictive.com). FibroTest uses five serum markers, Apo A1, Hap, α-2-M, gamma glutamyl transpeptidase (γGT) activity and Bil, together with the age and gender of the patient to calculate a score. In the original report, FibroTest scores from 0 to 0.10 provided 100% negative predictive value for the absence of significant fibrosis (defined as F2, F3 or F4 by Metavir) while scores from 0.60 to 1.00 had a >90% positive predictive value for significant fibrosis for hepatitis C patients. Scores from 0.11 to 0.59 were indeterminate and liver biopsy was recommended. In an independent validation of FibroTest, the negative predictive value of a score <0.10 was 85% and the positive predictive value of a score >0.60 was 78%.[22]

FibroTest has also been applied to detect liver fibrosis in patients with chronic hepatitis B infection.[23] For application in non-alcoholic fatty liver disease FibroTest has been modified and presented as NashTest by including the following additional parameters: height, weight, serum triglycerides, cholesterol, and both AST and ALT.[24]

Fibrospect

FIBROspect II was first described for hepatitis C patients in 2004 and is licensed by Prometheus Laboratories (California, US).[25] Fibrospect uses three serum markers, α-2-M, HA and TIMP, to calculate a score. When applied to 696 patients with hepatitis C, a score <0.36 excluded significant fibrosis with a negative predictive value of 76% and a score >0.36 detected significant fibrosis with a positive predictive value of 74%.

ELFG

In a thorough international multicentre study, the ELFG developed an algorithm combining age and three serum markers: HA, PIIINP and TIMP 1.[7] In the same paper, the algorithm was applied to three chronic liver diseases; hepatitis C, alcoholic liver disease and non-alcoholic fatty liver disease where it achieved areas under ROCC of 0.77, 0.94 and 0.87, respectively. When histologic grading obtained by three pathologists was compared, the agreement between pathologists ranged from very good to moderate (kappa scores 0.97-0.46).[7]

Hepascore

Hepascore requires the measurement of serum Bil, γGT activity, α-2-M and HA levels.[26] Hepascore is a score from 0.00 to 1.00 calculated from the results of these four analyses and the age and sex of the patient. Hepascore has been validated in hepatitis C patients, where a score ≥0.50 provided a positive predictive value of 88% for significant fibrosis (METAVIR score of F2 or above) and a score <0.5 had a negative predictive value of 95% for the absence of advanced fibrosis (METAVIR score of F3 or above).[26]

Fibrometer

In a thorough study Cales et al. measured a total of 51 serum markers and were able to calculate and compare five previously described serum models, including FibroTest, Fibrospect II and the European Liver Fibrosis models.[27] In addition they proposed Fibrometer, a new serum model that is claimed to outperform previous models. The six tests required to calculate Fibrometer are platelets, PT index, AST, α-2-M, HA and urea.

Assessing Serum Model Performance

Serum models are assessed against the prevailing liver biopsy gold standard, although it is a flawed standard. In a new approach, Poynard et al. assessed the risk factors for discordances between the FibroTest serum marker model and biopsy, and then classified them as attributable to either biopsy or marker failure.[28] Discordance was attributable to failure of serum markers in 2.4%, to biopsy failure in 18% and was not attributable in a further 8% of patients. The most frequent reason for marker failure was a false negative result due to inflammation affecting the serum results, whereas biopsy failures were usually due to false negative staging associated with smaller biopsy size, fragmented biopsy and steatosis. In a similar study, discordance was attributable to failure of FibroTest serum marker model in 5%, to biopsy failure in 4% and was not attributable in a further 9% of patients.[29]

There is five years experience with the first reported serum marker model and the five year prognostic value of the serum

model compared to that of biopsy staging has been reported using the endpoints of predicting decompensation of cirrhosis and patient survival.[30]Although only 64 patients with untreated severe fibrosis were studied, the serum model was a better predictor of complications of hepatitis C and patient survival than liver biopsy results.

Comparing Serum Models

An important systematic review of the literature up to 2004,[31] examined 10 serum models proposed for hepatitis C using the approved quality assessment of diagnostic accuracy studies tool (QADAS).[32] The results of receiver operator areas under the curve, likelihood ratios and diagnostic odds ratios were mostly below the values expected for robust tests. The models were found to perform with either high sensitivity and low specificity or vice versa. Somewhat disappointingly, clinically relevant predictive values either ruling in or ruling out fibrosis were obtained in only 35% of the hepatitis C patient population. This result is partly due to the lack of validation parameters in the publications describing the models. One of the review conclusions was to press for uniform reporting of likelihood ratios and diagnostic odds ratios so that these can be used as performance indicators.

Studies reporting actual head to head comparisons of serum models have also recently appeared. An especially thorough study measured a total of 51 serum markers in order to calculate and compare five previously described serum models and propose a new serum model called Fibrometer which is also claimed to assess a new parameter, the area of liver fibrosis.[27]

Comparisons are now available which include other non-invasive techniques such as transient elastography in comparison to serum models. For example, transient elastography gave similar performance in assessing liver fibrosis to FibroTest, but the best performance was given by combining transient elastography and FibroTest.[33] Using this combination, 84% of hepatitis C patients could have avoided biopsy.

The Future for Serum Models

At present, serum marker models are usually trialled in parallel with liver biopsy, rather than replacing biopsy. However there are indications that serum models can be applied in selected patients. For example, most models deliver a high negative predictive value when the scores are very low and it is felt appropriate to forego liver biopsy because the likelihood of significant fibrosis is correspondingly low.[34] As more studies are published further niche applications are likely to be found.

When the literature was reviewed up to 2004, it was concluded that serum marker models could have obtained clinically relevant predictive values either ruling in or ruling out fibrosis in only 35% of the hepatitis C patient population.[31] However, in more recent work, indications are that this has already been improved and given the level of interest and importance, will likely continue to improve.[27,33]

Competing Interests: The authors are party to a licensing agreement between the University of Western Australia and a US pathology company with regards to Hepascore.

The authors were the winners of the Research Organisation category of the 2006 Inventor of the Year award offered by the Western Australian Government Department of Industry and Resources for their development of Hepascore.

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