Around 4 to 5 million people suffer from chronic liver disease in Germany (1), which can lead to hepatic cirrhosis and in turn to complications such as ascites, bleeding oesophageal varices, hepatic encephalopathy, hepatorenal syndrome, hepatopulmonary syndrome and hepatocellular carcinoma (HCC). Patients with hepatic cirrhosis have a significantly reduced life expectancy relative to non-cirrhotic patients (2). Hepatic cirrhosis is considered a precursor to hepatocellular carcinoma. The high (1 to 6% per year) incidence of hepatocellular carcinomas secondary to hepatic cirrhosis contribute significantly to the high mortality seen in these patients, hence many expert bodies recommend regular screening for hepatocellular carcinoma in patients with cirrhosis of the liver (3).

The limitations of available diagnostic methods for hepatic cirrhosis (clinical signs, imaging techniques and liver biopsy) are presently driving interest in a range of non-invasive tests, which are currently under evaluation. The focus of this review is research relating to transient elastography.

Liver biopsy and ultrasound
Liver biopsy is a common element of diagnostic workup in hepatic cirrhosis, alongside clinical examination and abdominal ultrasound, and is the accepted diagnostic gold standard. Its sensitivity and specificity can be further increased by the combination of liver histology with macroscopic liver examination via laparoscopy (4). It should be noted that there is no unitary system of histological classification used to evaluate the degree of fibrosis, and individual systems are often validated only for individual disease entities (table 1). A fundamental difficulty with histological classification arises whenever a continuous process such as hepatic fibrosis is translated into an ordinally scaled system of points. This inevitably leads to incongruities in the histological evaluation of the stage of fibrosis. The variance in evaluation can be as high as 20% even among experienced pathologists (5). This is compounded by the fact that fibrotic change in liver tissue does not always occur homogeneously, so that a degree of error is introduced.
even at the level of the biopsy specimen. Hence in 33% of cases, differences of up to one stage of fibrosis are found within the same patient between biopsy specimens taken from the right and left lobes of the liver, respectively (6). A further disadvantage of liver biopsy is that it is an invasive and possibly painful intervention, with a serious complication rate of 1 to 3% (5).

Ultrasound allows accurate diagnosis of hepatic cirrhosis in 82 to 88% of cases (7). However, its value depends heavily on practitioner experience and the quality of the instrument. Ultrasonographic diagnosis of hepatic cirrhosis relies on indirect parameters such as evidence of portal hypertension.

**Serum markers and scores for fibrosis**

There are numerous laboratory measures which individually or in combination mark the extent of fibrosis (box). However, most of these markers bear no causal relation with fibrogenesis. In comparing the various non-invasive methods, it should be remembered that they are often derived from differing patient populations, often only as part of pilot studies, without independent validation, and often using differing diagnostic threshold values (table 2). In addition, these non-invasive markers and scores are measured against liver biopsy, itself a variable and error-prone gold standard.

Of all the individual measures, the platelet count is the most convenient rough guide to the evaluation of the stage of fibrosis. In advanced disease of the liver parenchyma, or cirrhosis, the platelet count often falls. This finding correlates moderately with the histologically determined degree of fibrosis, with a correlation coefficient of 0.46 to 0.50 (8). In addition to the platelet count, procollagen III peptide has found a place in routine investigation (box).

Another measure of serum fibrosis is the APRI (“aspartate aminotransferase to platelet ratio index”) score, which is calculated from the GOT level and the platelet count (box). The APRI score has thus far only been evaluated in patients with viral hepatitis. It is not suitable for the evaluation of the degree of fibrosis in other liver parenchymal diseases such as ethyltoxicity with high GOT levels. A threshold level for significant fibrosis has been

| **TABLE 1** |
| **Histological classification systems for evaluating the stage of fibrosis in chronic viral hepatitis (21)** |

<table>
<thead>
<tr>
<th>Stage of fibrosis</th>
<th>Desmet &amp; Scheuer</th>
<th>Knodell</th>
<th>Ishak</th>
<th>Metavi*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No increase in fibrosis</td>
<td>No fibrosis</td>
<td>No fibrosis</td>
<td>No fibrosis</td>
</tr>
<tr>
<td>1</td>
<td>Portal fibrosis, no septa</td>
<td>Portal fibrosis</td>
<td>Fibrosis of isolated portal areas with or without short septa</td>
<td>Portal fibrosis</td>
</tr>
<tr>
<td>2</td>
<td>Incomplete or complete portoportal septa, architecture preserved</td>
<td>n. d.</td>
<td>Increased fibrosis in most portal areas with or without short septa</td>
<td>Portal fibrosis with scattered septa</td>
</tr>
<tr>
<td>3</td>
<td>Fibrosis with septum formation and architectural disruption, but no evidence of complete cirrhotic change</td>
<td>Portoportal or portocentral septa</td>
<td>Portal fibrosis with portoportal septa</td>
<td>Numerous septa without cirrhosis</td>
</tr>
<tr>
<td>4</td>
<td>Probable or definite cirrhosis</td>
<td>Cirrhosis</td>
<td>Portal fibrosis with marked porportoportal or portocentral septa</td>
<td>Cirrhosis</td>
</tr>
<tr>
<td>5</td>
<td>n. d.</td>
<td>n. d.</td>
<td>Marked septum formation (portoportal or portocentral) with some nodule formation (incomplete cirrhosis)</td>
<td>n. d.</td>
</tr>
<tr>
<td>6</td>
<td>n. d.</td>
<td>n. d.</td>
<td>Probable or definite cirrhosis</td>
<td>n. d.</td>
</tr>
</tbody>
</table>

n. d. = not defined; * only validated in chronic hepatitis C
defined (Ishak score F3 to F6) as a score of > 1.5 (9), whereas a score of < 0.5 is said to rule out significant fibrosis.

In hepatic cirrhosis (Ishak score F5 to F6) the threshold for significant disease is > 2.0, whereas a score of < 1.0 is thought to exclude cirrhosis. The area under the receiver operator curve (AUROC: graphic representation of sensitivity and specificity) for the APRI index in identifying significant fibrosis or cirrhosis is in the order of 0.80 or 0.89, respectively (9, 10). The larger the area under the curve, the better the diagnostic test, where an area of 1.0 equates to a perfect test with a sensitivity and specificity of 100%.

An additional combined marker for serum fibrosis is the FibroTest, which is based on a mathematical algorithm made up of various serological values (box). Scores of 0 to 0.10 are held to exclude significant fibrosis (Metavir F2, F3 or F4), whereas values between 0.60 and 1.00 show at least F2 level fibrosis. These threshold levels yield a negative predictive

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**BOX**

**Laboratory tests for degree of hepatic fibrosis**

**Individual tests:**
- Platelet count
- Procollagen-III-peptide
- Type 4 collagen
- Hyaluronic acid
- Thrombopoetin
- TGFβ1
- Laminin

**Combined serological markers of fibrosis:**

- **Pohl score (13)**
  - AST/ALT and platelet count
  - Diagnostic range:
    - Advanced fibrosis (Metavir F3/F4): AST/ALT > 1 and platelets < 150,000/µL,
    - Exclusion of advanced fibrosis (F3/F4): AST/ALT < 1 and platelets > 150,000/µL

- **APRI index (9, 10)**
  - Relation of measured GOT [U/L] to reference value [U/L] divided by platelets [10^9/L] x 100
  - Diagnostic range:
    - Advanced fibrosis (Ishak ≥ 3): score > 1.5
    - Exclusion of advanced fibrosis (Ishak < 3): score ≤ 0.5

- **Fora’s index (12)**
  - \[7.181 – 3.131 \times \ln(\text{platelets} [10^9/\text{L}]) + 0.781 \times \ln(\text{gamma GT}) + 3.467 \times \ln(\text{age}) – 0.014 \times \text{cholesterol [mg/dL]}\]
  - Diagnostic range:
    - Advanced fibrosis (F2, F3, F4 according to Scheuer score): score > 6.9
    - Exclusion of advanced fibrosis: score < 4.21

- **FibroTest (10)**
  - \[F = 4.467 \times \log([\text{alpha 2 makroglobulin (g/L)}] – 1.357 \times \log([\text{Haptoglobin (g/L)}] + 1.017 \times \log([\text{gamma GT (IU/L)}] + 0.281 \times \text{age [years]} + 1.737 \times \log([\text{bilirubin (µmol/L)}] – 1.184 \times \text{apolipoprotein A1 (g/L)}] + 0.301 \times \text{sex (0 for female, 1 for male)} – 5.540\]
  - Diagnostic range:
    - Advanced fibrosis (Metavir F2, F3, F4): score 0.60 to 1.00
    - Exclusion of advanced fibrosis: score 0 to 0.10

AST, aspartate aminotransferase; ALT, alanine aminotransferase
value of 100% and a positive predictive value of > 90% for the diagnosis of advanced fibrosis. The AUROC values for the detection of significant fibrosis were in the region of 0.83 and 0.87 respectively (11). A more recent study reports AUROC values of 0.90 and 0.87 respectively for significant hepatic fibrosis (Metavir F3) or cirrhosis (Metavir F4) (10). These findings are roughly comparable with APRI score data.

The Forns index is calculated using the platelet count, the gamma GT, the age of the patient and the cholesterol level (box). A result of under 4.21 effectively rules out significant fibrosis (Metavir F2, F3 or F4), with a high degree of probability (negative predictive value 96%). The positive predictive value and hence the probability of fibrosis in the presence of a value over 6.9 was 79%, significantly lower (12) than for elastography.

The Pohl score, another combined serum marker of fibrosis, is derived from the GOT to GPT ratio, in combination with the platelet count (box). A GOT:GPT ratio > 1 and a platelet count below 150 000/µL yielded a positive predictive value for advanced fibrosis of 93.1% according to Pohl et al.’s data (Metavir F3/F4). The sensitivity, specificity and negative predictive values were 41.2 %, 99.1 % and 85.0 % respectively. The Pohl score was validated in patients with chronic HCV infection, and is not transferable to patients with alcohol abuse (13).

### TABLE 2

<table>
<thead>
<tr>
<th>Non-invasive tests for liver fibrosis</th>
<th>AUROC values for diagnosing cirrhosis</th>
<th>Sensitivity for cirrhosis diagnosis</th>
<th>Specificity for cirrhosis diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets (8)</td>
<td>0.89</td>
<td>77 %</td>
<td>88 %</td>
</tr>
<tr>
<td>APRI score (8, 22)</td>
<td>0.90–0.94</td>
<td>38–57 %</td>
<td>87–93 %</td>
</tr>
<tr>
<td>FibroTest (22)</td>
<td>0.87</td>
<td>50 %</td>
<td>93 %</td>
</tr>
<tr>
<td>Forns index (12)</td>
<td>No data</td>
<td>30 %</td>
<td>95 %</td>
</tr>
<tr>
<td>Pohl Score (13)</td>
<td>No data</td>
<td>18–41 %</td>
<td>98–99 %</td>
</tr>
<tr>
<td>Transient elastography (10, 14–19, 23–25)</td>
<td>0.91–0.97</td>
<td>77–100 %</td>
<td>82–97 %</td>
</tr>
</tbody>
</table>

**Transient elastography**

Transient elastography is a new imaging modality for detecting hepatic fibrosis. The measuring instrument comprises a computer driven control unit and a measuring probe containing a low frequency vibration emitter together with a 5 Mhz ultrasound probe.

Transient elastography is carried out with the patient supine, with his/her right arm behind their head. The measuring probe is positioned at the level of the xiphoid in the right midaxillary line, at 90 degrees to the body (diagram 1). The vibrating probe emits a mechanical signal on the body surface, which generates a low frequency elastic wave of 50 Hz, which is transmitted into liver tissue at a speed of around 1 m/s. Using the high frequency ultrasound wave of 1 500 m/s the transmission velocity of the elastic wave in the liver tissue can be measured (diagram 2). This allows liver stiffness to be measured, which correlates with the degree of fibrosis, a higher degree of fibrosis implying greater stiffness. Stiffness is measured in kPa, with maximal possible values of up to 75 kPa. At least 6 valid measurements should be taken. A single measurement takes no more than 15 seconds. A final reading is derived from the median of the individual readings, in order to exclude outlying measurements.

Transient elastography can be performed on an outpatient basis, and is both non-invasive and painless. It is risk free, comparable to ultrasound examination, and can be repeated freely. It has not been validated in children and adolescents under 18. The price of a measuring instrument is currently in the region of 80 000 euros, with minimal maintenance costs.

Some early large studies have generated threshold values for the diagnosis of hepatic cirrhosis of between 12.5 and 14.6 kPa with sensitivities of 77 to 87 % and specificities of 91 to 97 % (10, 14, 15). Our own results in 147 patients yield a sensitivity of 90% and a specificity of 82% using a diagnostic threshold value of 13 kPa (table 3). The resulting AUROC curve for patients with advanced fibrosis (Desmet und Scheuer stage F3) was
0.88, and for patients with cirrhosis, 0.92 (95% confidence interval 0.87 to 0.98). As optimal threshold values appear to vary between studies, it seems wise to establish individual threshold values for each newly acquired piece of equipment. Until adequate patient numbers have been investigated to generate these values, it seems advisable to use the lowest threshold values quoted in the literature of 12.5 kPa.

Transient elastography is not only helpful in diagnosing hepatic cirrhosis with viral hepatitis. In 380 patients with chronic alcohol abuse, positive predictive values for cirrhosis of 97% were achieved, using a threshold value of 13 kPa (16). A study of 150 patients with primary biliary cirrhosis reports AUROC values of 0.93 (17). In HIV/HCV coinfected patients similarly high AUROC values of 0.97 were reported for a diagnosis of hepatic cirrhosis (18) (table 3).

Elastography appears unreliable in differentiating between milder levels of fibrosis, however. AUROC values of between 0.72 and 0.81 have been reported (18). In our own studies, it was impossible to distinguish reliably between F0 and F1, between F1 and F2, and between F2 and F3 fibrosis (Desmet and Scheuer classification) (19). Elastography is also limited in patients with a high body mass index (BMI), primarily due to impeded penetration of the mechanical impulse into tissue. One large study reported invalid results in 4.5% of 2 114 patients (20). Both the univariate and multivariate analyses showed a significant correlation between invalid measurement and a BMI of over 28 kg/m². Other impediments to transient elastography include narrow intercostal spaces, ascites, space occupying lesions in the liver, acute hepatitis and scarring following liver resection, which can restrict the progress of the elastic wave. The effects of liver fat content, vascular changes or variations in portal pressure on liver stiffness have not been systematically evaluated.

Improvements in the sensitivity and specificity of non-invasive techniques for evaluating fibrosis could probably be achieved via a combination of individual methods. In patients with hepatic cirrhosis, the fibrosis test alone generated 80% agreement with the histological findings, for elastography alone this figure was 90%, but with a combination of the two, an
agreement of 94% was achieved (10). In summary, transient elastography, used in combination with other non-invasive tests and with refinement of mathematical methods, can therefore diagnose cirrhosis of the liver reliably, rendering liver biopsy unnecessary. The marginal value of transient elastography over and above history, examination findings, laboratory results and other imaging, where these are available, has not been studied and remains uncertain.

Conflict of Interest Statement
The authors declare no conflict of interests in the terms of the International Committee of Medical Journal Editors.


Translated from the original German by Dr Sandra Goldbeck-Wood.

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