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Non-invasive diagnosis of cirrhosis and the natural history of its complications

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Several methods have been studied in the attempt to reach a diagnosis of cirrhosis by non-invasive means. Although abdominal ultrasound can detect the hepatic and extra-hepatic changes consistent with cirrhosis, its ability to distinguish chronic hepatitis from compensated cirrhosis is limited. Serum markers can rule in or rule out fibrosis in up to 35% of patients but, in individual patients, cannot differentiate the stages of fibrosis reliably. Transient elastography (Fibroscan) might be of value for the non-invasive diagnosis of cirrhosis; however, its reproducibility needs to be further validated. Cirrhosis can be divided into 4 stages: stage 1, no varices, no ascites; stage 2, varices without ascites and without bleeding; stage 3, ascites ± varices; stage 4, bleeding ± ascites. Yearly mortality ranges from 1% in stage 1 to 57% in stage 4. The yearly incidence of oesophageal varices is 5–7%; their rate of enlargement is 10–12% per year. The incidence of variceal bleeding is about 25% at 2 years. Bleeding stops spontaneously in about 50% of cases but early rebleeding occurs in 30–40% of patients. Bleeding-related mortality has declined over time and is now around 20% at 6 weeks.

Key words: abdominal ultrasound; ascites; fibroscan; oesophageal varices; serum markers; variceal bleeding.

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NON-INVASIVE DIAGNOSIS OF CIRRHOSIS

In patients with chronic liver disease, histopathological examination of percutaneous biopsy samples has traditionally been considered the gold standard for establishing a precise diagnosis — by grading the severity of necroinflammation and the extent of fibrosis — and for detecting progression to cirrhosis. However, liver biopsy has limitations: it is invasive, costly and requires hospitalisation for at least 6–18 h; it is associated with small but significant morbidity and mortality rates; it can be subject to sampling error and inter- and intra-observer variation in pathology interpretation.[1,2] In addition, it is not suitable for repeat testing to assess progression of disease. For these reasons, non-invasive methods for evaluating the severity of liver disease, and especially for differentiating chronic hepatitis from compensated cirrhosis, have been evaluated over the years.

Abdominal ultrasound

Imaging techniques are attractive for their lack of invasiveness and their potential to detect structural changes in the liver parenchyma. Abdominal ultrasound can provide useful information on the size of the liver, the appearance of its surface and margin, and the echogenicity of the parenchymal texture. In addition, it can detect extra-hepatic changes (splenomegaly, ascites, portal collaterals, dilation of portal vessels) secondary to portal hypertension. However, most of these changes apply to advanced cirrhosis, for which a clinical diagnosis can be readily made. When discrimination between chronic hepatitis and compensated cirrhosis is attempted, the performance of ultrasound is only fair. This is nicely exemplified in a study by Gaiani et al,[3] who examined prospectively a sample of patients with chronic hepatitis (78%) or compensated cirrhosis (22%) and developed a diagnostic score based on seven ultrasonographic parameters (six morphological, one Doppler). In this study, the ultrasound score failed to identify cirrhosis in 21.3% of patients with the condition and classified as cirrhotic 19.4% of patients with chronic hepatitis.

Blood markers of liver fibrosis

Blood markers of liver fibrosis are attractive because they are non-invasive and suitable for repeated testing, thus allowing monitoring the evolution of liver disease. In recent years, several diagnostic indexes based on panels of blood markers have been proposed (Table 1).[4–11] In all the studies, the performance of the panels in grading fibrosis was compared with liver histology, which served as the gold standard. The studies vary widely with regard to number of patients and types of liver disease studied, although most have been carried out in patients with chronic hepatitis C (HCV) or HCV-related cirrhosis. Different histological grading systems have been used and, furthermore, there were differences in the degree of fibrosis considered as advanced in the various studies. This is important because different cut-off values lead to different estimates of sensitivity, specificity, positive and negative predictive values.

In a recent meta-analysis of 14 studies examining 10 panels of blood markers,[12] the diagnostic indexes were validated on samples from independent patients in 11 of the 14 studies. Overall, the sensitivity of the panels in distinguishing between mild and moderate–severe fibrosis ranged between 17% and 100%; the specificity varied between 24% and 100%. In the studies in which these data were available, the ranges