World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
doi:10.3748/wjg.v20.i2.445

World J Gastroenterol 2014 January 14; 20(2): 445-459
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (9): Hepatitis B virus

Non-invasive diagnosis of hepatitis B virus-related cirrhosis

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Supported by A grant of the South Korea Healthcare technology R and D project, Ministry of Health and Welfare, South Korea, No. HI10C2020
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Received: October 25, 2013 Revised: November 25, 2013
Accepted: December 5, 2013
Published online: January 14, 2014

Abstract

Chronic hepatitis B (CHB) infection is a major public health problem associated with significant morbidity and mortality worldwide. Twenty-three percent of patients with CHB progress naturally to liver cirrhosis, which was earlier thought to be irreversible. However, it is now known that cirrhosis can in fact be reversed by treatment with oral anti-nucleotide drugs. Thus, early and accurate diagnosis of cirrhosis is important to allow an appropriate treatment strategy to be chosen and to predict the prognosis of patients with CHB. Liver biopsy is the reference standard for assessment of liver fibrosis. However, the method is invasive, and is associated with pain and complications that can be fatal. In addition, intra- and inter-observer variability compromises the accuracy of liver biopsy data. Only small tissue samples are obtained and fibrosis is heterogeneous in such samples. This confounds the two types of observer variability mentioned above. Such limitations have encouraged development of non-invasive methods for assessment of fibrosis. These include measurements of serum biomarkers of fibrosis; and assessment of liver stiffness *via* transient elastography, acoustic radiation force impulse imaging, real-time elastography, or magnetic resonance elastography. Although significant advances have been made, most work to date has addressed the diagnostic utility of these techniques in the context of cirrhosis caused by chronic hepatitis C infection. In the present review, we examine the advantages afforded by use of non-invasive methods to diagnose cirrhosis in patients with CHB infections and the utility of such methods in clinical practice.

Key words: Chronic liver disease; Chronic hepatitis B; Hepatitis B virus; Cirrhosis; Liver stiffness measurement; Transient elastography; Acoustic radiation force impulse imaging; Real-time elastography; Magnetic resonance elastography; FibroTest; Aspartate aminotransferase to platelet ratio index

Core tip: Chronic hepatitis B (CHB) infection is associated with significant morbidity and mortality because it can progress to cirrhosis or hepatocellular carcinoma. Early diagnosis of liver cirrhosis in CHB patients is important to prevent the disease progression. Non-invasive diagnosis has been developed remarkably and showed high diagnostic accuracy for cirrhosis. New methods and the combination of non-invasive diagnosis tools may contribute to the improvement to diagnose the cirrhosis with CHB.

Lee S, Kim DY. Non-invasive diagnosis of hepatitis B virus-related cirrhosis. *World J Gastroenterol* 2014; 20(2): 445-459 Available from: URL: http://www.wjgnet.com/1007-9327/full/v20/i2/445.htm DOI: http://dx.doi.org/10.3748/wjg.v20.i2.445

INTRODUCTION

Serologically, hundreds of millions of people are chronic

hepatitis B (CHB) virus surface antigen (HBsAg) carriers and it is estimated that over 200000 CHB patients die worldwide each year from cirrhosis[1,2]. The prognosis is worse in those infected by hepatitis B virus (HBV) in areas in which the virus is endemic. The annual rate of progression from chronic hepatitis to cirrhosis is 2%-5% in HBV e antigen-positive and 3%-10% in e antigen-negative patients[3].

Early diagnosis of liver cirrhosis in CHB patients is important because cirrhosis per se is an independent predictor of mortality. The 1-year mortality rates vary from 1% in patients with early-stage cirrhosis to 57% in those with decompensated disease[4-6]. In addition, the 5-year cumulative risk that a cirrhotic patient will develop hepatocellular carcinoma is 10%-17%[3]. Diagnosis of cirrhosis in CHB patients may trigger early initiation of antiviral treatment, which improves clinical outcomes. Also, development of complications in such patients is monitored regularly[7,8].

Traditionally, cirrhosis has been diagnosed with the aid of clinical information, including laboratory and imaging data. However, such methods have their limitations, and a liver biopsy has usually been required to confirm a diagnosis of liver cirrhosis.

Cirrhosis occurs in response to chronic liver injury and constitutes the final stage of progressive hepatic fibrosis characterized by distortion of hepatic architecture and formation of regenerative nodules[9]. If a liver biopsy sample is to be adequately diagnostic, the sample should be at least 2-3 cm in length and contain more than 11 complete portal tracts[10]. However, it is usually difficult to fulfill these requirements. Also, the evaluation of simultaneous biopsies taken from the left and right lobes yielded different fibrosis scores in 33% of patients[11]. Intra- and inter-observer variation contribute to test variability[12]. Biopsy is associated with a bleeding risk of 1%[13] and a mortality rate of approximately 0.01%[14].

Therefore, it is necessary to investigate the new diagnostic methods for improving the limitations and complications of liver biopsy. Non-invasive modalities, including transient elastography (TE), acoustic radiation force impulse imaging (ARFI), real-time elastography (RTE), and magnetic resonance elastography (MRE), have been developed to overcome the problems discussed above. Also, markers of cirrhosis have been sought in blood. Such non-invasive modalities have attracted much attention[15-22]. In the present review, we examine the roles played by non-invasive diagnostic modalities in terms of assessment of cirrhosis and prediction of the prognosis of CHB patients.

CLASSICAL DIAGNOSIS OF LIVER CIRRHOSIS USING CLINICAL INFORMATION

Clinicians usually take a clinical history, conduct a physical examination, and review laboratory and imaging data to diagnose liver cirrhosis in CHB patients.

First, history-taking is a basic clinical approach. For example, a family or past history of HBV infection is an important clue to decide whether cirrhosis may or may not be caused by HBV. The histories of blood transfusion, needle injury, and sexual activity are important factors for the route of infection.

Second, physical examination is both simple and essential. Spider angioma, splenomegaly, hepatomegaly, a distended abdomen, the presence of shifting fluid, and pitting edema suggestive of portal hypertension, all aid in the diagnosis of liver cirrhosis in CHB patients. Blood samples should be evaluated for the presence of HBV surface antigen, platelet count, albumin level, prothrombin time, and total bilirubin concentration. Simple blood test data do not afford great sensitivity in diagnosis of cirrhosis, but one meta-analysis found that the presence of ascites [likelihood ratio (LR) = 7.2], a platelet count < 160000/mm^3 (LR = 6.3), and spider nevi (LR = 4.3) were all usefully predictive of cirrhosis[23]. These simple blood tests, and data from physical examination, are necessary to evaluate the severity of cirrhosis, being parameters used to derive Child-Pugh or Model for End-Stage Liver Disease (MELD) scores for cirrhotic patients.

Third, imaging modalities including ultrasound, abdominal computed tomography (CT), and magnetic resonance imaging (MRI), can aid in detection of cirrhosis or hepatocellular carcinoma in HBV patients. Liver cirrhosis is typically associated with splenomegaly, hepatomegaly, a coarse echo pattern of the liver parenchyma, nodularity of the liver surface, a blunt angle, ascites, and thrombus of the portal vein[24-27]. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of ultrasound used to predict the presence of HBV-related cirrhosis were 77.8%, 92.5%, 87.5%, 86.0%, and 86.6%, respectively, and were higher in CHB patients than in those with chronic hepatitis C (CHC)[27]. Such radiological findings are also important when abdominal CT or MRI is used to diagnose liver cirrhosis. Additionally, other radiological findings including the velocity of portal flow, the shape of the hepatic vein waveform (as revealed by Doppler testing), and the caudate lobe/right lobe ratio with use of the main or right portal vein to set the lateral boundary (as revealed on CT or MRI), are useful[24,28-30]. Of these parameters, a caudate lobe/right lobe ratio over 0.65 is suggestive of the presence of liver cirrhosis. The sensitivity, specificity, and accuracy of this measure were 84%, 100%, and 94%, respectively[30]. Liver surface nodularity, a platelet count less than 100000/mm^3, an albumin level less than 3.5 g/dL, and an international normalized prothrombin time ratio of 1.3 or more, are also associated with liver cirrhosis. Each of these findings is associated with a specificity and sensitivity of 90% and 61%, respectively, in terms of cirrhosis diagnosis[31].

An overview of clinical history, physical examination, and review of laboratory and imaging test data, combine to aid in the diagnosis of HBV-caused cirrhosis. The use

of clinical strategies that combine elements of these diagnostic modalities is crucial to diagnose cirrhosis in CHB patients and to plan suitable treatment.

TRANSIENT ELASTOGRAPHY

Measurement of liver stiffness

TE is a representative noninvasive method used to diagnose cirrhosis or assess the extent of fibrosis using ultrasound elastography. The propagation velocity of transient shear waves of low amplitude and frequency (50 Hz) is affected by the elasticity of the liver parenchyma. If the waves propagate rapidly, the fibrotic burden is large[32]. The outcome is expressed as a pressure (thus in kilopascals; kPa) and ranges from 2.5 to 75 kPa (normal, 5 kPa)[33-35]. The reliability of the technique has been reported to be over 60% and the median interquartile range less than 30%[36-38]. The generator is placed over an interspace of the ribcage of the right upper quadrant. The test usually takes 5-10 min. Typically, 10 or more measurements are taken but three valid measurements suffice to reliably diagnose liver fibrosis in CHB patients[39].

Diagnostic performance

Most studies have found that TE performs well when used to diagnose and measure the extent of liver fibrosis in patients with CHC infection or other liver conditions[40-42]. TE also afforded acceptable diagnostic accuracy in CHB patients[18-20]. Marcellin *et al*[20] reported that TE used to diagnose cirrhosis in CHB patients had a diagnostic accuracy of 94%, a sensitivity of 57%, a specificity of 97%, a PPV of 67%, and an NPV of 96%. When maximal sensitivity and specificity are required, the cutoff value falls to 11.0 kPa (sensitivity 93%, specificity 87%, PPV 38%, and NPV 99%). Chan *et al*[19] found that TE yielded a good diagnostic performance in clinical practice. The maximal diagnostic accuracy was associated with a cutoff of 13.4 kPa but this value was 12.0 kPa when the sum of sensitivity and specificity was maximized. A liver stiffness measurement (LSM) cutoff value can easily be determined for each particular clinical requirement. A highly sensitive cutoff is useful when screening for early-stage cirrhosis whereas a highly specific cutoff would aid in detection of significant fibrosis or cirrhosis. A cutoff affording a high diagnostic accuracy would be valuable to ensure correct diagnosis. Interestingly, the cutoffs obtained by maximizing the sum of sensitivity and specificity, the area under the receiver operating characteristic (AUROC) curve, and diagnostic accuracy, were slightly lower for CHB than CHC patients. This is because the extent of fibrosis is slightly less in the former patients[43]. Cirrhosis in CHB patients is more macronodular in nature than in patients with CHC or alcoholic liver disease.

Kim *et al*[44] found that LSMs and biopsy data were not in agreement with measures of necro-inflammatory activity in CHB patients. LSMs were significantly higher in cirrhotic patients in whom such activity was maximal (grades 3-4; grade 4 is termed F4) than when the activity was less (grades 1-2) (median of 19.2 kPa in the former patients *vs* 11.9 kPa in the latter; $P = 0.009$). The results of liver biopsy and LSM differed in CHB patients with cirrhosis, principally when necro-inflammatory activity of grades 3-4 significantly increased the LSMs.

In addition, serum levels of aminotransferases must be considered when interpreting TE data from hepatitis B patients because alanine aminotransferase (ALT) flares (which are frequent in CHB patients) cause TE values to be artificially inflated[45]. Thus, patients with higher ALT levels tend to have greater LSMs than do those with lower ALT levels, even when the stage of liver fibrosis is identical. Thus, TE values of CHB patients should be interpreted cautiously because it is possible that patients with low-grade fibrosis may score as false-negatives whereas those with high ALT levels may yield false-positive values. In patients with normal ALT levels, the optimal cutoff values for reliable detection of cirrhosis ranged from 8.4 to 12.0 kPa. However, in patients with elevated ALT levels [> 1-5-fold the upper limit of normal (ULN)], the optimal cutoff values ranged from 8.4 to 13.4 kPa[19]. Kim *et al*[46] suggested that an appropriate LSM cutoff value in CHB patients with ALT ≤ ULN was 10.1 kPa, but 15.5 in those with ALT > ULN and ALT < 2 × ULN. When only patients with ALT < ULN were studied, the cutoff values allowing discrimination of each stage of fibrosis were reduced, and the sum of LSM sensitivity and specificity increased.

Both the total bilirubin level and the time of performance of LSM have been explored in terms of the ability to predict development of cirrhosis in CHB patients. The total bilirubin level was significantly associated with changes in LSMs. However, the LSM was not reduced when measured soon after the levels of ALT and total bilirubin normalized[47]. This suggests that normalization of the LSM may occur only after laboratory measurements on serum return to normal. Therefore, biochemical findings should be well-stabilized before LSMs can be considered reliable.

LSM data did not differ when the detector was placed in the fifth, sixth, and seventh intercostal spaces[48]. All LSMs accurately predicted development of cirrhosis. It was not necessary that the site of LSM should correspond to the liver biopsy site in cirrhotic HBV patients.

A meta-analysis of 50 studies found that the mean AUROC for reliable diagnosis of significant fibrosis and cirrhosis was 0.94, with an optimal cutoff LSM of 13.01 kPa[49]. TE diagnosed severe fibrosis or cirrhosis more reliably than less advanced fibrotic stages. The data suggest that TE is an excellent tool for use in clinical practice to confirm the presence of cirrhosis when other clinical data are not definitive.

Another meta-analysis of the data of nine studies showed that use of TE to diagnose cirrhosis was associated with 87% sensitivity and 91% specificity[50]. TE affords good diagnostic accuracy when used to quantify the extent of liver fibrosis in patients with either CHB or CHC. Chon *et al*[51] performed a meta-analysis of 18 stud-

ies with 2772 patients and found that the cutoff value for detection of cirrhosis in Asian CHB patients was 11.7 kPa, with a sensitivity and specificity of 84.6% and 81.5%, respectively. The mean AUROC for diagnosis of cirrhosis was 0.929.

Advantages and disadvantages of TE

TE data are reproducible and the results have been validated in detail. The procedure time is less than 5 min. It is easy to evaluate patients either at the bedside or in the outpatient clinic. TE is useful when employed to follow-up disease progression and to predict hepatic events preceding cirrhosis[52].

However, it is difficult to obtain TE data from obese patients [those with a body mass index (BMI) above 28 kg/m^2] and patients with narrow intercostal spaces, ascites, space-occupying tissue abnormalities, extrahepatic cholestasis, or congestion[15,53,54]. The difficulty of reliably measuring liver stiffness in patients with ascites is a major disadvantage, because ascites is a typical sign of cirrhosis.

Recently, an XL TE probe (as distinct from the standard M probe) has been used to gather data from obese patients. The XL probe afforded the best diagnostic performance of all probes tested and a relatively low level of measurement failure[55]. Compared to the M probe, the XL probe operates at a lower frequency (3.5 MHz *vs* 5 MHz), is longer (ultrasound transducer focal length of 50 mm *vs* 35 mm), yields vibration of greater amplitude (peak-to-peak 3 mm *vs* 2 mm), and has a greater depth of measurement (35-75 mm *vs* 25-65 mm). Failure of LSM using the M probe occurred in 29.1% of patients with BMIs of 30 kg/m^2 or more, but the failure rate was only 6.8% when the XL probe was employed.

Interestingly, eating prior to performance of TE can compromise the accuracy of LSMs in both CHC patients and those with other conditions[56,57]. The impact of ingestion on liver stiffness values is proportional to the stage of fibrosis, being maximal in patients with cirrhosis. This is because liver stiffness increases as portal blood flow and the hepatic vein pressure gradient rise after a meal[58]. Therefore, it is necessary for a patient to fast for at least 2 h prior to performance of TE.

ACOUSTIC RADIATION FORCE IMPULSE IMAGING

Measurement of liver stiffness

ARFI, which employs conventional B-mode sonography, is an alternative to TE. ARFI mechanically excites tissue for a brief period *via* delivery of a high-intensity acoustic pulse to a region of interest (ROI). Shear waves propagate and generate localized tissue displacement[59]. The shear-wave velocity (SWV) is recorded in m/s and quantified in a region smaller than that examined when TE is employed (10 mm long and 6 mm wide). The ROI can be chosen by the operator. The SWV increases with stiffness. Thus, the SWV is an intrinsic and reproducible property of tissue[59-61].

The probe is usually placed between the ribs on the right side (*e.g.*, in segment 8) to reduce the effect of cardiac motion on measurement. Thus, the device is located approximately where a liver biopsy is usually performed 1 cm under the capsule. Minimal scanning pressure is applied and the patient is asked to stop breathing for a moment, to minimize motion[62-64]. Data can also be obtained from the left lobe, which always appears to be stiffer than the right lobe, although data from both lobes correlate well with the stage of fibrosis[65]. The difference in measurement may be explained by variation in the pressure with which the ultrasonographic probe is placed. The probe is not directly applied to the right lobe because the chest wall intervenes to prevent direct probe contact with the liver.

Diagnostic performance

ARFI SWV diagnostic cutoff values of 1.75-2.00 m/s have been reported in patients with liver cirrhosis[62-67]. Chen *et al*[68] explored the association between spleen stiffness and advanced liver fibrosis. The optimal cutoff value was 3.32 m/s for detection of cirrhosis (80.0% sensitivity, 88.4% specificity, 55.5% PPV, 96.0% NPV). However, these data should be interpreted with caution because the proportion of HBV patients in the tested population was too small to allow the diagnostic performance of ARFI in cirrhotic HBV patients to be evaluated. ARFI has been used to examine patients with a variety of liver diseases, principally hepatitis C infection.

Friedrich-Rust *et al*[69] were the first to use ARFI to assess the severity of liver fibrosis in HBV patients. In this prospective European multicenter study, the median SWV was 0.76-2.96 m/s in CHB patients. In terms of Metavir fibrosis scores, the median velocities were 1.10 m/s for F0 patients, 1.14 m/s for F1 patients, 1.23 m/s for F2 patients, 1.60 m/s for F3 patients, and 1.75 m/s for F4 patients. The accuracy of cirrhosis diagnosis was 0.97. The cutoff for diagnosis of significant fibrosis (F grade $\geqslant$ 2) was 1.39 m/s with a sensitivity of 50%, a specificity of 90%, a PPV of 67%, an NPV of 73%, a positive likelihood ratio of 5.125, and a negative likelihood ratio of 0.554. However, no optimal cutoff for diagnosis of cirrhosis in CHB patients was derived, because the number of patients with F3/F4 fibrosis was too small. The diagnostic accuracy of ARFI in HBV patients with different degrees of fibrosis was lower than reported in previous studies on CHC patients who had fibrosis ranging from mild to significant, or cirrhosis. The accuracy of ARFI when used to detect mild fibrosis was 66% in HBV patients compared to 73% in studies on patients with CHC and other liver diseases. The accuracy values were 73% and 82%-90% in patients with significant fibrosis, 94% and 90%-99% in those with severe fibrosis, and similar (97% and 87%-99%) in those with cirrhosis[62-72]. Further randomized prospective studies are required to determine whether ARFI data are influenced by underlying liver disease.

One meta-analysis reviewed 36 reports on ARFI im-

aging of CHB patients and those with other liver diseases. In terms of diagnosis of patients of F grade ⩾ 3, the mean AUROCs of studies including and excluding HBV patients were 0.87 (95%CI: 0.85-0.90) and 0.92 (95%CI: 0.89-0.95), respectively[73]. Thus, AFRI afforded good diagnostic accuracy when used to detect cirrhosis.

Advantages and disadvantages

In contrast to TE, ARFI yields real-time information on the extent of liver stiffness during observation using B-mode ultrasonography. Also, liver tissue can be directly targeted, with exclusion of small non-parenchymatous areas (for example, blood vessels). If a patient has a large right-side tumor or ascites, it is difficult to measure LSM using TE. In such instances, ARFI can be employed to diagnose cirrhosis. As ARFI is performed using a conventional ultrasound instrument, ARFI and standard ultrasound examination may be performed using the same machine in the same session. This is convenient for CHB patients, who are usually examined ultrasonographically once or twice per year.

The major disadvantage of ARFI is that no long-term follow-up validation studies have been performed. Also, ARFI values, in contrast to TE values, have a narrow range (0.5-4.4 m/s). This makes it difficult to define precise cutoff values that can be used to make decisions on patient management.

Cassinotto *et al*[55] reported that ARFI was (like TE) less efficient in obese patients. This is because the ultrasound beam travels poorly through thick fatty soft tissue. Thus, ARFI cannot be used as a first-line examination modality for obese patients.

An advantage of ARFI is the ability to measure LSM in both the right and left lobes of the liver. However, upon simultaneous liver biopsy of both lobes, a between-lobe difference of at least one fibrosis stage was noted in only 33% of patients, and liver cirrhosis was evident in only one biopsy in 14.5% of cases[11].

Acute cellular infiltration, increased central venous pressure, and cholestasis, can cause the extent of liver fibrosis to be overestimated. These possibilities should be considered when interpreting elastography data[74-76]. As is true of TE measurements, food intake also increases ARFI-measured liver stiffness[77].

REAL-TIME ELASTOGRAPHY

Measurement of liver stiffness

RTE is a novel noninvasive ultrasound modality measuring liver elasticity, and has recently been used to quantitatively assess the extent of liver fibrosis[78-81]. As with ARFI, RTE uses a modified version of standard ultrasound equipment. RTE propagates a shear wave through the liver and echo signals are captured in real time. Friedrich-Rust *et al*[79] and Kanamoto *et al*[82] examined the utility of RTE in evaluation of liver fibrosis.

No special skills are required. A patient is placed in a supine position with the right arm extended above the head to stretch the intercostal muscles. After B-mode examination, the elastographic mode is selected. It is easy to verify the position of the liver because the elastographic images may be superimposed on B-mode reference images. The probe pressure may be varied manually. A small compression plate is usually attached to the ultrasonic probe so that stable tissue compression is attained and the stress field transmitted more uniformly. Tissue elasticity is color-coded (red: soft; blue: hard) in terms of magnitude and superimposed on conventional two-dimensional (2D) images[83], allowing anatomical correspondence to be noted.

Diagnostic performance

Only a few reports on use of RTE to evaluate CHB patients have appeared. Xie *et al*[84] used RTE to calculate elastic strain ratios (elastic strain values of liver tissue in the ROI/strain values of intercostal muscle in the ROI) in patients with different degrees of liver fibrosis. The diagnostic cut-off ratios were 1.10 in patients with substantial liver fibrosis and 0.60 in those with cirrhosis. The detection sensitivities for substantial fibrosis and cirrhosis were 77.8% and 50.0%, respectively, and the specificities 80.0% and 96.7%. The positive predictive values were 80.0% and 71.4% and the negative predictive values 77.8% and 92.2%.

Wang *et al*[85] described the diagnostic performance of an elasticity index obtained using RTE, and the aspartate aminotransferase (AST) to platelet ratio index (APRI) used to stage liver fibrosis in CHB patients. The AUROCs for detection of cirrhosis were 0.66 and 0.23, respectively. The diagnostic accuracies of both tests used to assess the stage of liver fibrosis (except cirrhosis) in CHB patients were high. In terms of elasticity index distribution by Metavir fibrosis stage, the cut-off value was 90.31 for cirrhosis.

Advantages and disadvantages

RTE reveals relative tissue strain in real time by measuring tissue displacement. RTE can be used (as can ARFI) to evaluate liver fibrosis patients with ascites or who are severely obese. Eleven stiffness parameters are measured, and changes in tissue stiffness are thus evaluated systematically and sensitively.

However, RTE requires further clinical validation. Although strain images are usually clear, artifacts include multiple reflections at the surface of the liver; echo-free areas filled by thick blood vessels, ribs and lungs; and lack of wave penetration. Also, if the probe pressure is excessive, the elastic relationship will vary (elasticity is nonlinear). In addition, pressure is not uniformly transmitted to the liver because that tissue is slightly deformed by heartbeats. However, good images can be obtained simply by applying the probe lightly to right-side intercostal regions. New quantitative analysis systems can measure tissue compression caused by the rhythmic beats of the heart and blood vessels; no manual compression is required. This minimizes the capacity for human error.

MAGNETIC RESONANCE ELASTOGRAPHY

Measurement of liver stiffness

MRE is not yet widely available. The technique uses a modified phase-contrast method to image the propagative characteristics of a shear wave traversing the liver[86]. A probe is placed against the patient's back. Measurements are obtained from the anterior segment of the right lobe (the region of the liver that is usually biopsied). Liver stiffness is measured by delineating an ROI of at least 100 mm^2 in the liver parenchyma, avoiding the edges of the tissue, large vessels (> 3 mm in diameter), and fissures. Low-frequency vibrations are emitted and the MRI spin echo sequence is used to gather data. Mean liver stiffness is expressed in kPa using a formula deriving a shear modulus, which is one-third the modulus of Young used in TE evaluation[87].

Diagnostic performance

From a clinical viewpoint, MRE affords excellent accuracy when used to differentiate significant fibrosis from mild fibrosis or absence of fibrosis, and cirrhosis from other stages of liver fibrosis[88,89]. MRE has a high negative predictive value (97%) when used to exclude the presence of fibrosis[90]. A meta-analysis reviewing five studies employing MRE showed that the technique performed well diagnostically when used to evaluate liver cirrhosis attributable to different causes. The sensitivity of the technique was 92% and the specificity 96% when used differentiate F0-2 fibrosis from fibrosis of grades F3-4[91].

Venkatesh *et al*[92] found that MRE was an accurate non-invasive method when used to detect and stage fibrosis in CHB patients. The diagnostic performance of MRE was significantly higher than those of serum fibrosis markers. The optimally discriminatory cutoff MRE value was 4.33 kPa for diagnosis of cirrhosis in CHB patients, with a sensitivity of 100%, a specificity of 100%, a PPV of 91.3%, and an NPV of 100%. Use of MRE was associated with a 14.3% error rate. Therefore, MRE is a valuable non-invasive test when used to detect and stage liver fibrosis in CHB patients.

Interestingly, the MRE cutoff value for diagnosis of cirrhosis in CHB patients (4.33 kPa) was lower than that reported for CHC patients (6.20 kPa)[93] but similar to that associated with diagnosis of advanced fibrosis in NASH patients (4.3 kPa)[94]. This suggests that the cutoff values of diagnostic MRE data differ for diseases that vary in etiology. However, such results require confirmation in large-scale studies.

Advantages and disadvantages

MRE affords a significantly higher accuracy and technical success rate than other non-invasive modalities. MRE scans the entire liver and thus does not select an acoustic window. MRE can be used to evaluate obese patients or those with ascites. MRE can be easily incorporated into routine liver MRI; clinicians can simultaneously assess structural disease, liver stiffness, and fat and iron levels.

Serum ALT level is a known confounding factor when fibrosis is detected using TE; liver stiffness is positively correlated with serum ALT levels[95,96]. However, MRE has exhibited no such association[89], probably because MRE and TE assess different mechanical properties.

However, MRE is quite expensive, and is not yet widely available. MRE cannot be used to evaluate patients who are claustrophobic or fitted with heart pacemakers. MRE is more time-consuming than are other ultrasound-based elastographic methods. MRE cannot be performed on iron-overloaded livers because of signal-to-noise limitations.

SERUM BIOMARKERS

Measurement of liver stiffness

Diagnostic serum biomarkers of liver fibrosis and cirrhosis have been well-validated. Although marker levels are highly reproducible, they are not specific for liver disease and do not allow easy discrimination of intermediate stages of fibrosis[95]. Score panels based on combined blood test data are also of limited utility in differentiating the stages of fibrosis. Biomarkers detect cirrhosis more readily than intermediate stages of fibrosis[97,98]. However, the clinical utility of markers in diagnosis of liver cirrhosis requires further verification.

Diagnostic performance

Several serum markers have been evaluated in terms of the ability to diagnose liver cirrhosis. These include the FibroTest, the APRI, the prothrombin index (PI), the AST/ALT ratio (the AAR), the Lok index, and the Goteborg University cirrhosis index (the GUCI)[99,100]. The FibroTest and biopsy data performed similarly when used to diagnosis significant fibrosis in CHC patients[98,101-104]. One large study (of 913 CHC and 284 HBV patients) prospectively compared the most popular patented tests (the FibroTest, the Fibrometre, and the Hepacore) with a nonpatented test (the APRI); the AUROC values for cirrhosis ranged from 0.77 to 0.86 and no significant among-test differences in scores were evident[105]. Although nonpatented tests such as the Forns index, the FIB-4, and the APRI may lack the performance of the patented tests, the former tests are inexpensive, easy to perform, and widely available. However, few serum biomarkers have been evaluated in terms of the ability to define the stage of liver cirrhosis in CHB patients. The results of studies on CHC patients cannot be directly applied to CHB patients because CHB infection is associated with a specific type of pathogenesis. Thus, dedicated validation of marker utility in CHB patients is required.

The FibroTest has been studied extensively over the last 5 years and is currently the best-understood serum marker panel used to detect fibrosis[106]. Application of

the FibroTest to CHB patients was associated with AUROCs of 0.77-0.78 for detection of significant fibrosis and cirrhosis, with 85.0% sensitivity and 52.0% specificity[107,108].

The APRI is a simple test that combines AST level with platelet count to predict the occurrence of significant fibrosis and cirrhosis in CHC patients. Venkatesh *et al*[92] showed that serum AST levels differed significantly between patients with low-grade and advanced fibrosis, but ALT levels did not. The APRI was helpful for discriminating CHB patients with advanced fibrosis from those with mild-to-moderate conditions. When the APRI cutoff was set at 0.5 for CHB patients, the AUROC for prediction of significant fibrosis was 0.673[109] and the PPV and NPV 30% and 87%, respectively. In other words, the APRI can reliably be used to exclude the presence of significant fibrosis.

Hui *et al*[109] developed a predictive model based on body mass index (BMI) and the data of three routine laboratory tests, which had an AUROC of 0.79 when used to assess the fibrosis stage of CHB patients. The laboratory data were bilirubin, albumin, platelet, and ALP levels. The PPV was 38% when a cutoff of 0.15 was applied and 53% when the cutoff was 0.5. The results suggest that the model should be used primarily to identify patients lacking significant fibrosis.

Sebastiani *et al*[110] reported that sequential use of the APRI, the FibroTest, and liver biopsy data, greatly improved diagnostic performance compared to use of a single non-invasive test in CHB patients. The sequential combination was developed to detect cirrhosis in HBV patients. The need for liver biopsy was reduced by 50%-80%. All of the FibroTest, the APRI, the AAR, and the GUCI were only 77.5%-86.1% accurate in terms of cirrhosis detection when used individually. The FibroTest showed the best PPV, NPV, and AUROC for cirrhosis detection (90%, 87.1%, and 0.76, respectively). However, the sequential combination afforded excellent accuracy (100%) in terms of detection. Stepwise combination algorithms featuring the APRI, the FibroTest, and biopsy, afforded excellent performance (0.95 AUROC and 98.3% NPV for cirrhosis).

Montazeri *et al*[111] suggested that serum hyaluronate level might predict extensive liver fibrosis and inflammation in CHB patients. Zhang *et al*[112] suggested that use of the APRI test in combination with hyaluronic acid (HA) measurement could serve to detect moderate-to-severe fibrosis in CHB patients. When the APRI was used alone to this end, the sensitivity, specificity, PPV, and NPV were 44.7%, 84.3%, 41.3%, and 84.7%, respectively. The diagnostic performance of the APRI was low in terms of discrimination of fibrosis stages in such patients. However, when an APRI score of $\geqslant$ 1.5 was used in combination with an HA cutoff of > 300 ng/mL, moderate-to-severe fibrosis was accurately predicted in CHB patients (98.9% of specificity and 93.7% of PPV).

Lebensztejn *et al*[113] reported that the AUROC of combined hyaluronan and laminin measurements was 0.84. Zeng *et al*[114] developed a non-invasive combination model including age and measurements of serum alpha-2-macroglobulin, hyaluronan, and γ-glutamyl transpeptidase. The AUROCs were 0.77-0.84. The expected rate of misdiagnosis was around 20%, similar to that reported in hepatitis C patients. However, it may be inappropriate to apply the test in real clinical settings. Recently, "proteome" technology has been used to study liver fibrosis. A total of 30 features predictive of significant fibrosis and cirrhosis were identified in 46 CHB patients. The AUROCs were high, being 0.906 and 0.921 for detection of advanced fibrosis and cirrhosis, respectively[115]. However, the method is rather complicated and may not be applicable to large-scale testing.

A meta-analysis[116] of data from 30 studies using the FibroTest and biopsy (3501 CHC and 1457 CHB patients) found that the mean standardized AUROC for diagnosis of significant fibrosis was 0.84, and did not differ significantly between patients with CHC (0.85) and CHB (0.80).

Advantages and disadvantages

The inter-laboratory reproducibilities of the FibroMeter, FibroTest, and APRI tests, and combinations thereof, are excellent[117]. The APRI test is inexpensive and widely available (being nonpatented). However, these tests perform less well than does TE in terms of cirrhosis diagnosis. Also, test results are not immediately available[95]. The tests are not specific for liver disease and do not discriminate among the intermediate stages of fibrosis. Test results can be influenced by comorbidities, and critical data interpretation is required. False-positive FibroTest and Hepascore results are yielded by patients with Gilbert's syndrome or hemolysis, because such patients exhibit hyperbilirubinemia[118]. Similarly, acute hepatitis can produce false-positive results in the APRI, Forns index, FIB-4, or Fibrometer tests.

DIAGNOSIS OF DECOMPENSATED CIRRHOSIS

Recently, noninvasive ultrasound- and MRI-based elastographic techniques have allowed the relationships between liver or spleen stiffness and portal pressure to be explored. Use of TE revealed a statistically significant association of these parameters with the hepatic venous pressure gradient of CHC patients[119,120], and a correlation with the grade of esophageal varices was evident[121]. Talwalkar *et al*[122] used MRE to show that splenomegaly, mean spleen stiffness, and serum platelet count were potentially associated with the presence of esophageal varices. Neither the mean liver stiffness value nor the mean spleen volume was significantly associated with the presence of esophageal varices. A cutoff spleen stiffness value of over 10.5 kPa identified all cirrhotic patients with esophageal varices.

Ye *et al*[123] reported that the liver stiffness cutoff value of ARFI was 1.88 m/s for diagnosis of liver cirrhosis in

CHB patients (AUROC = 0.97; sensitivity, 95.7%; specificity, 91.8). Interestingly, spleen stiffness values were also determined in the cited study, to aid in diagnosis of cirrhosis and esophageal varices. The spleen stiffness cutoff value was 2.72 m/s for diagnosis of liver cirrhosis (AUROC = 0.96; sensitivity, 88.4%; specificity, 93.2%). The optimal spleen stiffness cutoff predicting varices was 3.16 m/s (AUROC = 0.83). In this report, portal hypertensions could not be graded according to liver stiffness, but a significant linear correlation was evident between spleen stiffness and varices grade.

COMPARISONS OF MODALITIES USED TO DIAGNOSE CIRRHOSIS

TE and ARFI

Lupsor *et al*[66] found that both ARFI and TE data were strongly correlated with the stage of fibrosis, and TE was superior when used to predict early-stage disease in patients with chronic hepatitis C. However, Ebinuma *et al*[65] found that the diagnostic powers of the two techniques were almost identical. Neither mode detected low-grade fibrosis effectively, but diagnostic capacities rose as the stage of fibrosis advanced.

ARFI and TE were compared in a meta-analysis of eight studies involving 518 patients. TE afforded a slightly higher diagnostic accuracy for cirrhosis (mean AUROC difference: 0.04)[124]. The mean AUROC of all published studies on the use of ARFI to detect cirrhosis in CHB patients was 0.90. However, most studies had small sample numbers and the study populations were heterogeneous.

Friedrich-Rust *et al*[69] found that ARFI and TE performed similarly when used to diagnose liver fibrosis in CHB patients. ARFI afforded excellent performance when used to diagnose advanced fibrosis, but differentiation of mild fibrosis was in need of improvement. When a low cutoff of 1.03 m/s was used to exclude significant fibrosis, and a high cutoff of 1.39 m/s to confirm significant fibrosis, 38% of patients were correctly classified using ARFI.

Cassinotto *et al*[55] compared the use of ARFI, TE with the M and XL probes, and the FibroTest, in evaluation of 321 patients (39 with HBV infections). In terms of cirrhosis diagnosis, no significant difference was evident between ARFI elastography and TE with the M or XL probes. However, the diagnostic performance of TE was significantly better than that of the FibroTest.

Comparison of TE and MRE

In a comparative study, MRE was superior to both TE and APRI when used to assess liver fibrosis, affording accuracies of over 98% in diagnosis of all categories of fibrosis[89]. The AUROC of MRE was 0.998 for diagnosis of liver cirrhosis and the technical success rate was higher than that associated with ultrasound elastography (AUROC = 0.930), APRI (AUROC = 0.820), and a combination of TE with APRI (AUROC = 0.944).

Comparison of RTE and other elastographic modalities

Colombo *et al*[125] compared the utility of TE, RTE, and ARFI in diagnosis of liver fibrosis. TE and ARFI exhibited high diagnostic accuracies (AUROCs 0.9) when used to diagnose cirrhosis. All three methods afforded fair (AUROC = 0.7) to good (AUROC = 0.8) diagnostic accuracy when used to diagnose all fibrosis (F1-4 Metavir grades) and significant fibrosis (F2-4 Metavir grades). Of the various modalities, TE exhibited the best diagnostic performance (AUROCs of 0.878 for fibrosis and 0.897 for significant fibrosis, respectively). TE and ARFI were highly accurate when used to diagnose cirrhosis.

Friedrich-Rust *et al*[79] found that the AUROCs for diagnosis of significant fibrosis and cirrhosis using TE and RTE were 0.84 *vs* 0.69, and 0.97 *vs* 0.65, respectively. RTE was less accurate than TE when used to predict liver fibrosis. However, upon direct comparison of TE, RTE, and ARFI in 74 Korean patients, the cut-off values for diagnosis of cirrhosis were 8.60 kPa (AUROC = 0.786; sensitivity, 81.0%; specificity, 64.2%); 1.39 m/s (AUROC = 0.807; sensitivity, 90.5%; specificity, 66.0%); and 2.79 (AUROC = 0.767; sensitivity, 81.0%; specificity, 64.2%), respectively[126]. TE and ARFI, rather than RTE, are the best modalities for non-invasive assessment of liver fibrosis. However, all three methods reliably predict cirrhosis.

Comparison of elastography and serum biomarker measurements

In terms of detection of cirrhosis, AUROC analysis indicated that the APRI test was superior to the elastic strain ratio determined using real-time elastography, and the Forns index[84]. This suggests that the APRI should be used to diagnose cirrhosis in preference to calculation of the elastic strain ratio. When the AUROCs of spleen stiffness measurement and APRI were compared, the overall diagnostic performance of the former test in prediction of liver fibrosis stages was superior to that of the APRI[68]. The diagnostic accuracy of the FibroTest was comparable to those of elastographic methods. APRI scoring has been shown to be inferior to FibroTest- and TE-based evaluations[127,128].

Other methods for diagnosis of liver cirrhosis

Hu *et al*[129] measured newly maximal accumulative respiration strain (MARS) values obtained from hepatic tissue image analysis of CHB patients. Each value represents the average strain of hepatic tissue in the ROI at different stages of the respiratory cycle. The MARS values were correlated with fibrotic stage. The diagnostic accuracy rate for cirrhosis had an AUROC of 0.75. However, the performance of MARS was inferior to that of TE.

COMBINATION OF LSM WITH OTHER MODELS OF FIBROSIS PREDICTION

The use of combination models has been proposed to

Table 1 Diagnostic performance of non-invasive diagnostic methods in predicting cirrhosis with chronic hepatitis B

Ref.	Year	Modality	Patients (*n*)	Cut-offs ≥ F4	Standard reference	AUROC	Se	Sp	Accuracy	PPV	NPV
Myers *et al*[107]	2003	Biomarkers	209	0.2[1]	Biopsy	0.780	85.0%	52.0%	-	43.0	92.0
				0.4[1]			54.0%	80.0%	-	53.0	81.0
				0.8[1]			18.0%	99.0%	-	92.0	75.0
Hui *et al*[109]	2005	Biomarkers	235	> 0.15[1]	Biopsy	0.791	88.0%	50.0%	93.0	38.0	92.0
				> 0.5[1]		0.791	37.0%	88.0%	-	53.0	81.0
Zeng *et al*[114]	2005	Biomarkers	200	> 3.0[1]	Biopsy	0.770	94.8%	44.1%	-	70.1	86.1
				> 8.7[1]		0.770	35.3%	95.2%	-	91.1	51.6
Marcellin *et al*[20]	2009	TE	173	18.2 kPa[2]	Biopsy	0.930	57.0%	97.0%	94.0	67.0	96.0
				11 kPa[2]	Biopsy	0.930	93.0%	87.0%	38.0	38.0	99.0
Chan *et al*[19]	2009	TE	161	13.4 kPa[2]	Biopsy	0.930	75.0%	93.0%	89.0	78.0	92.0
				12 kPa[3]			79.0%	92.0%	-	76.0	93.0
Kim *et al*[18]	2009	TE	91	10.3 kPa	Biopsy	0.803	59.0%	78.0%	-	68.0	72.0
Kim *et al*[52]	2010	TE	104	10.1 kPa	Biopsy	0.849	86.7%	88.1%	-	87.5	77.1
		TE	52	15.5 kPa		0.867	66.7%	100.0%	-	100.0	72.9
Kim *et al*[138]	2010	LSPI[4]	330	38[5]	Biopsy	0.956	98.0%	69.2%	-	82.9	95.7
				62[5]			85.9%	93.8%	-	95.5	81.3
				42[6]			96.3%	67.4%	-	73.3	95.1
				94[6]			67.5%	97.7%	-	96.4	76.4
Hu *et al*[129]	2010	MARS	28	20.32%	Biopsy	0.750	100.0%	-	-	-	-
Ye *et al*[123]	2011	ARFI	264	1.88 m/s	Biopsy	0.970	95.7%	91.8%	-	-	-
		Spleen ARFI		2.72 m/s		0.960	88.4%	93.2%	-	-	-
Xie *et al*[84]	2012	RTE[7]	71	-0.6	Biopsy	0.797	50.0%	96.7%	-	71.4	92.2
		APRI	71		Biopsy	0.930	-	-	-	-	-
Wang *et al*[85]	2012	RTE	75	90.31	Biopsy	0.660	71.4%	80.0%	-	93.8	40.0
		APRI	75		Biopsy	0.930	-	-	-	-	-
Cassinotto *et al*[55]	2013	TE[8]	285	14.1 kPa	Biopsy	0.910	77.0%	92.0%	89.0	74.0	93.0
		TE[9]	254	10.1 kPa	Biopsy	0.880	85.0%	82.0%	82.0	76.0	96.0
Friedrich-Rust *et al*[69]	2013	ARFI	92		Biopsy	0.970	-	-	-	-	-
		TE	92		Biopsy	0.930	-	-	-	-	-
Venkatesh *et al*[92]	2013	MRE	64	4.33 kPa	Biopsy	0.980	100.0%	95.2%	-	91.3	100.0

[1]Cut-off value for significant fibrosis; [2]Cut-off value with maximum of diagnosis accuracy; [3]Cut off value with a maximum sum of sensitivity and specificity; [4]Liver stiffness measurement × spleen diameter/platelet count; [5]Cut-off value with normal alanine aminotransferase (ALT); [6]Cut-off value with high ALT; [7]Elastic strand ratio; [8]M probe; [9]XL probe. LSPI: Liver stiffness measurement - spleen diameter to platelet ratio index; TE: Transient elastography; ARFI: Acoustic radiation force impulse imaging; RTE: Real-time elastography; MRE: Magnetic resonance elastography; MARS: Maximal accumulative respiration strain; Se: Sensitivity; Sp: Specificity; PPV: Positive predictive value; NPV: Negative predictive value; AUROC: Area under the receiver operating characteristic.

increase the diagnostic performance of tests for liver cirrhosis, although elastography alone accurately predicts histological cirrhosis. The combined use of the Enhanced Liver Fibrosis (ELF) test with either ARFI or TE in patients with multi-origin cirrhosis increased the diagnostic accuracy of liver cirrhosis[130]. The PPV and NPV of ARFI-plus-ELF were 73% and 100%, and those of TE-plus-ELF 64% and 100%, respectively.

The ultimate validation of liver fibrosis as a marker of liver injury is the prognostic value thereof in terms of morbidity and mortality. In recent studies on non-CHB patients, the TE test and measures of serum fibrosis markers were prognostically more valuable than liver biopsy data[131-133]. However, long-term follow-up studies on ARFI are required.

Chung *et al*[126] explored the efficacies of combinations of LSM modalities (TE, ARFI, and RTE) with platelet count in terms of increasing the diagnostic power for liver disease of varying etiology. Cutoff ratios of LSM/(platelet count) used to predict cirrhosis were no more effective than the LSM data alone. However, the ratios predicted significant fibrosis (grade ≥ F2) more effectively than did LSM data alone.

The diagnostic performance of TE in CHB patients can be improved by combining test data with those of fibrosis serum marker levels derived using the APRI, Fib-4, Fibrometer and FibroTest[134-136]. Wong *et al*[137] reported that agreement between a high LSM and a high Forns index value improved diagnostic specificity (from 99% to 100% and from 87% to 98% in training and validation cohorts, respectively). Kim *et al*[138] derived optimal predictive threshold values of the LSM/spleen diameter to platelet ratio index (LSPI; LSM × spleen diameter/platelet count) for detection of cirrhosis in terms of ALT level. The AUROC was 0.956, thus slightly higher than the AUROC of 0.919 afforded by use of TE data alone. When used to diagnose cirrhosis in patients with normal ALT levels, use of an LSPI predictive threshold value of 38 was associated with 98.0% sensitivity and 69.2% specificity, whereas a threshold value of 62 was associated with 85.9% sensitivity and 93.8% specificity. Similarly, in a high-level ALT group, an LSPI predictive threshold value of 42 was associated with 96.3% sensitivity and 67.4% specificity, whereas a threshold of 94 was associated with 67.5% sensitivity and 97.7% specificity.

Kim *et al*[46] found that optimal LSM cutoff values varied with ALT level, and use of an index (a ratio) combining data on age, spleen size, and platelet level, enhanced

LSM performance when used to diagnose cirrhosis in CHB patients (AUROCs = 0.917 in patients with ALT ⩽ upper ULN; 0.909 in those with ALT ⩽ 2 × ULN; and 0.894 in all patients).

Evaluation of hepatitis B patients using elastography increased the accuracy of these measures when used to diagnose cirrhosis. Increasing acceptance of the utility of combination modalities is expected to reduce the requirement for liver biopsy. The combination methods enhance diagnostic accuracy and reduce the number of liver biopsies needed to evaluate cirrhotic CHB patients. An optimal choice of diagnostic modality requires the conduct of large-scale validation studies in a variety of patient populations. Also, the cost-effectiveness of combination models requires future attention.

CONCLUSION

The last decade has seen significant progress in development of noninvasive liver disease assessment in CHB patients (Table 1). It has become accepted that liver biopsy has limitations when used to diagnose cirrhosis. TE, ARFI, RTE, and MRE are valuable for early diagnosis of cirrhosis in CHB patients because the AUROC values associated with use of these techniques are in excess of 0.8[139].

Routine use of TE in management of hepatitis C patients has significantly reduced the need for liver biopsy[140], but reliable detection of mild fibrosis and accurate differentiation of fibrotic stages remain problematic[141-143]. In addition, accurate measurements may be difficult to obtain from obese patients, those with ascites, and those exhibiting severe hepatic atrophy. Acoustic radiation force impulse imaging is a novel form of ultrasound providing *in vivo* information on the local mechanical properties of tissue[144,145]. However, ARFI cannot be used to evaluate patients who are obese or cirrhotic patients with very stiff tissue because imaging results are automatically rejected if detection of low-frequency acoustic wave propagation is inadequate[63]. RTE does not have such limitations and can be used to image almost all patients, including those who cannot be assessed by TE or ARFI. MRE was more accurate than either ultrasound-based elastography or measurement of serum markers of fibrosis[88,89,93]. However, most previous studies on RTE and MRE included patients with chronic liver disease of various etiologies. RTE and MRE should be validated in CHB cohorts (with macronodular cirrhosis) in particular.

TE is the most widely used method for diagnosis of cirrhosis in CHB patients, but ARFI and MRE may be equally valuable. Novel techniques including supersonic shear imaging[146,147] or measurement of spleen stiffness[148] may also be valuable in diagnosis of liver cirrhosis. A combination of elastography and biomarker measurements may improve diagnostic performance during surveillance of CHB patients for development of liver cirrhosis. However, clinical benefit must be weighed against cost when a combined approach is planned.

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ISSN 1007-9327