# Clinical Effectiveness of Three Noninvasive Methods for Detecting Hepatic Fibrosis

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**Target audience** includes clinicians and scientists who are interested in noninvasive technologies for the assessment of hepatic fibrosis.

**Introduction:** Chronic liver disease and cirrhosis remain a leading cause of mortality in the United States, with 143,000 hospitalizations, 11,000 in-hospital deaths and 6.7 billion dollars of total hospital charges in 2009 [1]. Currently, liver biopsy is the reference standard for detecting hepatic fibrosis. However, liver biopsy is an invasive method and has some significant limitations, such as sampling errors, interobserver variation, patient refusal, pain, bleeding and death [2-4]. Meanwhile, noninvasive technologies have been developed for assessing hepatic fibrosis. These include imaging methods (e.g., MR Elastography (MRE) and Fibroscan®) and serum markers (e.g., FIBRO*Spect* II®). Both MRE and Fibroscan use external vibrations to excite mechanical waves in the patient's liver; use MRI or ultrasound, respectively, to measure the wave speed; and ultimately calculate liver stiffness maps (elastograms) based on the wave speed. MRE measures the tissue shear modulus, while Fibroscan measures Young's modulus. FIBRO*Spect* II is a panel of serum markers that are sensitive to liver fibrosis. Different studies have shown that MRE, FIBRO*Spect* II, and Fibroscan have a diagnostic accuracy of 90.9-100%, 46.7-82.6% and 83.7-91.4%, respectively, for detecting hepatic fibrosis stage two and above, and have also compared their advantages and disadvantages [5-11]. Our purpose is to evaluate the clinical effectiveness of MRE, Fibroscan and FIBRO*Spect* II in a single patient population with a consideration for interobserver variation of liver pathology. Our hypothesis is that MRE is the most accurate method among the three noninvasive methods for detecting clinically significant liver fibrosis (F2-F4) in patients.

**Methods:** ***(1) Subjects:*** Our Institutional Review Board approved the study. A total of 113 patients with different liver disease causes (fatty liver, steatohepatitis, hepatitis virus C, Alpha-1 Antitrypsin; no iron overload or ascites) were enrolled in the study to undergo the three exams within one month (operators of each exam were blinded to the other results). Some data were not available for some patients for different reasons (e.g., scheduling availability and technique failures). ***(2) Liver biopsy:*** Liver biopsy was performed using either a percutaneous, transjugular, or intraoperative approach within our clinical practice. METAVIR (for hepatitis C) and Brunt (for nonalcoholic and alcoholic liver disease) were used to assess fibrosis stage. A first interpretation was done in the clinical practice by different pathologists (bx1), and a second interpretation was done by a single independent pathologist (bx2). ***(3) FIBROSpect II:*** Blood was collected and sent to Prometheus Laboratories, Inc. (San Diego, CA) for the FIBRO*Spect* II index (0-100) calculation using the serum levels of 3 fibrosis markers (serum hyaluronic acid, metalloproteinase-1, and alpha2-macroglobulin). ***(4) MRE:*** Technique details can be found in [5]. In brief, subjects underwent 2D, 60-Hz liver MRE performed in a 1.5-T MRI scanner (GE, Signa HDxt, Wisconsin, USA), with a MRE driver positioned on their chest wall close to the liver. ***(5) Fibroscan:*** Technique details can be found in [11]. In brief, subjects underwent Fibroscan (Echosens, France) in the supine position; one of two different sized probes (M and XL) was used depending on the skin-to-liver capsule distance (SCD) [12]. ***(6) Statistic analysis:*** Interobserver variation in the two biopsy interpretations was assessed. In the following analysis, subjects with an interobserver difference of two categories were excluded, and the second interpretation was used to avoid interobserver variations among the original pathologists. Diagnosis accuracy (>=F2) was calculated by Area Under Receiver Operating Characteristic (AUROC); optimal threshold is determined by maximizing the sum of specificity and sensitivity. JMP Pro (SAS, USA) software was used in the analysis.

Table 1 Performance for Diagnosis Fibrosis >= F2

| Methods | Threshold | Sens | Spec | PPV | NPV |
|---|---|---|---|---|---|
| MRE | 3.1 kPa | 84.6% | 85.7% | 78.6% | 90.0% |
| FIBRO*Spect* II | 23 | 80.9% | 80.0% | 72.3% | 86.7% |
| Fibroscan | 6.8 kPa | 86.5% | 67.9% | 65.3% | 87.8% |

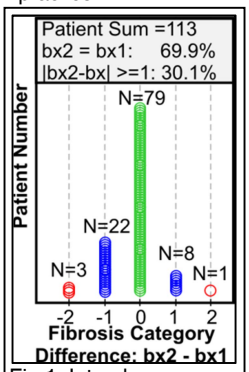

Fig.1. Interobserver variation of pathology

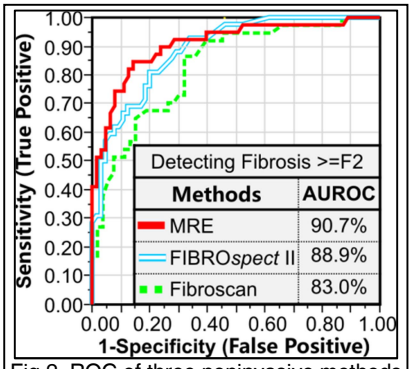

Fig.2. ROC of three noninvasive methods for detecting hepatic fibrosis stage > =F2

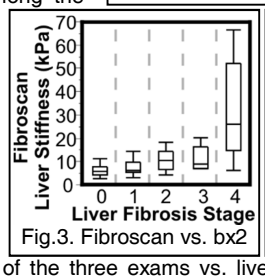

Fig.3. Fibroscan vs. bx2

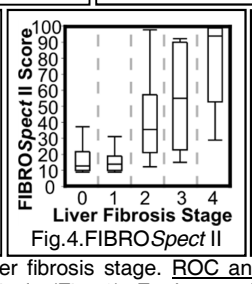

Fig.4.FIBRO*Spect* II

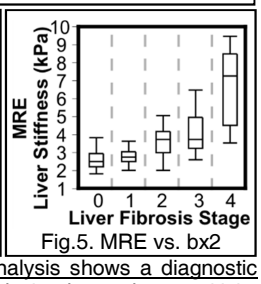

Fig.5. MRE vs. bx2

**Results:** Between the two biopsy interpretations for fibrosis stage, 79/113 patients had the same stage, 30/113 had a difference of one category, and 4/113 had a difference of 2 categories (Fig.1). This interobserver variation is consistent with the literature [3, 4]. After the 4 patients with interobserver differences of 2 categories were excluded, 107/109 had FIBRO*Spect* II data, 102/109 had MRE data, and 90/109 had Fibroscan data. Figs. 3-5 show the data distribution of the three exams vs. liver fibrosis stage. ROC analysis shows a diagnostic accuracy (>= F2) of 90.7%, 88.9% and 83.0% for MRE, FIBRO*Spect* II and Fibroscan, respectively (Fig. 2). Further analysis shows the sensitivity (Sens), specificity (Spec), positive predictive value (PPV), and negative predictive value (NPV) in Table 1.

**Discussions and Conclusions:** In this study, MRE has the highest diagnostic accuracy (90.7%) for detecting fibrosis stage >= F2. Its high negative predictive value (90.0%) suggests that patients without clinically significant liver fibrosis could be diagnosed by MRE and could avoid liver biopsy. However, MRE still has contraindications, such as claustrophobia. The optimal FIBRO*Spect* II index threshold (23) determined in this study is lower than a previous study [7], maybe due to the different patient populations. FIBRO*Spect* II needs only blood samples from patients, but requires samples sent to the company for analysis, resulting in extra exam time and medical cost. Fibroscan is a fast exam; it can report the measurements immediately and is not limited to patients with claustrophobia; its XL probe has reduced the technique failures previously reported in high BMI patients, which is consistent with other studies [12]. In summary, MRE has the highest diagnostic accuracy among the three noninvasive methods for detecting hepatic fibrosis.

**References:** **[1]** http://hcup.ahrq.gov/HCUPNet.asp2009, U.S. Dep. of Health & Human Serv. **[2]** World J Gastroenterol, 2008. 14(21): p. 3396-402. **[3]** Gut, 2006. 55(4): p. 569-78. **[4]** Am J Gastroenterol, 2002. 97(10): p. 2614-8. **[5]** Clin Gastroenterol Hepatol, 2007. 5(10): p. 1207-1213 e2. **[6]** Radiology,2007. 245(2): p. 458-66. **[7]** The American Journal of medicine. 2007. 120(3): p. 280 e9-14. **[8]** Obesity surgery, 2010. 20(12): p. 1647-53. **[9]** Gastroenterology, 2008. 135(1): p. 32-40. **[10]** Bohte, A.E., European radiology, 2013. **[11]** Ultrasound in medicine & biology, 2003. 29(12): p. 1705-13. **[12]** Liver international : official journal of the International Association for the Study of the Liver, 2010. 30(7): p. 1043-8.