

doi: 10.13241/j.cnki.pmb.2014.07.019

瞬时弹性成像对慢性乙肝肝纤维化诊断的研究*

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摘要 目的:探讨瞬时弹性成像(FibroScan)诊断慢性乙型肝炎肝纤维化的准确性。**方法:**选取慢性乙型肝炎患者 289 例,其中未做病理组 198 例,病理组 91 例,正常对照 50 例,病理组患者行病理肝纤维化检测,未做病理组患者检查 B 超,全部患者及正常对照应用 FibroScan 进行肝脏硬度检测(liver stiffness measurement,LSM)值测量。分析未做病理组慢乙肝组与正常对照组间及未做病理组慢乙肝组 B 超肝纤维化各级间 LSM 值的差异;病理慢乙肝组采用受试者工作特征(Receiver Operating haracteristic,ROC)曲线分析 FibroScan 诊断肝纤维化的准确性,并得出各期诊断界值;根据该诊断界值对未做病理慢乙肝组进行 FibroScan 肝纤维化分期,分析其与 B 超肝纤维化分级的一致性。**结果:**LSM 值在未做病理慢乙肝组和正常对照组间及 B 超肝纤维化各级间差别显著 ($P < 0.05$);其中病理组统计结果显示 F1、F2、F3、F4 期肝纤维化的 ROC 曲线下面积 (Area under Receiver Operating Characteristic,AUROC)分别为 0.726、0.847、0.806、0.864,诊断界值分别为 6.5、7.4、10.1、17.0 kPa,敏感性分别为 69.62 %、68.33 %、66.67 %、72.22 %,特异性分别为 66.67 %、87.10 %、85.71 %、91.78 %;肝纤维化的 FibroScan 分期和 B 超分级具有一致性 (Kappa 值 = 0.366, $P < 0.05$)。**结论:**FibroScan 对慢性乙型肝炎肝纤维化尤其是严重肝纤维化及肝硬化诊断准确性高,具有良好的临床应用价值。

关键词:慢性乙型肝炎;肝纤维化;瞬时弹性成像

中图分类号:R445.1,R575.2 文献标识码:A 文章编号:1673-6273(2014)07-1279-04

Study of FibroScan on Diagnosis of Liver Fibrosis in Patients with Chronic Hepatitis B*

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ABSTRACT Objective: To explore the accuracy of transient elastography (FibroScan) for the detection of liver fibrosis. **Methods:** A total of 289 patients diagnosed with chronic hepatitis B were involved in the study, non-pathology group (198 subjects), pathology group (91 subjects) and the control group (50 subjects). Pathology group were subjected to liver biopsy, Non-pathology group were examined by B-ultrasound, meanwhile, FibroScan was used for liver stiffness measurement (LSM) of everyone. The differences of LSM between control group and non-pathology group and LSM differences between B-ultrasound liver fibrosis levels of non-pathology were analyzed. In pathology group, the Receive Operating Characteristic (ROC) curve was adopted to analyze the accuracy of FibroScan for diagnosing liver fibrosis and the diagnostic cutoffs were counted. Liver fibrosis levels of non-pathology group were staged by cutoffs above and also classified by B-ultrasound, the consistency of them was analyzed. **Results:** LSM differences between control group and non-pathology group and that between B-ultrasound liver fibrosis levels of non-pathology were significantly different ($P < 0.05$). The statistical results pathology group show that the areas under the ROC curve were 0.726, 0.847, 0.806, 0.864 for patients with fibrosis F1, F2, F3, F4, the cutoff values were 6.5, 7.4, 10.1, 17.0 kPa, the sensitivities were 69.62%, 68.33 %, 66.67 %, 72.22 %, the specificities were 66.67 %, 87.10 %, 85.71 %, 91.78 %. Liver fibrosis staged by FibroScan was consistent with that classified B-ultrasound (Kappa=0.366, $P < 0.05$). **Conclusions:** The diagnosis of liver fibrosis of chronic hepatitis B especially severe fibrosis and cirrhosis by FibroScan has high accuracy. FibroScan is valuable for clinic application.

Key words: Chronic hepatitis B; Liver fibrosis; FibroScan

Chinese Library Classification(CLC): R445.1, R575.2 **Document code:** A

Article ID: 1673-6273(2014)07-1279-04

前言

肝纤维化是各种慢性肝病损伤修复过程的共同结果,最终

可发展成肝硬化。如果肝纤维化、甚至早期肝硬化如果能得到及时治疗,可发生逆转,因此,及时准确及时地判定肝纤维化的程度,对慢性肝病防治及其预后评价具有重要意义^[1]。目前病理

* 基金项目:中国肝炎防治基金会王宝恩肝纤维化研究基金 (20100039)

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(收稿日期:2013-09-22 接受日期:2013-10-15)

目前仍是判断肝脏纤维化的“金标准”,但其存在有创、取样局限及主观性等缺点^[2-4]。近年来,国内外学者致力于无创性肝纤维化评估系统的研究,肝脏弹性(硬度)测量是目前受到广泛关注的一种无创诊断方法。FibroScan 是利用超声技术发明的一项无创定量测量肝组织硬度的新方法,利用肝纤维化程度与肝脏硬度的相关性对肝纤维化程度进行评估。与肝穿刺相比,快速、无创、客观、易重复、价格低及患者依从性高等都是 FibroScan 的优势。目前,关于利用 Fibroscan 测定肝纤维化程度的研究主要集中在慢性丙型肝炎、脂肪肝、酒精肝、脂肪肝^[5-7]等疾病,对于乙型肝炎引起的纤维化或肝硬化的研究很少,笔者评估 FibroScan 诊断慢乙型肝炎纤维化的准确性。

1 材料与方法

1.1 临床资料

选择上海市公共卫生临床中心 2010 年 1 月~2012 年 6 月的慢性乙型肝炎患者 289 例,其中未做病理组 198 例,男性 135 例,女性 63 例,年龄 15~85 岁,平均年龄 44.1 岁。病理组 91 例,男性 57 例,女性 34 例;年 21~63 岁,平均年龄 37.8 岁。依据 2000 年西安会议修订的《病毒性肝炎防治方案》的标准进行诊断^[8]。排除标准:甲、丙、丁、戊型肝炎病毒重叠感染者;合并巨细胞病毒(cytomegalovirus, CMV)、EB 病毒(Epstein-Barr Virus, EBV)、人类免疫缺陷病毒(Human Immunodeficiency Virus, HIV)感染者;合并自身免疫性肝炎、脂肪肝及酒精性肝炎者。病理组同意接受肝脏病理检查,签署知情同意书。另选择无肝脏病史、体格检查正常、影像学检查正常,且肝炎生化系列阴性的健康志愿者 50 例作为正常对照组,其中男 30 例,女 20 例,年龄 20~67 岁,平均年龄 43.0 岁。

1.2 方法

1.2.1 超声检查 采用 philips HDI 5000 超声仪进行检测,患者取平卧位,对全部患者行 B 型超声检查,观察肝脏实质质地均匀度,表面平整度,柔韧程度,血管粗细及走行;观察脾脏情况。**1.2.2 超声判断指标** 肝纤维化判断:阴性:质地尚均匀,表面光滑,柔韧度好,血管走行自然,脾脏厚度 < 40 mm。早期纤维化:质地增粗不均匀,表面欠光整,柔韧度欠佳,血管较细,脾脏厚度 < 40 mm。严重肝纤维化:质地网格状,表面不光整,柔韧度

较差,血管变细,脾脏厚度 > 40 且 < 45 mm。肝硬化:质地呈结节状,表面凹凸不平,柔韧度差,血管变细扭曲,脾脏厚度:> 45 mm。

1.2.3 瞬时弹性成像检查 采用瞬时弹性扫描仪 FibroScanEcho-sens Paris France 对肝脏进行成像。患者取仰卧位,右手抱头,最大限度展现肋间隙,检查区域选择右侧腋前线至腋中线第 7、8、9 肋间,避开大血管,探头紧贴皮肤并与皮肤垂直,连续检查 10 次。成像均由操作熟练且取得上岗证的技术人员完成。

1.2.4 瞬时弹性成像检测指标 检测肝脏硬度 LSM 值,取中位数作为最终测定结果,并以弹性值 kPa 表示,检测要求成功率 60%,偏差值低于测量值中位数的 1/3。

1.2.5 病理学诊断 肝组织病理标本进行纤维化评分,评分标准参考 2000 年版《病毒性肝炎防治方案》^[8]。S0 无肝纤维化;S1 汇管区纤维化扩大,局限窦周及小叶内纤维化;S2 汇管区周围纤维化,纤维间隔形成,小叶结构保留;S3 纤维间隔伴小叶结构紊乱,无肝硬化;S4 早期肝硬化。

1.3 统计学方法

计量资料用均数±标准差表示。采用 SPSS13.0 和 MedCalc11.4 软件做统计分析,组间差异采用 t 检验和方差分析,诊断实验的评价使用受试者工作特征 ROC 曲线分析,一致性检验采用 Kappa 检验, P<0.05 为差异有统计学意义。

2 结果

2.1 LSM 值在各组间的差异

LSM 值在正常对照组和未做病理慢乙肝患者组中差别显著(P=0.000),见表 1。LSM 值在未做病理慢乙肝组 B 超肝纤维化各级中差别显著(P=0.000),肝硬化组与严重肝纤维化组、早期肝纤维化组、阴性组差别显著,严重肝纤维化组与早期肝纤维化组、阴性组差别显著(P 均 < 0.05),但早期肝纤维化组与阴性组差别不显著(P=0.325),见表 2。

2.2 受试者工作特征曲线的判定

病理慢乙肝组以病理为金标准根据 ROC 曲线推断 FibroScan 诊断各期肝纤维化如图 1-4 所示,具体性能指标见表 3,各期病理图片见图 5。

2.3 一致性检验

表 1 正常对照组和慢乙肝患者组 LSM 值($\bar{x} \pm s$)

Table 1 LSM of normal control and chronic hepatitis B patients($\bar{x} \pm s$)

Control group	Chronic hepatitis B group	T value	P value
5.09 ± 1.47	9.69 ± 8.37	7.291	0.000

表 2 B 超肝纤维化分级患者 LSM 值($\bar{x} \pm s$)

Table 2 LSM of liver fibrosis patients classified by B-ultrasound($\bar{x} \pm s$)

Negative group	Earlier fibrosis group	Severe fibrosis group	Cirrhosis group	F value	P value
6.36 ± 4.41	6.99 ± 3.76	13.44 ± 8.76	18.16 ± 12.32	29.039	0.000

根据以上所得诊断界值对未做病理慢乙肝组进行 FibroScan 肝纤维化分期, B 超诊断肝纤维化亦进行分级,两者进行一致性检验(Kappa 值=0.366, P<0.05),见表 4。

3 讨论

肝纤维化是肝脏炎症长期活动后的常见结局,肝纤维化病情尚可逆转^[9,10],肝硬化形成后仅能延缓疾病进程,所以及早发现肝纤维化并采取相应的治疗措施非常重要。肝纤维化是一个损伤修复的动态发展过程,因而需要反复检测观察纤维化进

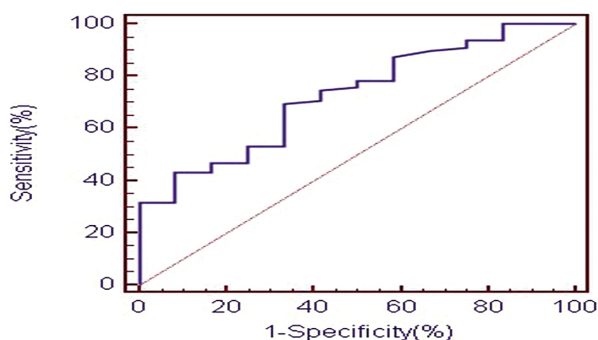


图1 FibroScan 检查诊断 s1 期肝纤维化的 ROC 曲线

Fig.1 ROC curves of FibroScan diagnosis for liver fibrosis of s1

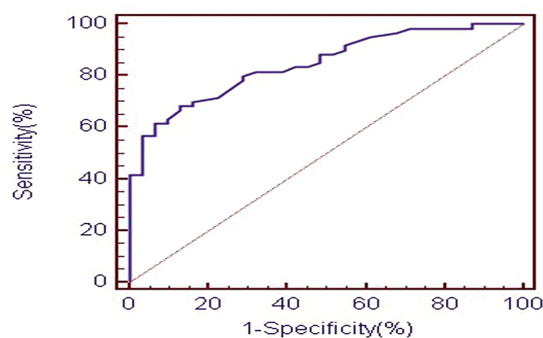


图2 FibroScan 检查诊断 s2 期肝纤维化的 ROC 曲线

Fig.2 ROC curves of FibroScan diagnosis for liver fibrosis of s2

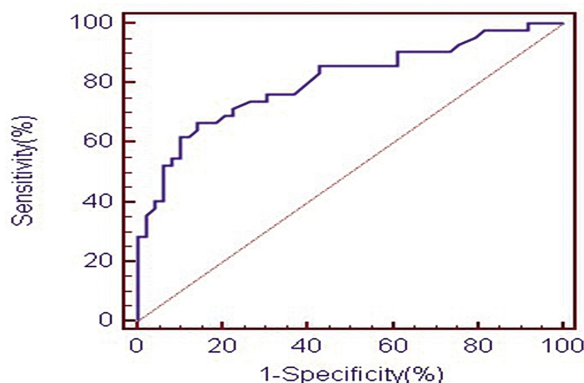


图3 FibroScan 检查诊断 s3 期肝纤维化的 ROC 曲线

Fig.3 ROC curves of FibroScan diagnosis for liver fibrosis of s3

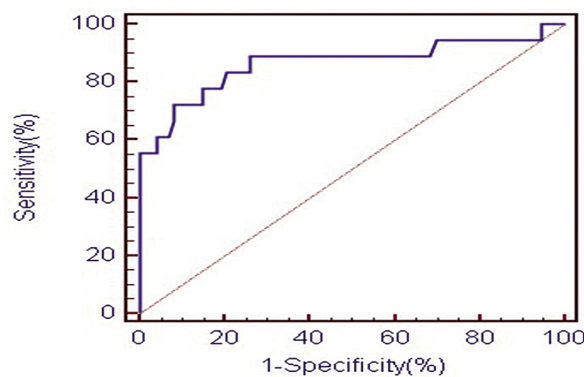


图4 FibroScan 检查诊断 s4 期肝纤维化的 ROC 曲线

Fig.4 ROC curves of FibroScan diagnosis for liver fibrosis of s4

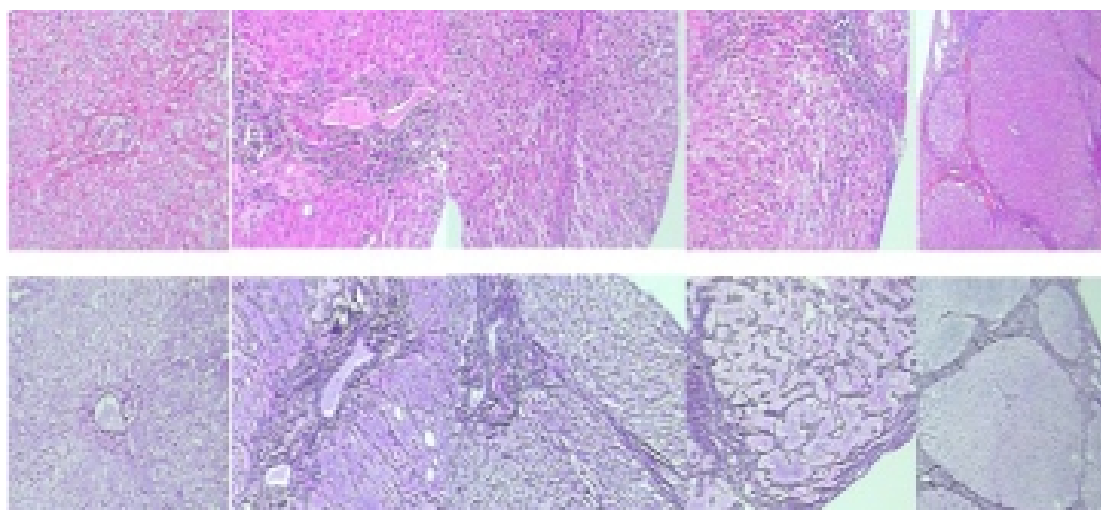


图5 慢乙肝肝纤维化病理图片,第一行从左至右为 HE× 100 染色 s0-4 期,第二行从左至右为对应的网染× 100 s0-4 期

Fig.5 Pathology images of liver fibrosis of chronic hepatitis B patients, the first row from left to right is s0-4 dyed by HE× 100, the second row from left to right is s0-4 reticulin dyeing× 100

展。病理是诊断肝纤维化的金标准,但存在有创、取材局限、不宜反复检查、主观性强等缺点,为寻找非创伤性定量诊断肝纤维化的方法,学者们已做了大量探索^[11-13],包括肝纤维化四项等血清学检查方法及谷草转氨酶/血小板比值(Aspartate aminotransferase To Platelet Ratio Index, APRI)等复合指标,但与肝穿刺活检相比效果不甚理想。FibroScan 是建立在超声诊断基础上的一种新型的、快速便捷、非侵袭性肝纤维化检测新技术,它通过测定肝脏瞬时弹性图谱来反映肝实质硬度^[14,15],我们对 FibroScan 诊断肝纤维化的准确性进行了评估。

通过对未做病理组慢乙肝患者与正常对照及未做病理组慢乙肝患者 B 超肝纤维化各级中 LSM 值差别的研究,结果显示慢乙肝患者组与正常对照组、肝硬化组与严重肝纤维化组、早期肝纤维化组、阴性组差别显著,严重肝纤维化组与早期肝纤维化组、阴性组差别显著($P < 0.05$)。B 超通过检测肝脏的质地、表面光整度、柔韧度、肝内血管是否狭窄、血管走行是否自然和脾肿大程度来综合判断肝纤维化程度。B 超是临床上现行评价肝纤维化的常用方法,B 超诊断肝纤维化各级中 LSM 值的差异说明 FibroScan 诊断肝纤维化有一定的准确性。

表 3 FibroScan 检查诊断试验评价结果
Table 3 Diagnostic value of FibroScan for liver fibrosis

Fibrosis staged by pathology	AUC	Diagnosis critical value(kPa)	Sensitivity	Specificity
S1-	S1-	6.5	69.62%	66.67%
S2-	S2-	7.4	68.33%	87.10%
S3-	S3-	10.1	66.67%	85.71%
S4	S4	17.0	72.22%	91.78%

表 4 肝纤维化 FibroScan 分期与 B 超分级
Table 4 Liver fibrosis staged by FibroScan and B-ultrasound

B ultrasound	FibroScan					Total
	F0	F1	F2	F3	F4	
Negative group	44	7	6	4	1	62
Earlier fibrosis group	20	32	8	14	1	75
Severe fibrosis group	3	3	9	3	5	23
Cirrhosis group	1	0	6	18	13	38
Total	68	42	29	39	20	198
Kappa value						0.366
P value						< 0.05

我们对病理组慢乙肝患者统计结果显示 F1、F2、F3、F4 期肝纤维化的 ROC 曲线下面积(AUROC)分别为 0.726、0.847、0.806、0.864, 诊断界值分别为 6.5、7.4、10.1、17.0 kPa, 灵敏度分别为 69.62%、68.33%、66.67%、72.22%, 特异度分别为 66.67%、87.10%、85.71%、91.78%。病理组织检查是评价肝纤维化程度的“金标准”, AUROC 均大于 0.7 进一步肯定了 FibroScan 诊断肝纤维化的准确性。

我们根据 AUROC 推断所得 FibroScan 诊断肝纤维化各期界值对未做病理组慢乙肝患者进行 FibroScan 肝纤维化分期, B 超诊断肝纤维化亦进行分级, 两者行 Kappa 检验得出肝纤维化 FibroScan 分期和 B 超分级之间具有一致性 (Kappa 值 = 0.366, $P < 0.05$)。FibroScan 与 B 超诊断肝纤维化的一致性进一步说明 FibroScan 诊断肝纤维化的价值, 并肯定了诊断界值的准确性。

在对未做病理组慢乙肝患者 B 超纤维化分级 LSM 值差别的研究中, 早期肝纤维化组与阴性组差别不显著 ($P = 0.325$); 而且对病理组慢乙肝患者统计结果显示, F1 期肝纤维化的 AUROC、特异度均较其他各期低, 说明 FibroScan 对严重肝纤维化或肝硬化的诊断具有较好的准确性, 而对于早期肝纤维化的诊断效果不理想, 这与一些研究结果相符^[16]。

FibroScan 诊断早期纤维化能力有限可能因为早期肝纤维化的病理改变主要在于肝脏微循环及血流动力学发生了变化, 但细胞外基质的合成不大明显, 所以肝脏硬度改变较小。但早期肝纤维化的诊断在临床工作中具有比较重要的意义, 该期进行治疗病情尚可逆转, 而在临床中经常会遇到症状较轻的患者, 他们大多不愿接受肝活检而无法判断肝纤维化程度, 从而不能及时有效的进行抗病毒治疗, 使肝硬化发展为肝癌的风险增高。学者们对早期肝纤维化的诊断做了大量的研究, CT 灌注成像及超声造影为功能性成像, 能反应肝脏微循环及血流动力

学改变, 在肝纤维化的早期诊断方面有一定的优势。无创性诊断方法的联合应用能提高肝纤维化早期诊断的特异性及敏感性, 研究表明 FibroScan 对肝纤维化的诊断价值明显优于其他指标, 可使部分患者免除不必要的肝活检^[17,18], 联合 FibroScan 及血清学、影像学检查能提高早期肝纤维化的诊断率^[19,20], 具有良好的应用前景, 有待进一步研究。

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