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声触诊弹性成像联合 APRI 对慢性乙型肝炎 肝纤维化的评估价值

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[摘要] 目的: 探讨声触诊弹性成像(sound touch elastography, STE)联合天冬氨酸转氨酶(aspartate aminotransferase, AST)/血小板比率指数(AST-to-platelet ratio index, APRI)对慢性乙型肝炎(chronic hepatitis B, CHB)患者肝纤维化的评估价值。方法: 选取2019年1月至2021年8月在海南医学院第二附属医院就诊的96例CHB患者。患者均完成STE检查(获得弹性模量值), 并完成肝功能生化指标[包括AST、血小板计数(platelet count, PLT)]的测定, 计算APRI。以肝组织病理学检查结果为金标准, 采用受试者工作特征(receiver operating characteristic, ROC)曲线评价各指标对肝纤维化的评估效能。结果: 随着肝纤维化程度加重, 患者弹性模量值和血清APRI逐渐增大, 差异有统计学意义($P < 0.05$)。Spearman相关性分析显示: 弹性模量值与肝纤维病理分期呈正相关($r = 0.589$, $P < 0.001$), APRI也与肝纤维病理分期呈正相关($r = 0.410$, $P < 0.001$)。STE弹性模量值诊断肝纤维化 $\geq S2$ 、 $\geq S3$ 及 $S4$ 期的曲线下面积(area under the curve, AUC)分别为0.852、0.954、0.959, APRI诊断的AUC分别为0.887、0.928、0.935, 二者联合诊断的AUC分别为0.918、0.974、0.984。结论: STE和血清APRI对CHB患者肝纤维化有较高评估价值, 且二者联合应用可提高诊断效能。

[关键词] 慢性乙型肝炎; 肝纤维化; 声触诊弹性成像; 天冬氨酸转氨酶/血小板比率指数

Evaluation value of sound touch elastography combined with APRI for liver fibrosis in patients with chronic hepatitis B

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Abstract **Objective:** To investigate the evaluation value of sound touch elastography (STE) combined with aspartate aminotransferase (AST)-to-platelet ratio index (APRI) on liver fibrosis in patients with chronic hepatitis B (CHB). **Methods:** A total of 96 CHB patients admitted to Second Affiliated Hospital of Hainan Medical College from January 2019 to August 2021 were selected. All patients completed STE examination (elastic modulus

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value), and the determination of biochemical indexes of liver function [including AST and platelet count (PLT)], then calculated APRI. The receiver operating characteristic (ROC) curve was used to evaluate the efficacy of each index on liver fibrosis with the results of liver histopathology as the gold standard. **Results:** With the aggravation of liver fibrosis, the elastic modulus and serum APRI of patients gradually increased, and the difference was statistically significant ($P < 0.05$). Spearman correlation analysis showed that the elastic modulus was positively correlated with the pathological stage of liver fiber ($r = 0.589, P < 0.001$), and APRI was also positively correlated with the pathological stage of liver fiber ($r = 0.410, P < 0.001$). The area under the curve (AUC) of STE elastic modulus in the diagnosis of liver fibrosis $\geq S2, \geq S3$, and $S4$ were 0.852, 0.954, and 0.959, respectively. The AUC of APRI were 0.887, 0.928, and 0.935, respectively. The AUC of combined diagnosis were 0.918, 0.974, and 0.984. **Conclusion:** STE and serum APRI have high evaluation value for liver fibrosis in CHB patients, and the combination of the two can improve the diagnostic efficacy.

Keywords chronic hepatitis B; liver fibrosis; sound touch elastography; aspartate aminotransferase-to-platelet ratio index

准确评估肝纤维化程度有助于管理慢性乙型肝炎(chronic hepatitis B, CHB)患者病情和制定精准治疗方案, 对于改善患者预后具有重要意义^[1]。肝组织病理活检是临床诊断肝纤维化的金标准, 是肝纤维化评估的常规手段^[2], 但作为有创性检查, 存在出血、感染等多种并发症风险, 难以被患者接受。近年来, 超声弹性成像技术被提出可作为肝纤维化的无创评估手段, 同时血清学诊断指标也成为临床研究热点。声触诊弹性成像(sound touch elastography, STE)作为一种二维剪切波弹性成像技术(two-dimensional shear-wave elastography, 2D-SWE), 能够在二维灰阶图像下获得弹性模量值, 可定量评估肝硬度, 反映肝纤维化程度^[3-4]。天冬氨酸转氨酶(aspartate aminotransferase, AST)/血小板比率指数(ASST-to-platelet ratio index, APRI)是新用于肝纤维化评估的血清学指标^[5], 但其在国内临床的应用价值仍有待进一步明确。

1 对象与方法

1.1 对象

本研究为回顾性研究, 经海南医学院第二附属医院医学伦理委员会审核批准(审批号: 2022026)。选取2019年1月至2021年8月在海南医学院第二附属医院就诊的96例CHB患者, 其中男69例, 女27例, 年龄21~60(36.11 ± 8.23)岁。纳入标准: 1)符合CHB诊断标准^[6]; 2)临床资料完整。排除标准: 1)合并其他类型肝炎; 2)合并酒精性肝病; 3)肝癌; 4)肝移植术后; 5)妊娠期或哺乳期女性。患者均完成STE检查, 并于

同1 d完成肝功能生化指标的测定, 并于2 d内接受肝组织病理学检查。所有检查均告知患者并取得同意。

1.2 方法

1.2.1 STE检查

仪器设备: 迈瑞Resona 7型彩色多普勒超声诊断仪和SC6-1U型凸阵探头(1~6 MHz)。受检者准备: 空腹2 h以上, 检查时采取平卧位, 右手臂上抬、外展, 使得右侧季肋部得以充分暴露。检查方法: 将探头置于右肋间肝右叶切面, 避开肝内血管长轴, 图像清晰显示肝实质后, 将取样框放置到肝包膜以下约1 cm, 嘱咐患者保持平静呼吸, 屏气3~5 s, 开启弹性成像功能, 图像稳定后, 冻结图像并测量感兴趣区(region of interest, ROI)内弹性模量值, 连续测量5次取平均值。单次检测成功标志: ROI区域内彩色充盈均匀, 不存在异常区域, 可信度指数 $\geq 95\%$ 。

1.2.2 血清学指标

患者均接受了常规肝功能血清生化指标测定, 仪器为迈瑞BS-2000M全自动生化分析仪, 包括AST、血小板计数(platelet count, PLT)水平, 并计算 $APRI = AST/PLT$ 。记录患者丙氨酸转氨酶(alanine transaminase, ALT)、总胆固醇(total cholesterol, TC)等生化指标。

1.2.3 病理检查

患者均采用16G组织切割活检针行肝穿刺活检。参照Scheuer标准^[7]进行病理肝纤维化分期, 可分为S1~S4期, $\geq S2$ 期为显著纤维化, $\geq S3$ 期为进展期纤维化, S4期为肝硬化。典型肝纤维化病理图像见图1。

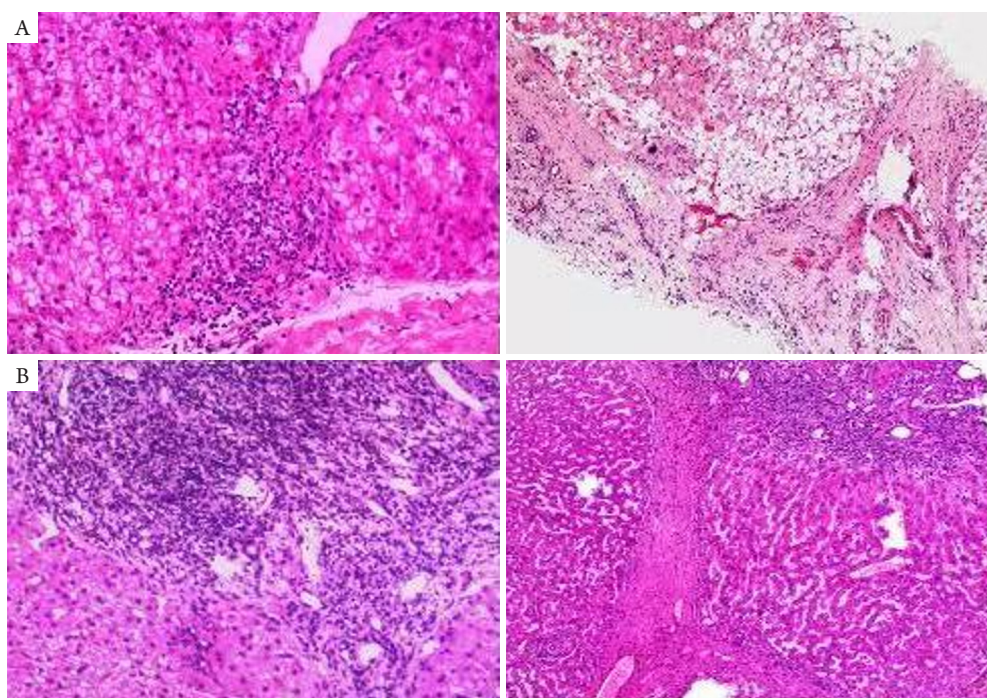


图1 CHB患者肝纤维化病理图像(HE染色, $\times 400$)

Figure 1 Pathological image of liver fibrosis in CHB patients (HE staining, $\times 400$)

(A)S1期(无肝纤维化), S2期(显著纤维化); (B)S3期(进展期纤维化), S4期(肝硬化)。

(A) S1 (no hepatic fibrosis), S2 stage (obvious fibrosis); (B) S3 stage (advanced fibrosis), S4 (liver cirrhosis).

1.3 统计学处理

采用SPSS 24.0统计学软件进行数据分析。计量资料(满足正态分布)采取 $(\bar{x} \pm s)$ 进行表示, 多组间比较用单因素方差分析, 两两比较用SNK(Student-Newman-Keuls)法; 计数资料比较用 χ^2 检验; 变量之间的相关性采用Spearman相关分析; 采用受试者工作特征(receiver operating characteristic, ROC)曲线评价STE弹性模量值、APRI及其联合对肝纤维化分期的诊断效能; 采用多元线性回归模型分析STE弹性模量值的影响因素。 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 不同肝纤维化分期CHB患者临床特征比较

96例患者的肝纤维化病理分期: S1期25例, S2期27例, S3期16例, S4期28例。随着肝纤维化程度加重, 患者弹性模量值和血清APRI均逐渐增大(均 $P < 0.05$, 表1)。

2.2 弹性模量值、APRI与肝纤维化病理分期的相关性

Spearman相关性分析显示: 弹性模量值与

肝纤维病理分期呈正相关($r = 0.589$, $P < 0.001$), APRI也与肝纤维病理分期呈正相关($r = 0.410$, $P < 0.001$)。

2.3 弹性模量值及APRI的诊断效能

构建ROC曲线显示: STE弹性模量值诊断肝纤维化 $\geq S2$ 、 $\geq S3$ 及S4期的临界值分别为10.0、11.75、14.74, 曲线下面积(area under the curve, AUC)分别为0.852、0.954、0.959; APRI诊断纤维化 $\geq S2$ 、 $\geq S3$ 及S4期的临界值分别为0.23、0.25、0.35, AUC分别为0.887、0.928、0.935。二者联合诊断各分期的AUC相比单一检测均提高, 分别为0.918、0.974、0.984(表2, 图2~4)。

2.4 STE弹性模量值的影响因素

体重指数(body mass index, BMI)、ALT、TC、肝纤维化分期与STE弹性模量的Spearman相关系数分别为0.323、0.471、0.547、0.565(分别 $P = 0.121$ 、0.015、0.105、0.009)。ALT、肝纤维化分期与STE弹性模量的Spearman相关系数分别为0.511、0.346(分别 $P = 0.019$ 、0.024)。

表1 不同肝纤维化分期CHB患者临床特征比较

Table 1 Comparison of clinical features of CHB patients with different stages of liver fibrosis

肝纤维化分期	<i>n</i>	性别(男/女)/例	年龄/岁	弹性模量值/kPa	APRI
S1	25	16/9	35.74 ± 6.58	8.56 ± 2.12	0.16 ± 0.05
S2	27	18/9	36.11 ± 7.23	10.98 ± 2.35 ^a	0.21 ± 0.09
S3	16	11/5	35.89 ± 6.94	13.36 ± 2.61 ^{ab}	0.31 ± 0.11
S4	28	24/4	36.58 ± 7.89	16.87 ± 2.44 ^{abc}	0.44 ± 0.10
<i>F/χ²</i>		3.859	0.291	17.514	19.541
<i>P</i>		0.277	0.796	<0.001	<0.001

与S1期相比, ^a*P*<0.05; 与S2期相比, ^b*P*<0.05; 与S3期相比, ^c*P*<0.05; 弹性模量值: S2、S3、S4与S1对比的*t*分别为3.888、6.460、11.544, 均*P*<0.001, S3、S4与S2相比的*t*分别为3.081、9.113, 分别*P*=0.004和<0.001; S4与S3相比的*t*为4.476, *P*<0.001; APRI: S2、S3、S4与S1对比的*t*分别为2.449、5.954、12.650, 分别*P*=0.018、<0.001、<0.001, S3、S4与S2相比的*t*分别为3.241、8.955, 分别*P*=0.002和<0.001; S4与S3相比的*t*为4.001, *P*<0.001。

Compared with S1 period, ^a*P*<0.05; compared with S2 period, ^b*P*<0.05; compared with S3, ^c*P*<0.05; elastic modulus values: *t* values of S2, S3, S4 compared with S1 were 3.888, 6.460 and 11.544, respectively, all *P*<0.001, *t* values of S3, S4 compared with S2 were 3.081 and 9.113, respectively, *P*=0.004 and <0.001, respectively; the *t* value of S4 compared with S3 was 4.476, *P*<0.001; APRI: *t* values of S2, S3, S4 compared with S1 were 2.449, 5.954, 12.650, *P*=0.018, <0.001, <0.001, *t* values of S3, S4 compared with S2 were 3.241, 8.955, *P*=0.002 and <0.001; the *t* value of S4 compared with S3 was 4.001, *P*<0.001.

表2 STE及APRI对肝纤维化的诊断效能

Table 2 Diagnostic efficacy of STE and APRI for liver fibrosis

方法	诊断临界点	AUC	敏感度/%	特异度/%
STE				
≥S2	10.0	0.852 (0.765~0.916)	78.9	84.0
≥S3	11.75	0.954 (0.890~0.986)	90.9	86.5
S4	14.74	0.959 (0.897~0.989)	89.3	92.6
APRI				
≥S2	0.23	0.887 (0.807~0.943)	74.6	100.0
≥S3	0.25	0.928 (0.857~0.971)	90.9	80.8
S4	0.35	0.935 (0.866~0.975)	92.9	83.8
STE联合APRI				
≥S2	—	0.918 (0.844~0.964)	83.1	92.0
≥S3	—	0.974 (0.919~0.996)	86.4	98.1
S4	—	0.984 (0.935~0.999)	100.0	91.2

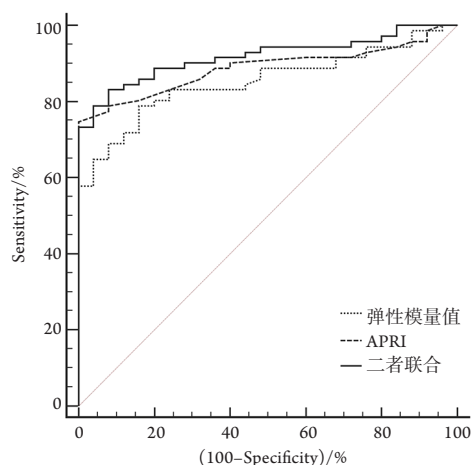


图2 STE弹性模量值及APRI诊断肝纤维化 \geq S2期的ROC曲线
Figure 2 ROC curve of STE elastic modulus and APRI in diagnosis of hepatic fibrosis \geq S2

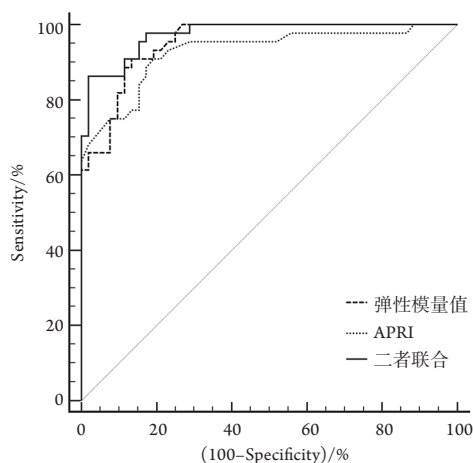


图3 STE弹性模量值及APRI诊断肝纤维化 \geq S3期的ROC曲线
Figure 3 ROC curve of STE elastic modulus and APRI in diagnosis of hepatic fibrosis \geq S3

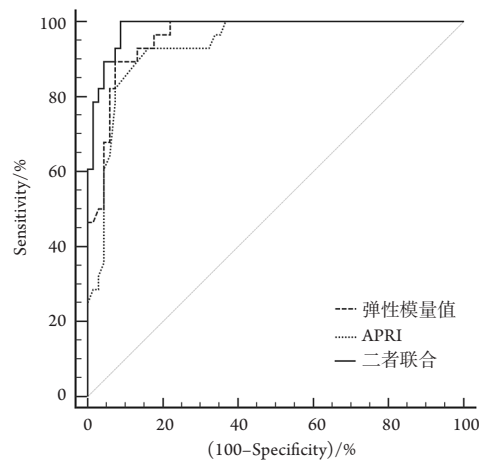


图4 STE弹性模量值及APRI诊断肝纤维化S4期的ROC曲线
Figure 4 ROC curve of STE elastic modulus and APRI in diagnosis of S4 hepatic fibrosis

3 讨论

超声弹性成像技术是一种非侵入性影像学新技术, 有着无创、操作便捷等优点, 由于可提供组织硬度信息, 使超声诊断产生了新的变革^[8-9]。目前, 在肝纤维化诊断中, 检测肝硬度的弹性成像是重要的无创诊断方法。近年剪切波弹性成像在肝纤维化无创评估中的应用发展迅速, 本研究采用STE技术, 同时呈现二维图像和弹性成像, 在ROI检测部位进行精准定位, 获取ROI的弹性模量值。瞬时弹性成像是较早被开展应用于肝纤维临床评估中的技术, 但由于易受腹水、肥胖等多种因素影响, 加之缺乏二维实时引导, 使得其应用存在不足; 而STE在二维灰阶图像的实时引导下检测较为容易, 检测成功率高, 能够获得满意的弹性图像^[10]。本研究患者均获得检测, 检测成功率为100%。Xia等^[11]采用STE和瞬时弹性成像对CHB患者肝纤维化程度进行评估, 发现STE的诊断效能相比TE更优, 并且100%的检测成功率同样优于瞬时弹性成像的97.3%。吴曼丽等^[12]研究表明STE检测成功率高, 重复性好, 相比二维剪切波弹性成像具有明显优势。由此可见, STE技术具有良好的应用前景。

本研究结果显示: 在不同肝纤维化病理分期患者的STE弹性模量值差异有统计学意义, 且随着肝纤维化分期提高, 患者弹性模量值逐渐增大, 同时弹性模量值与肝纤维化病理分期呈正相关, 说明STE弹性模量值与肝纤维化程度具有相关性。ROC曲线显示: STE弹性模量值对肝纤维化 \geq S2、 \geq S3和S4期均有较好诊断效能, AUC分别为0.852、0.954、0.959。与既往报道^[13]一致。

血清学诊断标志物的应用是临床关注的热点之一, 研究^[14]发现在血清ALT、AST正常时, 患者肝脏已出现了纤维化病变。这表明仅凭血清ALT、AST难以对病情做出准确判断。APRI由Wai等^[15]设计, 旨在放大AST、PLT在不同肝纤维化程度肝炎患者之间的差异, 其研究表明APRI与肝纤维化分期的相关性大于AST、PLT与肝纤维化分期的相关性。并且有研究^[16]显示APRI预测肝纤维化分期的AUC大于单独的AST或PLT。由于APRI相关指标获得简便, 有很好的性价比, 已成为欧洲肝病指南推荐的用于慢性丙肝患者肝纤维化诊断的标志物^[17]。但其在国内患者中的应用价值仍有待进一步验证。本研究显示: 随着肝纤维化分期的提高, CHB患者血清APRI逐渐增大, 相关性分析显示APRI与肝纤维化病理分期呈正相关, 且ROC曲线分析显示

APRI诊断 $\geq S2$ 、 $\geq S3$ 和 $S4$ 期的AUC分别为0.887、0.928、0.935。表明APRI与肝纤维分期具有相关性,对CHB患者肝纤维化程度具有较高诊断价值。沈崔琴等^[18]研究显示APRI对 $\geq S2$ 期和 $S4$ 期肝纤维化均有较高诊断准确性,这与本研究结果类似。

声弹性成像技术及血清学指标已成为肝纤维化无创评估的主要手段,二者的联合应用也成为研究的热点。本研究结果显示:二者联合诊断 $\geq S2$ 、 $\geq S3$ 和 $S4$ 期的AUC相比单一检测均提高,分别为0.918、0.974、0.984,说明STE联合APRI诊断可能有助于进一步提高肝纤维化的诊断效能。陈晓玲等^[19]研究表明:剪切波弹性成像技术联合血清 γ -谷氨酰转肽酶/血小板比值(γ -glutamyltranspeptidase-to-platelet ratio, GPR)可提高纤维化的诊断价值。由此可见,临床可通过联合应用超声弹性技术和血清学指标进行诊断,有望提高对肝纤维化评估的价值。

弹性模量值可能还受ALT、肝脂肪变等因素的影响,更多相关因素有待进一步探讨。综上所述,STE弹性模量值、血清APRI均与肝纤维化程度呈正相关,对CHB患者肝纤维化有较高评估价值,且二者联合应用有望进一步提高诊断效能,值得关注。但本研究存在不足,首先样本量较小,统计结果难免存在偏差;其次肝纤维化血清诊断标志物较多,由于条件限制,本研究仅纳入APRI进行分析,关于其他血清指标如GPR、纤维化指数等在肝纤维化诊断中的应用仍有待进一步研究。

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