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超声结合血清学指标对自身免疫性肝病相关肝硬化的预测价值*

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摘要 目的:本研究旨在结合二维剪切波弹性成像(2D-SWE)技术、超声特征及血清学指标构建自身免疫性肝病(AILD)相关肝硬化的预测模型并评估该模型的预测效能。**方法:**收集2019年月至2022年5月于福建医科大学孟超肝胆医院行肝脏活检确诊为AILD,并行肝胆脾超声、2D-SWE及相关血清学检查的患者。根据病理结果,分为肝硬化组与非肝硬化组。通过多因素logistic回归分析筛选出AILD相关肝硬化的独立风险因素,构建AILD相关肝硬化的列线图模型(AILDC)。采用Bootstrap法对模型进行内部验证,绘制ROC曲线,校准曲线及临床决策曲线评估模型的区分度、校准度及临床净获益。**结果:**共纳入AILD 255例,肝硬化组共45例。logistic回归分析结果显示:肝硬度(OR:1.322,95%CI:1.186-1.474),脾脏厚度 >4 cm(OR:5.154,95%CI:1.943-13.674),补体C4(OR:0.001,95%CI:0.000-0.674),高尔基体-73(OR:1.014,95%CI:1.002-1.027)均是AILD肝硬化独立预测指标。AILDC的最佳截断值为80,敏感度84.4%,特异度78.6%;曲线下面积(Area under curve, AUC)0.866。AILD肝硬度的最佳截断值为10 Kpa,敏感度为71.1%,特异度为85.2%,AUC为0.803。相较于其它无创指标,AILDC具有更高的净重新分类指数、综合判别改善指数及临床决策曲线。**结论:**AILDC具有较好的预测效能,优于其他无创指标,适于在临床中运用并进一步推广。

关键词:自身免疫性肝病相关肝硬化;超声;血清学;预测;无创模型

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Predictive Value of the Autoimmune Liver Disease Related Cirrhosis by Ultrasound Combined with Serological Indexes*

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ABSTRACT Objective: To construct a prediction model about the autoimmune liver disease (AILD) related cirrhosis based on two-dimensional shear wave elasticity (2D-SWE), ultrasound and serological indexes, and to evaluate the predicting efficiency. **Objective** To construct a prediction model about the autoimmune liver disease (AILD) related cirrhosis based on two-dimensional shear wave elasticity (2D-SWE), ultrasound and serological indexes, and to evaluate the predicting efficiency. **Methods:** Patients with AILD confirmed by liver biopsy with liver ultrasound, 2D-SWE and serological examination were collected from 2019.01 to 2022.05. Patients were divided into cirrhotic and non-cirrhotic groups. Independent risk factors for the AILD related cirrhosis were selected by multivariate logistic regression analysis, and a nomogram model (AILDC) of the AILD related cirrhosis was constructed. The internal was validated on the model by Bootstrap method, and the Receiver Operating Characteristic curve, calibration curve and clinical decision curve were drew to evaluate the differentiation degree, calibration degree and the clinical net benefit of the model. **Results:** A total of 255 patients, 45 had liver cirrhosis. Multivariate logistic regression analysis showed that liver stiffness (OR:1.322,95%CI:1.186-1.474), spleen thickness >4 cm (OR: 5.154,95%CI: 1.943-13.674), complement C4(OR:0.001,95%CI:0.000-0.674), and the Golgi apparatus protein-73 (OR: 1.014,95% CI: 1.002-1.027) were all independent predictors of AILD related cirrhosis. The optimal cut-off for AILDC was 80, sensitivity 84.4%, specificity 78.6%, the area under curve(AUC) was 0.866. The optimal cutoff value for AILD liver stiffness was 10 Kpa, with the sensitivity of 71.1%, and the specificity of 85.2%, and an AUC of 0.803. Compared with other non-invasive indicators, AILDC has a higher net reclassification index, comprehensive discriminant improvement index, and clinical decision curve. **Conclusion:** The AILDC has better predictive efficacy than other noninvasive indices, and worth further promotion in clinical practice.

Key words: Autoimmune liver disease related cirrhosis; Ultrasound; Serology; Prediction; Noninvasive model

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前言

自身免疫性肝病(autoimmune liver disease, AILD)包括自

身免疫性肝炎,原发性胆汁性胆管炎,原发性硬化性胆管炎,及以上疾病重叠所构成的重叠综合征^[1-3]。全球发病率约为1.3-9.4/100000,目前该病虽发病率较低,但目前尚无特效治疗,

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尤其在肝硬化阶段,肝脏对各种药物的应答性显著降低^[4-6],对患者家庭及社会医疗资源造成严重负担。故尽早诊断该病,及时调整用药方案,精准化治疗具有重要临床意义。肝脏活检穿刺虽作为肝硬化诊断的金标准,但费用昂贵且取材假阴性率高,且穿刺后并发症发病率高,具有一定局限性。随着无创及微创概念的普及,越来越多的无创指标用于评估肝纤维化等级^[7-10],较常用的血清学指标天冬氨酸氨基转移酶 (AST) 和血小板 (PLT) 比率 (APRI),肝纤维化 4 指数 (FIB-4) 等^[11,12],但上述血清学指标缺乏稳定性;超声检查指标则以肝组织弹性指标^[13]及超声声像图一般指标,如肝包膜光滑度,胆囊壁光滑度,脾脏厚度是否 $>4\text{ cm}$ 等^[14,15]。超声检查声像图异常表现及肝硬度值敏感性较差,且无法对评估肝脏功能进行评估。本研究结合超声特征及血清学指标构建诊断 AILD 相关肝硬化的预测模型以替代肝脏活检穿刺,早期预测该病的诊断以指导临床决策的调整使患者获益具有十分重要的意义。

1 材料与方法

1.1 一般资料

本研究经过医院伦理委员会审核,批准进行(伦理批号 2021-088-01)。回顾性分析 2019 年 1 月-2022 年 5 月于我院行肝脏穿刺、超声检查及血清学检查确诊为 AILD 患者 1526 例,根据纳排标准,255 例患者纳入研究,收集患者一般基线资料,如身高、体重指数、性别、年龄、糖尿病史。

纳入标准:① 肝脏穿刺活检,首次确诊为 AILD;② 穿刺前未行其他治疗,包括抗纤治疗、中药治疗;③ 病例资料完整;④ 征得患者或监护人同意。

排除标准:① 病理结果显示合并病毒感染(乙肝、丙肝等);② AILD 治疗史;③ 病理资料不完整(缺少肝脏超声检查指标或大量血清学指标)。

1.2 实验方法

1.2.1 超声指标收集 采用迈瑞 Resona R9 超声诊断仪,腹部凸阵探头,频率 2-6 MHz,检查前,患者空腹 8 小时,嘱患者仰卧或左侧卧位,上抬右上肢,首先行常规腹部超声检查,收集以下指标:右肝斜后径(正常值 10-14 厘米),肝脏包膜(主观评判是否光滑),肝脏实质回声(主观评判是否均匀),门静脉内径(于距肝门处约 1 厘米处测量),胆囊壁(主观评判是否光滑),脾脏尺寸(当厚径大于 4 厘米时,判断为脾肿大),侧支循环(胃左静脉、脐静脉、脾肾分流静脉,探及任一血管时,判断为侧支循环形成)。随后开启实时二维剪切波弹性成像(Two-dimensional shear wave elasticity, 2D-SWE)检测模式,进行肝硬度(Liver stiffness measurement, LSM)测量,避开气体、大血管、胆道及肋骨等组织结构;取样框大小 $4\text{ cm} \times 3\text{ cm}$,上缘置于肝包膜下 1-2 cm,最深不超过 6 cm;感兴趣区设定为 1.5 cm,置于预穿刺部位,使所测硬度值能最大程度的反映穿刺组织的真实情况。嘱患者于平静呼吸状态下屏住呼吸 3-5 秒(避免深吸后屏气),进行测量,待图像稳定后,激活该程序,取样框内完全被色彩充满,在取样框的不同部位连续测量五次,取中位数作为最终结果,以上操作均由 10 年以上超声工作经验医生承担。

1.2.2 血清学指标收集 收集穿刺前相关指标:白细胞(White

blood cell, WBC)计数、血红蛋白(Hemoglobin, Hb)、血小板(Platelet, PLT)、谷丙转氨酶(Alanine aminotransferase, ALT)、谷草转氨酶(Aspartate transaminase, AST)、谷氨酰转肽酶(Gamma glutamyl transpeptidase, GGT)、碱性磷酸酶(Alkaline phosphatase, ALP)、白蛋白(Albumin, ALB)、总胆红素(Total bilirubin, TBIL)、胆固醇(Cholesterol, CHO)、凝血酶原时间(Prothrombin time, PT)、国际标准化比值(International normalized ratio, INR)、补体 C3、补体 C4、高尔基体-73(Golgi apparatus, GP-73)

1.2.3 无创指标收集 根据以往文献报道,本研究共纳入了以下无创指标作为比较对象^[16]。

(1)谷草转氨酶/血小板比值指数(APRI): $\text{AST/正常值上限}/\text{PLT} \times 100$;

(2)体重指数谷草转氨酶/谷丙转氨酶比值、糖尿病评分(BARD): $\text{BMI} \geq 28$ 1 分, $\text{AST/ALT} \geq 0.8$ 2 分,糖尿病史 1 分;

(3)肝纤维化(FIB)-4: $(\text{年龄} \times \text{AST}) \div (\text{PLT} \times \text{ALT})$;

(4)非酒精性肝纤维化评分(NFS): $-1.675 + 0.037 \times \text{年龄} + 0.094 \times \text{BMI} + 1.13 \times \text{糖尿病史}(\text{有}=1, \text{无}=0) + 0.99 \times \text{AST/ALT} - 0.012 \times \text{PLT} - 0.66 \times \text{ALB}$;

(5)Forns 指数: $7.811 - 3.131 \times \ln \text{PLT} + 0.781 \times \ln \text{GGT} + 3.467 \times \ln \text{年龄} - 0.014 \times \text{CHO}$;

(6)谷氨酰转肽酶/血小板(GPR): GGT/PLT ;

(7)Lok 指数: $-5.56 - 0.0089 \times \text{PLT} + 1.26 \times \text{AST/ALT} + 5.27 \times \text{INR}$;

(8)谷草转氨酶/谷丙转氨酶(AAR): AST/ALT 。

1.2.4 病理学诊断标准 排除其他疾病,结合临床表现及自身抗体与病理检查结果,诊断为 AILD,肝纤维化分期采用 Metavir 分级方法,纤维化分级(以 S 表示),分为 S0-S4。当纤维化分级 S=4 时,诊断为肝硬化。

1.3 统计学处理

计量资料采用 $(\bar{x} \pm s)$ 表示,计数资料以百分比(%)表示,符合正态分布的两组变量间的比较,使用两独立样本 t 检验,不符合正态分布的两组变量间的比较,使用 Mann-Whitney U 检验。率的比较使用卡方检验或 Fisher 确切概率法。缺失值使用均值插补法进行填补。组间相关性分析采用 Pearson 或 Spearman 秩相关法。采用 logistic 回归分析筛选诊断 AILD 相关肝硬化的指标,构建列线图,绘制 ROC 曲线,计算 AUC、敏感度及特异度。同时绘制列线图的校准曲线及临床决策曲线,列线图与其它无创指标诊断 AILD 相关肝硬化的 AUC 的差异比较采用 Delong 法。计算 AILDC 与其他各指标的净重新分类指数(Net reclassification index, NRI)和综合判别改善指数(Integrated discrimination improvement, IDI)的改变量。以 $P < 0.05$ 认为差异具有统计学意义。

2 结果

2.1 一般情况

共 255 例,其中 AIH146 例, PBC71 例, PSC5 例, OLS33 例,肝硬化组 45 例,非肝硬化组 210 例,平均年龄为 52.9 ± 11.3 岁。硬化组肝包膜不光滑、脾肿大、胆囊壁毛糙、肝硬度值

的比例均高于非硬化组；硬化组 AST、GP73、TBIL、PT、INR 高（表 1）。
于非硬化组，硬化组 ALB、PLT、C4 低于非硬化组， P 均 <0.05 。

表 1 入组患者一般情况
Table 1 Basic characteristics

Name of index	Total (n=255)	Non-cirrhotic group (n=210)	Cirrhotic group (n=45)	P
Age (year)	52.9± 11.3	52.4± 10.9	55.0± 13.2	0.069
Gender				
Female	214 (83.9%)	175 (83.3%)	39 (86.7%)	0.66
Male	41 (16.1%)	35 (16.7%)	6 (13.3%)	
BMI	22.4± 2.8	22.4± 2.5	22.4± 3.7	0.69
Right liver size				
Normal	236 (92.5%)	196 (93.3%)	40 (88.9%)	0.34
Reduce	19 (7.5%)	14 (6.7%)	5 (11.1%)	
Liver echo				
Normal	140 (54.9%)	121 (57.6%)	19 (42.2%)	0.12
Thickening	85 (33.3%)	67 (31.9%)	18 (40.0%)	
Trrberculation	30 (11.8%)	22 (10.5%)	8 (17.8%)	
Diolame				
Smooth	214 (83.9%)	181 (86.2%)	33 (73.3%)	0.044
Coarse	41 (16.1%)	29 (13.8%)	12 (26.7%)	
Collateral circulation				
No	251 (98.4%)	208 (99.0%)	43 (95.6%)	0.14
Yes	4 (1.6%)	2 (1.0%)	2 (4.4%)	
Splenomegaly				
No	168 (65.9%)	153 (72.9%)	15 (33.3%)	< 0.001
Yes	87 (34.1%)	57 (27.1%)	30 (66.7%)	
Gallbladder wall				
Smoot	78 (30.6%)	70 (33.3%)	8 (17.8%)	0.049
Coarse	177 (69.4%)	140 (66.7%)	37 (82.2%)	
Pathological type				
Autoimmune hepatitis	146(57.3%)	123(58.6%)	23(51.1%)	0.72
Primary biliary cholangitis	71(27.8%)	58(27.6%)	13(28.9%)	
Primary sclerotic cholangitis	5(2.0%)	4(1.9%)	1(2.2%)	
Overlap syndrome	33(12.9%)	25(11.9%)	8(17.8%)	
ALT (U/L)	149.3 ± 430.1	159.4± 470.0	102.3± 124.3	0.32
Transaminase (U/L)	111.6 ± 121.3	107.7± 114.2	130.0± 150.3	0.049
Platelet count (/ L)	205.1 ± 79.4	212.3± 76.1	171.1± 86.0	< 0.001
Albumin (g/L)	38.7± 16.8	39.0± 17.7	37.4± 12.3	0.009
Glutayl transeptidase (μ/L)	284.7± 341.1	292.8± 361.3	246.9± 223.5	0.69
Cholesterol (mmol/L)	3.42± 1.14	3.46± 1.09	3.38± 1.02	0.82
Total bilirubin (μmol/L)	45.2± 60.9	40.6± 58.0	66.6± 69.8	0.002
Alkaline phosphatase (mmol/L)	242.5± 202.1	241.7± 206.3	246.1± 183.4	0.77
Golgi Body Protein 73 (μg/L)	96.1± 33.7	92.3± 27.7	113.5± 50.3	< 0.001
Prothrombin time (s)	12.8± 1.8	12.6± 1.5	13.6± 2.7	< 0.001
Prothrombin activity level (%)	102.5± 21.2	104.4± 20.6	93.6± 21.7	< 0.001
International normalized ratio	1.0± 0.2	1.0± 0.1	1.1± 0.4	0.003
Complementary C3(g/L)	1.1± 0.3	1.1± 0.3	1.1± 0.3	0.21
Complementary C4(g/L)	0.2± 0.1	0.2± 0.1	0.2± 0.1	0.01
Liver tissue hardness (kpa)	8.0± 4.9	6.8± 3.1	13.4± 7.5	< 0.001
Inner diameter of the main portal vein(cm)	1.1± 0.1	1.1± 0.1	1.1± 0.1	0.89

2.2 各个指标相关性

在所收集的指标中与 AILD 相关肝硬化有显著相关性的指标是 LSM ($r=0.528, P<0.001$), GP73 ($r=0.143, P=0.022$), Lokindex($r=0.267, P<0.001$), GPR($r=0.129, P=0.040$), NFS($r=0.$

145, $P=0.020$), Fornsindex ($r=0.152, P=0.015$), FIB-4 ($r=0.209, P=0.011$), APRI($r=0.159, P=0.011$), AAR($r=0.227, P<0.001$), 肝脏回声($r=0.151, P=0.016$)。(图 1)。

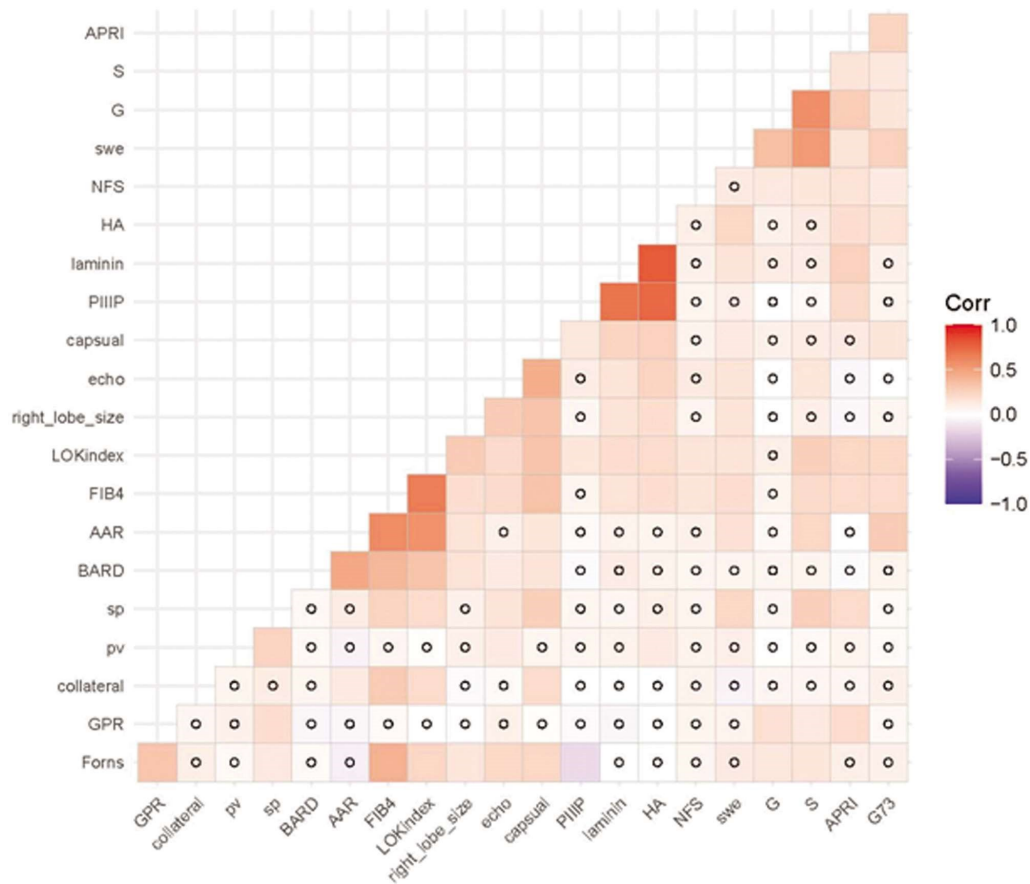


图 1 各指标相关性热图

Fig.1 Correlation Heat Map of Each Index

Note: S: liver fibrosis stage, G: inflammation stage, swe: liver stiffness, laminin: laminin, PIIP: type III procollagen telopeptide, HA: hyaluronidase, echo: liver echo, right-lobe-size: right hepatomegaly, sp: splenomegaly, PV: portal vein diameter, Collateral: collateral formation. circle means no correlation.

2.3 多因素分析

将单因素分析有意义的指标,排除共线性后纳入二元 logistic

回归分析(表 2),结果显示肝硬度,脾肿大,C4,GP73 是预测 AILD 肝硬化的独立风险因素。

表 2 AILD 相关性肝硬化二元 logistic 回归结果

Table 2 AILD related cirrhosis multivariable analysis result

Name of index	β	P	OR	95%CI
Albumin (g/L)	-0.004	0.747	0.996	0.972-1.021
Platelet count (/L)	-0.002	0.563	0.998	0.992-1.004
Total bilirubin ($\mu\text{mol/L}$)	0.002	0.518	1.002	0.995-1.009
Prothrombin time (s)	-0.028	0.821	0.972	0.760-1.243
Complement C4(g/L)	-6.565	0.037	0.001	0.000-0.674
Golgi Body Protein 73 ($\mu\text{g/L}$)	0.014	0.019	1.014	1.002-1.027
Capsula fibrosa	-0.124	0.821	0.883	0.302-2.583
The gallbladder wall is rough	-0.135	0.805	0.874	0.300-2.546
Splenic thickness was> 4 cm	1.64	0.001	5.154	1.943-13.674
Liver Hardness (kpa)	0.279	0	1.322	1.186-1.474
Constant	-4.025	0.144	0.018	

2.4 AILD 相关肝硬化的 nomogram 模型(AILDC)

将 Logistic 回归分析筛选的结果纳入独立风险因素,构建 Nomogram 模型(图 2)。

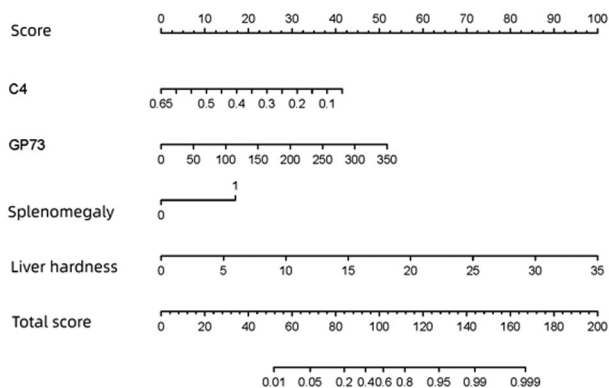


图 2 AILDC 可视化展示

Fig.2 Visual presentation of AILDC

2.5 AILDC 与其它无创指标的比较

Delong 检验显示 AILDC 的 ROC 曲线及 AUC(图 3,表 3)

明显优于其他指标及单纯肝硬度指标,差异具有统计学意义 ($P<0.05$),通过约登指数得出肝硬度预测肝硬化的最佳截断值为 10kpa,AUC 为 0.803 此时预测敏感度为 71.1 %, 特异度为 85.2 %。

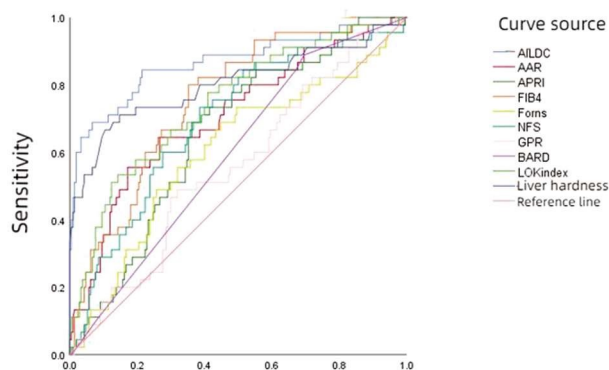


图 3 各个无创指标的 ROC 曲线

Fig.3 ROC curve of each index

表 3 各指标曲线下面积

Table 3 AUC of each index

Name of index	AUC	95% CI
AAR	0.707	0.619-0.794
APRI	0.656	0.575-0.736
FIB4	0.755	0.681-0.828
Fornsindex	0.603	0.507-0.698
NFS	0.693	0.609-0.778
GPR	0.557	0.466-0.647
BARD	0.593	0.508-0.677
LOKindex	0.745	0.664-0.826
LSM	0.803	0.715-0.892
AILDC	0.866	0.795-0.937

2.6 预测模型的校正和验证

预测概率沿 45° 线分布(图 4),具有较高的准确性。由各

指标的临床决策曲线(图 5)可见 AILDC 具有最大的净获益且较其他大部分指标有更好的 NRI 与 IDI(表 4)。

肝硬度

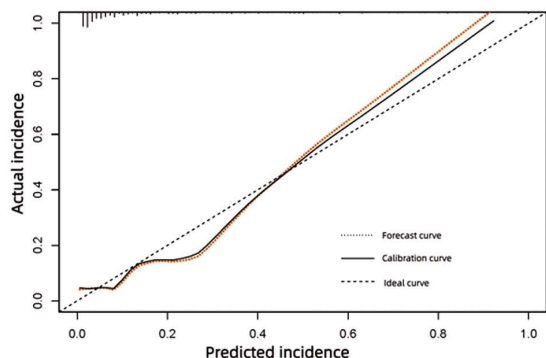


图 4 AILDC 校准曲线

Fig.4 The AILDC calibration curve

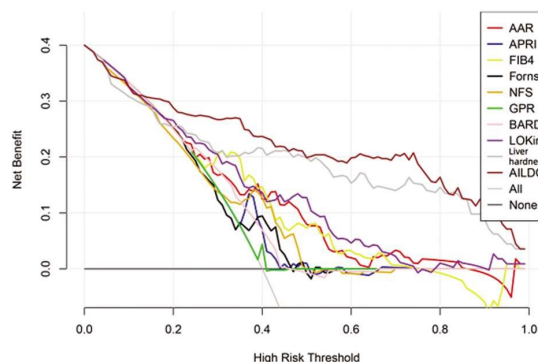


图 5 各个指标的临床决策曲线

Fig.5 Clinical decision curve for each index

3 讨论

本课题研究发现肝硬度测定、脾脏大小与 AILD 纤维化等级较其他常规指标相比,有更高的相关性;并将超声检查指标

与血清学指标进行融合,构建了无创预测模型--AILDC, NRI, IDI, 临床决策曲线方面都展现出较为明显的优势。AILDC 与其他常用的无创预测指标进行比较,在 AUC,

表 4 AILDC 模型与其他指标 NRI 与 IDI 相比的改变值

Table 4 NRI and IDI of each index

Name of index	NRI changes the value	Inspection value	P	IDI changes the value	Inspection value	P
AAR	0.251	2.287	0.022	0.148	1.955	0.051
APRI	0.308	3.069	0.002	0.197	2.853	0.004
FIB4	0.178	2.023	0.043	0.139	1.986	0.047
Forns	0.389	3.763	<0.001	0.225	3.333	0.001
NFS	0.278	2.748	0.006	0.186	2.628	0.009
GPR	0.456	4.083	<0.001	0.239	3.637	<0.001
BARD	0.6	4.527	<0.001	0.256	3.982	<0.001
Lokindex	0.235	2.059	0.039	0.125	1.568	0.117
LSM	0.824	1.83	0.041	0.65	1.421	0.253

2D-SWE 作为近现代的新兴技术,无创估测肝脏硬化程度,已在乙肝、丙肝、酒精肝、非酒精性脂肪肝领域作出了突出贡献,并且寻找出了最佳截断值^[11,17,18]。本研究中 AIL 肝硬化的诊断界值与其他慢性肝病的最佳截断值基本相符,但有部分学者联合肝脾硬度,截断值分别设置为 16.1kpa,29.8kpa 时,AUC 可达 0.93-0.95,该研究将硬度值设置过高,特异度显著提升,但敏感度却比较低,并且因部分未知原因,并未采用同一种弹性测量技术,这样必然导致测量误差^[19]。相较而言,本研究始终采用同一种弹性测量技术,并且在研究过程中,始终使用同一台仪器进行测量,执行测量的人员也局限于具有丰富经验的少数几名超声医生,因此稳定性更强,误差更小。

通过超声观察肝脏包膜及实质回声、胆囊壁、门静脉内径、侧支血管、脾脏大小等对肝脏纤维化程度可作出初步判断;多项研究显示肝包膜呈结节状改变、肝实质回声增粗、脾大可提示 AILD 肝硬化^[20-22]。但考虑评判肝实质回声主观因素影响较大,不能单独评估肝实质纤维化程度。本研究中肝实质回声在硬化组与非硬化组无统计学意义;但脾肿大是预测 AILD 肝硬化发生的独立风险因素。脾脏作为人体内最大的实质储血器官,当脾静脉回流不畅时,导致脾实质增生,因此脾脏肿大常能反映肝脏病变的持续时间与严重程度^[23,24]。

补体系统是先天性免疫系统重要组成部分,在 AILD 患者中,由于免疫系统紊乱,产生自身抗体,血清中补体含量也相应增加^[25,26]。补体 C4 作为 AILD 发病的重要辅助指标,在 AILD 的诊断中起到重要的提示意义^[27]。由于 AILD 发病初期,C4 常显著增高,而在硬化阶段,C4 显著降低,导致差异更加显著。GP73 是常驻高尔基体跨膜蛋白,广泛分布于机体组织内,尤其与肝脏疾病关系密切。以往研究中 GP73 在急慢性肝炎中都成正向表达,并且表达水平与疾病严重程度成正相关^[28]。在 Iftikhar 的研究中发现 GP73 在活化的星状细胞中表达活跃,并且与肝纤维化程度呈正相关^[29],这与本研究结果相似。在另一项 Gateslis 的研究中也发现了 GP73 与肝脏纤维化程度有明显相关性^[30]。

但本研究依然存在以下不足之处,第一本研究系回顾性研究,必然存在选择偏移;第二,病例数虽然较以往研究更多,但依然无法将 AILD 的各个亚型进行细分分析,这也拓宽了模型的应用场景;第三,本研究部分数据存在缺失,因总病例数稀缺,所以采用均值插补法对数据进行补充,补充数据主要为 GP73,在最终的回归结果中,GP73,OR 值 1.014,虽对最终模型影响较小,仍为不足之处;第四,该模型只经过了内部重抽样验证,外部适用性还不得而知,因此,增加研究中心,扩大样本量,对模型进行外部验证,显得尤为重要。

本研究将超声指标与血清学指标有机结合,不仅构建了可视化模型,还寻找了判断 AILD 肝硬化的最佳诊断界值。与其他无创指标相比,具有更高的预测准确性,值得在临床中进一步推广。

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