

• 临床研究 •

aCHANGE 模型: NAFLD 人群显著肝纤维化风险的预测模型

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[摘要] 目的: 针对非酒精性脂肪性肝病(non-alcoholic fatty liver disease, NAFLD)人群开发一个基于血清学标志物预测显著肝纤维化的模型。方法: 选择来自美国国家健康与营养调查(National Health and Nutrition Examination Survey, NHANES)数据库的2 543例NAFLD患者, 以7:3的比例将人群随机分为训练集和内部验证集, 采用SPSS 26.0对训练集和验证集的各项指标进行卡方检验、单因素分析以及二元Logistic回归分析(逐步分析), 得到预测模型, 再在R 4.3.1中进行模型的评价及验证。结果: 年龄、性别、臀围、铁蛋白、天门冬氨酸氨基转移酶(aspartate aminotransferase, AST)、 γ -谷氨酰转移酶(gamma-glutamyl transferase, GGT)、心脏代谢指数(cardiomatabolic index, CMI)是NAFLD患者发生显著肝纤维化的独立危险因素; 预测模型aCHANGE在训练集和验证集都有良好的表现, 其在训练集的受试者工作特征(receiver operating characteristic, ROC)曲线的曲线下面积(area under curve, AUC)为0.775, 在验证集的AUC为0.775, 校准曲线、决策曲线分析(decision curve analysis, DCA)结果均良好。结论: aCHANGE模型有助于预测NAFLD患者出现肝脏显著纤维化的风险。

[关键词] 非酒精性脂肪性肝病; 显著肝纤维化; 预测模型**[中图分类号]** R575.2**[文献标志码]** A**[文章编号]** 1007-4368(2024)08-1092-08**doi:** 10.7655/NYDXBNSN240250

aCHANGE model: a predictive model for the risk of significant liver fibrosis in NAFLD

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[Abstract] **Objective:** To develop a predictive model for significant liver fibrosis based on serological markers in the population with non-alcoholic fatty liver disease (NAFLD). **Methods:** A total of 2 543 NAFLD patients from the he National Health and Nutrition Examination Survey (NHANES) database in the United States were selected. These patients were randomly divided into a training set and an internal validation set in a 7:3 ratio. Chi-square tests, univariate analysis, and binary logistic regression analysis (stepwise) were performed on both sets using SPSS 26.0, followed by model evaluation and validation in R 4.3.1. **Results:** Age, gender, hip circumference, ferritin, aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), and cardiomatabolic index (CMI) were identified as independent risk factor for significant liver fibrosis in NAFLD patients, respectively the predictive model aCHANGE demonstrated good performance in both the training and validation sets, with an area under the curve (AUC) of the receiver operating characteristic (ROC) curve of 0.775 in both sets. The calibration curves and decision curve analysis (DCA) also showed good results. **Conclusion:** The aCHANGE model is useful for predicting the risk of significant liver fibrosis in NAFLD patients.

[Key words] non-alcoholic fatty liver disease; significant liver fibrosis; prediction model

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非酒精性脂肪性肝病(non-alcoholic fatty liver disease, NAFLD)是一种全球患病率约30%的代谢相关性肝病, 与胰岛素抵抗和遗传因素密切相关, 是肝硬化和肝细胞癌的主要原因之一^[1-4]。研究显

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示, NAFLD增加心血管疾病、心肌病、瓣膜钙化和心律失常的风险, 也与结直肠肿瘤的发生和转移相关^[5-7]。目前尚无获批的特效治疗药物, 只能通过改善生活方式和对症治疗进行干预。2020年有专家建议将NAFLD更名为代谢相关性脂肪性肝病(metabolic dysfunction-associated steatotic liver dis-

ease, MASLD), 2023年美国肝病研究学会(AASLD)、欧洲肝脏研究学会(EASL)以及拉丁美洲肝脏研究学会(ALEH)等3个国际区域肝病学会表明支持这一更名。近来研究表明,大多数NAFLD患者符合MASLD标准,研究结果及相关数据在新定义下仍有效^[8-9]。因此,本研究继续以NAFLD群体为对象进行探索。

肝纤维化是肝脏受损后胶原纤维过度沉积导致的肝组织结构和功能异常。研究显示,肝纤维化是预测NAFLD患者长期结局的最关键指标,其分期与总病死率、肝移植和肝相关不良事件紧密相关^[10]。肝活检虽为肝纤维化诊断的金标准,但因其创伤性、高成本和高风险,难以在NAFLD人群中针对肝纤维化进行筛查。此外,也有研究指出肝组织病变的不均匀分布使得肝活检结果不能全面反映肝脏病变^[11],该研究还指出肝纤维化指数(fibrosis 4 score, FIB-4)和天门冬氨酸氨基转移酶(aspartate aminotransferase, AST)与血小板的比值作为无创诊断模型,能够有效评估肝纤维化。但这两个目前广泛应用的模型主要基于慢性肝炎(如慢性病毒性肝炎)患者开发,未充分考虑NAFLD的特点,在NAFLD患者中的适用性和精确度有限。据Grau-pera等^[12]研究指出,当肝脏硬度测试(liver stiffness measurement, LSM) ≥ 8 kPa时,FIB-4的表现不如腰围,且上述两个模型均未涉及炎症指标等其他与NAFLD密切相关的因素,这些都提示临床迫切需求针对NAFLD人群建立有效评估疾病进展和肝纤维化程度及风险的无创诊断模型。鉴于此,探索融合腰围和炎症标志物等新指标建立有效可靠的无创诊断模型,以提高对NAFLD患者肝纤维化的诊断准确性已成为临床研究热点。

心脏代谢指数(cardiometabolic index, CMI)于2015年由Wakabayashi等^[13]提出,通过血脂参数甘油三酯(triglycerides, TG)、高密度脂蛋白(high density lipoprotein, HDL)和腰臀比(waist-to-hip ratio, WHR)评估内脏肥胖,定义为 $CMI = (TG/HDL) \times WHR$ 。已证实CMI与多种代谢疾病相关^[14-17],特别是心血管、肾脏疾病和高尿酸血症,是评估代谢疾病的重要预测指标。2022年的一项研究发现^[18], CMI是NAFLD的独立危险因素,但其与NAFLD肝纤维化的关系尚未明确。

C反应蛋白(C-reactive protein, CRP)是炎症时肝脏合成的急性期蛋白,而血清白蛋白(albumin, ALB)反映营养状态和肝功能,与炎症状态呈反比。CRP与ALB的比值(CAR)作为新型炎症指标,已关联

多种癌症和疾病预后^[19-22]。CALLY指数结合CRP、ALB和外周血淋巴细胞计数,反映炎症、免疫和营养状况,早期研究表明其与结肠癌预后相关^[23],但CAR和CALLY指数是否与NAFLD进展相关尚未被认知。

综上,为了探索上述新型指标在NAFLD人群中的诊断价值,本研究利用美国国家健康与营养调查(National Health and Nutrition Examination Survey, NHANES)中18~80岁人群的相关资料进行研究分析,并建立NAFLD人群进展为显著肝纤维化的风险预测模型。

1 对象和方法

1.1 对象

NHANES是一项针对美国全国人口的代表性调查,使用复杂、多阶段和概率抽样方法提供有关美国一般人口营养和健康的大量信息^[24]。本研究截取NHANES数据库中2017—2020年新冠病毒大流行前的所有人群的相关资料($n=15\,560$),在总样本中排除:①年龄 <18 岁;②没有完整CMI、ALB、CRP、臀围、LSM、瞬时弹性成像技术诊断的受控衰减参数(controlled attenuation parameter, CAP)资料;③既往诊断过乙型病毒性肝炎或者乙型肝炎病毒表面抗原(HBsAg)阳性,以及既往诊断过丙型病毒性肝炎以及丙型肝炎病毒(HCV)核酸或抗HCV抗体阳性;过量饮酒者(女性饮酒量 >14 标准杯/周或男性饮酒量 >21 标准杯/周)^[25];CAP <274 dB/m者。根据Eddowes等^[26]研究,CAP ≥ 274 dB/m被视为是NAFLD,其在检测所有程度的肝脂肪变性方面具有90%的灵敏度。最终纳入本研究的样本量为2 543例。

1.2 方法

NHANES的工作人员使用装备有502 V2探头的FibroScan[®]对受试者进行振动控制瞬时弹性成像(transient elastography, TE)检查,并记录受试者的CAP值和LSM值。根据Eddowes等^[26]研究,将LSM ≥ 8.2 kPa的人群定义为有显著肝纤维化的人群,LSM <8.2 kPa定义为无显著肝纤维化的人群。本研究的因变量为研究人群是否存在显著肝纤维化。自变量为性别、年龄、受教育程度、种族、臀围(hip circumference, HIP)、白细胞计数(white blood cell count, WBC)、铁蛋白(ferritin)、丙氨酸氨基转移酶(alanine aminotransferase, ALT)、AST、碱性磷酸酶(alkaline phosphatase, ALP)、 γ -谷氨酰转移酶(γ -glutamyl transferase, GGT)、球蛋白(globulin, GLO)、尿酸(uric acid, UA)、总胆固醇(total cholest-

terol, TC)、CMI、CAR、CALLY。

1.3 统计学方法

使用R语言4.3.1版本,对数据进行处理,以7:3随机拆分为训练集以及内部验证集。使用SPSS 26.0版本统计学软件,对训练集以及内部验证集的分类变量做卡方检验,对符合正态分布的连续变量做独立样本*t*检验,不符合正态分布的变量用中位数(四分位数)[*M*(*P*₂₅, *P*₇₅)]表示,最后根据卡方检验、*t*检验及秩和检验结果,并结合临床实际在训练集中调整混杂因素行多因素二元Logistic逐步回归分析,剔除了冗杂的自变量得到最终简化的临床预测模型。得到模型后使用R语言4.3.1版本,对模型

进行评价,包括绘制本临床预测模型的列线图、ROC曲线、校准曲线、临床决策曲线,并在内部验证集对预测模型进行验证。*P* < 0.05为差异有统计学意义。

2 结 果

2.1 研究人群的基线特征

根据LSM结果,将训练集和验证集的NAFLD患者分为无显著肝纤维化者(LSM<8.2 kPa)和显著肝纤维化者(LSM≥8.2 kPa)两类。所有纳入研究的NAFLD患者临床特征具体分析及单因素分析结果见表1。

表1 研究人群的临床特征
Table 1 Clinical characteristics of the study population

Index	Training set		<i>P</i>	Internal validation set		<i>P</i>
	No significant fibrosis (LSM<8.2 kPa, <i>n</i> =1 463)	Increased fibrosis and above (LSM≥8.2 kPa, <i>n</i> =317)		No significant fibrosis (LSM<8.2 kPa, <i>n</i> =626)	Increased fibrosis and above (LSM≥8.2 kPa, <i>n</i> =137)	
Sex(%)			0.016			0.830
Male	80.1	19.9		82.3	17.7	
Female	84.5	15.5		81.7	18.3	
Age(year, $\bar{x} \pm s$)	53.57 ± 16.48	56.56 ± 14.68	0.001	52.78 ± 16.84	54.84 ± 15.73	0.170
Race(%)			0.550			0.300
Mexican American	82.2	17.8		86.7	13.3	
Non-Hispanic Black	80.5	19.5		79.1	20.9	
Non-Hispanic White	81.4	18.6		81.3	18.7	
Other hispanic	84.3	15.7		77.8	22.2	
Other race	84.9	15.1		85.9	14.1	
Education(%)			0.140			0.430
Below high school level	82.4	17.6		84.4	15.6	
High school level	78.7	21.3		78.8	21.2	
Above high school level	83.2	16.8		82.2	17.8	
HIP(cm, $\bar{x} \pm s$)	111.03 ± 13.69	122.31 ± 17.16	<0.001	111.64 ± 13.73	124.55 ± 18.72	<0.001
WBC (10 ⁹ /L, $\bar{x} \pm s$)	7.37 ± 2.08	7.78 ± 2.22	0.003	7.42 ± 2.07	8.11 ± 2.48	0.003
Ferritin(ng/mL)	123.00(63.00, 219.00)	149.00(73.85, 256.50)	0.003	119.00(61.75, 227.50)	126.00(64.65, 243.50)	0.358
ALT[U/L, <i>M</i> (<i>P</i> ₂₅ , <i>P</i> ₇₅)]	20.00(15.00, 28.00)	23.00(16.00, 35.00)	<0.001	21.00(15.00, 29.25)	23.00(16.00, 37.50)	0.010
AST[U/L, <i>M</i> (<i>P</i> ₂₅ , <i>P</i> ₇₅)]	19.00(16.00, 24.00)	21.00(17.00, 28.00)	<0.001	20.00(16.00, 25.00)	21.00(17.00, 27.50)	0.026
ALP(U/L, $\bar{x} \pm s$)	80.32 ± 24.28	84.67 ± 28.78	0.013	80.56 ± 25.72	84.74 ± 25.69	0.086
GGT[U/L, <i>M</i> (<i>P</i> ₂₅ , <i>P</i> ₇₅)]	24.00(17.00, 34.00)	28.00(21.00, 52.00)	<0.001	24.00(17.00, 34.00)	31.00(20.00, 54.00)	<0.001
GLO(g/L, $\bar{x} \pm s$)	30.98 ± 4.16	31.58 ± 4.41	0.027	30.84 ± 4.15	32.50 ± 5.28	<0.001
UA(μmol/L, $\bar{x} \pm s$)	334.76 ± 84.32	367.65 ± 93.99	<0.001	343.38 ± 87.03	362.87 ± 101.97	0.022
TC(mmol/L, $\bar{x} \pm s$)	2.32 ± 0.10	2.32 ± 0.11	0.550	2.32 ± 0.09	2.33 ± 0.10	0.630
CMI[<i>M</i> (<i>P</i> ₂₅ , <i>P</i> ₇₅)]	0.81(0.49, 1.35)	1.07(0.70, 1.59)	<0.001	0.85(0.55, 1.34)	1.01(0.66, 1.55)	0.017
CAR[<i>M</i> (<i>P</i> ₂₅ , <i>P</i> ₇₅)]	0.06(0.03, 0.14)	0.10(0.04, 0.19)	<0.001	0.07(0.03, 0.13)	0.11(0.05, 0.23)	<0.001
CALLY[<i>M</i> (<i>P</i> ₂₅ , <i>P</i> ₇₅)]	3.44(1.66, 8.00)	2.41(1.15, 5.42)	<0.001	3.31(1.65, 6.72)	2.06(1.04, 4.50)	<0.001

*: Normally distributed data, expressed as $\bar{x} \pm s$. #: Non-normally distributed data, expressed as *M*(*P*₂₅, *P*₇₅).

2.2 对研究变量进行多因素二元Logistic分析

根据单因素分析及结合临床实际后,以性别、年龄、臀围、白细胞计数、铁蛋白、ALT、AST、ALP、GGT、尿酸、球蛋白、CALLY、CAR、CMI等因素为自变量,以NAFLD人群中是否存在显著肝纤维化为因变量行二元Logistic回归分析(逐步回归,表2)。

2.3 预测列线图的建立

本研究通过卡方检验及单因素分析初筛出14个变量,使用逐步Logistic回归分析确定了7个关键变量。这些变量被用于构建预测模型,称之为aCHANGE模型(a: age; C: CMI; H: HIP; A: AST; N: ferritin; G: GGT; E: sex),旨在预测NAFLD患者出现

表2 NAFLD患者是否显著肝纤维化的多因素二元Logistic逐步回归分析结果

Table 2 Results of multivariable binary Logistic stepwise regression analysis for significant liver fibrosis in NAFLD patients

Variable	B	Standard error	Walds	P	Exp(B)	95%CI
Age	0.029	0.005	39.16	<0.001	1.029	1.020-1.039
Sex(male)	0.624	0.153	16.66	<0.001	1.867	1.383-2.519
HIP	0.064	0.005	173.21	<0.001	1.067	1.056-1.077
Ferritin	0.001	0.000	3.99	0.046	1.001	1.000-1.001
AST	0.035	0.007	26.25	<0.001	1.035	1.022-1.049
GGT	0.005	0.002	9.61	0.002	1.005	1.002-1.008
CMI	0.137	0.058	5.59	0.018	1.146	1.024-1.284

显著肝纤维化的风险。模型采用列线图表示(图1),其中首行“Points”用于估算各变量的风险分数,通过变量在“Points”量表上的垂直对应值读取得分,最终在“Total Points”行累加得出总分。根据总分,在底行risk找到患者出现显著肝纤维化的风险百分比。

2.4 模型的验证

2.4.1 预测模型识别能力和准确性评估

对aCHANGE模型进行校准曲线和受试者工作特征(receiver operating characteristic, ROC)曲线分析以验证其准确性和鉴别力。校准曲线在训练集

中表现出良好的一致性(图2A)。ROC曲线分析显示,模型的曲线下面积(area under curve, AUC)为0.775(图3A),表明其具有良好的预测能力。在验证集上,模型的校准曲线(图2B)和ROC曲线(图3B)的结果与训练集相似,进一步确认了模型在预测NAFLD患者显著肝纤维化风险方面的有效性。

2.4.2 预测模型的临床效能评估

通过决策曲线分析(decision curve analysis, DCA)评估临床预测模型的实用性。结果显示,当阈值概率在0~0.975时,使用aCHANGE模型预测NAFLD

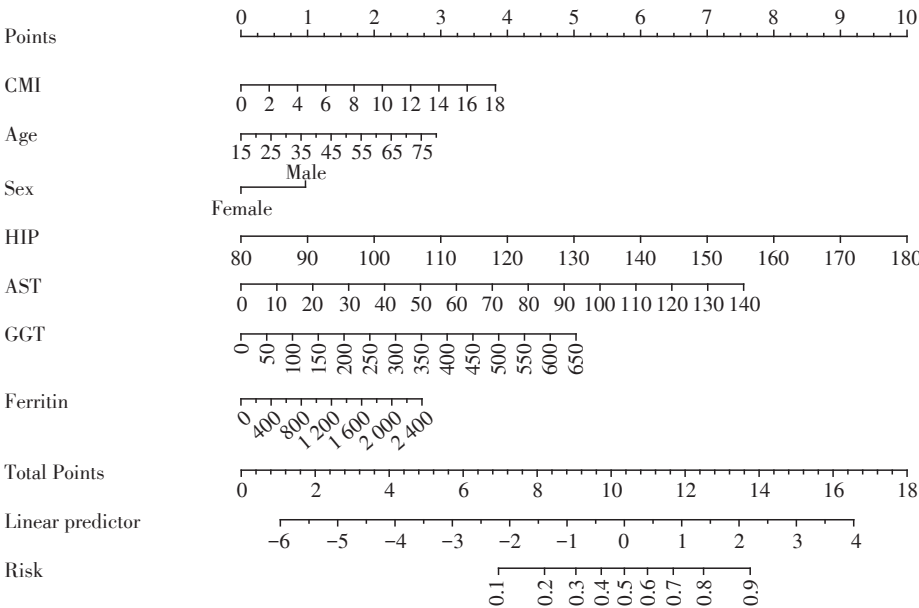
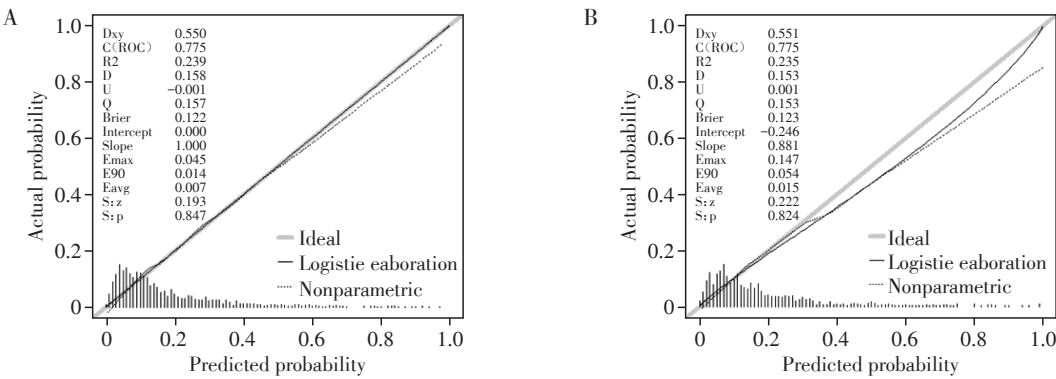


图1 aCHANGE模型的列线图
Figure 1 Nomogram of the aCHANGE model

患者显著肝纤维化的决策具有临床获益(图4)。模型的净获益曲线(红色)位于无干预(None, 蓝色横线)和全面干预(All, 绿色斜线)的极端情况之上, 说明aCHANGE模型比这两种极端假设更能临床提供价值, 有助于准确预测NAFLD患者出现显著肝纤

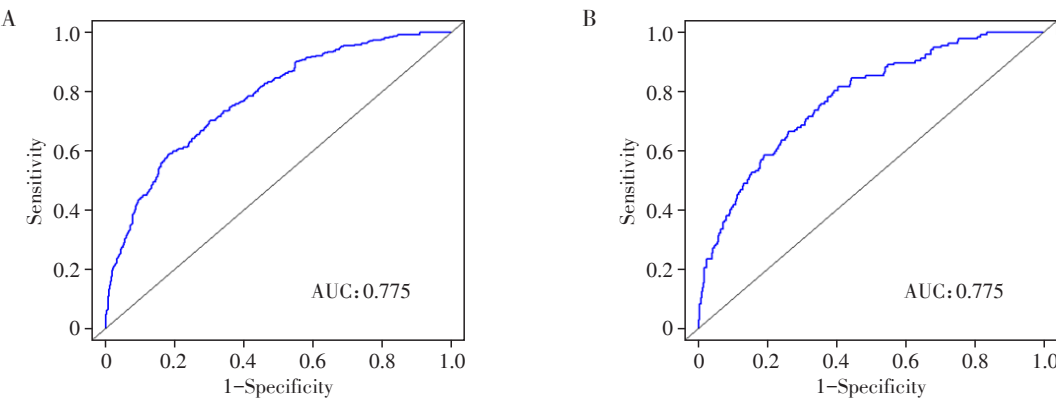
维化的风险。
2.4.3 aCHANGE模型与FIB-4模型预测能力的比较
在训练集以及验证集中计算出FIB-4, 计算公式: $FIB-4 = (AST \times 年龄) / (血小板计数 \times \sqrt{ALT})$, 后利用FIB-4对患者是否出现显著肝纤维化进行预



A: Calibration curve of the training set. B: Calibration curve of the internal validation set.

图2 aCHANGE模型的校准曲线

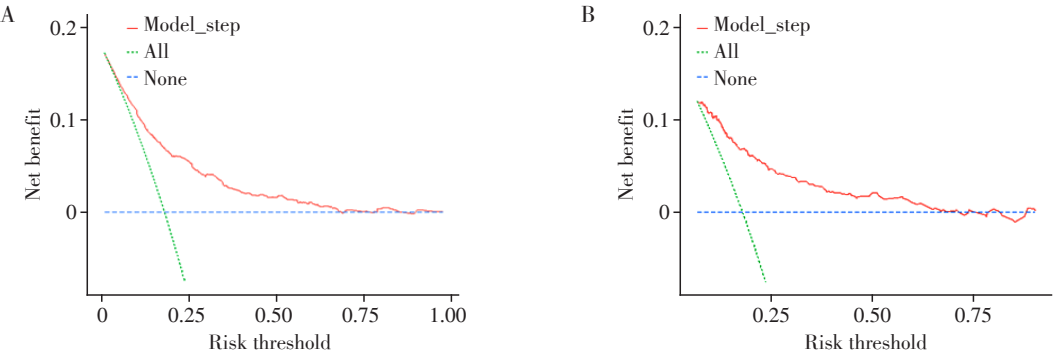
Figure 2 Calibration curve of the aCHANGE model



A: ROC curve of the training set (area under the curve approximately 0.775). B: ROC curve of the internal validation set (area under the curve approximately 0.775).

图3 aCHANGE模型的ROC曲线

Figure 3 ROC curve of the aCHANGE model



A: Clinical DCA on the training set. B: Clinical DCA on the internal validation set.

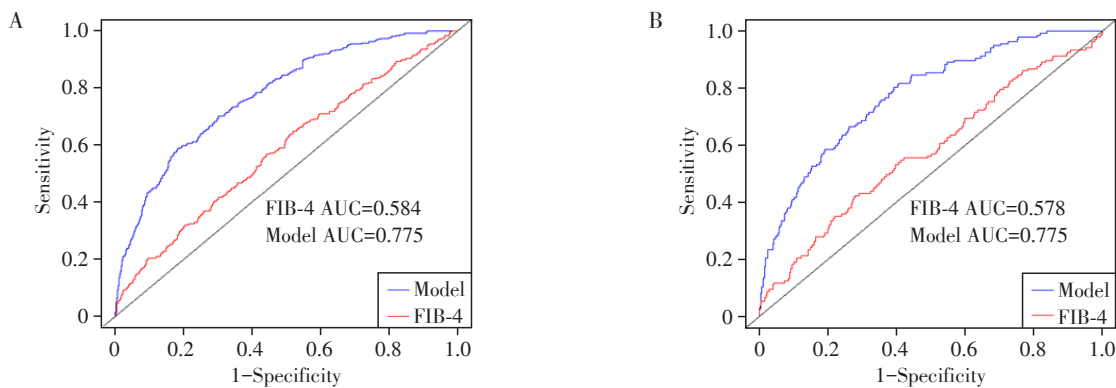
图4 aCHANGE模型的临床决策曲线分析

Figure 4 Clinical DCA of the aCHANGE model

测,并绘制ROC曲线,同时与aCHANGE模型的ROC曲线进行对比(图5),在训练集中aCHANGE模型的AUC为0.775、FIB-4的AUC为0.584,验证集中aCHANGE模型的AUC为0.775、FIB-4的AUC为0.578,可见所建立的模型在NAFLD人群中的预测能力似乎比FIB-4更为良好。

3 讨论

NAFLD是目前最普遍的慢性肝病,研究显示其与年龄增长密切相关^[27],与本研究一致。众多研究证明,NAFLD进展与炎症紧密相关,如肥胖会促进肝脏、脂肪组织和骨骼肌等多个器官组织的炎症反



A: ROC curve of the aCHANGE model and FIB-4 in the training set. B: ROC curve of the aCHANGE model and FIB-4 in the validation set.

图5 aCHANGE模型与FIB-4的ROC曲线比较图

Figure 5 Comparison of ROC curves between the aCHANGE model and FIB-4

应^[28-29],这种全身炎症反应会导致脂质沉积和肝脏脂肪变性,进而触发肝细胞死亡、炎症、纤维化和病理性血管生成^[30]。肥胖引起的全身性低度炎症是其与NAFLD之间的关键连接。可见CMI作为识别肥胖的新指标被纳入本模型中是合理的^[31]。这其中更关键的是慢性肝脏炎症,它在良性肝脏脂肪变性向非酒精性脂肪性肝炎(NASH)转换中发挥决定性作用,其通过持续的低水平促炎症因子如肿瘤坏死因子(tumor necrosis factor, TNF)、白介素(interleukin, IL)-6和IL-1 β 产生,导致肝损伤和纤维化,进而促进NASH发展。如上述,炎症在NAFLD发展中起着关键作用^[28-29, 32-36]。由于缺乏针对此炎症的特效药物,及时筛选出显著肝纤维化的高风险人群进行生活方式干预和治疗至关重要。本研究构建的aCHANGE模型是针对NAFLD人群开发的,包括了年龄、性别、臀围、铁蛋白、AST、GGT和CMI这7个与炎症、肥胖及年龄相关的变量,并据此绘制了列线图。

列线图是一种预后方法,可以提高准确性,使预后更容易理解,从而产生更好的临床决策,现在已广泛应用于肿瘤学和其他医学学科^[37-39]。列线图将复杂难懂且需要高级数学算法计算的统计回归方程转换为可视化图像,方便临床工作者无需使用计算机就可完成繁琐的临床预测,操作过程快速简

单,便于临床医生在评估患者状况时能及时获取相关疾病的数据信息。本研究将年龄、性别、臀围、铁蛋白、AST、GGT、CMI这7个变量纳入列线图预测模型用于预测NAFLD患者出现显著肝纤维化的风险,从而构建了针对NAFLD人群的aCHANGE预测模型。本研究构建的列线图预测模型经过验证队列验证,也提示本研究所建立的预测模型具有良好的鉴别能力和准确性。

即便是经过良好验证的临床预测模型,由于临床治疗方法以及疾病动态发展、尚未明确的危险因素等随时间变化,模型性能下降,即临床预测模型校准度出现了漂移^[40-41]。因此,临床预测模型需要定期更新和优化以保持其准确性。本研究针对NAFLD人群构建的模型为临床医生提供了一个有效的工具,帮助早期识别肝脏显著纤维化风险,从而实现早期预警、筛查和治疗,优化患者管理。本研究的优势:首先,样本量大且具有美国全国代表性,增加了结果的可信度;其次,所用变量易于基层医院获取,有助于NAFLD快速筛查和及时治疗;最后,模型包括代谢和炎症相关指标,是针对NAFLD人群所开发的。后续将继续完善研究,拓展至普通人群并进行肝活检验证。本研究仍然存在几个局限。首先,由于是横断面研究,无法确定因果关系;其次,NHANES数据库未包含用药情况,可能未完全

反映实际情况;第三,肝脏状况评估基于瞬时弹性成像技术诊断,而非金标准肝活检,可能存在偏差。

综上,年龄、性别、臀围、铁蛋白、AST、GGT、CMI均是NAFLD患者出现肝脏显著纤维化的独立危险因素。aCHANGE模型是基于逐步Logistic回归构建的临床预测模型,在训练集和验证集中均具有良好的区分度、准确性和临床实用性。该临床模型有助于预测NAFLD患者出现显著肝脏纤维化的风险。

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