

· 胰腺疾病 ·

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影像学定量参数联合血清肿瘤标志物对胰腺导管腺癌术后预后的评估价值

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摘要: **目的** 探讨影像学定量参数联合血清肿瘤标志物构建的预测模型在胰腺导管腺癌(PDAC)患者术后预后评估中的应用价值。**方法** 回顾性选取2020年4月—2023年3月于河北医科大学第四医院接受根治性切除术治疗的146例PDAC患者为研究对象,采用完全随机法将患者按照7:3的比例分为训练集($n=102$)和验证集($n=44$)。所有患者进行增强计算机断层成像(CT)以及多参数磁共振成像扫描,记录动脉期、静脉期和延迟期CT值以及b值为800 s/mm²的表观扩散系数(ADC)、T₂加权成像的信号强度(SI);检测患者血清糖类抗原19-9(CA19-9)及癌胚抗原(CEA)水平。计量资料两组间比较采用成组 t 检验;计数资料两组间比较采用 χ^2 检验。Kaplan-Meier法绘制生存曲线,生存情况的比较采用Log-rank检验;采用单因素及多因素Logistic分析评估各临床及影像学指标与预后的关系,并采用最小绝对值收敛和选择算子(LASSO)-Cox回归模型筛选影响患者预后的重要因素,构建预后预测模型。采用受试者操作特征曲线分析该模型在训练集和验证集中的预后预测价值。**结果** Kaplan-Meier生存曲线分析显示,训练集患者的中位生存时间为33.00个月,验证集患者的中位生存时间为32.00个月,差异无统计学意义($P>0.05$)。单因素分析结果显示,患者年龄、分化程度、淋巴结转移、肿瘤分期、血管侵犯、CA19-9、CEA、ADC及SI与患者生存预后有关(χ^2 值分别为5.906、13.116、12.807、17.277、14.611、7.275、14.339、9.506、13.137, P 值均 <0.05)。LASSO-Cox多因素回归分析显示,6个因素进入回归模型:肿瘤分期[风险比(HR)=8.934, 95%CI: 3.215 ~ 21.562, $P<0.001$]、淋巴结转移($HR=2.971$, 95%CI: 1.298 ~ 5.647, $P=0.002$)、CA19-9($HR=3.948$, 95%CI: 1.758 ~ 8.994, $P<0.001$)、CEA($HR=1.965$, 95%CI: 1.083 ~ 3.664, $P=0.039$)、ADC($HR=2.873$, 95%CI: 1.307 ~ 6.037, $P=0.003$)及SI($HR=3.107$, 95%CI: 1.264 ~ 7.339, $P=0.001$)。基于上述指标构建的列线图模型在训练集中的预测曲线下面积为0.845[95%置信区间(CI): 0.774 ~ 0.915],在验证集中的曲线下面积为0.919(95%CI: 0.870 ~ 0.967)。**结论** 基于LASSO-Cox回归构建的影像学定量参数-血清标志物联合模型可有效预测PDAC患者术后预后,有助于识别高风险患者,从而指导辅助治疗决策。

关键词: 胰腺肿瘤; 体层摄影术, X线计算机; 多参数磁共振成像; 生物标记, 肿瘤; 预后**基金项目:** 河北省医学科学研究课题(20260565)

Value of quantitative imaging parameters combined with serum tumor markers in prognostic evaluation after pancreatic ductal adenocarcinoma surgery

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Abstract: Objective To investigate the application value of a predictive model constructed based on quantitative imaging parameters and serum tumor markers in predicting the postoperative prognosis of patients with pancreatic ductal adenocarcinoma (PDAC). **Methods** A retrospective study was conducted among 146 patients with PDAC who underwent radical resection in Hebei Medical University Fourth Hospital from April 2020 to March 2023, and the patients were divided into a training set with 102 patients and a validation set of 44 patients at a ratio of 7:3 using the completely randomized method. All patients underwent

enhanced computed tomography (CT) and multi-parametric magnetic resonance imaging scans, and CT values in the arterial phase, the venous phase, and the delayed phase were recorded, as well as apparent diffusion coefficient (ADC) at $b = 800 \text{ s/mm}^2$ and signal intensity (SI) of T_2 weighted imaging. The serum levels of carbohydrate antigen 19-9 (CA19-9) and carcinoembryonic antigen (CEA) were also measured. The independent-samples t test was used for comparison of continuous data between groups, and the chi-square test was used for comparison of categorical data between groups. Kaplan-Meier survival curves were plotted for survival analysis; the univariate and multivariate Logistic regression analysis was used to investigate the association of clinical and imaging indicators with prognosis; the least absolute shrinkage and selection operator (LASSO)-Cox regression model was used to identify the important influencing factors for prognosis, and a prognostic prediction model was constructed. The receiver operating characteristic (ROC) curve was used to analyze the predictive value of the model in predicting prognosis in both the training set and the validation set. **Results** The Kaplan-Meier survival curve analysis showed a median survival time of 33.00 months in the training set and 32.00 months in the validation set, with no significant difference between the training set and the validation set ($P > 0.05$). The univariate analysis showed that patient age, degree of tumor differentiation, lymph node metastasis, tumor stage, vascular invasion, CA19-9, CEA, ADC value, and SI value were significantly associated with the survival prognosis of patients ($\chi^2 = 5.906, 13.116, 12.807, 17.277, 14.611, 7.275, 14.339, 9.506$, and 13.137 , all $P < 0.05$). The LASSO-Cox multivariate regression analysis showed that six factors were incorporated into the regression model, i.e., tumor stage ($HR = 8.934$, $95\%CI: 3.215 - 21.562$, $P < 0.001$), lymph node metastasis ($HR = 2.971$, $95\%CI: 1.298 - 5.647$, $P = 0.002$), CA19-9 ($HR = 3.948$, $95\%CI: 1.758 - 8.994$, $P < 0.001$), CEA ($HR = 1.965$, $95\%CI: 1.083 - 3.664$, $P = 0.039$), ADC value ($HR = 2.873$, $95\%CI: 1.307 - 6.037$, $P = 0.003$), and SI value ($HR = 3.107$, $95\%CI: 1.264 - 7.339$, $P = 0.001$). The nomogram model constructed based on these factors had an area under the ROC curve of 0.845 ($95\%CI: 0.774 - 0.915$) in the training set and 0.919 ($95\%CI: 0.870 - 0.967$) in the validation set. **Conclusion** The combined model of quantitative imaging parameters and serum tumor markers constructed based on LASSO-Cox regression can effectively predict the postoperative prognosis of PDAC patients, thereby helping to identify high-risk patients and guide decision-making for adjuvant therapy.

Key words: Pancreatic Neoplasms; Tomography, X-Ray Computed; Multiparametric Magnetic Resonance Imaging; Biomarkers, Tumor; Prognosis

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胰腺导管腺癌(pancreatic ductal adenocarcinoma, PDAC)是一种起源于胰腺导管上皮的高度恶性肿瘤,约占全部胰腺恶性肿瘤的90%,具有极高致死率^[1-2]。目前,根治性切除术是PDAC患者实现远期生存获益的唯一方法,但术后肿瘤局部复发或远处转移的发生率较高,导致患者术后5年生存率仅为20%~25%^[3-4]。现阶段,PDAC患者的预后评估主要依赖TNM分期系统和血清肿瘤标志物[如糖类抗原(carbohydrate antigen, CA)19-9、CA242],但单一指标存在明显局限性:血清肿瘤标志物易受胆道梗阻等非肿瘤因素干扰,特异性仅为61.7%~83.3%;同时,对于同一分期的患者预后也存在较大差异^[5]。医学影像学检查,如计算机体层成像(computed tomography, CT)、磁共振成像(magnetic resonance imaging, MRI)等,在PDAC的临床诊疗中具有重要作用,但传统影像学对微转移灶的识别敏感度较低,对淋巴结转移的术前误判率高达40%。随着精准医学的发展,多参数MRI通过提取肿瘤异质性特征[如表

观扩散系数(apparent diffusion coefficient, ADC)、纹理参数等],对淋巴结转移的预测准确率已达92.3%^[6-7]。

为进一步提高PDAC患者术后预后的预测效能,本研究旨在构建基于影像学定量参数与血清标志物的预后模型,提高对患者术后预后的预测准确性,从而为术后早期个体化辅助治疗提供客观依据,改善患者临床预后。

1 资料与方法

1.1 研究对象 采用回顾性研究设计,选取2020年4月—2023年3月河北医科大学第四医院收治的146例接受根治性切除术的PDAC患者为研究对象。参考机器学习及临床预测模型构建中常用的样本拆分方式,采用完全随机法将患者按照7:3的比例分为训练集($n=102$)和验证集($n=44$)。

1.2 纳入与排除标准 纳入标准:(1)术后病理诊断确认为PDAC;(2)术前2周内完成增强CT与多参数MRI检查,且图像质量符合影像组学分析要求;(3)术前或穿

刺检查前72 h内完成血清肿瘤标志物CA19-9、癌胚抗原(carcinoembryonic antigen, CEA)检测;(4)临床、随访资料完整。排除标准:(1)术前接受过全身或局部抗肿瘤治疗;(2)合并其他恶性肿瘤;(3)围术期死亡(生存期<30 d);(4)合并活动性胰腺炎或胆道梗阻未解除。

1.3 检查方法 (1)增强CT扫描:采用GE 256层 Revolution CT扫描仪对患者进行扫描,管电压设置为120 kV,管电流200~250 mA,层厚0.6~1.0 mm,螺距0.8~1.0,视野300 mm×300 mm。常规扫描完成后,经指静脉注射对比剂碘佛醇(350 mgI/mL),注射速度为2.0~2.5 mL/s。分别于注射后25、40~60和180 s进行动脉期、静脉期与延迟期扫描,并记录不同时期CT值。(2)多参数MRI扫描:采用3.0 T MRI扫描仪(Discovery MR 750, GE, 美国),分别对患者胰腺横断面进行T₂加权成像(T₂-weighted imaging, T₂WI)及T₁WI扫描,扫描序列采用自旋回波-平面回波成像,回波时间73 ms,重复时间6 000 ms,层厚5 mm,视野380 mm×380 mm,层间距1 mm。分别测量b值为800 s/mm²的ADC、T₂WI信号强度(signal strength indication, SI)。

1.4 随访 患者出院后采取来院回访、电话、邮件、微信等多种方式进行随访,以患者死亡作为随访终点事件,随访截止日期为2025年3月1日,记录患者总体生存时间。

1.5 统计学方法 采用SPSS 27.0统计软件进行数据分析。计量资料以 $\bar{x} \pm s$ 表示,两组间比较采用成组 t 检验;计数资料两组间比较采用 χ^2 检验。Kaplan-Meier法绘制生存曲线,生存情况比较采用Log-rank检验;采用R语言中Glmnet包进行最小绝对值收敛和选择算子(least absolute shrinkage and selection operator, LASSO)特征筛选,采用Cox多因素回归分析筛选预后影响因素,并使用R语言构建预后列线图模型;采用受试者操作特征曲线评估模型对患者预后的预测价值。 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 一般资料 训练集与验证集患者在临床资料、血清肿瘤标志物水平、CT值、ADC、SI方面比较,差异均无统计学意义(P 值均>0.05)(表1)。

2.2 生存曲线分析 训练集患者的中位生存时间为33.00个月,验证集患者的中位生存时间为32.00个月,两组间差异无统计学意义($P>0.05$)(图1、2)。

2.3 训练集患者生存预后的单因素分析 单因素分析

结果显示,性别、高血压、糖尿病、肿瘤最大径、肿瘤位置、平扫CT值、动脉期CT值、门静脉期CT值和延迟期CT值与患者生存预后无关(P 值均>0.05),而患者年龄、分化程度、淋巴结转移、肿瘤分期、血管侵犯、CA19-9、CEA、ADC和SI是影响患者生存预后的因素(P 值均<0.05)(表2)。

2.4 基于LASSO回归的特征参数筛选 基于训练集,采用LASSO回归模型筛选特征参数,共筛选出6个与患者预后相关的特征参数,包括肿瘤分期、淋巴结转移、CA19-9、CEA、ADC和SI(图3)。

2.5 基于LASSO-Cox回归的多因素分析 基于上述LASSO回归筛选出的6个参数进一步建立Cox回归模型,结果显示,肿瘤分期、淋巴结转移、CA19-9、CEA、ADC和SI为影响患者生存预后的危险因素(P 值均<0.05)(表3)。

2.6 列线图预后预测模型的构建 采用R语言的rms包构建列线图模型,并对模型进行可视化。模型的一致性指数为0.820(95%CI:0.800~0.839),提示模型具有较好的预测精度(图4)。

2.7 列线图模型对患者预后的预测效能评估 采用受试者操作特征曲线评估列线图模型对训练集和验证集患者预后的预测效能。结果显示,该模型对训练集患者预后的预测曲线下面积(area under curve, AUC)为0.845(95%CI:0.774~0.915),对验证集患者预后的AUC为0.919(95%CI:0.870~0.967)(图5)。

3 讨论

PDAC作为恶性程度最高的消化道肿瘤之一,患者术后5年生存率较低,且手术切除后仍面临较高的复发风险^[8]。传统的预后评估主要依赖患者病理分期以及血清CA19-9水平,但仍存在评估维度单一、预测精度不足等缺点^[9]。近年来,影像组学通过高通量提取CT及MRI图像的纹理特征、功能参数等,可量化肿瘤异质性^[10-12];而血清肿瘤标志物如CA19-9、CEA则可反映肿瘤生物学行为,二者联合应用有望突破现有预后评估的瓶颈,提升对PDAC患者术后预后的预测效能^[13]。本研究通过整合多模态影像组学参数与血清肿瘤标志物,构建预后预测模型,从而为个性化评估患者预后提供新的思路。

相关研究显示,单纯影像学检查对早期PDAC的敏感度仅为60%~70%,而血清CA19-9在胆道梗阻等非肿瘤因素影响下易出现假阳性结果^[14-16]。多层螺旋CT虽

表1 训练集及验证集患者临床资料比较
Table 1 Comparison of clinical data of patients in the training set and the validation set

临床资料	训练集(<i>n</i> =102)	验证集(<i>n</i> =44)	统计值	<i>P</i> 值
性别[例(%)]			$\chi^2=0.186$	0.666
男	48(47.06)	19(43.18)		
女	54(52.94)	25(56.82)		
年龄(岁)	55.23±8.64	54.58±6.59	<i>t</i> =0.446	0.656
高血压[例(%)]	25(24.51)	13(29.55)	$\chi^2=0.405$	0.525
糖尿病[例(%)]	17(16.67)	6(13.64)	$\chi^2=0.213$	0.645
分化程度[例(%)]			$\chi^2=0.251$	0.617
中高分化	67(65.69)	27(61.36)		
低分化	35(34.31)	17(38.64)		
肿瘤最大径(cm)	3.57±1.21	3.74±1.30	<i>t</i> =0.762	0.448
肿瘤位置[例(%)]			$\chi^2=0.059$	0.812
胰头颈部	67(65.69)	28(63.64)		
胰体尾部	35(34.31)	16(36.36)		
淋巴结转移[例(%)]	39(38.24)	15(34.09)	$\chi^2=0.227$	0.634
肿瘤分期[例(%)]			$\chi^2=0.133$	0.715
I期	38(37.25)	15(34.09)		
II~III期	64(62.75)	29(65.91)		
血管侵犯[例(%)]	41(40.20)	17(38.64)	$\chi^2=0.031$	0.860
CA19-9(U/mL)	185.43±53.02	189.28±31.64	<i>t</i> =0.448	0.655
CEA(U/mL)	12.56±4.21	13.04±3.15	<i>t</i> =0.678	0.499
CT值(HU)				
平扫期	34.83±3.19	36.04±3.95	<i>t</i> =1.953	0.053
动脉期	43.87±5.52	41.96±6.03	<i>t</i> =1.865	0.064
门静脉期	54.58±7.93	54.02±8.49	<i>t</i> =0.383	0.702
延迟期	60.21±5.68	59.38±6.10	<i>t</i> =0.792	0.430
ADC(×10 ⁻³ mm ² /s)	1.21±0.31	1.27±0.28	<i>t</i> =1.104	0.272
SI(×10 ⁻³)	0.45±0.09	0.46±0.12	<i>t</i> =0.555	0.580

注:CA19-9,糖类抗原19-9;CEA,癌胚抗原;CT,计算机断层扫描;ADC,表观扩散系数;SI,信号强度。

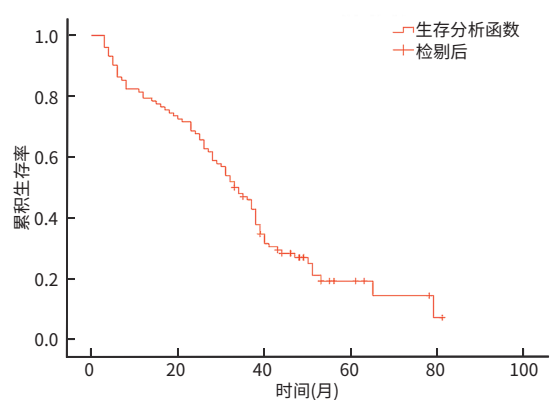


图1 训练集患者生存曲线

Figure 1 Survival curve of patients in the training set

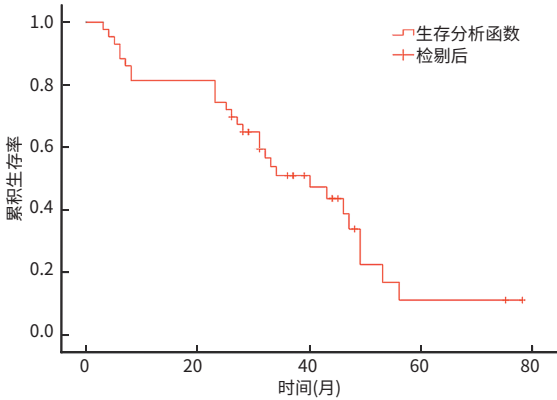


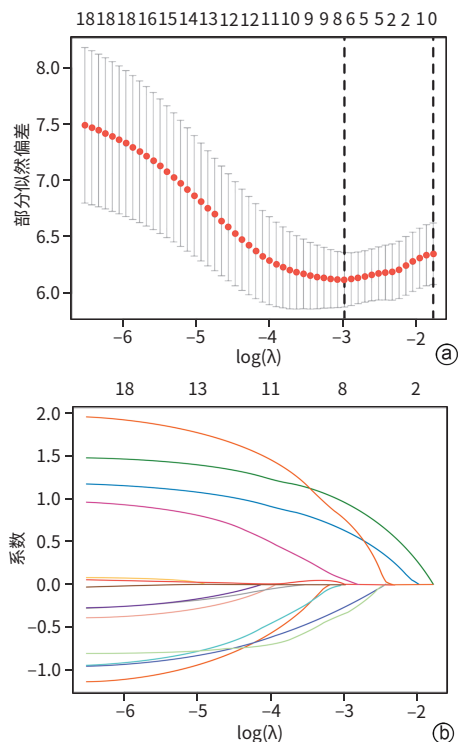
图2 验证集患者生存曲线

Figure 2 Survival curve of patients in the validation set

表2 训练集患者生存预后单因素分析
Table 2 Univariate analysis of survival prognosis of patients in the training set

因素	例数	中位生存期(月)	95%CI	χ^2 值	P值
性别				0.159	0.690
男	48	34.00	27.512 ~ 40.488		
女	54	32.00	22.398 ~ 41.602		
年龄				5.906	0.015
≥55岁	53	28.00	22.650 ~ 33.350		
<55岁	49	38.00	34.193 ~ 41.807		
高血压	25	32.00	23.840 ~ 40.160	0.438	0.508
糖尿病	17	31.00	18.899 ~ 43.101	0.823	0.364
分化程度				13.116	<0.001
中高分化	67	38.00	35.669 ~ 40.331		
低分化	35	23.00	14.443 ~ 31.557		
肿瘤最大径				0.233	0.629
≥3.5 cm	55	34.00	28.627 ~ 39.373		
<3.5 cm	47	28.00	14.806 ~ 41.194		
肿瘤位置				0.273	0.602
胰头颈部	67	34.00	28.092 ~ 39.908		
胰体尾部	35	33.00	22.706 ~ 43.294		
淋巴结转移	39	24.00	16.658 ~ 31.342	12.807	<0.001
肿瘤分期				17.277	<0.001
I期	38	43.00	34.006 ~ 51.994		
II ~ III期	64	28.00	23.569 ~ 32.431		
血管侵犯	41	25.00	19.772 ~ 30.228	14.611	<0.001
CA19-9				7.275	0.007
≥185 U/mL	56	26.00	19.714 ~ 32.286		
<185 U/mL	46	39.00	33.412 ~ 44.588		
CEA				14.339	0.001
≥12 U/mL	54	24.00	17.827 ~ 30.173		
<12 U/mL	48	40.00	37.408 ~ 42.592		
平扫期CT值				1.170	0.279
≥34 HU	59	32.00	23.577 ~ 40.423		
<34 HU	43	35.00	29.493 ~ 40.507		
动脉期CT值				0.830	0.362
≥43 HU	61	36.00	30.265 ~ 41.735		
<43 HU	41	29.00	20.934 ~ 37.066		
门静脉期CT值				0.072	0.788
≥54 HU	63	34.00	28.920 ~ 39.080		
<54 HU	39	32.00	21.115 ~ 42.885		
延迟期CT值				0.802	0.370
≥60 HU	57	37.00	26.994 ~ 47.006		
<60 HU	45	32.00	26.840 ~ 37.160		
ADC				9.506	0.002
≥ $1.2 \times 10^{-3} \text{ mm}^2/\text{s}$	60	38.00	35.501 ~ 40.499		
< $1.2 \times 10^{-3} \text{ mm}^2/\text{s}$	42	27.00	20.649 ~ 33.351		
SI				13.137	0.001
≥ 0.45×10^{-3}	58	26.00	19.506 ~ 32.494		
< 0.45×10^{-3}	44	39.00	35.856 ~ 42.144		

注:CA19-9,糖类抗原19-9;CEA,癌胚抗原;CT,计算机体层成像;ADC,表观扩散系数;SI,信号强度;CI,置信区间。



注:a,交叉验证曲线;b,系数路径图。

图3 胰腺导管腺癌术后预后最小绝对值收敛和选择算子回归变量筛选

Figure 3 The minimum absolute contraction and selection operator regression variable screening for prognosis after pancreatic ductal carcinoma surgery

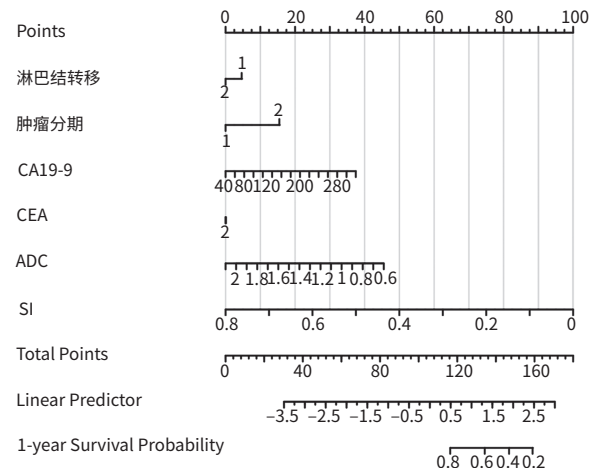
表3 胰腺导管腺癌术后预后Cox多因素回归分析
Table 3 Cox multivariate regression analysis of prognosis after pancreatic ductal adenocarcinoma surgery

因素	HR	95%CI	P值
肿瘤分期	8.934	3.215 ~ 21.562	<0.001
淋巴结转移	2.971	1.298 ~ 5.647	0.002
CA19-9	3.948	1.758 ~ 8.994	<0.001
CEA	1.965	1.083 ~ 3.664	0.039
ADC	2.873	1.307 ~ 6.037	0.003
SI	3.107	1.264 ~ 7.339	0.001

注:CA19-9,糖类抗原19-9;CEA,癌胚抗原;ADC,表观扩散系数;SI,信号强度;HR,风险比;CI,置信区间。

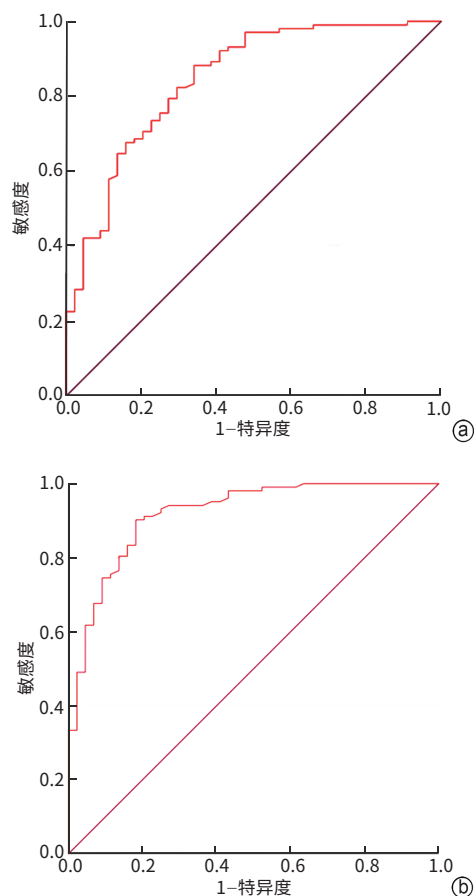
然可评估肿瘤形态学特征,但难以捕捉肿瘤内部的分子水平异质性^[17-18];弥散加权成像-MRI可通过ADC反映细胞密度,但无法全面评估肿瘤代谢活性^[19-21]。本研究通过整合不同时期CT值、ADC、SI等多参数影像特征,同时结合CA19-9、CEA血清学数据,实现了结构与功能维度的互补验证。

本研究采用LASSO-Cox回归模型,通过正则化过程有效控制了模型过拟合风险,并筛选出具有独立预后价



注:CA19-9,糖类抗原19-9;CEA,癌胚抗原;ADC,表观扩散系数;SI,信号强度。

图4 胰腺导管腺癌术后预后预测列线图模型
Figure 4 Nomogram model for predicting prognosis after pancreatic ductal adenocarcinoma surgery



注:a,训练集;b,验证集。

图5 模型对训练集和验证集患者预后预测价值的受试者操作特征曲线分析
Figure 5 ROC curve analysis of the model to evaluate its predictive value for the prognosis of patients in the training set and patients in the validation set

值的6个关键因素。尽管单因素分析提示,年龄与血管侵犯是患者预后的影响因素(P 值均 <0.05),但在多因素框架下,其预测信息可能已被其他更强或相关性更高的变量(如肿瘤分期、淋巴结转移等)所覆盖,因此未纳入最终模型。该结果提示,在综合模型中,肿瘤分期、淋巴结转移、CA19-9、CEA、ADC及SI对患者预后具有更强的独立贡献。模型纳入的6个关键因素中,ADC与SI作为影像学的代表参数,与血清肿瘤标志物CA19-9、CEA共同构成预测模型的核心。值得注意的是,ADC($b=800\text{ s/mm}^2$)与肿瘤细胞密度呈显著负相关,低ADC提示细胞增殖活跃、预后较差,这与弥散加权成像研究理论一致^[22-23]; T_2 WI的SI则可反映肿瘤间质纤维化程度,高SI往往对应更强的局部侵袭性^[24-25]。血清CA19-9升高时患者预后显著恶化,其机制可能涉及肿瘤负荷增加以及胆道排泄障碍的双重作用^[26-27]。基于上述独立预后因素构建的列线图模型,将抽象的风险概率可视化,更利于临床医师对患者进行术后分层管理。该模型在训练集和验证集中,对患者预后预测的AUC均超过0.8,提示该模型可有效提升对PDAC患者术后预后的预测价值。通过该模型快速分辨高风险患者,以1年生存率80%作为临界值,将模型评分 <115 分作为低风险组, ≥ 115 分作为高风险组。针对高风险患者,需加强患者临床监测,并采取积极的治疗手段,以尽可能改善患者生存预后。

本研究存在一定局限性。作为单中心研究,纳入样本量相对较小,研究结果可能存在选择偏倚。未来研究将扩大样本量且开展多中心验证,以进一步提升模型的稳定性及临床应用价值。此外,本研究的动脉期、静脉期及延迟期CT值在单因素分析中均未显示出与PDAC患者术后预后的关系(P 值均 >0.05)。这一结果与部分既往研究结论存在差异,可能与纳入对象以及CT扫描设备、对比剂注射方案、扫描时相等因素有关。本研究纳入的均为接受根治性切除术的患者,肿瘤相对局限,其血供特征可能与晚期肿瘤存在差异。此外,胰腺癌具有高度异质性,单纯依靠CT值难以全面反映其血流动力学特征,尤其是微血管浸润及肿瘤间质成分的影响。尽管多时相CT值在本研究队列中未显示出独立预后价值,但其在术前肿瘤分期、可切除性评估及鉴别诊断中仍具有重要临床意义。未来研究可进一步结合动态增强CT定量参数、能谱CT特征以及影像组学方法,更全面地评估肿瘤血流及组成特征,从而提高其对预后预测的贡献价值。

综上所述,本研究基于LASSO-Cox回归构建的影像

学定量参数-血清标志物联合模型,可有效预测PDAC患者术后预后,有助于临床识别高风险患者,从而指导辅助治疗决策。

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