

儿童腺病毒肺炎严重程度预测列线图的构建及验证

孙小艳 赵淑玲 王晓莹

【摘要】目的 开发一款用于指导临床准确评估儿童腺病毒肺炎严重程度的列线图模型, 并进行验证。**方法** 采用回顾性、横断面临床观察法, 纳入2019年8月至2021年8月于徐州医科大学附属徐州儿童医院诊断为腺病毒肺炎患儿共128例为研究对象, 均符合儿童腺病毒性肺炎诊断和治疗指南(2019版)的标准; 住院期间参照社区获得性肺炎诊断标准分为重症组(50例)和非重症组(78例), 比较两组患儿的性别、年龄、体重、是否早产、发热持续时间、体温峰值、有无基础疾病、血清白细胞计数、中性粒细胞和淋巴细胞百分比、C-反应蛋白(CRP)、乳酸、白细胞介素(IL)-6、乳酸脱氢酶(LDH)、降钙素原(PCT)、CD4⁺T和CD8⁺T淋巴细胞百分比、CD4⁺/CD8⁺T、CD16⁺CD56⁺和CD19⁺T淋巴细胞百分比、有无混合感染。采用LASSO回归法对危险因素进行降维处理, 采用多因素Logistic回归分析筛选独立危险因素, 根据回归系数(β)绘制列线图预测模型。采用受试者工作曲线(ROC)计算模型预测重症腺病毒肺炎(SAP)曲线下面积(AUC), Hosmer-Lemeshow检验评估模型的拟合优度, Calibration曲线和Decision曲线评估模型的一致性和获益性。**结果** 与非重症组比较, 重症组患儿发热持续时间延长[5.2(3.0, 8.5) d vs. 2.9(1.0, 5.0) d: $Z = 8.326, P < 0.001$], IL-6 [45.6(35.4, 56.9) pg/ml vs. 30.2(25.2, 38.6) pg/ml: $Z = 15.326, P < 0.001$]和LDH水平[452.6(385.6, 523.4) U/L vs. 365.9(302.1, 445.2) U/L: $Z = 9.625, P < 0.001$]升高、CD4⁺T [31.2(27.8, 34.2)% vs. 35.5(33.2, 38.9)%: $Z = 7.526, P < 0.001$]和CD4⁺/CD8⁺T水平[1.2(1.0, 1.4) vs. 1.4(1.1, 1.6): $Z = 5.230, P = 0.004$]下降、混合感染率增多[46.0%(23/50) vs. 19.2%(15/78): $\chi^2 = 10.460, P = 0.001$]。LASSO回归共筛选出4个具有非零系数特征的变量, 即发热持续时间、IL-6浓度、CD4⁺T淋巴细胞百分比和混合感染。多因素Logistic回归分析显示, 发热持续时间(OR = 3.125, 95%CI: 2.565~3.896, $P < 0.001$)、IL-6浓度(OR = 2.012, 95%CI: 1.428~2.639, $P < 0.001$)、CD4⁺T淋巴细胞百分比(OR = 0.369, 95%CI: 0.124~0.678, $P = 0.009$)和混合感染(OR = 1.457, 95%CI: 1.124~1.895, $P = 0.001$)均为SAP的独立危险因素。建立列线图模型总分160分, ROC显示列线图预测SAP的AUC值为0.852(95%CI: 0.779~0.901, $P < 0.001$)。Hosmer-Lemeshow检验值为0.786, 提示模型拟合优度较高。Calibration曲线和Decision曲线显示模型一致性和获益性尚可。**结论** 影响儿童腺病毒肺炎严重程度的主要因素有发热持续时间、IL-6浓度、CD4⁺T淋巴细胞百分比和混合感染, 以此开发的列线图预测模型来评估SAP, 操作简单、可视化效果强, 有较高的效能和拟合优度, 一致性和获益性尚好, 具有较好的临床应用价值。

【关键词】 腺病毒肺炎; 列线图; 白细胞介素-6; 危险因素

Construction and validation of a nomogram for predicting the severity of adenovirus pneumonia in children Sun Xiaoyan, Zhao Shuling, Wang Xiaoying. Department of Respiratory Medicine, Xuzhou Children's Hospital Affiliated to Xuzhou Medical University, Xuzhou 221000, China
Corresponding author: Sun Xiaoyan, Email: doctorsunys@163.com

【Abstract】Objective To develop a nomogram model for guiding clinical accurate evaluation on the severity of adenovirus pneumonia in children, and carry out the internal validation. **Methods** Total of 128 children with adenoviral pneumonia diagnosis in Xuzhou Children's Hospital Affiliated to Xuzhou Medical University from August 2019 to August 2021 were included, retrospectively, who all met the criteria of

the guideline for the diagnosis and treatment of adenoviral pneumonia in children (2019 Edition). During hospitalization, according to the diagnostic criteria of community-acquired pneumonia, 128 cases were divided into severe group (50 cases) and non-severe group (78 cases). The gender, age, weight, premature delivery, duration of fever, peak body temperature, basic diseases, serum leukocyte count, percentage of neutrophils and lymphocytes, C-reactive protein (CRP), lactic acid, interleukin (IL)-6, lactate dehydrogenase (LDH), procalcitonin (PCT), percentage of CD4⁺ T and CD8⁺ T lymphocytes, CD4⁺/CD8⁺, CD16⁺CD56⁺ and CD19⁺ T lymphocytes, and mixed infection were compared between the two groups. The dimension of risk factors was reduced by LASSO regression, then the independent risk factors were screened by multivariate Logistic regression analysis, nomogram predictive model was drawn according to the regression coefficient (β). The area under the curve (AUC) of model for severe adenovirus pneumonia (SAP) prediction was calculated by receiver operating curve (ROC), and the goodness of fit of the model was evaluated by Hosmer-Lemeshow test, consistency and benefit of the model were evaluated by calibration curve and decision curve. **Results** Compared with non-severe group, Univariate comparison showed that the duration of fever was longer [5.2 (3.0, 8.5) d vs. 2.9 (1.0, 5.0) d; $Z = 8.326$, $P < 0.001$], concentrations of IL-6 [45.6 (35.4, 56.9) pg/ml vs. 30.2 (25.2, 38.6) pg/ml; $Z = 15.326$, $P < 0.001$] and LDH were higher [452.6 (385.6, 523.4) U/L vs. 365.9 (302.1, 445.2) U/L; $Z = 9.625$, $P < 0.001$], levels of CD4⁺ T [31.2 (27.8, 34.2)% vs. 35.5 (33.2, 38.9)%; $Z = 7.526$, $P < 0.001$] and CD4⁺/CD8⁺ were lower [1.2 (1.0, 1.4) vs. 1.4 (1.1, 1.6); $Z = 5.230$, $P = 0.004$], and the rate of mixed infection was higher in severe group [46.0% (23/50) vs. 19.2% (15/78); $\chi^2 = 10.460$, $P = 0.001$]. LASSO regression screened four variables with non-zero coefficients, namely duration of fever, IL-6 concentration, CD4⁺ T lymphocyte percentage and mixed infection. Multivariate Logistic regression analysis showed that duration of fever (OR = 3.125, 95%CI: 2.565-3.896, $P < 0.001$), IL-6 concentration (OR = 2.012, 95%CI: 1.428-2.639, $P < 0.001$), CD4⁺ T lymphocyte percentage (OR = 0.369, 95%CI: 0.124-0.678, $P = 0.009$) and mixed infection (OR = 1.457, 95%CI: 1.124-1.895, $P = 0.001$) were the independent risk factors for SAP. The total score of nomogram model was 160. ROC showed that the AUC value of nomogram for predicting SAP was 0.852 (95%CI: 0.779-0.901, $P < 0.001$). The Hosmer-Lemeshow test value was 0.786, suggesting that the goodness of fit of the model was high. The calibration curve and decision curve showed that the consistency and benefit of the model were acceptable. **Conclusions** The main factors affecting the severity of adenovirus pneumonia in children are the duration of fever, the concentration of IL-6, the percentage of CD4⁺ T lymphocytes and mixed infection. The developed nomogram prediction model to evaluate SAP has simple operation and strong visualization effect. It has high efficacy and goodness of fit, good consistency and benefit, and has good clinical application value.

【Key words】 Adenovirus pneumonia; Nomograph; Interleukin-6; Risk factor

腺病毒是上呼吸道感染的主要病原体,也是急性胃肠炎和结膜炎的重要致病菌^[1]。腺病毒肺炎约占急性下呼吸道感染的5%~10%,在学龄前儿童中发病率较高,临床上约1/3的腺病毒肺炎儿童可进展为严重疾病,即重症腺病毒肺炎(severe adenovirus pneumonia, SAP),易引发多系统并发症,病死率高,给社会和家庭带来沉重负担^[2-3]。及早诊断SAP对快速阻断腺病毒肺炎的进程,指导临床采取恰当有效的干预策略,改善患儿预后具有积极意义。目前,国内外鲜有关于SAP发生危险因素的报道。基于此,本研究通过回顾性总结单中心临床病例资料,筛选SAP有关的主要危险因素,并建立列线图预测模型指导临床实践,现报道如下。

资料与方法

一、一般资料

本研究采用回顾性、横断面临床观察法,纳入2019年8月至2021年8月于徐州医科大学附属徐州儿童医院诊断为腺病毒肺炎患儿共128例为研究对象。纳入标准:①年龄1~18岁;②符合儿童腺病毒性肺炎诊断和治疗指南(2019版)^[4]的标准,即鼻咽拭子病毒抗原阳性、核酸阳性、特异性IgM抗体阳性,支气管肺泡灌洗液中腺病毒基因测序阳性;③根据指南推荐进行综合的药物治疗;④临床资料完整。本研究获得医院伦理委员会批准[批号:(2019)伦审第(021)号]。

排除标准：①遗传代谢性疾病、免疫功能缺陷性疾病；②中途要求转院；③需要应用免疫抑制剂；④明确诊断肺结核。

二、研究方法

1. 分组：住院期间参照社区获得性肺炎诊断标准^[5]分为重症组（50例）和非重症组（78例）。符合下面任何一项即归属为重症组，包括一般情况差；拒绝进食或脱水；意识障碍；更快的呼吸频率（ > 50 次/min）；发绀；呼吸困难（呻吟、三凹征、鼻翼扇）；肺浸润（多肺叶或 $\geq 2/3$ 肺）；胸腔积液；经皮血氧饱和度 $\leq 92\%$ ；肺外疾病（脑脓肿、脑膜炎、心包炎、骨髓炎、心内膜炎、关节炎、溶血性尿毒症综合征、败血症等）。

2. 收集指标：比较两组患儿性别、年龄、体重、是否早产（妊娠孕周小于37周）、发热持续时间、体温峰值、营养不良、肝炎、肾病、血清白细胞计数、中性粒细胞和淋巴细胞百分比、C-反应蛋白（C-reactive protein, CRP）、乳酸、白细胞介素（interleukin, IL）-6、乳酸脱氢酶（lactate dehydrogenase, LDH）、降钙素原（procalcitonin, PCT）、 $CD4^+$ T和 $CD8^+$ T淋巴细胞百分比、 $CD4^+/CD8^+$ T、 $CD16^+CD56^+$ 和 $CD19^+$ T淋巴细胞百分比、有无混合感染。所有患儿入院24 h内完成抽血和呼吸道分泌物采样，采样德国罗氏诊断分析仪及配套试剂检测血常规、乳酸和LDH，放射免疫法检测CRP、IL-6和PCT，试剂购自美国Sigma公司，美国BD公司流式细胞仪及配套试剂检测T淋巴细胞，所有步骤均严格根据说明书进行。检测病原微生物包括A型和B型流感病毒、呼吸道合胞病毒、柯萨奇B组病毒、腺病毒、肺炎支原体、肺炎衣原体和细菌，任何两种类型的病原体共同感染定义为混合感染。

三、统计学处理

采用SPSS 20.0统计软件对数据进行统计学分析。计数资料以[例（%）]表示，两组间比较用Pearson χ^2 检验或连续校正卡方检验；不符合正态分布的计量资料采用中位数和四分位[M（P25，P75）]表示，比较采用Mann-Whitney U检验；采用最小绝对收缩选择算子（LASSO）回归法对存在一定相关性变量进行降维处理，筛选具有非零系数特征的变量，然后采用多因素Logistic回归模型（逐步后退法）筛选独立危险因素，Hosmer-Lemeshow检验评估模型拟合优度。R软件及相关程序包根据回归系数（ β ）绘制列线图预测模型，

受试者工作曲线（receiver operating curve, ROC）下面积（area under the curve, AUC）评估模型预测效能，Calibration曲线和Decision曲线评估模型一致性和获益性。以 $P < 0.05$ 为差异有统计学意义。

结 果

一、两组患儿的临床资料

重症组较非重症组患儿发热持续时间延长、IL-6和LDH浓度升高、 $CD4^+$ T和 $CD4^+/CD8^+$ T水平下降、混合感染率增多，差异均有统计学意义（ $P < 0.05$ ）。非重症组混合感染中合并病毒感染10例，支原体3例，细菌2例；重症组患儿混合感染中合并病毒感染16例，支原体5例，细菌2例。见表1。

二、SAP危险因素的LASSO回归分析

LASSO回归法从上述单因素比较差异有统计学意义的6个指标中筛选出4个具有非零系数特征的变量，即发热持续时间、IL-6浓度、 $CD4^+$ T淋巴细胞百分比和混合感染，见图1。

三、SAP危险因素的Logistic回归分析

将发热持续时间、IL-6浓度、 $CD4^+$ T淋巴细胞百分比和混合感染作为自变量，SAP（否=0、是=1）为应变量纳入多因素Logistic回归模型，自变量赋值：发热持续时间（ < 3.5 d=0、 ≥ 3.5 d=1）、IL-6浓度（ < 37.8 pg/ml=0、 ≥ 37.8 pg/ml=1）和 $CD4^+$ T淋巴细胞百分比（ $\geq 30\%$ =0、 $< 30\%$ =1）均作为连续性变量，混合感染（否=0、是=1）。结果显示，发热持续时间、IL-6浓度、 $CD4^+$ T淋巴细胞百分比和混合感染均为SAP的独立危险因素，差异均有统计学意义（ P 均 < 0.05 ）。见表2。

四、SAP的列线图模型

根据Logistic回归分析筛选独立危险因素对应回归系数（ β ）绘制列线图预测模型，总分160分，每个变量对应上方评分标尺的评分，累积分值对应下方风险比例。举例说明：一位腺病毒肺炎患儿发热持续了5 d，对应分值为45分；血清IL-6水平为50 pg/ml，对应分值为25分； $CD4^+$ T细胞百分比为30%，对应分值为12分；混合感染阳性，对应分值为35分；各项分值相加得到总分为117分，对应风险为0.89，提示SAP的风险极高，见图2。

五、列线图的内部验证

ROC显示，列线图预测SAP的AUC值为0.852（95%CI: 0.779~0.901、 $P < 0.001$ ），提示模型

表1 两组患儿的临床资料

临床资料	非重症组 (78例)	重症组 (50例)	统计量	P值
男/女	41/37	28/22	$\chi^2 = 0.145$	0.704 ^a
年龄 [M (P25, P75), 岁]	3.8 (1.5, 8.0)	3.5 (1.0, 7.0)	$Z = 0.563$	0.501
体重 [M (P25, P75), kg]	6.9 (4.0, 20.5)	6.6 (3.5, 18.5)	$Z = 0.869$	0.223
早产 [例 (%)]	4 (5.1)	3 (6.0)	$\chi^2 = 0.045$	0.832 ^b
发热持续时间 [M (P25, P75), d]	2.9 (1.0, 5.0)	5.2 (3.0, 8.5)	$Z = 8.326$	< 0.001
体温峰值 [M (P25, P75), °C]	39.7 (39.0, 40.0)	39.9 (39.2, 41.5)	$Z = 0.965$	0.102
营养不良 [例 (%)]	7 (9.0)	5 (10.0)	$\chi^2 = 0.038$	0.745 ^b
肝炎 [例 (%)]	4 (5.1)	3 (6.0)	$\chi^2 = 0.045$	0.869 ^b
肾病 [例 (%)]	3 (3.8)	2 (4.0)	$\chi^2 = 0.002$	0.965 ^b
白细胞计数 [M (P25, P75), $\times 10^9/L$]	9.6 (7.5, 12.5)	10.2 (7.9, 14.0)	$Z = 0.785$	0.253
中性粒细胞 [M (P25, P75), %]	70.5 (66.9, 74.5)	72.3 (68.5, 75.5)	$Z = 0.635$	0.421
淋巴细胞 [M (P25, P75), %]	32.3 (30.1, 35.4)	35.6 (30.8, 36.6)	$Z = 0.741$	0.326
CRP [M (P25, P75), mg/L]	13.0 (8.5, 16.5)	13.5 (9.0, 18.2)	$Z = 0.596$	0.522
乳酸 [M (P25, P75), mmol/L]	2.5 (2.2, 2.8)	2.6 (2.3, 2.9)	$Z = 0.326$	0.648
IL-6 [M (P25, P75), pg/ml]	30.2 (25.2, 38.6)	45.6 (35.4, 56.9)	$Z = 15.326$	< 0.001
LDH [M (P25, P75), U/L]	365.9 (302.1, 445.2)	452.6 (385.6, 523.4)	$Z = 9.625$	< 0.001
PCT [M (P25, P75), $\mu g/L$]	0.2 (0.1, 0.3)	0.3 (0.1, 0.5)	$Z = 0.669$	0.421
CD4 ⁺ T [M (P25, P75), %]	35.5 (33.2, 38.9)	31.2 (27.8, 34.2)	$Z = 7.526$	< 0.001
CD8 ⁺ T [M (P25, P75), %]	26.6 (25.0, 30.1)	26.8 (25.5, 30.9)	$Z = 1.002$	0.121
CD4 ⁺ /CD8 ⁺ T [M (P25, P75)]	1.4 (1.1, 1.6)	1.2 (1.0, 1.4)	$Z = 5.230$	0.004
CD16 ⁺ CD56 ⁺ T [M (P25, P75), %]	13.0 (11.8, 14.5)	12.6 (11.5, 13.9)	$Z = 0.653$	0.302
CD19 ⁺ T [M (P25, P75), %]	19.9 (18.5, 22.5)	21.2 (19.0, 23.5)	$Z = 0.845$	0.203
混合感染 [例 (%)]	15 (19.2)	23 (46.0)	$\chi^2 = 10.460$	0.001 ^a

注: CRP: C-反应蛋白; IL: 白细胞介素; LDH: 乳酸脱氢酶; PCT: 降钙素原; ^a: Pearson 卡方检验, ^b: 连续校正卡方检验

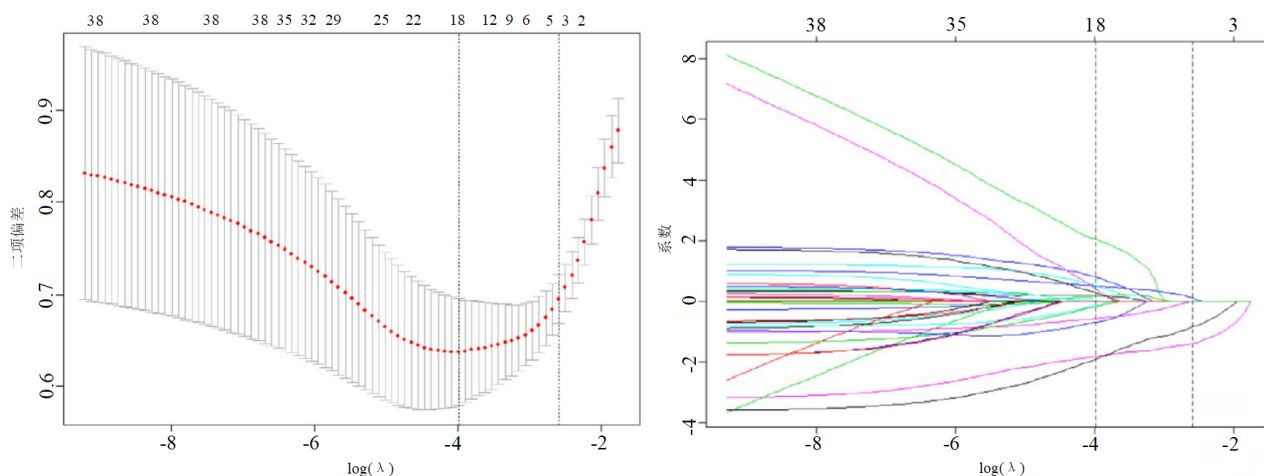


图1 SAP危险因素LASSO回归分析

表2 SAP 危险因素 Logistic 回归分析

危险因素	β 值	SE值	Wald χ^2 值	P值	OR值	95%CI
发热持续时间	1.326	0.895	21.503	< 0.001	3.125	2.565~3.896
IL-6	0.854	0.458	10.102	< 0.001	2.012	1.428~2.639
CD4 ⁺ T	-0.102	0.052	5.165	0.009	0.369	0.124~0.678
混合感染	0.526	0.301	7.071	0.001	1.457	1.124~1.895
常数项	0.085	0.033	6.659	0.001	—	—

预测效能较高, 见图3。Hosmer-Lemeshow检验值为0.786, 提示模型拟合优度较高。Calibration曲线显示

模型一致性尚可, 见图4。Decision曲线显示模型获益性尚可, 临界概率值为0.02~0.66, 见图5。

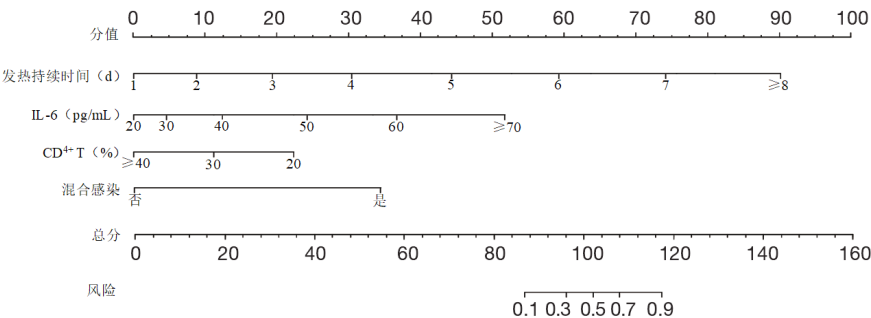


图2 SAP的列线图模型

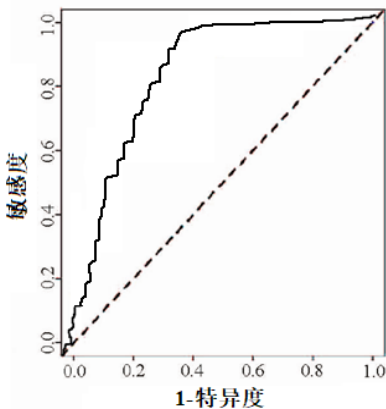


图3 列线图模型预测SAP的ROC曲线

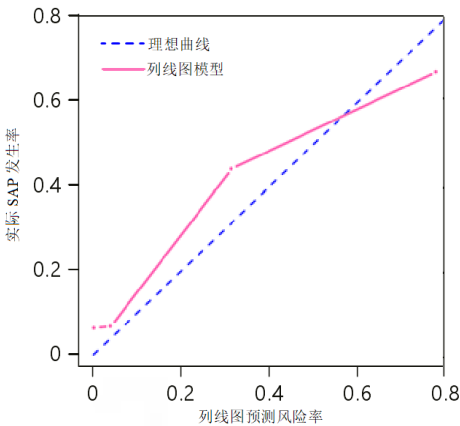
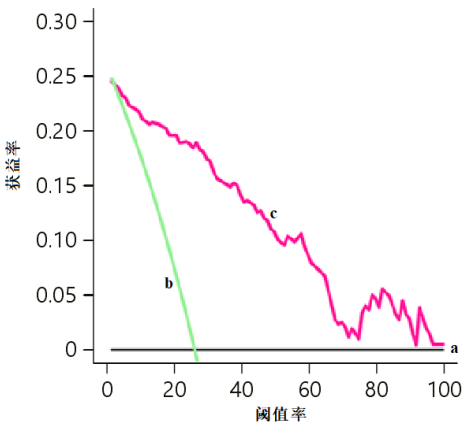


图4 列线图模型预测SAP发生的Calibration曲线



注：^a：假设所有患儿均未采用列线图模型评估SAP发生风险；^b：假设所有患儿均采用列线图模型评估SAP发生风险；^c：列线图模型的决策曲线

图5 列线图模型预测SAP发生的Decision曲线

讨 论

腺病毒共有7个亚基因型, 103多种类型, 人群普遍易感。腺病毒是引起儿童社区获得性肺炎的常见病原体之一, 住院儿童呼吸感染性疾病中腺病毒感染的阳性率为3.5%~9.4%, 其中SAP发生率可高达53.9%^[6-8]。本研究显示, 腺病毒肺炎患儿进展至SAP发生率为39.1% (50/128)。当SAP继发多器官功能障碍综合征时, 病死率高于50%^[9]。因此, 本研究主要开发一款用于指导临床准确评估儿童腺病毒肺炎严重程度的列线图模型, 并进行验证。

本研究显示, 重症组较非重症组患儿发热持续时间延长、IL-6和LDH浓度升高、CD4⁺T和CD4⁺/CD8⁺T水平下降、混合感染率增多。高热往往是腺病毒肺炎的重要临床特征, 高热持续时间越长提示

病毒繁殖能力较强,越易损伤儿童免疫功能,导致肺部症状加重,病情恶化^[10-12]。先天性免疫反应是宿主对腺病毒感染的重要防御机制,CD4⁺ T细胞能够识别腺病毒的衣壳蛋白并引起阳性免疫反应^[13]。CD4⁺ T细胞根据不同的细胞因子谱被分为Th1和Th2,其中Th1能够通过分泌细胞因子增强对感染的抵抗力,而Th2通过分泌细胞因子实现体液免疫帮助B淋巴细胞活化,并产生抗体^[14]。当发生SAP时,机体外周循环中CD4⁺ T细胞显著减少,导致体内细胞免疫抑制^[15-16]。IL-6是促进B淋巴细胞产生抗体,促进肝脏合成多种急性时相蛋白的重要信号源,IL-6水平显著升高往往与严重的腺病毒感染一致^[17-18]。研究证实^[19-20],IL-6水平与肺部炎症反应有关,过度表达往往提示腺病毒感染诱发紊乱的免疫-炎症反应,进而加重肺损伤。腺病毒引起的炎症风暴对治疗决策具有重要的临床意义,SAP临床症状类似于成人新型冠状病毒肺炎^[21]。低淋巴细胞计数和高血清LDH与儿童腺病毒引起的呼吸道感染严重程度有高度吻合性^[22-24]。

本研究进一步采用LASSO回归法筛选出4个具有非零系数特征的变量,即发热持续时间、IL-6浓度、CD4⁺ T淋巴细胞百分比和混合感染,保证各变量间的独立性。多因素Logistic回归分析显示,发热持续时间、IL-6浓度、CD4⁺ T淋巴细胞百分比和混合感染均为SAP的独立危险因素,差异均有统计学意义。发热持续时间延长者SAP的发生风险升高为3.125倍,IL-6水平升高者SAP的发生风险升高为32.012倍,CD4⁺ T细胞百分比升高者SAP的发生风险下降为0.369倍,混合感染者SAP的发生风险升高为1.457倍。最后,建立列线图预测模型,根据各指标对应评分然后相加得到总分,对应风险值即SAP发生率。列线图具有可视化效果强,操作简单的优点,在临床中多个领域已广泛应用。列线图模型能有效区分个体化预测,便于个体化治疗。通过多个维度对列线图模型进行验证,发现模型预测SAP的效能和拟合优度较高,一致性和获益性尚可。本研究显示,列线图模型对所有阈值概率都有净效益,尤其在20%~60%更为突出,进行腺病毒肺炎的严重程度评估获益明显;阈值概率为10%~20%积极评估腺病毒肺炎的严重程度依然获益;然而,在阈值概率<10%时,列线图的净效益与所有参与者的预测阳性结果相当。如ICU收治1例腺病毒患儿,通过列线图进行危重程度评分,

假设评估结果危重风险为30%,临床医生应高度警惕此患儿是否会进展为SAP,从而做出相应决策,对提升临床疗效将产生积极影响。

但本研究存在一定局限性:本研究结果建立在单中心、回顾性病例总结的基础上,可能存在病例选择的偏倚性,影响结果稳定性,通过多中心、前瞻性病例对照随机试验能够对本研究结果进行验证和校正;此外,临床诊断腺病毒肺炎还需借助影像学检查,本研究筛选因素中并未纳入影像学指标;包括腺病毒分型,3、7型比较危重;脏器功能受累,肺及肺外情况等^[25];最后,临床治疗方式包括药物种类、辅助器械等也会对疾病进展产生重要影响。

综上,影响儿童腺病毒肺炎严重程度的主要因素有发热持续时间、IL-6浓度、CD4⁺ T淋巴细胞百分比和混合感染,列线图预测模型评估SAP,具有操作简单、可视化效果强的优势,基于上述4项临床指标建立的模型有较高的效能和拟合优度,一致性和获益性尚好,具有较好的临床应用价值。

参 考 文 献

- [1] Zhong L, Lin J, Dai J. Risk factors for the development of bronchiolitis obliterans in children with severe adenovirus pneumonia: A retrospective study with dose-response analysis[J]. J Med Virol, 2020, 92(10):3093-3099.
- [2] 林静, 陈志敏. 儿童重症腺病毒肺炎早期识别的研究进展[J]. 浙江大学学报(医学版), 2019, 48(5):567-572.
- [3] 靳丹丹, 周卫芳, 李嫣, 等. 儿童腺病毒肺炎的混合感染特点和重症病例的危险因素分析[J]. 临床肺科杂志, 2019, 24(10):1747-1750.
- [4] National Health Commission of the People's Republic of China, State Administration of Traditional Chinese Medicine. Guideline for diagnosis and treatment of adenovirus pneumonia in children (2019 version)[J]. Chin J of Clin Infect Dis, 2019, 12(2):161-166.
- [5] 李昌崇, 尚云晓, 沈叙庄, 等. 儿童社区获得性肺炎管理指南(2013修订)[J]. 中华儿科杂志, 2013, 51(11):856-862.
- [6] 王心静, 王仲元, 刘晓, 等. 48例腺病毒55型所致急性呼吸系统感染者的临床特点[J/CD]. 中华实验和临床感染病杂志(电子版), 2021, 15(2):124-128.
- [7] Zampoli M, Mukuddem-Sablay Z. Adenovirus-associated pneumonia in South African children: Presentation, clinical course and outcome[J]. S Afr Med J, 2017, 107(16):123-126.
- [8] 荣道香, 宣爱丽, 方姗姗, 等. 儿童腺病毒肺炎120例临床特征分析[J]. 中华全科医学, 2020, 18(7):1096-1098, 1142.
- [9] Cheng JL, Peng CC, Chiu NC, et al. Risk factor analysis and molecular epidemiology of respiratory adenovirus infections among children in northern Taiwan, 2009-2013[J]. J Microbiol Immunol Infect, 2017, 50(10):418-426.
- [10] Gu J, Su QQ, Zuo TT, et al. Adenovirus diseases: a systematic review and meta-analysis of 228 case reports[J]. Infection, 2021, 49(8):1-13.
- [11] Park JY, Kim BJ, Lee EJ, et al. Clinical features and courses of

- adenovirus pneumonia in healthy young adults during an outbreak among Korean Military Personnel[J]. PLoS One,2017,12(1):e0170592.
- [12] Yoo H, Oh J, Park C. Characteristics of fever and response to antipyretic therapy in military personnel with adenovirus-positive community-acquired pneumonia[J]. Mil Med Res,2020,7(2):6-8.
- [13] Chowdhury F, Shahid ASMSB, Ghosh PK, et al. Viral etiology of pneumonia among severely malnourished under-five children in an urban hospital, Bangladesh[J]. PLoS One,2020,15(3):e0228329.
- [14] Barnadas C, Schmidt DJ, Fischer TK, et al. Molecular epidemiology of human adenovirus infections in Denmark, 2011-2016[J]. J Clin Virol,2018,104(11):16-22.
- [15] Ye Q, Wang B, Mao J. The pathogenesis and treatment of the 'Cytokine Storm' in COVID-19[J]. J Infect,2020,80(13):607-613.
- [16] Wu PQ, Zeng SQ, Yin GQ, et al. Clinical manifestations and risk factors of adenovirus respiratory infection in hospitalized children in Guangzhou, China during the 2011-2014 period[J]. Medicine (Baltimore),2020,99(6):e18584.
- [17] Sun J, Xiao Y, Zhang M, et al. Serum inflammatory markers in patients with adenovirus respiratory infection[J]. Med Sci Monit,2018,24(9):3848-3855.
- [18] Chen X, Lv J, Qin L, et al. Severe adenovirus pneumonia requiring extracorporeal membrane oxygenation support in immunocompetent children[J]. Front Pediatr,2020,8(4):162-164.
- [19] Zhang R, Wang H, Tian S, et al. Adenovirus viremia may predict adenovirus pneumonia severity in immunocompetent children[J]. BMC Infect Dis,2021,21(1):213-215.
- [20] Moon SM, Choe J, Na SJ, et al. Comparative study on the effect of cidofovir treatment for severe adenovirus pneumonia[J]. J Intensive Care Med,2021,36(12):1436-1442.
- [21] 廖蕊, 代继宏, 钟林平, 等. 基于决策曲线和剂量反应分析评估腺病毒载量对儿童感染重症腺病毒肺炎后发展为闭塞性细支气管炎的预测价值[J]. 中国循证儿科杂志,2019,14(5):342-346.
- [22] Jiang J, Wan R, Pan P, et al. Comparison of clinical, laboratory and radiological characteristics between COVID-19 and adenovirus pneumonia: A retrospective study[J]. Infect Drug Resist,2020,13(10):3401-3408.
- [23] 黄淼, 罗蓉, 符州. 儿童重症腺病毒肺炎不良预后的危险因素分析[J]. 中国当代儿科杂志,2017,19(2):159-162.
- [24] 彭力, 钟礼立, 黄振, 等. 儿童肺炎支原体肺炎合并腺病毒感染的临床观察[J]. 中国当代儿科杂志,2021,23(10):1033-1037.
- [25] Lou Q, Zhang SX, Yuan L. Clinical analysis of adenovirus pneumonia with pulmonary consolidation and atelectasis in children[J]. J Int Med Res,2021,49(2):154-157.

(收稿日期: 2022-04-27)
(本文编辑: 孙荣华)

孙小艳, 赵淑玲, 王晓莹. 儿童腺病毒肺炎严重程度预测列线图的构建及验证[J/CD]. 中华实验和临床感染病杂志(电子版), 2022,16(5):337-343.