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血清 D-二聚体、IL-6、IL-18 对儿童难治性肺炎支原体肺炎的预测价值

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[摘要] 目的: 探讨血清D-二聚体、白细胞介素-6(interleukin 6, IL-6)、白细胞介素-18(interleukin 18, IL-18)对儿童难治性肺炎支原体肺炎(refractory mycoplasma pneumoniae pneumonia, RMPP)的预测价值。方法: 以2020年5月至2021年5月北京怀柔医院收治的150例肺炎支原体肺炎(mycoplasma pneumoniae pneumonia, MPP)患儿为研究对象, 根据临床诊断标准将其分为RMPP组($n=52$)与普通肺炎支原体肺炎(general mycoplasma pneumoniae pneumonia, GMPP)组($n=98$), 比较2组一般基础资料、胸部CT影像学资料及治疗前的血清指标[D-二聚体、C反应蛋白(C-reactive protein, CRP)、降钙素原(procalcitonin, PCT)、肿瘤坏死因子- α (tumor necrosis factor- α , TNF- α)、IL-6、IL-18]水平。采用logistic回归分析RMPP的独立影响因素, 并绘制受试者工作特征(receiver operator characteristic, ROC)曲线评估D-二聚体、IL-6、IL-18诊断RMPP的临床价值。结果: RMPP组患儿胸腔积液、肺实变、肺不张比例及血清D-二聚体、CRP、PCT、IL-6、IL-18水平显著高于GMPP组($P<0.05$), 2组一般基础资料、血清TNF- α 水平比较, 差异无统计学意义(均 $P>0.05$)。Logistic回归分析显示: 肺实变、胸腔积液、肺不张及血清D-二聚体、CRP、PCT、IL-6、IL-18表达升高是预测RMPP的独立危险因素($P<0.05$)。ROC曲线显示: 血清D-二聚体、IL-6、IL-18预测RMPP的曲线下面积分别为0.830、0.825、0.860, 截断值分别为0.56 mg/L、24.96 pg/mL、393.51 pg/mL。结论: 血清D-二聚体、IL-6、IL-18可作为儿童RMPP的早期预测指标。

[关键词] 难治性肺炎支原体肺炎; D-二聚体; IL-6; IL-18; 免疫功能

Predictive value of serum D-Dimer, IL-6 and IL-18 for refractory mycoplasma pneumoniae pneumonia in children

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Abstract **Objective:** To investigate the predictive value of serum D-Dimer, interleukin-6 (IL-6) and interleukin-18 (IL-18) on refractory mycoplasma pneumoniae pneumonia (RMPP) in children. **Methods:** A total of 150 children with mycoplasma pneumoniae pneumonia (MPP) admitted to our hospital from May 2020 to May 2021 were

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selected as the research subjects and divided into a RMPP group ($n=52$) and a general mycoplasma pneumoniae pneumonia (GMPP) group ($n=98$) according to the clinical diagnostic criteria. The general basic data, chest CT imaging data and serum indexes before treatment [*D*-Dimer, C-reactive protein (CRP), procalcitonin (PCT), tumor necrosis factor- α (TNF- α), IL-6, and IL-18] were compared between the 2 groups. Logistic regression was used to analyze the independent influencing factors of RMPP, and receiver operating characteristic curve (ROC) was drawn to evaluate the clinical value of *D*-Dimer, IL-6 and IL-18 in the diagnosis of RMPP. **Results:** The proportion of pleural effusion, pulmonary consolidation, atelectasis and serum levels of *D*-Dimer, CRP, PCT, IL-6 and IL-18 in RMPP group were significantly higher than those in the GMPP group ($P<0.05$). Logistic regression analysis showed Pulmonary consolidation, pleural effusion, atelectasis and increased expression of serum *D*-Dimer, CRP, PCT, IL-6 and IL-18 were independent risk factors for RMPP ($P<0.05$). ROC curve showed that the areas under the curve of serum *D*-Dimer, IL-6 and IL-18 for predicting RMPP were 0.830, 0.825 and 0.860, respectively, and the cut-off values were 0.56 mg/L, 24.96 pg/mL and 393.51 pg/mL, respectively. **Conclusion:** Serum *D*-Dimer, IL-6 and IL-18 can be used as early predictors of RMPP in children.

Keywords refractory mycoplasma pneumoniae pneumonia; *D*-Dimer; interleukin-6; interleukin-18; immune function

肺炎支原体肺炎(mycoplasma pneumoniae pneumonia, MPP)是儿童常见的呼吸系统疾病,主要采取大环内酯类抗生素治疗,但随着抗生素耐药性增强、免疫损伤加重,部分患儿对常规抗生素无反应,进一步发展为难治性MPP(refractory mycoplasma pneumoniae pneumonia, RMPP)^[1]。临床^[2]发现:RMPP患儿不仅肺部存在明显病变,还会累及皮肤黏膜、消化系统、中枢神经系统等,严重危害患儿生命健康。因此, RMPP的早期诊断和针对性治疗至关重要,可减少患儿并发症发生风险。相关研究^[3-4]发现:免疫损伤与RMPP的发生、发展密切相关,免疫相关的细胞因子如白细胞介素-6(interleukin 6, IL-6)、白细胞介素-18(interleukin 18, IL-18)等可能有助于预测RMPP。研究^[5]显示:社区获得性肺炎患者血清D-二聚体水平显著升高,且可用于衡量病情程度及远期预后。基于此,本研究探讨血清D-二聚体、IL-6、IL-18对儿童RMPP的预测价值,以期临床建立高效的RMPP早期诊断方案提供参考。

1 对象与方法

1.1 对象

选取2020年5月至2021年5月在北京怀柔医院住院治疗的150例MPP患儿为研究对象。纳入标准:1)年龄6个月~12岁;2)符合MPP临床诊断标准^[6];3)支原体耐药基因检测显示不存在耐药基因。排除标准:1)患有肺结核、支气管哮喘、结缔组织疾病等肺部疾病者;2)患有血液性疾

病或免疫系统疾病者;3)患有恶性肿瘤者;4)临床资料不全者。根据RMPP及普通肺炎支原体肺炎(general mycoplasma pneumoniae pneumonia, GMPP)的临床诊断依据将其分为2组,其中RMPP组52例,GMPP组98例。

GMPP诊断依据^[7]:胸部CT影像学显示肺部有高密度阴影,伴有胸腔积液、肺实变、肺不张等,查体发现肺部哮鸣音、湿啰音,且支原体病原学检查呈阳性;采用大环内酯类抗生素规范化治疗5 d疗效显著。

RMPP诊断依据^[8]:采用大环内酯类抗生素规范化治疗7 d, MPP患儿体征、肺部CT征象无好转或持续加重。

1.2 方法

搜集患儿一般基础资料及胸部CT影像学资料,同时于治疗前采集患儿空腹肘静脉血5 mL,离心分离后,采用酶联免疫吸附法检测血清中D-二聚体、C反应蛋白(C-reactive protein, CRP)、降钙素原(procalcitonin, PCT)、肿瘤坏死因子- α (tumor necrosis factor- α , TNF- α)、IL-6、IL-18水平。

1.3 统计学处理

采用SPSS 22.0统计学软件进行数据分析,计量资料符合正态分布且方差齐,以均数 \pm 标准差($\bar{x}\pm s$)表示,比较采用独立样本 t 检验;计数资料以[例(%)]表示,采用 χ^2 检验或Fisher精确概率法;采用logistic回归分析RMPP的独立危险因素;通过绘制受试者工作特征(receiver operator characteristic,

ROC)曲线分析血清D-二聚体、IL-6、IL-18预测RMPP的临床价值。 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 2组一般资料比较

2组性别、年龄、体重、病程、体温、合并全身炎症反应综合征(systemic inflammatory response syndrome, SIRS)、合并感染性休克及气促、湿啰音情况的差异均无统计学意义(均 $P > 0.05$); RMPP组胸腔积液、肺实变、肺不张发生比例均显著高于GMPP组, 差异均有统计学意义(均 $P < 0.05$, 表1)。

2.2 2组血清指标比较

RMPP组血清D-二聚体、CRP、PCT、IL-6、IL-18水平均显著高于GMPP组(均 $P > 0.05$), TNF- α 水平与GMPP组比较, 差异无统计学意义

($P < 0.05$, 表2)。

2.3 多因素 logistic 回归分析

将上述指标中有统计学意义的因素作为自变量, RMPP为因变量, 经logistic回归分析显示: 胸腔积液、肺实变、肺不张及血清D-二聚体、CRP、PCT、IL-6、IL-18水平升高是预测RMPP的独立危险因素($P < 0.05$, 表3)。

2.4 血清D-二聚体、IL-6、IL-18预测RMPP的ROC曲线

血清D-二聚体、IL-6、IL-18预测RMPP的截断值分别为0.56 mg/L、24.96 pg/mL、393.51 pg/mL, 曲线下面积(area under the curve, AUC)分别为0.830、0.825、0.860, 灵敏度分别为94.23%、86.54%、96.15%, 特异度分别为88.78%、95.92%、89.80%(表4, 图1)。

表1 2组一般资料比较

Table 1 Comparison of general information between the 2 groups

项目	RMPP组($n=52$)	GMPP组($n=98$)	χ^2/t	P
性别(男/女)/例	29/23	45/53	1.319	0.251
年龄/岁	6.15 \pm 2.74	6.27 \pm 2.56	0.267	0.790
体重/kg	19.83 \pm 3.65	20.18 \pm 3.92	0.533	0.595
病程/d	7.44 \pm 1.59	7.26 \pm 1.48	0.691	0.491
体温/ $^{\circ}\text{C}$	38.22 \pm 1.08	38.45 \pm 1.20	0.156	0.250
合并SIRS/[例(%)]	5 (9.62)	3 (3.06)	—	0.126*
合并感染性休克/[例(%)]	1 (1.92)	0 (0.00)	—	0.347*
胸腔积液/[例(%)]	35 (67.31)	29 (32.69)	19.756	0.001
肺实变/[例(%)]	42 (80.77)	41 (41.84)	20.835	0.001
肺不张/[例(%)]	16 (30.77)	10 (10.20)	10.027	0.002
气促/[例(%)]	21 (40.38)	37 (37.76)	0.099	0.753
湿啰音/[例(%)]	18 (34.62)	31 (31.63)	0.137	0.711

*Fisher精确概率法。

*Fisher exact probability method.

表2 2组血清指标比较

Table 2 Comparison of serum indexes between the 2 groups

组别	n	D-二聚体/($\text{mg}\cdot\text{L}^{-1}$)	CRP/($\text{mg}\cdot\text{L}^{-1}$)	PCT/($\text{ng}\cdot\text{L}^{-1}$)	TNF- α /($\text{ng}\cdot\text{L}^{-1}$)	IL-6/($\text{pg}\cdot\text{mL}^{-1}$)	IL-18/($\text{pg}\cdot\text{mL}^{-1}$)
RMPP组	52	1.39 \pm 0.30	31.28 \pm 5.69	0.22 \pm 0.05	3.17 \pm 0.64	31.28 \pm 6.24	378.52 \pm 119.69
GMPP组	98	0.44 \pm 0.12	14.06 \pm 3.17	0.13 \pm 0.02	3.04 \pm 0.56	17.71 \pm 3.50	311.50 \pm 72.66
t		27.531	23.828	15.649	1.235	17.079	4.263
P		0.001	0.001	0.001	0.219	0.001	0.001

表3 RMPP的多因素logistic回归分析

Table 3 Multivariate logistic regression analysis of RMPP

变量	β	SE	Wald χ^2	OR	95%CI	P
胸腔积液	0.246	0.108	5.188	1.279	1.035~1.580	0.023
肺实变	0.573	0.185	9.580	1.773	1.234~2.548	0.002
肺不张	0.205	0.087	5.552	1.228	1.035~1.456	0.020
D-二聚体	2.014	0.557	13.074	7.493	2.515~22.325	0.001
CRP	0.139	0.048	8.386	1.149	1.046~1.262	0.004
PCT	0.215	0.065	10.941	1.240	1.092~1.408	0.001
IL-6	1.587	0.549	8.356	4.889	1.667~14.340	0.004
IL-18	1.760	0.485	13.169	5.812	2.247~15.038	0.001

表4 血清D-二聚体、IL-6、IL-18预测RMPP的价值

Table 4 Value of serum D-Dimer, IL-6 and IL-18 in predicting RMPP

变量	AUC	截断值	Youden指数	灵敏度/%	特异度/%	95%CI	P
D-二聚体	0.955	0.56	0.830	94.23	88.78	0.908~0.982	0.001
IL-6	0.946	24.96	0.825	86.54	95.92	0.894~0.975	0.001
IL-18	0.944	393.51	0.860	96.15	89.80	0.897~0.976	0.001

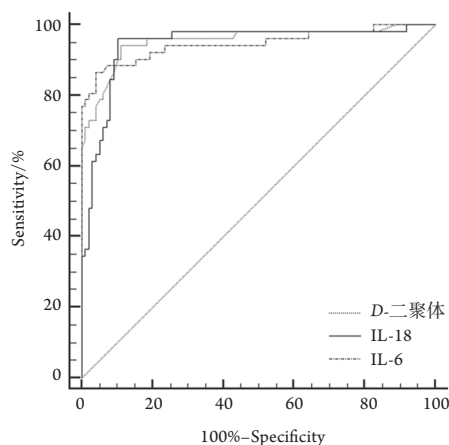


图1 血清D-二聚体、IL-6、IL-18预测RMPP的ROC曲线

Figure 1 ROC curve of serum D-Dimer, IL-6, IL-18 to predict RMPP

3 讨论

MPP是儿童、青少年高发呼吸道疾病,大多数患者临床表现轻微自限,但有少部分患者常规治疗无效,可发展为RMPP。近年研究^[9]显示:RMPP患儿对大环内酯类内抗生素的耐药率逐年升高,这给RMPP的治疗带来一定的难度。因此,探寻儿童RMPP早期诊断方法是临床提高治疗有效率

的关键。

本研究结果显示:2组患儿性别、年龄、体重、病程、体温、SIRS、感染性休克、气促、湿啰音情况比较,差异均无统计学意义,RMPP组胸腔积液、肺实变、肺不张占比显著高于GMPP组,血清D-二聚体、CRP、PCT、IL-6、IL-18水平均显著高于GMPP组,血清TNF- α 水平与GMPP组比较无差异,提示RMPP与GMPP患儿肺部影像学征象、机体免疫炎症反应存在显著差异。从RMPP定义上可以看出,该类型的患儿肺部影像学征象持续性加重,而且既往研究^[10]也显示:胸腔积液、肺实变等是发生RMPP的高危影响因素,这是因为RMPP患儿所受的免疫损伤更严重,肺部影像学征象更复杂。据相关报道^[11]显示:支原体在侵犯机体过程中,可携带黏附分子并与靶细胞上的神经氨酸受体发生结合,导致肺组织丧失细胞吞噬功能,介导机体免疫炎症反应。本研究中2组SIRS、感染性休克发生率无差异,可能是因为二者属于小儿MPP危及症状,而本研究纳入病例数少,未能显现出差异^[12]。CRP、PCT、TNF- α 、IL-6为临床常见的炎症因子,当机体受到感染或损伤时,其表达水平显著升高,而且与炎症反应程度呈正相关^[13]。本研究中,2组血清TNF- α 水平差异无统

计学意义, 可能是TNF- α 在肺炎支原体感染后的1周内达到峰值, 之后缓慢下降, 所以未显示出差异。D-二聚体、IL-18是近年研究RMPP机制的热点, D-二聚体是临床评估机体凝血情况的敏感性指标。研究^[14]显示: MPP患者肺内外并发症的发生与机体持续高凝状态有关, 可用于预测患者预后。IL-18具有多种生物学功能, 可诱导机体免疫细胞分泌干扰素, 加重机体免疫损伤, 是预测RMPP的潜在生物学指标^[15]。

进一步logistic回归分析显示: 肺实变、胸腔积液、肺不张及血清D-二聚体、CRP、PCT、IL-6、IL-18水平是预测RMPP的独立危险因素, 这与既往研究^[16]结论一致。王红连等^[16]的研究显示: 血清CRP ≥ 40 mg/L是RMPP的独立危险因素。CRP、PCT是评估机体感染的早期指标, 其表达水平与感染的严重程度呈正相关, 可用于指导感染性疾病的诊断及治疗。胸部CT表现是目前诊断儿童MPP最直接、最敏感的依据, RMPP肺部支原体感染更为严重, 因此CT大多表现为大片高密度影, 即肺实变; 因肺实变位置大多处于肺野外带, 可导致胸腔积液渗出; 因此儿童RMPP肺部CT多表现为肺实变、胸腔积液、肺不张等特征^[17]。

CRP、PCT是目前临床鉴别RMPP的主要指标, 为进一步优化诊断方法, 本研究仅选取血清D-二聚体、IL-6、IL-18作为评估儿童RMPP的备选指标, 通过绘制ROC曲线显示: 血清D-二聚体、IL-6、IL-18对儿童RMPP的预测均具有较高的价值, 可作为新型的RMPP早期诊断指标应用于临床, 而且ROC曲线还明确了这3种指标的具体数值, 为临床应用与实践提供了数据参考。本研究结果同时也说明: 过度免疫性炎症可能是RMPP发生、发展的机制之一, 降低血清D-二聚体、IL-6、IL-18可能有助于提高RMPP的治疗效果。梁世佳^[18]对比喹诺酮类、大环内酯类抗生素治疗儿童RMPP的临床效果发现: 喹诺酮类抗生素治疗效果更好, 且对患者血清D-二聚体、CRP水平及T淋巴细胞亚群改善作用更明显。

综上, 血清D-二聚体、IL-6、IL-18对儿童RMPP的预测价值较高, 在诊疗过程中应予以重点关注, 积极采取有效措施改善患儿预后。

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