

特发性肺动脉高压患儿血清 miR-182 和 ICAM-1 表达水平及其与预后相关性分析

杨春光^a, 刘海红^a, 王凤东^a, 王晓静^a, 张学郁^b, 张海波^c

(承德市妇幼保健院 a. 新生儿科; b. 检验科; c. 儿科, 河北承德 067020)

摘要: 目的 探讨血清微小核糖核酸 (micro RNA, miR) -182、细胞间黏附分子 (intercellular adhesion molecule-1, ICAM) -1 在特发性肺动脉高压 (idiopathic pulmonary arterial hypertension, IPAH) 患儿中的表达及其预后预测价值。方法 选取 2016 年 6 月 ~ 2020 年 12 月就诊于承德市妇幼保健院肺动脉高压中心的 76 例 IPAH 患儿为研究对象 (观察组), 另选取同期在医院进行体检的健康儿童 30 例作为对照组, 比较二组血清 miR-182, ICAM-1 水平。收集 IPAH 患儿常规实验室检查、心脏超声检查及心导管检查等资料, 并进行随访, 随访的终点事件定义为死亡或行肺移植治疗, 根据患儿预后情况将其分为存活组和死亡组。采用 Logistic 回归分析筛选影响 IPAH 患儿预后的危险因素, 绘制受试者工作特征 (receiver operating characteristic, ROC) 曲线评价血清 miR-182, ICAM-1 单独及联合检测对 IPAH 患儿预后的预测价值。结果 观察组血清 miR-182 (1.91 ± 0.20), ICAM-1 (305.67 ± 32.46 ng/ml) 水平均高于对照组 (0.15 ± 0.02 , 203.22 ± 21.51 ng/ml), 差异具有统计学意义 ($t = -73.624$, -33.698 , 均 $P < 0.05$)。72 例患儿获得随访, 其中死亡 21 例 (29.17%), 存活 51 例 (70.83%)。死亡组 NYHA 心功能分级 (III ~ IV 级) 占比、脑钠肽 (brain natriuretic peptide, BNP)、总胆红素 (total bilirubin, TB)、红细胞分布宽度 (red cell volume distribution width, RDW)、肺动脉收缩压 (systolic pulmonary artery pressure, sPAP)、全肺阻力 (total pulmonary resistance, TPR)、miR-182 和 ICAM-1 水平均高于存活组, 差异具有统计学意义 ($\chi^2 = 4.138$, $t' = -75.584$, $t = 7.231$, 6.197 , 2.464 , 3.930 , $t' = 6.782$, 3.328 , 均 $P < 0.05$)。NYHA 心功能分级 (高级) (OR=1.681, 95%CI=1.370 ~ 5.128), RDW (OR=2.112, 95%CI=1.212 ~ 5.135), sPAP (OR=2.597, 95%CI=1.052 ~ 6.1425), miR-182 (OR=3.587, 95%CI=1.249 ~ 6.125) 和 ICAM-1 (OR=3.634, 95%CI=1.135 ~ 5.153) 是影响 IPAH 患儿预后的危险因素 (均 $P < 0.05$)。血清 miR-182 和 ICAM-1 预测 IPAH 患儿预后的曲线下面积 (AUC) 分别为 0.761, 0.770, 联合预测的 AUC 为 0.883, 优于各指标单独预测 ($Z = -3.236$, -3.211 , 均 $P < 0.05$)。结论 血清 miR-182 和 ICAM-1 在 IPAH 患儿中呈现异常高表达, 二者与患儿预后存在一定关系, 在一定程度上可作为有效预测指标。

关键词: 特发性肺动脉高压; 微小核糖核酸 -182; 细胞间黏附分子 -1

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Analysis of Serum miR-182 and ICAM-1 Expression Levels in Children with Idiopathic Pulmonary Hypertension and Their Correlation with Prognosis

YANG Chun-guang^a, LIU Hai-hong^a, WANG Feng-dong^a, WANG Xiao-jing^a, ZHANG Xue-yu^b, ZHANG Hai-bo^c

(a. Department of Neonatology; b. Department of Clinical Laboratory; c. Department of Pediatrics, Chengde Maternal and Child Health Hospital, Hebei Chengde 067020, China)

Abstract: Objective To investigate the expression of serum micro RNA (miR) -182 and intercellular adhesion molecule-1 (ICAM)-1 in children with idiopathic pulmonary arterial hypertension (IPAH) and their the prognostic value of ICAM-1 in children with idiopathic pulmonary arterial hypertension (IPAH). **Methods** 76 children with IPAH who attended the Pulmonary Hypertension Center of Chengde Maternal and Child Health Hospital from June 2016 to November 2020 were selected for the study (observation group), and another 30 healthy children who underwent physical examination at the hospital during the same period were selected as the control group to compare the serum miR-182 and ICAM-1 levels in the two groups. Routine laboratory tests, cardiac ultrasonography and cardiac catheterization were collected from children with IPAH and followed up with an endpoint event defined as death or undergoing lung transplantation, and the children were divided into survival and death groups according to their prognosis. Logistic regression analysis was used to screen the risk factors affecting the prognosis of

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作者简介: 杨春光 (1982-), 女, 本科, 主治医师, 研究方向: 新生儿疾病, E-mail: haytes3@21cn.com。

children with IPAH, and receiver operating characteristic(ROC) curves were drawn to evaluate the individual and combined predictive value of serum miR-182 and ICAM-1 on the prognosis of children with IPAH. **Results** The levels of serum miR-182 (1.91 ± 0.20) and ICAM-1 levels (305.67 ± 2.46 ng/ml) were higher in the observation group than in the control group (0.15 ± 0.02 , 203.22 ± 21.51 ng/ml), and the differences were statistically significant ($t=-73.624$, -33.698 , all $P<0.05$). 72 children were followed up, of which 21 (29.17%) died and 51 (70.83%) survived. The percentage of NYHA cardiac function class (III ~ IV) in the death group, brain natriuretic peptide (BNP), total bilirubin (TB), red blood cell distribution width (RDW), systolic pulmonary artery pressure (sPAP), total pulmonary resistance (TPR), miR-182 and ICAM-1 levels were higher than those in the survivor group, all with statistically significant differences ($\chi^2=4.138$, $t'=-75.584$, $t=7.231$, 6.197 , 2.464 , 3.930 , $t'=6.783$, 3.328 , all $P<0.05$). NYHA cardiac function class (advanced) (OR=1.681, 95%CI=1.370 ~ 5.128), RDW (OR=2.112, 95%CI=1.212 ~ 5.135), sPAP (OR=2.597, 95%CI=1.052 ~ 6.1425), miR-182 (OR=3.587, 95%CI=1.249 ~ 6.125) and ICAM-1 (OR=3.634, 95%CI=1.135 ~ 5.153) were risk factors affecting the prognosis of children with IPAH (all $P<0.05$). The area under the curve (AUC) of serum miR-182, ICAM-1 to predict the prognosis of children with IPAH was 0.761 and 0.770, respectively, and the combined AUC was 0.883, which was better than each index alone ($Z=-3.236$, -3.211 , all $P<0.05$). **Conclusion** Serum miR-182 and ICAM-1 show abnormally high expression in children with IPAH, both of which would be related to the prognosis of the children and could be used as effective predictors to some extent.

Keywords: idiopathic pulmonary arterial hypertension; miR-182; intercellular adhesion molecule-1

特发性肺动脉高压 (idiopathic pulmonary arterial hypertension, IPAH) 成人发病率为 15 ~ 50 例/100 万人/年, 无特异性临床症状, 易引起右心功能衰竭甚至死亡^[1-2]。相较于成人, 儿童处于生长发育状态, 肺血管生理和病理改变更加特殊, IPAH 患儿的肺动脉压力、肺血管阻力和心脏指数升高更明显, 预后更差, 未经治疗者平均存活时间仅为 10 个月, 1, 3, 5 年生存率分别为 89%, 84% 和 75%^[3]。目前认为 IPAH 可能与遗传多态性、多基因缺陷、细胞因子和生长因子分泌异常有关^[4-5]。微小核糖核酸 (micro RNA, miR) -182 对细胞增殖、分化和凋亡等生物效应具有关键的调控作用, 与肺癌关系密切^[6]。细胞间黏附分子-1 (intercellular adhesion molecule-1, ICAM-1) 表达于血管内皮细胞、气道柱状上皮细胞及肺泡上皮细胞表面, 主要作用是介导细胞黏附、参与免疫应答和调节炎症反应^[7]。既往研究^[8]显示, 微小核糖核酸 (micro RNA) miRNA 可能通过某种机制对 ICAM-1 表达产生影响。本研究旨在探究血清 miR-182 和 ICAM-1 在 IPAH 患儿中的表达及对患儿预后的预测价值, 以期临床诊治、改善 IPAH 患儿预后提供指导。

1 材料与方法

1.1 研究对象 选取 2016 年 6 月 ~ 2020 年 12 月就诊于承德市妇幼保健院肺动脉高压中心的 76 例 IPAH 患儿为研究对象 (观察组), 其中男性 45 例, 女性 31 例; 年龄 1 ~ 10 (5.63 ± 4.26) 岁。纳入标准: ①诊断均符合 PAH 指南^[9]; ②超声心动图检查估测肺动脉收缩压 (systolic pulmonary artery pressure, sPAP) >36 mmHg (1 mmHg=0.133kPa); ③静息状态下右心导管检查肺毛细血管楔压 (pulmonary capillary wedge pressure, PCWP) ≤ 15 mmHg, 肺

血管阻力 (pulmonary vascular resistance, PVR) >3 Wood·U, 肺动脉平均压 (mean pulmonary artery pressure, mPAP) >25 mmHg; ④均具备用药指征; ⑤患儿监护人对本研究均知情同意并签字确认。排除标准: ①诊断为先天性心脏病、结缔组织病相关性 PAH 者; ②由原发肺部疾病或肺栓塞及其他原因引起的 PAH 者; ③并发严重的肝肾功能不全者; ④中途转院或放弃治疗者; ⑤存在用药禁忌证者。另选取同期在医院进行体检的健康儿童 30 例作为对照组, 其中男性 18 例, 女性 12 例; 年龄 1 ~ 9 (5.27 ± 3.82) 岁。两组一般资料比较差异均无统计学意义 ($P>0.05$), 具有可比性。本研究经医院医学伦理委员会审批通过。

1.2 仪器与试剂 SpectraMax M5 多功能酶标仪 (美国 Molecular Devices 公司); miR-182, ICAM-1 试剂盒 (上海江莱生物科技有限公司)。

1.3 方法

1.3.1 治疗方案: 参照儿童 PAH 指南^[10] 给予治疗。

1.3.2 血清 miR-182, ICAM-1 检测: 抽取健康对照组儿童及 IPAH 患儿入院 24h 内的外周静脉血 3 ml, 离心收集上层血清。以 U6 为内参, 提取血清总 RNA, 反转录 cDNA, PCR 共进行 40 个循环, 重复三次, 采用 $2^{-\Delta\Delta Ct}$ 法计算血清 miR-182 相对表达水平。miR-182 上游引物: 5'-GCGCGTGGTTCTAGACTTGC-3', 下游引物: 5'-ATCCAGTGCAGGGTCCGAGG-3'; U6 上游引物: 5'-GCTTCGGCAGCACA TATACTAAAT-3'; 下游引物: 5'-AACGCTTCACG AATTTGCGT-3', 均由上海生工生物工程有限公司合成。采用酶联免疫吸附测定法 (enzyme-linked immuno sorbent assay, ELISA) 测定血清 ICAM-1 水平。

1.3.3 随访及预后分组: 随访至2021年12月, 主要以电话、微信及门诊等形式进行, 记录终点事件(随访终点为全因死亡或接受肺移植术)^[10], 根据终点事件发生与否将所有入组患儿分为存活组和死亡组。

1.3.4 资料收集: 收集IPAH患儿的相关临床资料, 包括性别、年龄、体重、临床症状(青紫、晕厥、咯血、水肿)、P波高尖、NYHA心功能分级、脑钠肽(brain natriuretic peptide, BNP)、尿酸(uric acid, UA)、总胆红素(total bilirubin, TB)、乳酸脱氢酶(lactate dehydrogenase, LDH)、红细胞分布宽度(red cell volume distribution width, RDW)、sPAP, mPAP, 全肺阻力(total pulmonary resistance, TPR)、肺血管阻力指数(pulmonary vascular resistance index, PVRI)、心脏指数(cardiac index, CI)、经皮血氧饱和度、三尖瓣反流速率、左心室舒末径、X线心胸比、治疗方案(单药治疗、双药联合治疗、三药联合治疗)、血清miR-182和ICAM-1水平。

1.4 统计学分析 应用SPSS26.0统计软件处理数据。计数资料以率(%)表示, 组间比较采用 χ^2 检验; 计量资料经正态分布和方差齐性检验后采用均数 \pm 标准差($\bar{x} \pm s$)表示, 组间比较采用独立样本 t 检验, 若方差不齐, 则采用 t' 检验; 预测效能分析采用ROC曲线, 获取曲线下面积、95%可信区间、敏感度、特异度及cut-off值, 不同预测方案间曲线下面积(area under curve, AUC)比较采用DeLong检验, 联合诊断实施Logistic二元回归拟合, 返回预测概率logit(p), 将其作为独立检验变量。 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 观察组与对照组血清miR-182, ICAM-1水平比较 观察组血清miR-182(1.91 ± 0.20), ICAM-1(305.67 ± 32.46 ng/ml)水平均高于对照组(0.15 ± 0.02 , 203.22 ± 21.51 ng/ml), 差异具有统计学意义($t' = -73.624$, -33.698 , 均 $P < 0.001$)。

表1 存活组与死亡组IPAH患儿临床资料比较 [$\bar{x} \pm s$, n (%)]

类别	存活组($n=51$)	死亡组($n=21$)	$\chi^2/t/t'$ 值	P 值
性别				
男性	27 (52.94)	15 (71.43)	2.092	0.148
女性	24 (47.06)	6 (28.57)		
年龄(岁)	5.58 ± 1.35	5.65 ± 1.42	0.197	0.844
体重(kg)	19.58 ± 9.24	19.23 ± 9.86	0.143	0.887
临床症状				
青紫	19 (37.25)	7 (33.33)	0.099	0.753
晕厥	15 (29.41)	6 (28.57)	0.005	0.943
咯血	9 (17.65)	7 (33.33)	2.118	0.146
水肿	8 (15.69)	1 (4.76)	1.623	0.203
P波高尖	10 (19.61)	7 (33.33)	1.554	0.213
NYHA心功能分级				
低级(I~II级)	28 (54.90)	6 (28.57)	4.138	0.042
高级(III~IV级)	23 (45.10)	15 (71.43)		
BNP(ng/L)	322.15 ± 32.54	869.47 ± 70.13	-75.584	< 0.001
UA(μ mol/L)	385.69 ± 40.12	402.52 ± 41.31	1.604	0.113
TB(μ mol/L)	12.52 ± 1.31	15.57 ± 2.23	7.231	< 0.001
LDH(U/L)	290.32 ± 30.15	302.14 ± 31.25	1.496	0.139
RDW[%]	12.42 ± 1.27	14.86 ± 2.01	6.197	< 0.001
sPAP(mmHg)	88.82 ± 12.36	96.41 ± 10.58	2.464	0.016
mPAP(mmHg)	66.85 ± 7.56	70.12 ± 8.13	1.632	0.107
TPR(Wood \cdot U)	27.12 ± 3.01	30.25 ± 3.22	3.930	< 0.001
PVRI(Wood \cdot U \cdot m ²)	15.68 ± 1.83	16.56 ± 2.20	1.741	0.086
CI[L/(min \cdot m ²)	3.71 ± 0.42	3.55 ± 0.36	1.528	0.131
经皮血氧饱和度[%]	96.32 ± 1.23	95.86 ± 1.52	1.345	0.183
三尖瓣反流速率(cm/s)	450.23 ± 46.12	453.68 ± 47.51	0.286	0.776
左心室舒末径(mm)	31.42 ± 6.11	30.64 ± 5.67	0.502	0.617
X线心胸比	0.56 ± 0.06	0.54 ± 0.07	1.224	0.225
治疗方案				
单药治疗	26 (50.98)	14 (66.67)	2.425 ^a	0.298
双药联合治疗	22 (43.14)	5 (23.81)		
三药联合治疗	3 (5.88)	2 (9.52)		
miR-182	1.81 ± 0.19	2.16 ± 0.22	6.782	< 0.001
ICAM-1(ng/ml)	297.64 ± 31.23	325.17 ± 33.54	3.328	< 0.001

2.2 随访结果 对76例IPAH患儿进行随访,共获得72例随访结果,总体随访率为94.74%,失访4例,失访率为5.26%;获得随访的72例IPAH患儿死亡21例(29.17%),其中因感染、腹泻等所致右心衰竭死亡15例(71.43%),因大咯血窒息死亡6例(28.57%),存活51例(70.83%)。

2.3 存活组与死亡组IPAH患儿临床资料比较 见表1。死亡组NYHA心功能分级(高级)占比、BNP、TB、RDW、sPAP、TPR、miR-182、ICAM-1水平均高于存活组,差异有统计学意义(均 $P < 0.05$);两组性别、年龄、体重、临床症状、P波高尖、UA、LDH、mPAP、PVRI、CI、经皮血氧饱和度、三尖瓣反流速率、左心室舒末径、X线心胸比、治疗方案比较差异无统计学意义(均 $P > 0.05$)。

2.4 影响IPAH患儿预后的多因素Logistic回归分析 见表2。多因素Logistic回归分析显示,NYHA心功能分级(高级)、RDW、sPAP、miR-182、ICAM-1是影响IPAH患儿预后的危险因素(P

< 0.05)。

表2 影响IPAH患儿预后的多因素Logistic回归分析

变量	β	S.E	Wals	OR (95%CI)	P值
NYHA心功能分级	0.537	0.081	15.637	1.681 (1.370 ~ 5.128)	< 0.001
BNP	-0.463	0.169	3.878	0.575 (0.085 ~ 1.064)	0.168
TB	-0.276	0.167	3.052	0.638 (0.251 ~ 1.305)	0.203
RDW	0.552	0.053	26.391	2.112 (1.212 ~ 5.135)	< 0.001
sPAP	0.478	0.062	28.937	2.597 (1.052 ~ 6.142)	< 0.001
TPR	-0.214	0.183	2.861	0.779 (0.370 ~ 1.157)	0.223
miR-182	0.452	0.071	32.532	3.587 (1.249 ~ 6.125)	< 0.001
ICAM-1	0.481	0.067	33.368	3.634 (1.135 ~ 5.153)	< 0.001

2.5 血清miR-182、ICAM-1对IPAH患儿预后的预测价值 见表3,图1。血清miR-182、ICAM-1预测IPAH患儿预后具有较高的敏感度和特异度,同时联合检测的效能高于独立检测($Z = -3.236$, $P = 0.012$; $Z = -3.211$, $P = 0.009$)。

表3 血清miR-182、ICAM-1对IPAH患儿预后的预测价值

项目	AUC	95%CI	P值	截断值	敏感度(%)	特异度(%)
miR-182	0.761	0.673 ~ 0.849	< 0.001	1.95	74.30	66.10
ICAM-1	0.770	0.683 ~ 0.856	< 0.001	308.62 ng/ml	75.70	67.90
二者联合	0.883	0.824 ~ 0.941	< 0.001		87.10	62.50

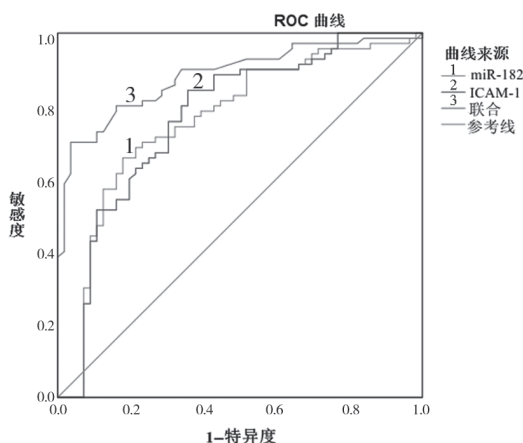


图1 血清miR-182、ICAM-1对IPAH患儿预后的预测价值

3 讨论

目前研究认为特发性肺动脉高压(IPAH)发病机制主要与细胞、体液介质、分子遗传等多个因素有关^[11]。肺血管系统较复杂,易受多种血管活性物质影响,如血管紧张素II、血栓素A2等能使肺循环微动脉收缩,心房利钠肽、一氧化氮等可使肺血管舒张,上述血管介质一旦失衡就易引发IPAH^[12]。相关资料^[13]显示,大部分IPAH患者的血清炎症细胞因子呈现异常高表达,且免疫指标(如抗核抗体)为阳性,并具有免疫系统疾病特有的雷

诺现象,推测免疫炎症紊乱可能参与了IPAH的发病机制。国外报道儿童IPAH发病率为10例/100万,但该病起病隐匿,患儿症状差异较明显,临床诊断难度较大,极易导致漏诊和误诊^[5]。故寻找安全高效的血清学诊断或预后预测指标尤为重要。

在本研究中,IPAH患儿血清miR-182和ICAM-1水平明显高于健康儿童,提示血清miR-182和ICAM-1水平在IPAH患儿中呈现异常高表达,上述指标可能与IPAH发病机制有关,临床诊断或治疗中需要给予重点监测。miR-182通常被认为是原癌基因在肿瘤的高表达,并促进肿瘤细胞增殖,例如miR-182在乳腺癌中高表达,通过靶向叉头蛋白F2促进肿瘤细胞增殖和迁移;在结肠癌中高表达,通过磷脂酰肌醇3激酶/蛋白激酶B信号通路维持肿瘤细胞的干细胞状态;在胶质瘤中高表达,通过靶向果糖-2,6-二磷酸酶2提高肿瘤细胞增殖及侵袭能力^[14-16]。近年来大量临床研究或基础研究均表明,miRNA在心血管系统信号网络调控中起到重要作用,参与IPAH中血管收缩和重构中多物质的调控^[17-18]。此外,研究者发现还有更多的miRNA在IPAH患者中存在异常表达,但迄今为止,仅有数种miRNA被通过实验证明确实在IPAH的发生、发展中发挥一定的作用。目前研究显示,IPAH患

者 miRNA 表达谱中共有 78 个差异表达位点, 其中 62 个显示上调, 16 个下调, 包括 miR-17-92, miR-143/145, miR-21 和 miR-124 等, 在肺血管收缩和重构各个环节中发挥功能, 不仅调控血管内皮细胞和成纤维细胞的增殖、凋亡、促进血管新生, 还参与血管平滑肌细胞增殖、凋亡及表型转化等过程^[19]。如郭天聪等^[20]研究发现, miR-182 在 IPAH 患者中上调, 并通过调节肌细胞增强因子 2C 促进平滑肌细胞增殖, 参与 IPAH 发病机制。在 IPAH 患者中, 内皮细胞无序增殖即为肺血管重塑形成, 显示为丛状病灶, 而肺组织学检查发现该病灶周围存在 T 细胞、B 细胞、巨噬细胞及树突状细胞浸润, 提示炎症细胞可能参与 IPAH 发生发展^[21]。ICAM-1 是一种细胞表面糖蛋白, 参与并介导细胞与细胞、细胞与细胞外基质间的相互黏附, 是炎症反应形成的基础, 在体外循环肺损伤的炎症反应过程中起重要作用^[22]。如钟士杰等^[23]研究显示, 车前草提取物可通过降低缺氧性肺动脉高压 SD 大鼠模型泡灌液液中 ICAM-1 等炎症因子水平, 改善肺动脉及气道重塑。基于上述分析不难发现, miR-182 与 ICAM-1 极有可能参与 IPAH 发生发展, 当然这需要进一步验证。

随着 PAH 靶向药物的应用, 发达国家 IPAH 患儿的生存率得到了明显改善, 但不同国家对这些药物的使用并不完全相同, 我国 IPAH 患儿的预后也尚未完全清楚。在本研究中, 获得随访的 72 例 IPAH 患儿死亡率为 29.17% (21/72), 与朱燕等^[24]报道的 28.9% (11/38) 基本一致。死亡组 NYHA 心功能分级 (高级) 占比, BNP, TB, RDW, sPAP, TPR, miR-182 和 ICAM-1 水平均高于存活组, Logistic 回归分析显示, NYHA 心功能分级 (高级)、RDW, sPAP, miR-182 和 ICAM-1 是影响 IPAH 患儿预后的危险因素。上述研究结果再次提示 miR-182 和 ICAM-1 在 IPAH 的发生发展中占据重要地位, 两种因子联合预测 IPAH 患儿预后的 AUC 为 0.883, 敏感度和特异度分别为 87.10%, 62.50%, 优于各指标单独预测, 提示 miR-182, ICAM-1 与 IPAH 患儿预后关系密切, 可能是反映 IPAH 患儿预后的敏感指标, 联合检查可在一定程度上提高预测效能, 为临床预测 IPAH 患儿预后提供更准确的数据参考, 对该类 IPAH 预防、控制与治疗具有重要意义。但本研究病例样本有限, 可能存在一定的数据偏倚, 后续需收集更多病例做更深入研究, 以获取更为可靠的数据支持。

综上所述, IPAH 患儿血清 miR-182 和 ICAM-1 表达水平较高, 二者联合检测在预测其预后情况方面具有较高临床应用价值, 可为 IPAH 患儿的诊断、

预防及治疗提供参考。

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