

doi: 10.13241/j.cnki.pmb.2022.05.030

血清 miR-34b-5p、miR-155 表达与早产儿急性呼吸窘迫综合征炎症因子和预后的关系分析 *

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摘要 目的:探讨血清微小核糖核酸(miR)-34b-5p、miR-155 表达与早产儿急性呼吸窘迫综合征(ARDS)炎症因子和预后的关系。**方法:**选择 2019 年 2 月至 2021 年 3 月我院收治的 92 例 ARDS 早产儿,根据 ARDS 病情严重程度将其分为轻度组(31 例)、中度组(43 例)和重度组(18 例),追踪患儿临床结局,根据院内死亡情况将其分为存活组(51 例)和死亡组(41 例)。检测所有患儿的血清 miR-34b-5p、miR-155 表达水平以及白细胞介素-1 β (IL-1 β)、肿瘤坏死因子- α (TNF- α)、白细胞介素-6(IL-6)水平,比较各组间上述指标差异,分析 ARDS 早产儿血清 miR-34b-5p、miR-155 表达与炎症因子的相关性以及 miR-34b-5p、miR-155 预测 ARDS 早产儿预后的价值。**结果:**重度组 miR-155 表达水平及 IL-1 β 、TNF- α 、IL-6 水平均高于中度组和轻度组,且中度组高于轻度组($P<0.05$),重度组 miR-34b-5p 表达水平低于中度组和轻度组,且中度组低于轻度组($P<0.05$)。死亡组 miR-155 表达水平及 IL-1 β 、TNF- α 、IL-6 水平高于存活组($P<0.05$),死亡组 miR-34b-5p 表达水平低于存活组($P<0.05$)。ARDS 早产儿 miR-155 表达水平与 IL-1 β 、TNF- α 、IL-6 水平均呈正相关,而 miR-34b-5p 表达水平与 IL-1 β 、TNF- α 、IL-6 水平均呈负相关($P<0.05$)。联合 miR-34b-5p、miR-155 预测 ARDS 早产儿死亡的曲线下面积(AUC)为 0.853,高于两指标单独预测的 0.688、0.649。**结论:**ARDS 早产儿血清 miR-34b-5p、miR-155 表达水平与患儿血清炎症因子水平以及预后有关,可作为 ARDS 早产儿病情评估以及预后预测的潜在指标。**关键词:**早产儿;急性呼吸窘迫综合征;miR-34b-5p;miR-155;炎症因子;预后
中图分类号:R714.21 **文献标识码:**A **文章编号:**1673-6273(2022)05-945-05

Relationship Analysis between Expression of Serum miR-34b-5p and miR-155 and Inflammatory Factors and Prognosis of Premature Infants with Acute Respiratory Distress Syndrome*

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ABSTRACT Objective: To investigate the relationship between the expression of serum micro ribonucleic acid (miR)-34b-5p and miR-155 and the inflammatory factors and prognosis of premature infants with acute respiratory distress syndrome (ARDS). **Methods:** 92 premature infants with ARDS who were admitted to our hospital from February 2019 to March 2021 were selected, and they were divided into mild group (31 cases), moderate group (43 cases) and severe group (18 cases) according to the severity of ARDS, follow up the clinical outcome of children, according to the death in hospital, they were divided into survival group (51 cases) and death group (41 cases). The expressions of serum miR-34b-5p and miR-155, as well as interleukin-1 β (IL-1 β), tumor necrosis factor - α (TNF- α) and interleukin-6 (IL-6) in all the children were detected. The differences of the above indexes among the groups were compared, the correlation between the expressions of serum miR-34b-5p and miR-155 and inflammatory factors and the value of miR-34b-5p and miR-155 in predicting the prognosis of premature infants with ARDS were analyzed. **Results:** The expression levels of serum miR-155 and the levels of IL-1 β , TNF- α and IL-6 in the severe group were higher than those in the moderate group and mild group, and those in moderate group were higher than those in mild group ($P<0.05$). The expression level of serum miR-34b-5p in the severe group was lower than that in moderate and mild groups, and that in moderate group was lower than that in mild group ($P<0.05$). The expression level of serum miR-155 in the death group was higher than that in the survival group ($P<0.05$), and the expression level of miR-34b-5p in the death group was lower than those in the survival group ($P<0.05$). The expression level of miR-155 was positively correlated with the levels of IL-1 β , TNF- α and IL-6 in premature infants with ARDS($P<0.05$), and the expression level of miR-34b-5p was negatively correlated with the levels of IL-1 β , TNF- α and IL-6($P<0.05$). The area under curve(AUC) of miR-34b-5p and miR-155 predicting premature infant death

* 基金项目:山东省医药卫生科技发展计划项目(2019WSB03007)

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(收稿日期:2021-07-22 接受日期:2021-08-17)

in ARDS was 0.853, which was higher than 0.688 and 0.649 predicted by the two indexes alone. **Conclusion:** The expression levels of serum miR-34b-5p and miR-155 in premature infants with ARDS are related to the levels of serum inflammatory factors and prognosis, which can be used as potential indexes for condition evaluation and prognosis prediction of premature infants with ARDS.

Key words: Premature infants; Acute respiratory distress syndrome; miR-34b-5p; miR-155; Inflammatory factors; Prognosis

Chinese Library Classification(CLC): R714.21 **Document code:** A

Article ID: 1673-6273(2022)05-945-05

前言

早产儿肺组织发育不成熟,缺乏足够的表面活性剂,易发生急性呼吸窘迫综合征(ARDS),是新生儿早期死亡和残疾的主要原因^[1]。ARDS是以肺气体交换功能突然下降和难治性低氧血症为特征的临床综合征,其主要病理特征是肺血管内皮通透性和血管外肺水增加。炎症因子和介质大量释放和激活,促炎和抗炎因子失衡导致肺组织损害是ARDS发病的主要病理基础^[2,3]。微小核糖核酸(miRNAs)转录后水平调节多种蛋白质表达,参与炎症反应调节,在肺损伤中发挥重要作用^[4,5]。miR-34b-5p在脂多糖诱导的ARDS大鼠模型中表达下调,参与肺部炎症反应过程^[6],miR-155在脓毒症ARDS患者血浆中高表达,诊断ARDS具有较高的敏感性和特异性^[7]。鉴于此,本研究拟检测ARDS早产儿血清miR-34b-5p、miR-155表达水平,分析其与ARDS早产儿血清炎症因子以及预后的关系,旨在为早产儿ARDS病情评估以及预后预测提供参考。

1 资料与方法

1.1 临床资料

选择2019年2月至2021年3月我院收治的92例ARDS早产儿,其中男59例,女33例;胎龄28~36周,平均(31.93±2.69)周。纳入标准:①符合《新生儿急性呼吸窘迫综合征蒙特勒标准(2017年版)》中的诊断标准^[8];②经相关检查(胸部X线片检查提示双肺弥散性透光度下降、渗出或白肺,肺部超声检查提示肺水肿,动脉血气分析氧合指数(PaO₂/FiO₂)下降,低于300 mmHg)结合症状确诊;③胎龄在28~36周;④急性起病,入住重症监护室治疗。排除标准:①先天性心脏病、先天性肺和胸壁畸形;②原发性肺泡表面活性物质缺乏;③合并严重的肺外感染,自身免疫疾病和血液疾病;④临床资料缺失,中途转院无法追踪临床结局。根据氧合指数将患儿分为轻度组(201~300 mmHg,31例)、中度组(101~200 mmHg,43例)和重度组(≤100 mmHg,18例)^[9]。轻度组,男19例,女12例,胎龄28~36周,平均(32.02±2.28)周;出生体质量1.02~2.49 kg,平均(2.01±0.35)kg;病因:窒息3例,胎粪吸入6例,肺炎16例,败血症6例。中度组:男29例,女14例,胎龄29~36周,平均(31.85±2.31)周;出生体质量1.05~2.40 kg,平均(1.98±0.32)kg;病因:窒息6例,胎粪吸入10例,肺炎20例,败血症7例。重度组:男11例,女7例,胎龄28~36周,平均(31.97±2.40)周;出生体质量1.10~2.411 kg,平均(2.09±0.34)kg;病因:窒息2例,胎粪吸入4例,肺炎10例,败血症2例。三组患儿家属均知情同意签署同意书,基线资料比较无统计学差异($P>0.05$),本研究获得我院伦理会批准。

1.2 miR-34b-5p、miR-155和炎症因子检测

(1)血标本采集和处理:确诊次日采集所有患儿空腹静脉血3 mL注入干燥试管,待血液凝固后取上层液离心(1500 rpm,半径10 cm,时间5 min),取上清液-20℃保存备检。(2)miR-34b-5p、miR-155检测:取血清样本,加入1 mL TRIzol(美国Invitrogen公司),根据说明书流程提取总RNA,Agilent 2100生物分析仪(美国Agilent公司)评估RNA质量,M-MLV逆转录酶(美国Promega公司)将RNA逆转录为cDNA。采用StepOnePlus™实时荧光定量PCR系统(美国赛默飞Applied Biosystems)进行三次重复qRT-PCR分析,反应体系包括:DNA模板2 μL,上下游引物各1 μL,Premix Ex Taq DNA聚合酶25 μL,RNase-Free ddH₂O 21 μL。反应条件:95℃预变性3 min,98℃变性2 s,67℃退火15 s,72℃延伸20 s,循环30次。采用比较循环阈值(2^{-ΔΔCt})法计算miR-34b-5p、miR-155相对表达水平。引物设计上海捷瑞公司合成,引物序列:miR-34b-5p,上游:5'-AGGCAGUGUAAUAGCUGAUUGU-3',下游:5'-AAUC-AGCUAAUACACUGCCUUU-3',扩增133bp。miR-155,上游:5'-CCTGCACTCAGGGCTGCCAACACT-3',下游:5'-GGCAT-CATTGCCGCACGAATCAGC-3',扩增105bp。β-actin(内参)上游:5'-TGTCCACCTTCCAGCAGATGT-3',下游:5'-GCT-CAGTAACAGTCCGCCTAGA-3'。(3)炎症因子检测:仪器选用SuPerMax 3000FA型多功能酶标仪(上海闪谱生物科技有限公司),取血清样本,采用酶联免疫吸附试验检测血清白细胞介素-1β(IL-1β)、肿瘤坏死因子-α(TNF-α)、白细胞介素-6(IL-6)水平,试剂盒购自上海酶联生物有限公司。

1.3 临床结局追踪

所有患儿自数字化病历系统追踪临床结局,统计住院期间死亡情况,并据此将患儿分为死亡组(41例)和存活组(51例)。

1.4 统计学分析

应用SPSS 25.0软件进行数据分析,计量资料经Kolmogorov-Smirnov检验符合正态分布,以($\bar{x} \pm s$)表示,比较采用单因素方差分析(两两对比采用LSD-t检验)或独立样本t检验。以率(%)表示计数资料,比较采用 χ^2 检验。采用Pearson相关分析ARDS早产儿血清miR-34b-5p、miR-155表达与炎症因子相关性。采用受试者工作特征曲线(ROC)分析miR-34b-5p、miR-155预测ARDS早产儿死亡的价值,检验水准 $\alpha=0.05$ 。

2 结果

2.1 不同病情严重程度ARDS早产儿血清miR-34b-5p、miR-155表达及炎症因子水平比较

重度组血清miR-155表达水平及IL-1β、TNF-α、IL-6水平均高于中度组和轻度组,且中度组高于轻度组($P<0.05$);重度组血清miR-34b-5p表达水平低于中度组和轻度组,且中度组低于轻度组($P<0.05$)。见表1。

表 1 不同病情严重程度 ARDS 早产儿血清 miR-34b-5p、miR-155 表达及炎症因子水平比较($\bar{x} \pm s$)Table 1 Comparison of expressions of serum miR-34b-5p, miR-155 and the levels of inflammatory factor in premature infants with ARDS of different severity($\bar{x} \pm s$)

Groups	n	miR-34b-5p($2^{-\Delta\Delta C_t}$)	miR-155($2^{-\Delta\Delta C_t}$)	IL-1 β (pg/mL)	TNF- α (μ g/L)	IL-6(pg/mL)
Mild group	31	1.39 $\pm$ 0.22	1.02 $\pm$ 0.35	58.12 $\pm$ 9.25	5.98 $\pm$ 1.35	9.65 $\pm$ 2.03
Moderate group	43	0.92 $\pm$ 0.30 [°]	2.62 $\pm$ 0.69 [°]	65.08 $\pm$ 11.37 [°]	8.13 $\pm$ 2.49 [°]	13.05 $\pm$ 3.17 [°]
Severe group	18	0.75 $\pm$ 0.23 ^{° °}	3.32 $\pm$ 0.74 ^{° °}	80.12 $\pm$ 13.45 ^{° °}	12.06 $\pm$ 3.75 ^{° °}	16.35 $\pm$ 4.59 ^{° °}
F		43.025	98.902	22.268	33.818	26.162
P		0.000	0.000	0.000	0.000	0.000

Note: compared with mild group, [°] $P < 0.05$. Compared with the moderate group, [°] $P < 0.05$.

2.2 不同预后 ARDS 早产儿血清 miR-34b-5p、miR-155 表达及炎症因子水平比较 高于存活组($P < 0.05$);死亡组 miR-34b-5p 表达水平低于存活组($P < 0.05$)。见表 2。

死亡组血清 miR-155 表达水平及 IL-1 β 、TNF- α 、IL-6 水平表 2 不同预后 ARDS 早产儿血清 miR-34b-5p、miR-155 表达及炎症因子水平比较($\bar{x} \pm s$)Table 2 Comparison of expressions of serum miR-34b-5p, miR-155 and the levels of inflammatory factor in premature infants with ARDS with different prognosis($\bar{x} \pm s$)

Groups	n	miR-34b-5p($2^{-\Delta\Delta C_t}$)	miR-155($2^{-\Delta\Delta C_t}$)	IL-1 β (pg/mL)	TNF- α (μ g/L)	IL-6(pg/mL)
Survival group	51	1.45 $\pm$ 0.46	1.58 $\pm$ 0.39	54.06 $\pm$ 5.49	5.85 $\pm$ 1.69	10.71 $\pm$ 3.02
Death group	41	0.54 $\pm$ 0.12	3.01 $\pm$ 0.36	80.13 $\pm$ 6.35	11.06 $\pm$ 2.17	14.84 $\pm$ 1.69
t		12.322	18.085	21.101	12.949	7.841
P		0.000	0.000	0.000	0.000	0.000

2.3 ARDS 早产儿血清 miR-34b-5p、miR-155 表达与炎症因子的相关性分析 IL-6 水平均呈正相关($P < 0.05$), 而 miR-34b-5p 表达水平与 IL-1 β 、TNF- α 、IL-6 水平均呈负相关($P < 0.05$)。见表 3。

ARDS 早产儿血清 miR-155 表达水平与 IL-1 β 、TNF- α 、

表 3 ARDS 早产儿血清 miR-34b-5p、miR-155 表达与炎症因子的相关性分析

Table 3 Correlation analysis between serum miR-34b-5p, miR-155 expression and inflammatory factors in premature infants with ARDS

Indexes	IL-1 β		TNF- α		IL-6	
	r	P	r	P	r	P
miR-34b-5p	-0.538	0.000	-0.468	0.002	-0.507	0.001
miR-155	0.602	0.000	0.513	0.000	0.461	0.003

2.4 血清 miR-34b-5p、miR-155 预测 ARDS 早产儿死亡的价值分析 积(AUC)分别为 0.688、0.649,而联合 miR-34b-5p、miR-155(取各自界值)预测 ARDS 早产儿死亡的 AUC 为 0.853,见表 4 和图 1。

miR-34b-5p、miR-155 预测 ARDS 早产儿死亡的曲线下

表 4 血清 miR-34b-5p、miR-155 预测 ARDS 早产儿死亡的价值分析

Table 4 Value analysis of serum miR-34b-5p and miR-155 in predicting death of premature infants with ARDS

Factors	AUC(95%CI)	Threshold	Sensitivity	Specificity	Youden index
miR-34b-5p	0.688(0.577~0.798)	1.03	28/41	35/51	0.4252
miR-155	0.649(0.528~0.770)	2.45	29/41	38/51	0.3374
Two unite	0.853(0.758~0.947)	-	35/41	45/51	0.7998

3 讨论

早产可引起支气管肺发育不良、肺炎、呼吸暂停、肺间质肺气肿、ARDS 等呼吸系统并发症^[9],其中 ARDS 是最为严重的呼

吸系统并发症,是新生儿死亡的主要原因^[10,11]。ARDS 是肺部急性炎症反应过程,肺泡中性粒细胞聚集释放大趋化因子、炎症因子,诱导局部剧烈炎症反应,损伤肺泡毛细血管膜,导致血管通透性增加,肺间质和肺泡水肿,从而导致急性低氧性呼吸衰竭^[12,13]。miRNAs 是一类天然存在的小非编码 RNA,作为基因表达的转录后调节剂,miRNAs 可调节靶向信使 RNA 的稳定性和翻译,参与所有细胞过程,包括炎症反应,与 ARDS 发病密切相关^[14,15]。

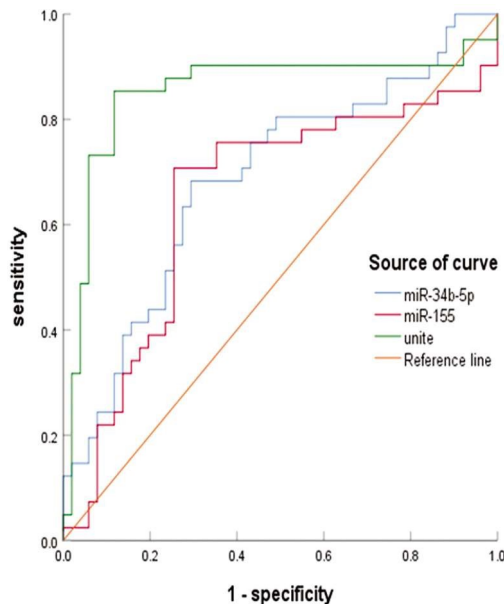


图1 miR-34b-5p、miR-155 预测 ARDS 早产儿死亡的 ROC 图

Fig.1 ROC diagram of miR-34b-5p and miR-155 predicting premature infant death in ARDS

miR-34b-5p 属于 miR-34 家族,是众所周知的抑癌因子,可下调血管内皮生长因子 A 表达抑制新生血管形成^[16],抑制细胞增殖活力、迁移和侵袭^[17]。除了抑癌作用外,miR-34b-5p 可调控肌管形成^[18],还可调控核因子- κ B 信号传导^[19],核因子- κ B 是调节免疫应答和炎症反应的重要因子^[20],miR-34b-5p 可能通过调控核因子- κ B 参与免疫应答和炎症反应的调节。miR-34b-5p 亦广泛表达于肺组织中,可抑制其下游靶基因 TIMP3 表达,抵抗博来霉素诱导的肺纤维化进程^[21],miR-34b-5p 还可下调黏蛋白表达基因 MUC5AC 表达,其表达缺失则导致气道黏液过度分泌和积累,纤毛细胞减少,引起气道阻塞、黏膜瘀滞,增加呼吸道合胞病毒感染风险^[22]。本研究结果显示 ARDS 早产儿血清 miR-34b-5p 表达水平随着患儿病情加重而降低,且与患儿院内结局有关,说明 miR-34b-5p 可作为 ARDS 早产儿病情评估和预后预测的指标。本研究相关性分析结果显示 miR-34b-5p 表达与血清 IL-1 β 、TNF- α 、IL-6 水平呈负相关,提示 miR-34b-5p 表达缺失可能导致其抗炎作用减弱,进而加剧炎症反应参与早产儿 ARDS 发病过程。

miR-155 是炎症和免疫反应的主要调节因子,可调节树突状细胞、巨噬细胞、B 细胞以及 CD8⁺ 和 CD4⁺T 细胞分化^[23,24],在宿主防御病原体和防止过度炎症介导的损伤中发挥重要作用^[25]。miR-155 可通过调控 CCAAT/ 增强子结合蛋白 β 、含 SH2 结构域的肌醇 5- 磷酸酶 1 和白细胞 -13 受体 α 2 促使巨噬细

胞向 M1 表型转化诱导炎症反应^[26],miR-155 还受 Toll 样受体信号调节,参与炎症性疾病进展^[27],miR-155 表达缺失可阻止酒精诱导的脂肪性肝炎,阻止肝纤维化进程^[28]。miR-155 与呼吸系统疾病亦存在密切关系,现有研究显示 miR-155 分别通过靶向含 SH2 结构域的肌醇 5- 磷酸酶 1 和细胞因子信号抑制因子 -1 促进巨噬细胞增殖,刺激核因子 κ B 活化,诱导 TNF- α 和 IL-6 的产生,导致急性肺炎发病^[28]。本研究发现 miR-155 同样与早产儿 ARDS 发病有关,血清 miR-155 表达水平随着 ARDS 病情加重而升高,死亡组血清 miR-155 表达高于存活组,提示 miR-155 可能参与早产儿 ARDS 发病和进展过程,可能的机制为:首先,miR-155 通过靶向调控干扰素调节因子 2 结合蛋白 2 表达,激活活化 T 细胞核因子 1,导致诱导型一氧化氮合酶引起炎症反应,进一步导致急性肺损伤^[29]。其次,miR-155 还可通过调节促血管生成素-1、-2 及其受体 Tie2 通路诱导炎症反应,促使肺中性粒细胞浸润,肺血管渗漏和肺水肿^[30]。本研究相关性分析显示 miR-155 与 IL-1 β 、TNF- α 、IL-6 呈正相关,也支持 miR-155 通过诱导炎症反应参与早产儿 ARDS 发病过程的结论。

本研究 ROC 曲线分析结果还验证了 miR-34b-5p、miR-155 在 ARDS 早产儿预后中的预测价值,且联合两项指标后预测效能更高,提示 miR-34b-5p、miR-155 可作为早产儿 ARDS 疾病进展结局的辅助性预测指标。

综上,ARDS 早产儿血清 miR-34b-5p、miR-155 表达与 ARDS 病情加重以及不良预后有关。miR-34b-5p、miR-155 可能通过调控炎症反应参与早产儿 ARDS 发病和进展过程。

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