

高血压并发冠状动脉粥样硬化性心脏病患者血清 miR-27a-3p 和 HOXC6 水平表达与冠状动脉病变的相关性研究

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摘要: 目的 探讨高血压并发冠状动脉粥样硬化性心脏病(冠心病)患者血清微小核糖核酸-27a-3p(miR-27a-3p)和同源异型盒C6(homeobox C6, HOXC6)水平表达与冠状动脉病变的相关性,为高血压并发冠心病的防治提供一定参考。方法 选取北大荒集团总医院2021年6月~2023年6月接诊的246例高血压患者为研究对象,其中129例高血压并发冠心病患者作为并发组,117例单纯高血压患者作为未并发组。采用实时荧光定量PCR(quantitative real time PCR, qRT-PCR)检测血清miR-27a-3p和HOXC6表达水平;运用Spearman法分析高血压并发冠心病患者血清miR-27a-3p和HOXC6水平与冠状动脉病变的相关性;多因素Logistic回归分析高血压并发冠心病的影响因素;受试者工作特征(receiver operating characteristic, ROC)曲线分析血清miR-27a-3p, HOXC6水平对高血压并发冠心病的预测价值。结果 并发组高血压病程(6.69 ± 1.35 年)、总胆固醇(total cholesterol, TC)(5.96 ± 0.86 mmol/L)、低密度脂蛋白-胆固醇(low-density lipoprotein cholesterol, LDL-C)(3.36 ± 0.51 mmol/L)均显著高于未并发组(5.87 ± 1.32 年, 5.42 ± 0.67 mmol/L, 2.98 ± 0.48 mmol/L),并发组血清miR-27a-3p(1.35 ± 0.34), HOXC6(1.29 ± 0.33)水平均显著高于未并发组(1.06 ± 0.23 , 1.03 ± 0.25),差异具有统计学意义($t=4.808, 5.454, 6.001, 7.755, 6.911$, 均 $P < 0.05$);轻度组、中度组、重度组患者血清miR-27a-3p($0.54 \pm 0.13, 1.19 \pm 0.31, 2.18 \pm 0.55$)和HOXC6($0.47 \pm 0.12, 1.12 \pm 0.31, 2.13 \pm 0.52$)表达水平逐渐升高,差异具有统计学意义($F=191.026, 191.026$, 均 $P < 0.05$)。高血压并发冠心病患者血清miR-27a-3p, HOXC6与SYNTAX评分呈正相关性($r=0.563, 0.517$, 均 $P < 0.05$);血清miR-27a-3p[OR(95%CI: 1.627(1.177 ~ 2.248))、HOXC6[OR(95%CI: 1.715(1.069 ~ 2.750))]是影响高血压并发冠心病的独立危险因素($P < 0.05$);血清miR-27a-3p和HOXC6联合预测高血压并发冠心病的AUC为0.896(95%CI: 0.851 ~ 0.931),优于各自单独诊断($Z=2.133, 2.815$, 均 $P < 0.05$)。结论 高血压并发冠心病患者血清miR-27a-3p, HOXC6水平均显著升高,且与冠状动脉病变密切相关,二者联合对高血压并发冠心病具有较高的预测价值。

关键词: 微小核糖核酸-27a-3p; 同源异型盒C6; 高血压; 冠状动脉粥样硬化性心脏病; 冠状动脉病变

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Correlation between Serum miR-27a-3p and HOXC6 Levels and Coronary Artery Disease in Patients with Hypertension Complicated with Coronary Atherosclerotic Heart Disease

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Abstract: Objective To investigate the correlation between serum microRNA (miR)-27a-3p and homeobox C6 (HOXC6) levels expression and coronary artery disease in patients with hypertension complicated by coronary atherosclerotic heart disease (CHD), and provide some references for the prevention and treatment of hypertension complicated with coronary heart disease.

Methods A total of 246 hypertensive patients accepted by Beidahuang Group General Hospital from June 2021 to June 2023 were collected as the study subjects, with 129 hypertensive patients complicated with coronary heart disease as the concurrent group and 117 simple hypertensive patients as the non concurrent group. Quantitative real time fluorescent PCR (qRT-PCR) was applied to detect the expression levels of miR-27a-3p and HOXC6 in serum. Spearman method was applied to analyze the correlation between serum miR-27a-3p and HOXC6 levels and coronary artery disease in hypertensive patients with coronary heart disease. Multivariate logistic regression was applied to analyze the influencing factors of hypertension complicated with coronary heart disease. Receiver operating characteristic (ROC) curve was applied to analyze the predictive value of serum miR-27a-3p and HOXC6 levels for hypertension complicated with coronary heart disease. **Results** The course of

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hypertension(6.69 ± 1.35 年), total cholesterol (TC)(5.96 ± 0.86 mmol/L) and low-density lipoprotein cholesterol (LDL-C)(3.36 ± 0.51 mmol/L) in the concurrent group were higher than those in the non concurrent group(5.87 ± 1.32 年, 5.42 ± 0.67 mmol/L, 2.98 ± 0.48 mmol/L), the serum levels of miR-27a-3p(1.35 ± 0.34) and HOXC6(1.29 ± 0.33) in the concurrent group were higher than those in the non concurrent group(1.06 ± 0.23 , 1.03 ± 0.25), and the differences were statistically significant ($t=4.808$, 5.454 , 6.001 , 7.755 , 6.911 , all $P<0.05$). The expression levels of miR-27a-3p (0.54 ± 0.13 , 1.19 ± 0.31 , 2.18 ± 0.55) and HOXC6 (0.47 ± 0.12 , 1.12 ± 0.31 , 2.13 ± 0.52) in mild, moderate and severe groups were gradually increased, and the differences were significant ($F=191.026$, 191.026 , all $P<0.05$). There were positive correlations between serum miR-27a-3p, HOXC6, and SYNTAX scores in patients with hypertension complicated by coronary heart disease ($r=0.563$, 0.517 , all $P<0.05$). Serum miR-27a-3p [OR(95%CI): $1.627(1.177 \sim 2.248)$] and HOXC6 [OR(95%CI): $1.715(1.069 \sim 2.750)$] were independent risk factors for hypertension complicated with coronary heart disease (all $P<0.05$). The combination of miR-27a-3p and HOXC6 levels had an area under the curve (AUC) of 0.896 (95%CI: $0.851 \sim 0.931$) for predicting hypertension complicated with coronary heart disease, which was superior to their respective individual diagnoses ($Z=2.133$, 2.815 , all $P<0.05$).

Conclusion The serum levels of miR-27a-3p and HOXC6 in patients with hypertension complicated by coronary heart disease were increased, which was closely related to coronary artery disease. The combination of the two has a high predictive value for hypertension complicated with coronary heart disease.

Keywords: micro RNA-27a-3p; homeobox C6; hypertension; coronary atherosclerotic heart disease; coronary artery disease

高血压是缺血性心脏病、卒中、其他心血管疾病及痴呆等最重要的危险因素之一,亦是全球和世界大多数地区心血管疾病死亡和疾病负担的主要原因^[1-2]。血压若长期处于偏高状态会使动脉血管逐渐硬化,有助于动脉粥样硬化斑块形成,导致动脉血管狭窄甚至闭塞出现供血不足,从而引发冠状动脉粥样硬化性心脏病(冠心病)和脑血管疾病等^[3]。大约有65%冠心病患者伴有高血压疾病,且高血压患者并发冠心病比血压正常者的发生概率要高^[4]。因此,探寻敏感血清指标协助评估高血压并发冠心病发生风险,对降低高血压患者的死亡率有重要意义。微小核糖核酸(microRNA, miRNA, miR)由内源性、小的单链天然存在的非编码RNA组成,在心血管疾病、炎症反应、免疫系统中扮演重要角色^[5]。miRNA-27a-3p在乳腺癌、肝细胞癌及多种炎症性疾病均有表达,且在其中促进癌细胞和炎症的发展过程^[6]。同源盒基因6(homeobox C6, HOXC6)属于HOX基因家族,是一种进化上高度保守的多基因家族,也是调节胚胎发育以及体内细胞生长和分化的重要基因^[7]。然而,关于血清miR-27a-3p和HOXC6在高血压并发冠心病中的研究较少^[8-9],因此本研究通过测定血清miR-27a-3p和HOXC6的表达水平,并分析其与冠状动脉病变相关性,从而为高血压并发冠心病的防治提供一定参考。

1 材料与方法

1.1 研究对象 选取北大荒集团总医院2021年6月~2023年6月接诊的246例高血压患者为研究对象,其中129例高血压并发冠心病患者作为并发组,117例单纯高血压患者作为未并发组。未并发组中男性60例,女性57例,年龄46~80(61.53 ± 6.22)岁,体质质量指数(body mass index,

BMI) 22.16 ± 2.28 kg/m²,高血压病程 5.87 ± 1.32 年,收缩压 147.52 ± 15.03 mmHg,舒张压 94.58 ± 9.52 mmHg;吸烟史52例,饮酒史58例,糖尿病史29例。并发组中男性67例,女性62例,年龄45~80(60.78 ± 6.25)岁,BMI 22.27 ± 2.31 kg/m²;高血压病程 6.69 ± 1.35 年;收缩压 149.64 ± 15.07 mmHg;舒张压 95.12 ± 9.63 mmHg;吸烟史61例,饮酒史60例,糖尿病史35例。两组性别、年龄、BMI,收缩压、舒张压、吸烟史、饮酒史、糖尿病史比例比较,差异均无统计学意义($\chi^2/t=0.918$, 0.011 , 0.375 , 1.103 , 0.442 , 0.200 , 0.230 , 0.175 , 均 $P>0.05$),其中并发组高血压病程显著长于未并发组($t=4.808$, $P<0.001$)。

纳入标准:①所有患者均符合《中国高血压防治指南(2018年修订版)》^[10]中有关高血压诊断标准,并确诊为原发性高血压;②冠心病诊断参照《实用内科学》^[11]中相关诊断标准;③近期内未服用代谢药物、免疫抑制剂药物。**排除标准:**①近期做过重大外科手术;②并发肝脏、肾功能异常者;③并发先天性心脏病、心力衰竭及其他恶性肿瘤者;④有精神异常、沟通交流障碍者;⑤并发心脏器质性病变和严重感染性疾病者。所有患者及其家属均知情且签署同意书,本研究已通过北大荒集团总医院医学伦理委员会审核批准(批号:202105110609)。

1.2 仪器与试剂 7500 PCR仪(广州维基科技有限公司);总RNA提取试剂(Trizol)(北京凯诗源生物科技有限公司,货号abs9331);逆转录试剂盒(上海羽喙生物科技有限公司,货号YDTEZ436);miR-27a-3p, HOXC6及内参U6, GAPDH的引物(锐博生物科技有限公司);全自动生化分析仪(武汉尚宜康健科技有限公司,型号:

KEA-TR100)。

1.3 方法

1.3.1 实时荧光定量 PCR (quantitative real time PCR, qRT-PCR) 法检测血清 miR-27a-3p 和 HOXC6 水平: 采集所有患者空腹静脉血 4 ~ 5 ml, 以 3 500 r/min 离心 8 min 后, 留取血清置于 -80℃ 冰箱储存。miR-27a-3p, HOXC6 及内参 U6, GAPDH

上游、下游引物序列见表 1。按照 Trizol 试剂盒说明书分离提取血清总 RNA, 参照逆转录试剂盒说明书逆转录合成 cDNA, 使用 PCR 仪检测血清中 miR-27a-3p, HOXC6 相对表达量。反应程序共 40 个循环。使用 $2^{-\Delta\Delta Ct}$ 方法 (Ct 为循环阈值), 并计算基因 miR-27a-3p, HOXC6 的相对表达量。

表 1 qRT-PCR 引物序列

| 基因 | 上游引物 | 下游引物 |
|------------|------------------------------|------------------------------|
| miR-27a-3p | 5'-AGTGGCTAAGTTCGCAA-3' | 5'-CTCAACTGCTGCTGGA-3' |
| U6 | 5'-CAGCACATATACAATTGGAACG-3' | 5'-ACGAATTTGCGTGTCATCC-3'' |
| HOXC6 | 5'-GCGGAAAAGAGAAAAGCGG-3' | 5'-AAGAGAGACTTGTGCGGGTAGG-3' |
| GAPDH | 5'-GGAGTCCACTGGCGTCTTCA-3' | 5'-GTCATGAGTCCTCCACGATACC-3' |

1.3.2 临床资料收集: 收集所有患者年龄、性别、BMI, 吸烟史、饮酒史、糖尿病史比例、高血压病程、收缩压、舒张压、尿酸、三酰甘油 (triglyceride, TG)、总胆固醇 (total cholesterol, TC)、低密度脂蛋白 - 胆固醇 (low-density lipoprotein cholesterol, LDC-C)、高密度脂蛋白 - 胆固醇 (high density lipoprotein cholesterol, HDL-C) 等资料, 进行组间比较。

1.3.3 冠状动脉病变严重程度评估: 采用 SYNTAX 评分^[12] 分别从冠状动脉病变位置、狭窄程度、分叉类型、有无钙化等角度评判, 以一般计分、分叉病变计分、其他情况计分相加的总分确定冠状动脉病变严重程度, 将并发组以 ≤ 21 分为轻度组 ($n=36$), > 21 且 ≤ 28 分为中度组 ($n=48$) 和 > 28 分为重度组 ($n=45$)。

1.4 统计学分析 使用 SPSS 25.0 统计软件分析数据。计量资料以均数 \pm 标准差 ($\bar{x} \pm s$) 表示, 两组间比较采用 t 检验; 计数资料以例或百分率 n (%) 表示, 组间比较采用 χ^2 检验; 三组及以上组间比较采用单因素方差分析 (进一步两两比较采用 SNK- q 检验); 运用 Spearman 法分析高血压并发冠心病患者血清 miR-27a-3p, HOXC6 水平与冠状动脉病变的相关性; 采用多因素 Logistic 回归方法分析高血压并发冠心病的影响因素; 运用 MedCalc 软件绘制受试者工作特征 (receiver operating characteristic, ROC) 曲线分析血清 miR-27a-3p, HOXC6 水平对高血压并发冠心病的预测价值。以

$P < 0.05$ 为差异有统计学意义。

2 结果

2.1 两组患者实验室指标及血清 miR-27a-3p, HOXC6 比较 见表 2。未并发组与并发组 TG, HDL-C, 尿酸比较, 差异均无统计学意义 (均 $P > 0.05$), 并发组 TC, LDC-C 及血清 miR-27a-3p, HOXC6 水平均显著高于未并发组, 差异具有统计学意义 (均 $P < 0.05$)。

表 2 两组患者实验室指标及血清 miR-27a-3p, HOXC6 比较 ($\bar{x} \pm s$)

| 项目 | 未并发组 ($n=117$) | 并发组 ($n=129$) | t | P |
|-------------------|---------------------|--------------------|-------|--------|
| TG (mmol/L) | 1.98 \pm 0.26 | 2.02 \pm 0.27 | 1.181 | 0.239 |
| TC (mmol/L) | 5.42 \pm 0.67 | 5.96 \pm 0.86 | 5.454 | <0.001 |
| LDC-C (mmol/L) | 2.98 \pm 0.48 | 3.36 \pm 0.51 | 6.001 | <0.001 |
| HDL-C (mmol/L) | 1.06 \pm 0.28 | 1.03 \pm 0.24 | 0.905 | 0.367 |
| 尿酸 (μ mol/L) | 341.26 \pm 35.17 | 343.39 \pm 36.25 | 0.467 | 0.641 |
| miR-27a-3p | 1.06 \pm 0.23 | 1.35 \pm 0.34 | 7.755 | <0.001 |
| HOXC6 | 1.03 \pm 0.25 | 1.29 \pm 0.33 | 6.911 | <0.001 |

2.2 不同程度冠状动脉病变患者血清 miR-27a-3p, HOXC6 水平比较 见表 3。重度组血清 miR-27a-3p 和 HOXC6 表达水平均显著高于轻度组 ($q=27.129$, 28.651) 和中度组 ($q=17.648$, 18.786), 且中度组血清 miR-27a-3p 和 HOXC6 表达水平均显著高于轻度组 ($q=10.905$, 11.378), 差异具有统计学意义 (均 $P < 0.05$)。

表 3 不同程度冠状动脉病变患者血清 miR-27a-3p, HOXC6 水平比较 ($\bar{x} \pm s$)

| 项目 | 轻度组 ($n=36$) | 中度组 ($n=48$) | 重度组 ($n=45$) | F 值 | P 值 |
|------------|-----------------|-----------------|-----------------|---------|--------|
| miR-27a-3p | 0.54 \pm 0.13 | 1.19 \pm 0.31 | 2.18 \pm 0.55 | 191.026 | <0.001 |
| HOXC6 | 0.47 \pm 0.12 | 1.12 \pm 0.31 | 2.13 \pm 0.52 | 213.542 | <0.001 |

2.3 高血压并发冠心病患者血清 miR-027a-3p, HOXC6 水平与 SYNTAX 评分的相关性 高血压并发冠心病

病患者 SYNTAX 评分平均得分为 26.38 ± 3.12 分, 经 Spearman 相关分析显示, 高血压并发冠心病患者血清 miR-27a-3p, HOXC6 与 SYNTAX 评分均呈正相关性 ($r=0.563, 0.517$, 均 $P < 0.05$)。

2.4 多因素 Logistic 回归分析高血压并发冠心病的影响因素 见表 4。将高血压病程和表 2, 3 有显著性差异的因素纳入多因素 Logistic 回归分析, 以

表 4 多因素 Logistic 回归分析高血压并发冠心病的影响因素

| 因素 | β | SE | Wald | P | OR | 95%CI |
|------------|---------|-------|-------|-------|-------|---------------|
| miR-27a-3p | 0.486 | 0.165 | 8.702 | 0.003 | 1.627 | 1.177 ~ 2.248 |
| HOXC6 | 0.539 | 0.241 | 5.010 | 0.025 | 1.715 | 1.069 ~ 2.750 |
| 高血压病程 | 0.197 | 0.243 | 0.659 | 0.417 | 1.218 | 0.756 ~ 1.961 |
| TC | 0.306 | 0.265 | 1.333 | 0.248 | 1.358 | 0.808 ~ 2.283 |
| LDC-C | 0.760 | 0.462 | 2.709 | 0.099 | 2.139 | 0.865 ~ 5.290 |

2.5 血清 miR-27a-3p, HOXC6 水平对高血压并发冠心病的预测价值 见表 5 和图 1。血清 miR-27a-3p, HOXC6, 二者联合预测高血压并发冠心病的曲线下面积 (area under curve, AUC) 分别为 0.835, 0.806 和 0.896, 二者联合优于血清 miR-27a-3p, HOXC6 各自单独诊断 ($Z=2.133, 2.815$, $P=0.033, 0.005$)。

表 5 血清 miR-27a-3p, HOXC6 水平对高血压并发冠心病的预测价值

| 项目 | AUC | 截断值 | 95%CI | 敏感度 (%) | 特异度 (%) | Youden 指数 |
|------------|-------|------|-------------|---------|---------|-----------|
| miR-27a-3p | 0.835 | 1.34 | 0.783~0.879 | 61.24 | 94.02 | 0.553 |
| HOXC6 | 0.806 | 1.24 | 0.751~0.853 | 65.12 | 87.18 | 0.523 |
| 二者联合 | 0.896 | - | 0.851~0.931 | 80.62 | 86.32 | 0.669 |

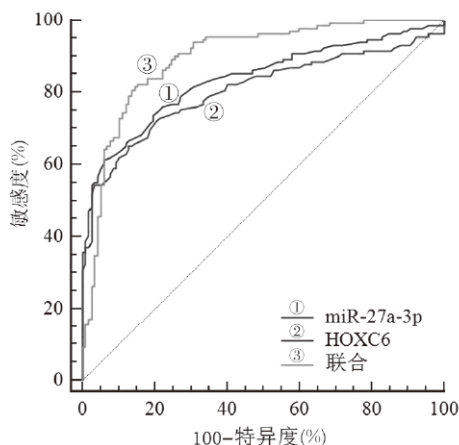


图 1 血清 miR-27a-3p, HOXC6 预测高血压并发冠心病的 ROC 曲线

3 讨论

高血压是临床上较为常见的心脑血管疾病, 长期处于高血压状态, 易导致动脉粥样硬化斑块形成, 从而引发冠心病、脑卒中、心律失常及心力衰竭等

是否发生并发冠心病为因变量 (并发 =1, 未并发 =0), miR-27a-3p (连续变量)、HOXC6 (连续变量)、高血压病程 (连续变量)、TC (连续变量)、LDC-C (连续变量) 为自变量。结果显示, 血清 miR-27a-3p, HOXC6 是影响高血压并发冠心病的独立危险因素 ($P < 0.05$)。

心血管疾病, 此类疾病的致残率和死亡率较高^[13-14]。高血压可诱发内皮功能障碍, 加剧动脉粥样硬化过程, 并使动脉粥样硬化斑块更加不稳定, 可能导致高血压并发冠心病发生风险更大。因此, 尽早寻找敏感血清指标协助预测高血压并发冠心病的概率, 对提升患者的生存率有一定参考价值。

循环 miRNA 可作为许多疾病的诊断标志物, 如心血管疾病^[16]。近几年, 研究表明, miR-27a 水平在小鼠的动脉粥样硬化斑块中增加, 推测 miR-27a-3p 表达水平可能在动脉粥样硬化斑块中发挥重要作用, 与高血压并发冠心病的发生、发展密切相关^[17]。本研究发现, 高血压并发冠心病患者血清 miR-27a-3p 水平均显著高于单纯高血压患者, 且随着患者病变严重程度的升高而逐渐升高, 提示 miR-27a-3p 水平异常变化促进疾病的发展方向。动脉粥样硬化是一种慢性炎症性疾病, 脊髓损伤患者中血清 miR-27a-3p 表达水平是升高的, miR-27a-3p 可通过负调节 Toll 样受体 4 来抑制脊髓损伤的炎症反应, 说明 miR-27a-3p 与疾病损伤程度、炎症有一定联系^[18]。本研究中, 高血压并发冠心病患者血清 miR-27a-3p 与 SYNTAX 评分呈正相关性, 表明血清 miR-27a-3p 与冠状动脉病变有着紧密联系。此外, 血清 miR-27a-3p 是影响高血压并发冠心病的独立危险因素, 且血清 miR-27a-3p 单独预测高血压并发冠心病的 AUC 为 0.835, 表明 miR-27a-3p 对高血压并发冠心病有一定预测价值。已有研究发现^[19], 与正常健康者相比, 冠状动脉疾病组 miR-27a-3p 的表达水平显著升高, 且与动脉粥样硬化病变形成有关, 促进动脉粥样硬化斑块的发展进程, 这与本研究结果 miR-27a-3p 高表达促进高血压并发冠心病的发展过程类似。

同源盒基因 6 (HOXC6) 是 HOXC 家族成员,

其中部分氨基酸构成介导 HOXC6 与靶基因启动子区结合的经典同源结构域^[20]。HOXC6 在多个肿瘤组织中呈高表达,影响癌细胞的恶性生物学行为,并且 HOXC6 在心外膜脂肪组织参与冠状动脉疾病病理过程发挥着至关重要的作用^[9, 21]。血管内皮细胞的凋亡在动脉粥样硬化的发生和发展中起着十分重要的作用。本研究中,高血压并发冠心病患者血清 HOXC6 水平高于单纯高血压患者,且血清 HOXC6 表达水平随着病变严重程度的升高而逐渐升高;高血压并发冠心病患者血清 HOXC6 与 SYNTAX 评分均呈正相关性,表明血清 HOXC6 与不同程度冠状动脉病变患者密切相关,这与既往发现相类似。已有研究表明^[22],HOXC6 在动脉粥样硬化大鼠的主动脉壁和冠心病大鼠中呈高表达,提示 HOXC6 可能参与冠心病及动脉粥样硬化的发生、发展。血清 HOXC6 是影响高血压并发冠心病的独立危险因素,其预测高血压并发冠心病的 AUC 为 0.806,表明 HOXC6 高表达与高血压并发冠心病相关,可能参与疾病的发展进程,HOXC6 表达水平异常升高可增加高血压并发冠心病的风险,对高血压并发冠心病具有较好的预测价值。本研究 ROC 曲线联合分析显示,血清 miR-27a-3p 和 HOXC6 联合预测高血压并发冠心病的 AUC 为 0.896,均优于二者各自单独预测,具有更高的预测价值,能够为高血压患者并发冠心病的防治提供新方向。

综上所述,高血压并发冠心病患者血清 miR-27a-3p 和 HOXC6 水平显著升高,二者均是高血压并发冠心病的独立危险因素,且与不同程度冠状动脉病变密切相关。血清 miR-27a-3p 和 HOXC6 水平对高血压患者并发冠心病具有更高的预测价值,为临床上疾病防治提供一定理论指导,能够为临床医师评估病情程度作参考。然而,血清 miR-27a-3p 和 HOXC6 水平在高血压并发冠心病中的具体作用机制仍不清楚,需后续扩大样本量和增加研究指标深入探究。

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