

急性主动脉夹层患者血浆 miR-30a 及 D-二聚体水平检测对临床预后判断价值

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摘要:目的 探讨血浆微小核糖核酸(miR)-30a及D-二聚体(D-dimer, D-D)水平对急性主动脉夹层(acute aortic dissection, AAD)预后判断价值。方法 选取2018年1月~2020年12月海口市第三人民医院收治的AAD患者152例和65例健康对照组作为研究对象,根据AAD患者住院期间的预后情况分为存活组($n=107$ 例)和死亡组($n=45$ 例),检测各组血浆miR-30a及D-二聚体水平。应用受试者工作特征(ROC)曲线分析血浆miR-30a及D-二聚体水平预测AAD死亡的价值。结果 AAD组血浆miR-30a(1.93 ± 0.78)及D-二聚体($6.28 \pm 1.72 \mu\text{g/ml}$)水平均明显高于对照组(0.72 ± 0.25 , $0.36 \pm 0.08 \mu\text{g/ml}$),差异有统计学意义($t=13.758$, 16.814 , 均 $P<0.001$)。死亡组血浆miR-30a(2.42 ± 1.13)及D-二聚体($8.62 \pm 2.24 \mu\text{g/ml}$)水平均明显高于存活组(1.30 ± 0.56 , $3.64 \pm 1.35 \mu\text{g/ml}$),差异有统计学意义($t=11.624$, 14.735 , 均 $P<0.001$)。ROC曲线显示,miR-30a及D-二聚体两项联合预测AAD死亡的曲线下面积(0.936, 95%CI: 0.875~0.992)最大,其敏感度和特异度分别为94.0%, 88.6%。结论 AAD患者血浆miR-30a及D-二聚体水平明显升高,两项联合检测对AAD预后判断具有较好的价值。

关键词: 急性主动脉夹层; 微小核糖核酸; D-二聚体

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Clinical Prognostic Value of Plasma miR-30a and D-dimer Levels in Patients with Acute Aortic Dissection

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Abstract: Objective To investigate the value of plasma miR-30a and D-dimer(D-D) levels in prognosis of acute aortic dissection (AAD). **Methods** The 152 AAD patients and 65 healthy controls in the Third People's Hospital of Haikou from January 2018 to December 2020 were selected as the research objects. According to the prognosis of AAD patients during hospitalization, they were divided into survival group ($n=107$) and death group ($n=45$). The levels of plasma miR-30a and D-dimer were detected in each group. The value of plasma miR-30a and D-dimer levels in prediction of death in AAD were analyzed by ROC curve. **Results** The levels of miR-30a (1.93 ± 0.78) and D-dimer ($6.28 \pm 1.72 \mu\text{g/ml}$) in AAD group were significantly higher than those in control group (0.72 ± 0.25 , $0.36 \pm 0.08 \mu\text{g/ml}$), the differences were statistically significant ($t=13.758$, 16.814 , all $P<0.001$). The levels of miR-30a (2.42 ± 1.13) and D-dimer ($8.62 \pm 2.24 \mu\text{g/ml}$) in the dead group were significantly higher than those in the survival group (1.30 ± 0.56 , $3.64 \pm 1.35 \mu\text{g/ml}$), the differences were statistically significant ($t=11.624$, 14.735 , all $P<0.001$). ROC curve showed that the area under the curve (0.936, 95%CI: 0.875~0.992) of the two combined predictors of AAD death were the largest, with sensitivity and specificity of 94.0%, 88.6%. **Conclusion** The levels of plasma miR-30a and D-dimer in patients with AAD were significantly increased, and the combined of the two items has a better value in the prognosis of AAD.

Keywords: acute aortic dissection; miR-30a; D-dimer

急性主动脉夹层(acute aortic dissection, AAD)是一种极为严重的心血管急症,其病情凶险、病死率高,若未能及时诊断治疗,AAD发生后48h内的病死率高达50%^[1]。准确地对AAD进行预后判断,并采取有效的治疗措施,对降低患者的病死率具有

重大帮助。微小核糖核酸(microRNA, miRNA)是一类单链非编码小分子RNA,参与多种信号通路的调节,在AAD的发生发展中起到重要的作用^[2]。有研究发现,miR-30a在AAD中异常表达,参与细胞外基质重塑、氧化应激等重要功能的调节,有

望成为治疗AAD的潜在靶点^[3]。D-二聚体(D-dimer, D-D)作为反映体内纤溶活性的重要指标,对评估AAD患者的病情及预后具有一定的价值^[4]。本研究通过检测AAD患者血浆miR-30a及D-二聚体水平,分析其对AAD预后判断的价值,旨在为AAD的救治提供参考依据。

1 材料与方法

1.1 研究对象 选取2018年1月~2020年12月海口市第三人民医院收治的AAD患者152例,其中男性114例,女性38例,年龄36~79(54.80±11.24)岁。纳入标准:①经主动脉CT血管成像明确诊断为AAD;②临床病例资料记录完整。排除标准:①并发其他心血管疾病及严重基础病;②不愿意配合本次研究者。152例AAD患者根据住院期间存活情况分为存活组($n=107$)和死亡组($n=45$)。另选取65例体检正常者作为对照组,其中男性47例,女性18例,年龄35~78(53.70±9.82)岁。各组的性别、年龄及体质指数比较,差异均无统计学意义(均 $P>0.05$)。本研究与患者签署知情同意书。

1.2 仪器与试剂 7500型荧光定量PCR仪(美国ABI公司);PCR试剂盒,RNeasy试剂盒,miRNA Easy试剂盒和Trizol试剂盒(博士德生物有限公司);贝克曼ACL7000全自动凝血分析仪。

1.3 方法

1.3.1 miR-30a检测:采集静脉血3 ml于EDTA抗凝管中,离心分离血浆,在ABI 7500型荧光定量PCR仪上检测miR-30a水平。逆转录反应体系为15 μ l: 5 μ l RNA模板,3 μ l U6及miRNA特异性茎环引物,0.15 μ l 100mmol/L脱氧核糖核苷酸,1.00 μ l 逆转录酶,1.50 μ l 10 \times 反转录缓冲液,0.19 μ l RNase抑制剂,4.16 μ l 双蒸水;反应体系为20 μ l: 1 μ l 引物及探针 Mix (20 \times), 10 μ l TaqMan通用混合物溶液(2 \times), 1.33 μ l 反向转录脱氧核糖核苷酸,7.67 μ l 双蒸馏水。采用 $2^{-\Delta\Delta Ct}$ 法计算miR-30a水平。

1.3.2 D-二聚体检测:采用贝克曼ACL 7000全自动凝血分析仪及配套试剂盒检测D-二聚体水平。

1.4 统计学分析 采用SPSS20.0统计软件,计量

资料以均数±标准差($\bar{x}\pm s$)表示,采用校正 t 检验(t' 检验)。计数资料组间比较采用 χ^2 检验。应用受试者工作特征曲线(ROC)分析血浆miR-30a及D-二聚体水平预测AAD死亡的价值。 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 AAD组和对照组血浆miR-30a及D-二聚体水平比较 AAD组血浆miR-30a(1.93±0.78)及D-二聚体(6.28±1.72 μ g/ml)水平均明显高于对照组(0.72±0.25, 0.36±0.08 μ g/ml),差异有统计学意义($t=13.758, 16.814$, 均 $P<0.001$)。

2.2 死亡组和存活组血浆miR-30a及D-二聚体水平比较 死亡组血浆miR-30a(2.42±1.13)及D-二聚体(8.62±2.24 μ g/ml)水平均明显高于存活组(1.30±0.56, 3.64±1.35 μ g/ml),差异有统计学意义($t=11.624, 14.735$, 均 $P<0.001$)。

2.3 血浆miR-30a及D-二聚体水平预测AAD患者死亡的价值 见表1和图1。血浆miR-30a及D-二聚体水平预测AAD患者死亡的最佳截断值分别为1.97, 6.36 μ g/ml。两项联合预测AAD患者死亡的曲线下面积(0.936, 95%CI: 0.875~0.992)明显高于单项检测miR-30a(0.852, 95%CI: 0.793~0.913)及D-二聚体(0.824, 95%CI: 0.767~0.885),差异均有统计学意义(均 $P<0.05$),其敏感度和特异度分别为94.0%和88.6%。

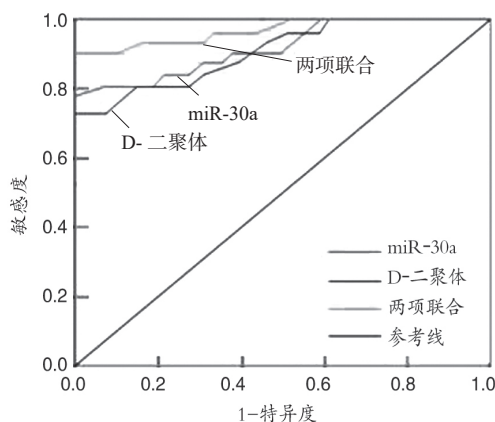


图1 血浆miR-30a及D-二聚体水平预测AAD患者死亡的ROC曲线

表1 血浆miR-30a及D-二聚体水平预测AAD患者死亡的价值

| 项目 | 最佳截断值 | AUC (95%CI) | 敏感度 (%) | 特异度 (%) | 阳性预测值 (%) | 阴性预测值 (%) | 阳性似然比 | 阴性似然比 |
|---------|-----------------|-----------------------|---------|---------|-----------|-----------|-------|-------|
| miR-30a | 1.97 | 0.852 (0.793 ~ 0.913) | 86.0 | 81.7 | 83.5 | 84.2 | 4.699 | 0.171 |
| D-二聚体 | 6.36 μ g/ml | 0.824 (0.767 ~ 0.885) | 83.5 | 78.0 | 81.2 | 80.6 | 3.795 | 0.212 |
| 两项联合 | - | 0.936 (0.875 ~ 0.992) | 94.0 | 88.6 | 92.4 | 90.2 | 8.246 | 0.068 |

3 讨论

急性主动脉夹层(AAD)是一种严重的致命性疾病,已成为严重危及人类生命健康的重要疾病

之一。miRNA在不同生理或病理状态下呈现差异性表达,具有组织器官特异性,可作为AAD诊断或预后预测的潜在标志物^[5-6]。LI等^[7]研究发现,

miRNA在主动脉夹层组织中表达下调,且与AAD患者的生存有关,miRNA的过表达促进血管平滑肌细胞增殖、抑制细胞凋亡,从而抑制AAD的发生发展。XUE等^[8]研究认为,miRNA在主动脉夹层中的表达水平较对照组明显升高,miRNA的过度表达通过靶向SMAD4诱导血管平滑肌细胞增殖和迁移,可能参与主动脉夹层的发生发展。D-二聚体是反映机体内纤溶亢进、高凝状态的可靠标志物,在血栓性疾病的诊断中发挥了重要作用^[9]。LI等^[10]研究表明,主动脉夹层患者D-二聚体显著升高,不同病期主动脉夹层的二聚体存在显著差异,并可反映主动脉夹层的稳定情况,在主动脉夹层的早期筛查中具有较好的价值。

本研究显示,AAD组血浆miR-30a及D-二聚体水平均明显高于对照组,且死亡组血浆miR-30a及D-二聚体水平均明显高于存活组,提示血浆miR-30a及D-二聚体水平升高与AAD患者病情的严重程度有关,可能参与AAD的发生发展,有望作为判断AAD患者病情严重程度的生物学指标。分析其原因,一方面可能是miR-30a通过调控多个信号通路,如细胞增殖、迁移及血管炎症等,参与了AAD的发病机制;另一方面死亡的AAD患者主动脉中层撕裂程度较严重,激活凝血系统及后续的纤溶过程比较活跃,使血浆中D-二聚体水平升高。WANG等^[11]研究发现,miRNA的过度表达显著降低了多囊蛋白-1和转化生长因子- β 1下游靶蛋白的表达,对AAD的早期诊断具有较高特异度和敏感度,miRNA可作为AAD的诊断标志物,并可能参与AAD的发病机制。潘小高等^[12]研究认为,D-二聚体水平升高是AAD患者院内死亡的独立危险因素($OR=1.04$,95%CI:1.00~1.08, $P<0.05$),是预测AAD预后的可靠指标。

本研究进一步应用ROC曲线分析,结果显示miR-30a及D-二聚体两项联合预测AAD死亡的AUC最大,其敏感度和特异度较好,说明miR-30a及D-二聚体可能是AAD预后判断的可靠指标,两项联合检测对AAD预后判断的价值较高。DONG等^[13]研究显示,AAD患者miRNA表达水平明显高于对照组,与AAD严重程度相关,miRNA在诊断AAD中具有良好的临床应用价值。湛镇伊等^[14]研究发现,miRNA的差异表达在AAD的发生及发展过程中起着重要作用,可能是AAD的潜在诊断标志物,同时也为了解AAD的发病机制及治疗提供新的指导。另有研究表明,AAD患者的D-二聚体水平升高,检测D-二聚体水平是排除AAD的良好预测指标,对AAD鉴别诊断具有重要的意义^[15]。

综上所述,AAD患者血浆miR-30a及D-二聚

体水平明显升高,其水平升高与AAD患者的病情严重程度及预后相关,两项联合检测弥补了单项检测的不足,对AAD预后判断具有较好价值,同时也为AAD的早期治疗提供了新的思路。但本研究仍存在一些不足,如病例来源较单一,缺乏多中心的研究结果,未来仍需更进一步深入研究。

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