



· 论 著 ·

血清miR-135及miR-601在胃癌患者中的表达及其诊断价值

田雯¹, 陈珑¹, 马艳华¹, 吴开李², 符国宏²

1. 三亚中心医院肿瘤内科, 海南 三亚 572000;
2. 三亚中心医院普外科, 海南 三亚 572000

[摘要] 背景与目的: 胃癌是消化内科常见的恶性肿瘤。探讨血清miR-135及miR-601在胃癌患者中的表达及其诊断价值。方法: 选取2016年1月1日—2019年9月30日三亚中心医院收治的胃癌患者152例, 根据胃癌病情进展及临床病理学分期分为早期胃癌组($n=62$)和进展期胃癌组($n=90$), I~II期($n=65$)和III~IV期($n=87$), 无淋巴结转移组($n=73$)和淋巴结转移组($n=79$)。另选择96例非胃癌患者作为非胃癌组, 60例健康体检正常者作为对照组。采用实时荧光定量聚合酶链反应(real-time fluorescence quantitative polymerase chain reaction, RTFQ-PCR)检测各组血清miR-135及miR-601表达水平, 化学发光法测定糖类抗原72-4(carbohydrate antigen 72-4, CA72-4)及糖类抗原19-9(carbohydrate antigen 19-9, CA19-9)水平, 分析其对早期胃癌的诊断价值。采用Pearson相关分析来分析胃癌患者血清miR-135、miR-601水平与CA72-4及CA19-9的相关性。结果: 与非胃癌组和对照组比较, 胃癌组血清miR-135、miR-601、CA72-4及CA19-9水平均明显升高($P < 0.001$)。进展期胃癌组血清miR-135(5.70 ± 1.84 vs 3.83 ± 1.12)、miR-601(11.28 ± 3.73 vs 7.36 ± 2.15)、CA72-4 [(41.75 ± 10.14) U/mL vs (17.82 ± 4.93) U/mL]及CA19-9 [(63.72 ± 17.50) U/mL vs (35.84 ± 10.36) U/mL]水平均明显高于早期胃癌组(均 $P < 0.001$)。III~IV期胃癌患者血清miR-135(6.10 ± 1.90 vs 3.74 ± 1.08)、miR-601(12.14 ± 3.92 vs 7.05 ± 2.04)、CA72-4 [(44.68 ± 12.35) U/mL vs (16.40 ± 4.52) U/mL]和CA19-9 [(68.53 ± 19.13) U/mL vs (33.75 ± 10.60) U/mL]水平均明显高于I~II期(均 $P < 0.001$), 而且II期胃癌患者血清miR-135、miR-601、CA72-4及CA19-9水平均明显高于对照组($P < 0.05$)。淋巴结转移组血清miR-135(6.24 ± 1.95 vs 3.65 ± 0.97)、miR-601(12.60 ± 4.13 vs 6.84 ± 1.92)、CA72-4 [(48.70 ± 12.37) U/mL vs (14.85 ± 4.20) U/mL]和CA19-9 [(72.36 ± 20.25) U/mL vs (31.60 ± 10.17) U/mL]水平均明显高于无淋巴结转移组(均 $P < 0.001$)。受试者工作特征(receiver operating characteristic, ROC)曲线分析结果显示, 血清miR-135、miR-601、CA72-4及CA19-9水平诊断早期胃癌的最佳截断值分别为3.78、7.14、17.63 U/mL、35.70 U/mL, 四项联合诊断早期胃癌的曲线下面积(area under curve, AUC)(0.920, 95% CI: 0.860~0.978)最大, 其灵敏度和特异度分别为98.6%和77.4%。相关分析显示, 胃癌患者血清miR-135、miR-601水平与CA72-4及CA19-9均呈正相关($r=0.748, P < 0.001, r=0.694, P < 0.001; r=0.815, P < 0.001; r=0.716, P < 0.001$)。结论: 胃癌患者血清miR-135、miR-601、CA72-4及CA19-9水平明显升高, 四项联合检测有助于提高早期胃癌的诊断价值。

[关键词] 胃癌; miR-135; miR-601; 诊断价值

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Expressions of serum miR-135 and miR-601 and their diagnostic value in patients with gastric cancer TIAN Wen¹, CHEN Long¹, MA Yanhua¹, WU Kaili², FU Guohong² (1. Department of Medical Oncology, Sanya Central Hospital, Sanya 572000, Hainan Province, China; 2. Department of General Surgery, Sanya Central Hospital, Sanya 572000, Hainan Province, China)

Correspondence to: TIAN Wen E-mail: tianwen279@163.com

[Abstract] **Background and purpose:** Gastric cancer is a common malignant tumor in gastroenterology. This study aimed to investigate the expressions of serum miR-135 and miR-601 and their diagnostic value in patients with gastric cancer. **Methods:** According to the progression of gastric cancer and clinical pathological stages, 152 gastric cancer patients treated in Sanya Central

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通信作者: 田雯 E-mail: tianwen279@163.com

Hospital from Jan. 2016 to Sep. 2019 were divided into early gastric cancer group ($n=62$) and advanced gastric cancer group ($n=90$), stage I - II group ($n=65$) and stage III - IV group ($n=87$), non-lymph node metastasis group ($n=73$) and lymph node metastasis group ($n=79$). In addition, 96 non-gastric cancer patients were selected as the non-gastric cancer group, and 60 healthy persons with normal physical examination were selected as the control group. Real-time fluorescence quantitative polymerase chain reaction (RTFQ-PCR) was used to detect the expression levels of serum miR-135 and miR-601 in each group, and chemiluminescence was used to determine the levels of carbohydrate antigen 72-4 (CA72-4) and carbohydrate antigen 19-9 (CA19-9), to analyze their diagnostic value in early gastric cancer. Pearson correlation analysis showed that the levels of miR-135 and miR-601 were correlated with CA72-4 and CA19-9. **Results:** Compared with the non-gastric cancer group and the control group, the average serum levels of miR-135, miR-601, CA72-4 and CA19-9 in gastric cancer group were significantly higher (all $P<0.001$). The levels of miR-135 (5.70 ± 1.84 vs 3.83 ± 1.12), miR-601 (11.28 ± 3.73 vs 7.36 ± 2.15), CA72-4 [(41.75 ± 10.14) U/mL vs (17.82 ± 4.93) U/mL] and CA19-9 [(63.72 ± 17.50) U/mL vs (35.84 ± 10.36) U/mL] in advanced gastric cancer group were significantly higher than those in early gastric cancer group (all $P<0.001$). The serum levels of miR-135 (6.10 ± 1.90 vs 3.74 ± 1.08), miR-601 (12.14 ± 3.92 vs 7.05 ± 2.04), CA72-4 [(44.68 ± 12.35) U/mL vs (16.40 ± 4.52) U/mL] and CA19-9 [(68.53 ± 19.13) U/mL vs (33.75 ± 10.60) U/mL] were significantly higher in stage III - IV group than in stage I - II group (all $P<0.001$). The serum levels of miR-135, miR-601, CA72-4 and CA19-9 in stage II gastric cancer patients were significantly higher than those in control group ($P<0.05$). The serum levels of miR-135 (6.24 ± 1.95 vs 3.65 ± 0.97), miR-601 (12.60 ± 4.13 vs 6.84 ± 1.92), CA72-4 [(48.70 ± 12.37) U/mL vs (14.85 ± 4.20) U/mL] and CA19-9 [(72.36 ± 20.25) U/mL vs (31.60 ± 10.17) U/mL] in the lymph node metastasis group were significantly higher than those in the non-lymph node metastasis group ($P<0.001$). The receiver operating characteristic (ROC) curve showed that the optimal cut-off values of serum miR-135, miR-601, CA72-4 and CA19-9 in the diagnosis of early gastric cancer were 3.78, 7.14, 17.63 U/mL and 35.70 U/mL, respectively. The area under the curve (AUC) (0.920, 95% CI: 0.860-0.978) in the four combined diagnosis of early gastric cancer was the largest, with the sensitivity and specificity of 98.6% and 77.4%, respectively. Correlation analysis showed that the levels of miR-135 and miR-601 were positively correlated with CA72-4 and CA19-9 respectively ($r=0.748$, $P<0.001$; $r=0.694$, $P<0.001$; $r=0.815$, $P<0.001$; $r=0.716$, $P<0.001$). **Conclusion:** The serum levels of miR-135, miR-601, CA72-4 and CA19-9 are significantly increased in patients with gastric cancer, and the combined detection of the four items is useful in improving the diagnostic value in early gastric cancer.

[Key words] Gastric cancer; miR-135; miR-601; Diagnostic value

胃癌是消化系统常见的恶性肿瘤, 早期大多数患者的临床症状不明显, 不容易被发现, 在出现明显的临床症状时, 已到进展期胃癌, 导致其预后较差, 病死率较高^[1]。因此, 寻找一种能早期筛查胃癌的生物学标志物对改善胃癌患者的预后具有很大的帮助。微小核糖核酸 (microRNA, miRNA) 是一类内源性、非编码的小分子RNA, 在细胞增殖、分化及凋亡中发挥重要的作用, 可能参与胃肠道肿瘤的发生、发展^[2]。近年来的研究发现, 胃肠道肿瘤存在 miR-135 及 miR-601 的异常表达, 对胃肠道肿瘤的诊断及预后判断具有重要的帮助^[3-4]。糖类抗原 72-4 (carbohydrate antigen 72-4, CA72-4) 及糖类抗原 19-9 (carbohydrate antigen 19-9, CA19-9) 是胃肠道肿瘤常用的血清肿瘤标志物, 对胃肠道肿瘤的诊断、术后复发监测及预后评估具有一定的作用^[5-6]。然而, 关于血清 miR-135 及 miR-60 水平对早期胃癌诊断的研究鲜有报道。

本研究通过检测不同胃疾病中的血清 miR-135、miR-601、CA72-4 及 CA19-9 水平, 探讨其对早期胃癌的诊断价值, 以期对胃癌的诊疗提供指导。

1 资料和方法

1.1 一般资料

收集 2016 年 1 月 1 日—2019 年 9 月 30 日三亚中心医院收治的胃癌患者 152 例, 其中男性 104 例, 女性 48 例, 年龄 31 ~ 78 岁, 中位年龄 58.50 岁。纳入标准: ① 胃癌的诊断依据胃镜检查及组织病理学检查结果; ② 在接受治疗前进行各指标检测。排除标准: ① 有肿瘤复发, 无法配合本研究; ② 合并其他恶性肿瘤, 血液系统疾病、免疫系统疾病及严重肝肾疾病。另选取同期因胃部疾病于三亚中心医院就诊的 96 例非胃癌患者 (萎缩性胃炎 25 例、非萎缩性胃炎 38 例、胃溃疡 33 例), 其中男性 64 例, 女性 32 例, 年龄 28 ~ 75 岁, 中位年龄 57 岁; 同期选择对照组 60 例健康体检者 (男性

38例, 女性22例), 年龄35~76岁, 中位年龄60.40岁。本研究通过三亚中心医院伦理委员会批准后, 与患者或其家属签署知情同意书。

1.2 方法

1.2.1 分组方法

根据胃癌患者病情进展程度, 分为早期胃癌组(62例)和进展期胃癌组(90例)。肿瘤局限于胃黏膜的黏膜层和黏膜下层, 未突破基底膜为早期胃癌; 癌组织浸润到黏膜下层, 进入肌层或已穿过肌层达浆膜为进展期胃癌。根据世界卫生组织(World Health Organization, WHO)肿瘤的TMN分期分为: I期28例, II期37例, III期63例, IV期24例。根据胃癌患者是否发生淋巴结转移, 分为淋巴结转移组79例和无淋巴结转移组73例。

1.2.2 miR-135及miR-601检测

采用实时荧光定量聚合酶链反应(real-time fluorescence quantitative polymerase chain reaction, RTFQ-PCR)检测各组血清miR-135及miR-601表达水平。miR-135基因上游引物为5'-ATGTACGCTACTGTGAGCTG-3', 下游引物为5'-GTCAGCGAGTGAGCATAG-3'; miR-601上游引物为5'-GATGACTGTATGACTCTCAG-3', 下游引物为5'-AGTGTACTACATAGTACG-3'。采集所有研究对象空腹静脉血5 mL, 分离血清, -80 °C低温冰箱保存待测。RTFQ-PCR在ABI 7500 RTFQ-PCR仪上进行。反应体系为20.00 μL: TaqMan 2×Universal PCR Master Mix 10.00 μL, TaqMan MicroRNA Assay 1.00 μL,

cDNA 1.33 μL, ddH₂O 7.67 μL, 混合后离心放入RTFQ-PCR仪。扩增条件: 95 °C预变性10 min、95 °C变性15 s、60 °C复性60 s, 45个循环, 实验重复3次。采用 $2^{-\Delta\Delta Ct}$ 法($\Delta Ct=Ct_{\text{目的基因}}-Ct_{U6}$)计算miR-135及miR-601的相对表达水平。

1.2.3 CA72-4及CA19-9检测

采用化学发光法测定CA72-4及CA19-9水平, 在罗氏E601电化学发光免疫分析仪上进行。

1.3 统计学处理

采用SPSS19.0统计软件分析, 计量资料以 $\bar{x}\pm s$ 表示, 单因素方差分析进行多组间比较, 采用SNK-*q*检验进行组内两两比较; 采用*t*检验进行两组间比较。miR-135、miR-601、CA72-4及CA19-9对早期胃癌的诊断价值应用受试者工作特征(receiver operating characteristic, ROC)曲线进行分析, 采用Z检验进行曲线下面积(area under curve, AUC)比较。应用Pearson相关分析各指标之间的相关性。 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 各组血清miR-135、miR-601、CA72-4及CA19-9水平比较

与非胃癌组和对照组比较, 胃癌组血清miR-135、miR-601、CA72-4及CA19-9水平均明显升高($P<0.001$)。与对照组比较, 非胃癌组血清miR-135、miR-601、CA72-4及CA19-9水平无明显升高, 差异均无统计学意义($P>0.05$, 表1)。

表1 各组血清miR-135、miR-601、CA72-4及CA19-9水平比较

Tab. 1 Comparison of serum levels of miR-135, miR-601, CA72-4 and CA19-9 in each group

Group	<i>n</i>	miR-135	miR-601	CA72-4 $\rho_B/(U\cdot mL^{-1})$	CA19-9 $\rho_B/(U\cdot mL^{-1})$
Control group	60	2.46 ± 0.82	4.17 ± 1.35	3.42 ± 0.96	15.84 ± 5.72
Non-gastric cancer group	96	2.71 ± 0.86	4.38 ± 1.40	4.15 ± 1.13	17.30 ± 6.15
Gastric cancer group	152	4.85 ± 1.63 ^{#Δ}	9.52 ± 2.84 ^{#Δ}	31.48 ± 7.62 ^{#Δ}	50.26 ± 13.28 ^{#Δ}
<i>F</i>		11.724	16.350	14.830	8.752
<i>P</i> value		<0.001	<0.001	<0.001	<0.001

[#]: $P<0.001$, compared with control group; ^Δ: $P<0.001$, compared with non-gastric cancer group

2.2 进展期胃癌组和早期胃癌组血清miR-135、miR-601、CA72-4及CA19-9水平比较

与早期胃癌组比较, 进展期胃癌组血清miR-135、miR-601、CA72-4及CA19-9水平明显升高($P<0.001$, 表2)。

2.3 不同TNM分期胃癌患者血清miR-135、miR-601、CA72-4及CA19-9水平比较

III~IV期胃癌患者血清miR-135、miR-601、CA72-4及CA19-9水平均明显高于I~II期和对照组, 差异均有统计学意义($P<0.001$)。I~II

期胃癌患者血清miR-135、miR-601、CA72-4及CA19-9水平均明显高于对照组, 差异均有统计学意义 ($P < 0.05$, 表3)。

2.4 两组血清miR-135、miR-601、CA72-4及CA19-9水平比较

与无淋巴结转移组比较, 淋巴结转移组血清miR-135、miR-601、CA72-4及CA19-9水平明显升高 ($P < 0.001$, 表4)。

2.5 血清miR-135、miR-601、CA72-4及CA19-9水平对早期胃癌的诊断价值

血清miR-135、miR-601、CA72-4及

CA19-9水平诊断早期胃癌的最佳截断值分别为3.78、7.14、17.63 U/mL、35.70 U/mL, 四项联合诊断早期胃癌的AUC (0.920, 95% CI: 0.860~0.978) 明显高于单项miR-135 (0.804, 95% CI: 0.748~0.862)、miR-601 (0.846, 95% CI: 0.787~0.906)、CA72-4 (0.815, 95% CI: 0.754~0.873) 及CA19-9 (0.714, 95% CI: 0.658~0.776), 差异有统计学意义 ($Z = 5.417$ 、4.938、5.108、7.804, $P < 0.05$), 其灵敏度和特异度为98.6%和77.4% (表5和图2)。

表 2 进展期胃癌组和早期胃癌组血清miR-135、miR-601、CA72-4及CA19-9水平比较

Tab. 2 Comparison of serum levels of miR-135, miR-601, CA72-4 and CA19-9 between advanced gastric cancer group and early gastric cancer group

Group	n	miR-135	miR-601	CA72-4 ρ_B /(U·mL ⁻¹)	CA19-9 ρ_B /(U·mL ⁻¹)
Early gastric cancer group	62	3.83 ± 1.12	7.36 ± 2.15	17.82 ± 4.93	35.84 ± 10.36
Advanced gastric cancer group	90	5.70 ± 1.84	11.28 ± 3.73	41.75 ± 10.14	63.72 ± 17.50
T		9.615	13.426	11.225	7.160
P value		<0.001	<0.001	<0.001	<0.001

表 3 不同TNM分期胃癌患者血清miR-135、miR-601、CA72-4及CA19-9水平比较

Tab. 3 Comparison of serum levels of miR-135, miR-601, CA72-4 and CA19-9 in patients with gastric cancer of different TNM stages

TNM stage	n	miR-135	miR-601	CA72-4 ρ_B /(U·mL ⁻¹)	CA19-9 ρ_B /(U·mL ⁻¹)
Control group	60	2.46 ± 0.82	4.17 ± 1.35	3.42 ± 0.96	15.84 ± 5.72
I - II	65	3.74 ± 1.08 [#]	7.05 ± 2.04 [#]	16.40 ± 4.52 [#]	33.75 ± 10.60 [#]
III-IV	87	6.10 ± 1.90 ^{△△}	12.14 ± 3.92 ^{△△}	44.68 ± 12.35 ^{△△}	68.53 ± 19.13 ^{△△}
F		10.270	15.118	12.406	8.141
P value		<0.001	<0.001	<0.001	<0.001

[#]: $P < 0.05$, compared with control group; [△]: $P < 0.001$, compared with control group; ^{△△}: $P < 0.001$, compared with stage I - II

表 4 两组血清miR-135、miR-601、CA72-4及CA19-9水平比较

Tab. 4 Comparison of serum levels of miR-135, miR-601, CA72-4 and CA19-9 between lymph node metastasis group and non-lymph node metastasis group

Group	n	miR-135	miR-601	CA72-4 ρ_B /(U·mL ⁻¹)	CA19-9 ρ_B /(U·mL ⁻¹)
No-lymph node metastasis group	73	3.65 ± 0.97	6.84 ± 1.92	14.85 ± 4.20	31.60 ± 10.17
Lymph node metastasis group	79	6.24 ± 1.95	12.60 ± 4.13	48.70 ± 12.37	72.36 ± 20.25
t		10.538	15.704	13.161	8.442
P value		<0.001	<0.001	<0.001	<0.001

表 5 血清miR-135、miR-601、CA72-4及CA19-9水平对早期胃癌的诊断价值

Tab. 5 Diagnostic value of serum levels of miR-135, miR-601, CA72-4 and CA19-9 in early gastric cancer

Project	Optimum truncation	AUC (95% CI)	Sensitivity/%	Specificity/%	Positive predictive value/%	Negative predictive value/%
miR-135	3.78	0.804 (0.740-0.862)	81.0	75.7	78.4	79.6
miR-601	7.14	0.846 (0.787-0.906)	86.5	80.8	83.7	84.0
CA72-4 ρ_B /(U·mL ⁻¹)	17.63	0.815 (0.754-0.873)	82.4	77.0	80.6	79.5
CA19-9 ρ_B /(U·mL ⁻¹)	35.70	0.714 (0.658-0.776)	74.6	70.8	73.5	71.7
Four combinations	-	0.920 (0.860-0.978)	98.6	77.4	82.5	86.0

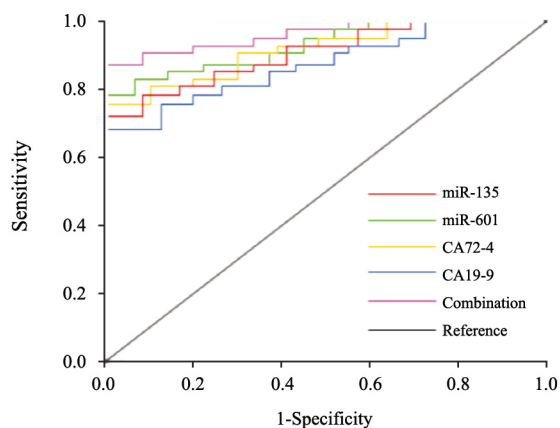


图1 血清miR-135、miR-601、CA72-4及CA19-9水平诊断早期胃癌的ROC曲线

Fig. 1 ROC curve of serum miR-135, miR-601, CA72-4 and CA19-9 in the diagnosis of early gastric cancer

2.6 胃癌患者血清miR-135、miR-601水平与CA72-4及CA19-9的相关性

Pearson相关分析结果显示，胃癌患者血清miR-135水平与CA72-4及CA19-9均呈正相关 ($r=0.748$, $P<0.001$, $r=0.694$, $P<0.001$)，miR-601水平与CA72-4及CA19-9均呈正相关 ($r=0.815$, $P<0.001$, $r=0.716$, $P<0.001$, 图2)。

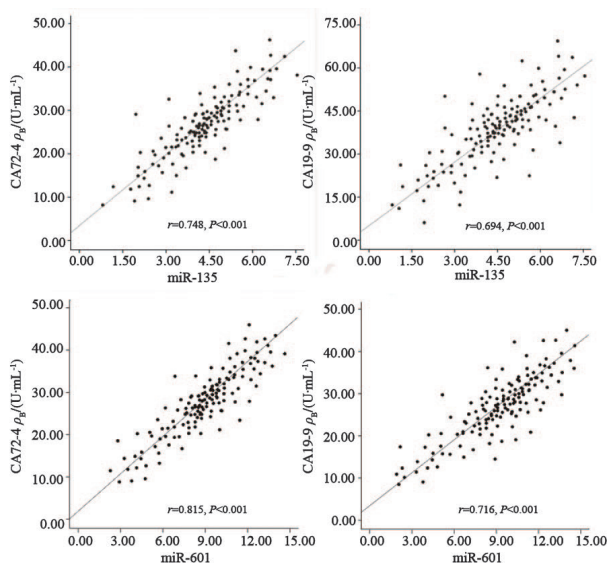


图2 血清miR-135、miR-601水平与CA72-4及CA19-9的相关性

Fig. 2 Correlation of serum miR-135 and miR-601 levels with CA72-4 and CA19-9

3 讨论

胃癌是中国常见的恶性肿瘤之一，CA72-4

及CA19-9是常用的传统肿瘤标志物，广泛应用于胃癌的诊断、转移监测及预后判断^[7]，但这些肿瘤标志物在早期胃癌诊断中的灵敏度较低，单项指标诊断早期胃癌的价值有限，联合应用生物学标志物对于早期胃癌的诊疗提供了新的思路。miRNA是一类高度保守的内源性非编码单链RNA，广泛存在于真核生物中，其调控靶基因的表达参与细胞的增殖、凋亡、侵袭及分化，对恶性肿瘤诊断及指导治疗具有很大的帮助^[8]。近期的研究表明，在多种恶性肿瘤中存在miR-135及miR-601的异常表达，有可能作为恶性肿瘤的诊断、转移及预后判断的重要指标^[9-10]。

本研究显示，与非胃癌组和对照组比较，胃癌组血清miR-135、miR-601、CA72-4及CA19-9水平均明显升高，而非胃癌组和对照组比较，差异无统计学意义。提示血清miR-135、miR-601、CA72-4及CA19-9水平在胃癌患者中异常高表达，其可能具有癌基因的作用，参与胃癌的发生、发展过程。有研究显示，miRNA有可能是一类新的癌基因，在胃癌的发病机制中发挥关键作用^[11]。Yu等^[12]研究也发现，胃癌患者血清CA72-4及CA19-9水平高于胃良性疾病组和对照组，而胃良性疾病组与对照组之间差异无统计学意义，提示其水平变化与胃癌进程有关。本研究中血清miR-135及miR-601水平在进展期胃癌组明显高于早期胃癌组，在Ⅲ~Ⅳ期患者明显高于在Ⅰ~Ⅱ期患者，有淋巴结转移组明显高于无淋巴结转移组，提示miR-135及miR-601在胃癌的发生、发展过程中起到重要的作用，其高表达对促进胃癌的病情进展和淋巴结转移具有重要的作用。有研究发现，miR-135b在胃癌组织中的表达水平升高，miR-135b的高表达与分化程度、浸润深度和TNM分期密切相关，可能参与胃癌的发生、发展^[13]。Kong等^[14]研究表明，miRNA在胃癌患者中明显升高，肿瘤复发和淋巴结转移与miRNA表达密切相关，是影响胃癌患者总生存率的独立预后因素。

本研究ROC曲线显示，血清miR-135、miR-601、CA72-4及CA19-9水平诊断早期胃癌的最佳截断值分别为3.78、7.14、17.63 U/mL、

35.70 U/mL, 四项联合诊断早期胃癌的AUC (0.920, 95% CI: 0.860~0.978) 最大, 其灵敏度较高。相关分析显示, 胃癌患者血清miR-135、miR-601水平与CA72-4及CA19-9均呈正相关 ($P<0.001$)。这说明miR-135及miR-601有望作为诊断早期胃癌的新型生物标志物, 四项联合检测有助于提高早期胃癌诊断的灵敏度。Yin等^[15]研究显示, miR-135在胃癌患者中明显升高, 其高表达与肿瘤标志物CA19-9相关, 对胃癌诊断具有较好的价值。Min等^[16]研究发现, miR-601在胃癌组织和细胞中的表达明显高于对照组, miR-601的高表达可促进胃癌的进展, 是胃癌患者生存率低的一个新的指标, 有可能作为胃癌预后预测的生物学标志物。另有研究表明, 胃癌发生、发展与血清miRNA表达水平上调有关, 对胃癌诊断的价值较好, miRNA有望作为一种非侵入性生物标志物应用于早期胃癌的筛查^[17]。

综上所述, 胃癌患者血清miR-135及miR-601表达水平明显升高, 且与胃癌的进展相关, 联合传统肿瘤标志物CA72-4及CA19-9检测有助于提高胃癌早期诊断的灵敏度, 同时也为了解胃癌的发病机制提供新的思路。

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