Cite as: He F, Niu ZX, Liu S. Expression levels of miR-212-5p and miR-576-5p in the serum of patients with colorectal cancer and prognosis [J]. Chin J Clin Res, 2025, 38(7):999-1004.

DOI: 10.13429/j.cnki.cjcr.2025.07.005

Expression levels of miR-212-5p and miR-576-5p in the serum of patients with colorectal cancer and prognosis

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Abstract: Objective To analyze the levels of serum microRNA (miR)-212-5p and miR-576-5p in colorectal cancer (CRC) patients and their clinical value in prognosis. **Methods** A total of 117 CRC patients admitted to First Hospital of Qinhuangdao from April 2019 to April 2021 and 50 healthy volunteers were enrolled as subjects. Postoperative follow-up was conducted for 3 years to record the survival outcomes of the patients. According to the survival status at the end of the follow-up, the patients with colorectal cancer were divided into survival group (n=91) and death group (n=26).The real-time fluorescence quantitative PCR (qRT-PCR) was used to measure the expression levels of serum miR-212-5p and miR-576-5p in each group. Pearson's correlation test was employed to analyze the correlation between the expression levels of serum miR-212-5p and miR-576-5p in CRC patients. The relationship between serum miR-212-5p, miR-576-5p levels and the clinicopathological characteristics of the patients was examined. **Results** Compared with the control group, the expression level of serum miR-212-5p in the observation group was decreased, while the expression level of miR-576-5p was increased (P <0.05). Compared with the survival group, the deceased group exhibited lower serum miR-212-5p expression and higher miR-576-5p expression (P <0.05). Serum miR-212-5p and miR-576-5p levels in CRC patients showed a significant negative correlation (r=-0.598, P<0.05). The serum levels of miR-212-5p and miR-576-5p in CRC patients were closely associated with TNM staging and lymph node metastasis (P <0.05). The area under the curve (AUC) values for serum miR-212-5p and miR-576-5p, both individually and in combination, in diagnosing CRC were 0.764, 0.827, and 0.907, respectively, with the combined detection outperforming individual detection ($Z_{combination-miR-212-5p}$=3.902, $Z_{combination-miR-576-5p}$=3.170, P<0.05). The AUC values for predicting CRC patient mortality using serum miR-212-5p and miR-576-5p individually and in combination were 0.861, 0.720, and 0.937, respectively, with the combined detection being superior to individual detection ($Z_{combination-miR-212-5p}$=2.460, $Z_{combination-miR-576-5p}$=4.377, P<0.05). **Conclusion** Serum miR-212-5p expression is reduced and miR-576-5p expression is increased in CRC patients. The combination of the two can provide clinical evidence for early diagnosis and prognosis of CRC.

Keywords: Colorectal cancer; MicroRNA-212-5p; MicroRNA-576-5p; Diagnosis; Prognosis

Fund program: Qinhuangdao Science and Technology Research and Development Program (201902A137)

Colorectal cancer (CRC) is one of the digestive system malignancies with high global incidence and mortality rates, and its incidence is increasing year by year in developing countries[1]. In the pathogenesis of CRC, environmental and genetic factors play a dominant role, while nutritional factors exert protective effects[2]. In recent years, due to advancements in screening technologies and optimization of treatment methods, the global mortality of CRC has shown a positive downward trend[3]. Therefore, early diagnosis is crucial for patient survival. However, traditional diagnostic methods often have insufficient sensitivity and specificity in early screening and prognostic evaluation of CRC[4], necessitating the exploration of new biomarkers to address this limitation. MicroRNAs (miRNAs), as a class of non-coding RNAs, play important regulatory roles in the development and metastasis of CRC[5]. Serum miRNAs have emerged as a new research hotspot in oncology due to their easy acquisition, good stability, and potential clinical application value[6]. miR-212-5p, a unique tumor suppressor, has been previously reported[7] to be closely associated with the metastatic process of CRC. Moreover, the expression level of miR-212-5p shows a significant downregulation trend in CRC cell lines, further highlighting its value as a therapeutic target in CRC progression. miR-576-5p, on the other hand, exhibits pro-cancer potential in various types of tumors. Studies have reported that miR-576-5p promotes the invasive behavior of colon adenocarcinoma cells by regulating the expression of neural growth regulator 1 (NEGR1)[8]. It has been found that miR-576-5p is highly expressed in CRC patients, thereby inhibiting the apoptosis of CRC cells[9]. Currently, there are limited clinical reports on the combined use of miR-212-5p and miR-576-5p in predicting the prognosis of CRC. Based on this, this study aims to analyze the expression changes of miR-212-5p and miR-576-5p in CRC and their relationships with disease occurrence and prognosis, with the expectation of providing a scientific basis for the diagnosis and prognostic evaluation of CRC.

1 Materials and methods

1.1 General data

Prior to the trial, approval was obtained from the Ethics Committee with the ethical batch number (2019H026). A total of 117 CRC patients admitted to the First Hospital of Qinhuangdao from April 2019 to April 2021 were enrolled as the study group, including 64 males and 53 females, with an age of (51.97±9.53) years.

Inclusion criteria: (1) Met the diagnostic criteria for CRC[10] and were confirmed by pathology; (2) None had received immunotherapy, radiotherapy, or chemotherapy before enrollment; (3) Age >18 years; (4) Staging I-IV according to relevant staging criteria[11]; (5) Complete clinical data; (6) Patients were informed, voluntarily participated, and signed informed consent forms.

Exclusion criteria: (1) With other intestinal diseases; (2) With dysfunction of vital organs such as kidneys, heart, or liver; (3) With severe infections, congenital diseases, or autoimmune diseases; (4) Pregnant or lactating women; (5) With other malignancies.

Additionally, 50 healthy volunteers undergoing physical examinations meanwhile were selected as the control group, with all physical examination indicators within normal ranges. The control group included 32 males and 18 females, with an age of (51.37±9.14) years. There were no statistically significant differences in gender and age between the two groups (P>0.05).

1.2 Research methods

1.2.1 Detection of relative expression levels of serum miR-212-5p and miR-576-5p by quantitative re-verse transcriptase polymerase chain reaction (qRT-PCR)

A total of 3 mL of fasting venous blood were collected from all subjects in the morning. After centrifugation for 10 minutes, the supernatant was collected and stored in a low-temperature environment for later use. Total RNA was isolated from serum samples using the Trizol Total RNA Extraction Kit (Shanghai Kanglang Biotechnology Co., Ltd., Cat. No.: KL001). An ultraviolet spectrophotometer was used to measure the absorbance (A value) of RNA samples, and their concentration and purity were calculated. Samples with an A260/A280 ratio between 1.7 and 2.1 were considered qualified. The selected total RNA was reverse-transcribed using a reverse transcription kit [Asia-Pacific Hengxin Biotechnology (Beijing) Co., Ltd., Cat. No.: AORT-0100]. The reaction system was configured according to the real-time fluorescent quantitative PCR (qRT-PCR) kit (Shanghai Baishenyue Biotechnology Co., Ltd., Cat. No.: BR1000207), and PCR amplification was performed in a qRT-PCR system. The reaction program was set as follows: pre-denaturation at 95 ℃ for 2 min, denaturation at 95 ℃ for 15 s, annealing at 60 ℃ for 30 s, and extension at 72 ℃ for 30 s, with 40 cycles in total. U6 was used as an internal reference gene for normalization, and the 2-ΔΔCt method was applied to calculate the relative expression levels of miR-212-5p and miR-576-5p. All primer sequences were designed by NCBI and synthesized by Bio-engineering (Shanghai) Co., Ltd. Specific sequence information is shown in **Table 1**.

Tab.1 Primer sequences

Title of gene	Forward primer (5'→3')	Reverse primer(5'→3')
miR-212-5p	GCT TAC GCT TCG AGC CCA C	GAC ACC ACG GCC CAC TCT GCA
miR-576-5p	GCG CGA TTC TAA TTT CTC CAC	AGT GCA GGG TCC GAG GTA TT
U6	CTC GCT TCG GCA GCA CA	AAC GCT TCA CGA ATT TGC GT

1.2.2 Collection of clinical characteristics

Key clinical characteristics of patients were recorded, including tumor location (73 cases in colon, 44 cases in rectum), tumor diameter (<5 cm in 61 cases, ≥5 cm in 56 cases), TNM staging (53 cases in stage I-II, 64 cases in stage III-IV), degree of differentiation (39 cases with low differentiation, 78 cases with moderate/high differentiation), and presence of lymph node metastasis (31 cases with lymph node metastasis, 86 cases without lymph node metastasis).

1.2.3 Follow-up

All patients underwent a 3-year postoperative follow-up through outpatient visits and telephone follow-up, and their prognostic survival status was recorded. The follow-up end date was March 2024. Based on survival status, patients were divided into a survival group (n=91) and a death group (n=26).

1.3 Statistical methods

Data were processed using SPSS 27.0 software. Measurement data were described as $\bar{x}\pm s$, and t-test was used for intergroup comparison; enumeration data were described as frequency (n), and chi-square test was applied. Pearson correlation analysis was performed to evaluate the correlation between serum miR-212-5p and miR-576-5p expression levels in CRC patients. Multivariate Cox regression analysis was used to identify factors influencing the prognosis of CRC patients. Receiver operating characteristic (ROC) curves were plotted to assess the early diagnostic value and prognostic predictive efficacy of serum miR-212-5p and miR-576-5p levels for CRC. P<0.05 was considered statistically significant.

2 Results

2.1 Comparison of serum miR-212-5p and miR-576-5p expression between the two groups

The results of qRT-PCR showed statistically significant differences in serum miR-212-5p and miR-576-5p expression between the two groups (P<0.05). Compared with the control group, the expression level of serum miR-212-5p was decreased, while the expression

level of miR-576-5p was increased in the observation group (P<0.05). **[Table 2]**

Tab.2 Comparison of the expressions of serum miR-212-5p and miR-576-5p between two groups（$\bar{x}\pm s$）

Groups	Case	miR-212-5p	miR-576-5p
Control group	50	1.02±0.24	1.00±0.23
Observational group	117	0.76±0.21	1.37±0.31
t value		7.016	7.589
P value		＜0.001	＜0.001

2.2 Comparison of serum miR-212-5p and miR-576-5p expression in CRC patients with different prognoses

There were statistically significant differences in serum miR-212-5p and miR-576-5p expression between patients with different prognoses (P<0.05): compared with the survival group, the death group showed lower serum miR-212-5p expression levels and higher miR-576-5p expression levels (P<0.05). **[Table 3]**

Tab.3 Comparison of serum miR-212-5p and miR-576-5p expressions in CRC patients with different prognostic outcomes（$\bar{x}\pm s$）

Groups	Case	miR-212-5p	miR-576-5p
Survival group	91	0.82±0.21	1.28±0.26
Death group	26	0.55±0.17	1.69±0.37
t value		6.011	6.413
P value		＜0.001	＜0.001

2.3 Correlation between serum miR-212-5p and miR-576-5p levels in CRC patients

Pearson correlation analysis revealed a significant negative correlation between serum miR-212-5p and miR-576-5p expression levels in CRC patients (r=-0.598, P<0.05). **[Figure 1]**

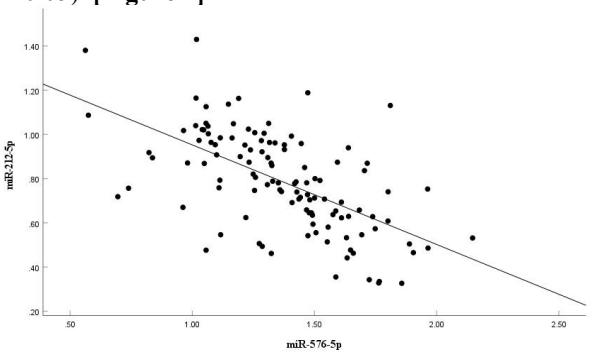

Fig.1 Correlation of serum miR-212-5p and miR-576-5p levels in patients with CRC

2.4 Relationship between serum miR-212-5p and miR-576-5p levels and clinicopathological characteristics of CRC patients

Using the mean expression levels of serum miR-212-5p and miR-576-5p as the cutoff value, CRC patients were divided into miR-212-5p high-expression group (n=54) and miR-212-5p low-expression group (n=63), as well as miR-576-5p high-expression group (n=61) and miR-576-5p low-expression group (n=56). There were statistically significant differences between the high-expression and low-expression groups of miR-212-5p and miR-576-5p in terms of TNM staging and lymph node metastasis (P<0.05). **[Table 4]**

Tab.4 Relationship between serum miR-212-5p and miR-576-5p levels and the clinicopathological characteristics of patients with CRC [case (%)]

Clinical charaterristics	n	miR-212-5p		χ^2 value	*P* value	miR-576-5p		χ^2 value	*P* value
		High expression（n=54）	Low expression（n=63）			High expression（n=61）	Low expression（n=56）		
Gender									
Male	64	30（55.56）	34（53.97）	0.030	0.860	33（54.10）	31（55.36）	0.019	0.891
Female	53	24（44.44）	29（46.03）			28（45.90）	25（44.64）		
Age (years)									
＜60	67	30（55.56）	37（58.73）	0.120	0.729	35（57.38）	32（57.14）	0.001	0.980
≥60	50	24（44.44）	26（41.27）			26（42.62）	24（42.86）		
Tumor location									
Colon	73	33（61.11）	40（63.49）	0.070	0.791	38（62.30）	35（62.50）	0.001	0.982
Rectum	44	21（38.89）	23（36.51）			23（37.70）	21（37.50）		
Tumor diameter（cm）									
＜5	61	29（53.70）	32（50.79）	0.099	0.753	31（50.82）	30（53.57）	0.089	0.766
≥5	56	25（46.30）	31（49.21）			30（49.18）	26（46.43）		
TNM staging									
Stage I-II	53	19（35.19）	34（53.97）	4.140	0.042	35（57.38）	18（32.14）	7.503	0.006
Stage III-IV	64	35（64.81）	29（46.03）			26（42.62）	38（67.86）		
Differentiation degree									
Poorly differentiated	39	17（31.48）	22（34.92）	0.155	0.694	20（32.79）	19（33.93）	0.017	0.896
Moderately/well differentiated	78	37（68.52）	41（65.08）			41（67.21）	37（66.07）		
Lymph node metastasis									
Yes	31	9（16.67）	22（34.92）	4.975	0.026	11（18.03）	20（35.71）	4.687	0.030
No	86	45（83.33）	41（65.08）			50（81.97）	36（64.29）		

2.5 Diagnostic value of serum miR-212-5p and miR-576-5p levels in early-stage CRC

ROC curve analysis was performed with the presence of

CRC (no=0, yes=1) as the state variable and serum miR-212-5p and miR-576-5p levels as independent variables. The results showed that the area under the curve (AUC) values for individual and combined diagnosis of CRC by serum miR-212-5p and miR-576-5p were 0.764 (95%*CI*: 0.692-0.826), 0.827 (95%*CI*: 0.760-0.881), and 0.907 (95%*CI*: 0.853-0.947), respectively. Moreover, the combined detection was superior to individual detection of miR-212-5p and miR-576-5p ($Z_{combination\text{-}miR\text{-}212\text{-}5p}$ =3.902, $Z_{combination\text{-}miR\text{-}576\text{-}5p}$=3.170, P<0.05). **[Table 5 & Figure 2]**

2.6 Influencing factors of CRC prognosis by multivariate Cox regression analysis

Multivariate Cox regression analysis was performed with death within 3 years in patients with CRC as the dependent variable and TNM staging, lymph node metastasis, miR-212-5p, and miR-576-5p as independent variables. The results showed that TNM staging, lymph node metastasis, and elevated miR-576-5p were risk factors for death in CRC patients (P<0.05), while decreased miR-212-5p was a protective factor for death in bladder cancer patients (P<0.05). **[Table 6]**

2.7 Predictive efficacy of serum miR-212-5p and miR-576-5p levels for CRC prognosis

ROC curve analysis was performed with the prognostic survival status of CRC patients (survival=0, death=1) as the state variable and serum miR-212-5p and miR-576-5p levels as independent variables. The results showed that the area under the curve (AUC) values for individual and combined prediction of death in CRC patients by serum miR-212-5p and miR-576-5p were 0.861 (95%*CI*: 0.785-0.918), 0.720 (95%*CI*: 0.630-0.799), and 0.937 (95%*CI*: 0.877-0.974), respectively. Moreover, the combined detection was superior to individual detection of miR-212-5p and miR-576-5p ($Z_{combination\text{-}miR\text{-}212\text{-}5p}$=2.460, $Z_{combination\text{-}\ miR\text{-}576\text{-}5p}$=4.377, P<0.05). **[Table 7 & Figure 3]**

Tab.5 The early diagnostic value of serum miR-212-5p and miR-576-5p levels for CRC

Item	AUC	95%*CI*	Sensitivity (%)	Specificity (%)	Youden index	Cut-off value
miR-212-5p	0.764	0.692-0.826	88.03	56.00	0.440	0.92
miR-576-5p	0.827	0.760-0.881	72.65	82.00	0.547	1.19
Combined detection	0.907	0.853-0.947	82.05	92.00	0.741	-

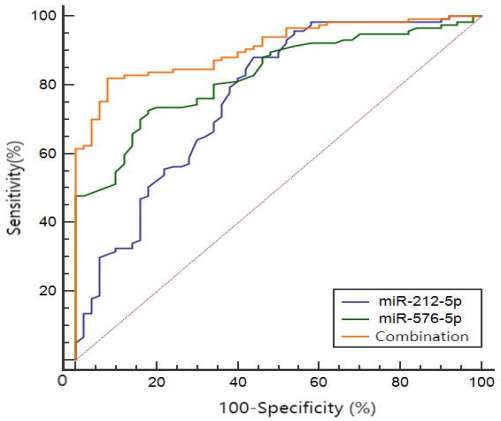

Fig.2 ROC curves of serum miR-212-5p and miR-576-5p levels in the diagnosis of CRC

Tab.6 Multivariate Cox regression analysis of influencing factors of prognosis of CRC

Influencing factors	*β*	*SE*	*Wald* χ^2	*P* value	*OR* ratio	*95%CI*
TNM stage III-IV	0.516	0.241	4.592	0.032	1.676	1.045-2.688
Lymph node metastasis	0.768	0.357	4.631	0.031	2.156	1.071-4.340
miR-212-5p	-0.543	0.209	6.750	0.009	0.581	0.386-0.875
miR-576-5p	0.499	0.179	7.778	0.005	1.647	1.160-2.340

Tab.7 The predictive efficacy of serum miR-212-5p and miR-576-5p levels for the prognosis of CRC

Item	AUC	95%*CI*	Sensitivity (%)	Specificity (%)	Youden index	Cut-off value
miR-212-5p	0.861	0.785-0.918	96.15	58.24	0.544	0.80
miR-576-5p	0.720	0.630-0.799	53.85	82.42	0.363	1.64
Combined detection	0.937	0.877-0.974	88.46	93.41	0.819	-

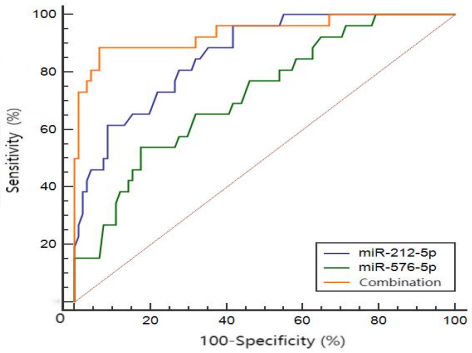

Fig.3 ROC curves of serum miR-212-5p and miR-576-5p levels for predicting the prognosis of patients with CRC

3 Conclusion

CRC, one of the most prevalent malignancies in the digestive system, has shown rising global incidence and mortality, with its age distribution gradually shifting toward younger populations [12]. Early-stage CRC often lacks significant specific symptoms, and its latent period during disease progression can exceed 10 years, posing major challenges to early identification and intervention [13]. The development of CRC is influenced by epigenetic regulatory mechanisms, among which miRNA play a critical role as core regulatory factors [14]. Extensive research has demonstrated that miRNAs take the potential as diagnostic biomarkers for various tumors and diseases [15].

miRNAs, acting as tumor suppressors or oncogenes, participate in regulating key biological processes, including cell proliferation, apoptosis, chemoresistance, and angiogenesis [16]. Therefore, miRNAs are promising biomarkers for early diagnosis, prognostic assessment, and personalized treatment of CRC. miR-212-5p, a member of the miR-212 family, has been proven to act as a tumor suppressor in multiple cancers. Downregulation of its expression is often closely associated with malignant behaviors such as accelerated tumor cell proliferation, enhanced invasiveness, and increased metastatic capacity [17]. Studies have found that downregulated miR-212-5p effectively inhibits the migration and invasion of CRC cells by promoting the upregulation of SMAD4 [18]. Consistent with these reports, our study revealed that serum miR-212-5p expression levels in the observation group were lower than those in the control group, and levels in the death group were lower than those in the survival group. These findings suggest that low serum miR-212-5p expression is closely related to CRC progression. Further analysis showed that miR-212-5p expression levels were significantly associated with the TNM staging and lymph node metastasis, indicating its potential involvement in CRC metastasis. ROC curve analysis indicated that the AUC of serum miR-212-5p expression for predicting CRC prognosis was 0.861. When serum miR-212-5p expression is below 0.80, it suggests a higher likelihood of poor CRC prognosis, prompting clinicians to adjust treatment regimens promptly to reduce adverse outcomes and provide references for preventing disease progression.

miR-576-5p, another member of the miRNA family, has been reported in previous studies to exhibit oncogenic effects [19]. Zhang *et al.* [20] reported that miR-576-5p expression is significantly upregulated during the pathological progression of esophageal carcinoma, making it a potential prognostic marker for assessing disease progression. Luo *et al.* [21] observed high miR-576-5p expression in CRC cells. Consistent with these findings, our study found that serum miR-576-5p expression levels were significantly elevated in CRC patients compared to healthy controls, and were closely associated with TNM staging and lymph node metastasis. Moreover, miR-576-5p levels were higher in the death group than in the survival group. These results suggest that miR-576-5p levels are involved in CRC progression and correlate with poor prognosis. ROC curve analysis further revealed that the AUC of serum miR-576-5p expression for predicting CRC prognosis was 0.720. When serum miR-576-5p expression exceeds 1.64, it indicates a higher risk of poor CRC prognosis, necessitating early adjustment of treatment strategies and preparation for countermeasures.

Further analysis demonstrated a negative correlation between serum miR-212-5p and miR-576-5p expression levels in CRC patients, and both were closely associated with TNM staging and lymph node metastasis. TNM staging is a key indicator for assessing the severity of CRC [22], while lymph node metastasis is an important predictor of poor prognosis [23]. These findings suggest that miR-212-5p and miR-576-5p may participate in CRC progression and hold promise as novel indicators for evaluating CRC malignancy and predicting prognosis. ROC curve analysis further confirmed that both individual and combined detection of miR-212-5p and miR-576-5p exhibited high diagnostic value, with the AUC of combined detection reaching 0.907, significantly higher than that of individual detection. Additionally, this study explored the potential value of serum miR-212-5p and miR-576-5p in CRC prognostic assessment. ROC curves further validated their role in predicting CRC patient prognosis, with the combined AUC for predicting death reaching 0.937, indicating excellent predictive efficacy. Collectively, these results highlight the critical role of serum miR-212-5p and miR-576-5p in CRC diagnosis and prognosis prediction.

In summary, decreased serum miR-212-5p expression and increased miR-576-5p expression in CRC patients are factors influencing CRC prognosis, and both are promising effective indicators for diagnosing CRC occurrence and predicting patient survival. However, this study has limitations, including a relatively small and single-center sample size, and a lack of in-depth exploration of the specific molecular mechanisms. Future research should expand the sample size, integrate molecular biology experiments and bioinformatics analysis, and further investigate the mechanistic roles of miR-212-5p and miR-576-5p in CRC development, as well as their potential value as biomarkers.

Conflict of interest None

Reference

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Submission Received:2025-04-08/**Revised:**2025-05-29

·论 著·

miR-212-5p和miR-576-5p在结直肠癌患者血清中表达水平及与预后的关系

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摘要：目的 分析血清微小RNA(miR)-212-5p和miR-576-5p在结直肠癌血清中水平及预后的临床价值。**方法** 选取2019年4月至2021年4月秦皇岛市第一医院收治的117例结直肠癌患者(观察组)和体检的50例健康志愿者(对照组)作为研究对象，术后随访3年，记录患者的预后生存状况。按随访结束时生存情况将结直肠癌患者分为生存组(n=91)和死亡组(n=26)。实时荧光定量PCR(qRT-PCR)法测定各组血清miR-212-5p和miR-576-5p的表达量；Pearson法分析结直肠癌患者血清miR-212-5p、miR-576-5p表达水平间的相关性；分析血清miR-212-5p、miR-576-5p与患者临床病理特征之间的关系；受试者工作特征(ROC)曲线评估血清miR-212-5p、miR-576-5p对结直肠癌的早期诊断价值及预后预测效能。**结果** 与对照组相比，观察组血清miR-212-5p表达水平降低，miR-576-5p表达水平则升高(P<0.05)；与生存组相比，死亡组血清miR-212-5p表达水平更低，miR-576-5p表达水平更高(P<0.05)。结直肠癌患者血清miR-212-5p与miR-576-5p表达水平呈显著负相关(r=−0.598，P<0.05)；结直肠癌患者血清miR-212-5p、miR-576-5p水平与患者的TNM分期和有无淋巴结转移密切相关(P<0.05)；血清miR-212-5p和miR-576-5p单独及联合诊断结直肠癌的曲线下面积(AUC)分别为0.764、0.827、0.907，联合检测优于二者单独检测($Z_{二者联合\text{-}miR\text{-}212\text{-}5p}$=3.902，$Z_{二者联合\text{-}miR\text{-}576\text{-}5p}$=3.170，$P$<0.05)；血清miR-212-5p和miR-576-5p单独及联合预测结直肠癌患者死亡的AUC分别为0.861、0.720、0.937，联合检测优于二者单独检测($Z_{二者联合miR\text{-}212\text{-}5p}$=2.460，$Z_{二者联合\text{-}miR\text{-}576\text{-}5p}$=4.377，$P$<0.05)。**结论** 结直肠癌患者血清miR-212-5p表达降低，miR-576-5p表达升高，二者联合可为结直肠癌的早期诊断及预后提供临床依据。

关键词： 结直肠癌；微小RNA-212-5p；微小RNA-576-5P；诊断；预后
中图分类号： R735.34 **文献标识码：** A **文章编号：** 1674-8182(2025)07-0999-06

Expression levels of miR-212-5p and miR-576-5p in the serum of colorectal cancer patients and their relationship with prognosis

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Abstract: Objective To analyze the levels of serum microRNA (miR)-212-5p and miR-576-5p in colorectal cancer (CRC) patients and their clinical value in prognosis. **Methods** A total of 117 CRC patients (observation group) admitted to First Hospital of Qinhuangdao from April 2019 to April 2021 and 50 healthy volunteers (control group) were enrolled as subjects. Postoperative follow-up was conducted for 3 years to record the survival outcomes of the patients. According to the survival status at the end of the follow-up, the patients with colorectal cancer were divided into survival group (n=91) and death group (n=26). The real-time fluorescence quantitative PCR (qRT-PCR) was used to measure the expression levels of serum miR-212-5p and miR-576-5p in each group. Pearson's correlation test was employed to analyze the correlation between the expression levels of serum miR-212-5p and miR-576-5p in CRC patients. The relationship between serum miR-212-5p, miR-576-5p levels and the clinicopathological characteristics of the patients was examined. Receiver operating characteristic (ROC) curve analysis was used to evaluate the early

DOI:10.13429/j.cnki.cjcr.2025.07.005
基金项目： 秦皇岛市科学技术研究与发展计划(201902A137)
出版日期： 2025-07-20

QR code for English version

diagnosis value and prognostic predictive efficacy of serum miR-212-5p and miR-576-5p in colorectal cancer. **Results** Compared with the control group, the expression level of serum miR-212-5p in the observation group was decreased, while the expression level of miR-576-5p was increased ($P < 0.05$). Compared with the survival group, the death group exhibited lower serum miR-212-5p expression and higher miR-576-5p expression ($P < 0.05$). Serum miR-212-5p and miR-576-5p levels in CRC patients showed a significant negative correlation (r=−0.598, P<0.05). The serum levels of miR-212-5p and miR-576-5p in CRC patients were closely associated with TNM stage and lymph node metastasis ($P < 0.05$). The area under the curve (AUC) for serum miR-212-5p and miR-576-5p individually and in combination for diagnosing CRC were 0.764, 0.827, and 0.907, respectively, with the combined detection outperforming each individual detection ($Z_{combination-miR-212-5p}$=3.902, $Z_{combination-miR-576-5p}$=3.170, P<0.05). The AUC for predicting CRC patient mortality using serum miR-212-5p and miR-576-5p individually and in combination were 0.861, 0.720, and 0.937, respectively, with the combined detection outperforming each individual detection ($Z_{combination-miR-212-5p}$=2.460, $Z_{combination-miR-576-5p}$=4.377, P<0.05). **Conclusion** Serum miR-212-5p expression is reduced and miR-576-5p expression is increased in CRC patients. The combination of these two can provide clinical evidence for early diagnosis and prognosis of CRC.

Keywords: Colorectal cancer; microRNA-212-5p; microRNA-576-5p; Diagnosis; Prognosis

Fund program: Qinhuangdao Science and Technology Research and Development Program (201902A137)

结直肠癌是全球范围内发病率和死亡率均居前列的消化系统恶性肿瘤之一，其发病率在发展中国家正逐年上升[1]。在结直肠癌的发病机制中环境和遗传因素发挥着主导作用，而营养因素则发挥保护作用[2]。近年来，由于筛查技术的进步与治疗方法的优化，结直肠癌的死亡率在全球范围内呈现出积极的下降趋势[3]。因此，早期诊断对于患者生存至关重要。然而，传统诊断手段在结直肠癌的早期筛查及预后评估中往往存在灵敏度与特异度不足的问题[4]，亟须探索新的生物标志物以弥补这一缺陷。微小RNA（microRNA，miRNA，miR）作为一类非编码RNA，在结直肠癌发展和转移过程中具有重要调控作用[5]。血清中miRNA因其具有易于获取、稳定性好及潜在的临床应用价值，成为肿瘤研究的新热点[6]。miR-212-5p作为一种独特的肿瘤抑制因子，先前已被报道与结直肠癌的转移过程密切相关，且miR-212-5p的表达水平在结直肠癌细胞系中呈现出显著的下调趋势，进一步强调了其在结直肠癌进展中作为治疗靶点的价值[7]。miR-576-5p则在多种类型肿瘤中展现出促癌潜力，研究发现miR-576-5p在结直肠癌患者中高表达，进而抑制结直肠癌细胞凋亡[8-9]。目前，临床关于miR-212-5p和miR-576-5p联合预测结直肠癌预后的相关报道有限，基于此，本研究通过分析miR-212-5p和miR-576-5p在结直肠癌中的表达变化及其与疾病发生、预后的关系，以期为结直肠癌的诊断及预后评估提供科学依据。

1 资料与方法

1.1 一般资料 试验开展前已获得伦理委员会审批伦理批号（2019H026），选取2019年4月至2021年4月秦皇岛市第一医院收治的117例结直肠癌患者作为研究组，其中男64例，女53例，年龄（51.97±9.53）岁。纳入标准：（1）符合结直肠癌相关诊断标准[10]，经病理确诊；（2）入组前均未经历免疫治疗干预，未接受放射治疗和化学药物治疗；（3）年龄>18岁；（4）根据相关分期标准[11]，属于Ⅰ~Ⅳ期；（5）临床资料完整；（6）患者均知情，自愿入职，签署同意书。排除标准：（1）合并其他肠道疾病者；（2）伴随有肾脏、心脏、肝脏等重要脏器功能损害者；（3）合并严重感染、先天性疾病和自身免疫性疾病者；（4）妊娠期或哺乳期妇女；（5）合并其他恶性肿瘤者。另选取同期体检的50例志愿者作为对照组，各项体检指标均处于正常范围之内。其中男32例，女18例，年龄（51.37±9.14）岁。两组性别、年龄差异无统计学意义（P>0.05）。

1.2 *研究方法*

1.2.1 实时荧光定量聚合酶链反应（quantitative reverse transcriptase polymerase chain reaction，qRT-PCR）法检测血清miR-212-5p和miR-576-5p相对表达水平 采集所有受试者清晨空腹静脉血3 mL，离心处理10 min后取上层清液，置于低温环境保存备用。利用Trizol Total RNA提取试剂盒（上海康朗生物科技有限公司，货号：KL001）从血清样本中分离出总RNA。使用紫外分光光度计测量RNA样品的吸光度（A值），并计算其浓度及纯度，A_{260}/A_{280}比值在1.7~2.1为合格。选用反转录试剂盒[亚太恒信生物科技（北京）有限公司，货号：AORT-0100]逆转录筛选出的总RNA。按照qRT-PCR试剂盒（上海百生跃生物科技有限公司，货号：BR1000207）配置反应体系，并在qRT-

PCR系统中执行PCR扩增。反应程序设置为:95 ℃预变性2 min,95 ℃变性15 s,60 ℃退火30 s,72 ℃延伸30 s,共进行40个循环。U6作为内参基因进行标准化,采用$2^{-\Delta\Delta Ct}$法计算miR-212-5p、miR-576-5p的相对表达水平。所有引物序列均由NCBI设计,并交由生物工程(上海)股份有限公司进行合成,具体序列信息见表1。

1.2.2 临床特征收集 记录患者的关键临床特征,包括肿瘤位置(结肠73例,直肠44例)、肿瘤直径(<5 cm 61例,≥5 cm 56例)、TNM分期(Ⅰ~Ⅱ期53例,Ⅲ~Ⅳ期64例)、分化程度(低分化39例,中高分化78例)以及有无淋巴结转移(有淋巴结转移31例,无淋巴结转移86例)。

1.2.3 随访 所有患者通过门诊复诊与电话随访,经历为期3年的术后跟踪,并记录每位患者的预后生存状况。随访截止时间为2024年3月,基于预后生存状况将患者划分为生存组(n=91)与死亡组(n=26)。

1.3 统计学方法 采用SPSS 27.0软件处理数据。计量资料以$\bar{x}\pm s$描述,组间比较采用t检验;计数资料用频数描述,采用χ^2检验。Pearson法分析结直肠癌患者血清miR-212-5p和miR-576-5p表达水平之间的相关性;结直肠癌患者预后的影响因素采用多因素Cox回归分析;绘制受试者工作特征(receiver operating characteristic,ROC)曲线评估血清miR-212-5p和miR-576-5p水平对结直肠癌的早期诊断价值和预后预测效能。P<0.05为差异有统计学意义。

2 结 果

2.1 两组血清miR-212-5p、miR-576-5p表达比较 qRT-PCR结果显示,与对照组相比,观察组血清miR-212-5p表达水平降低,miR-576-5p表达水平升高(P<0.05)。见表2。

2.2 不同预后结直肠癌患者血清miR-212-5p、miR-576-5p表达比较 与生存组相比,死亡组血清miR-212-5p表达水平更低,miR-576-5p表达水平更高(P<0.05)。见表3。

2.3 结直肠癌患者血清miR-212-5p、miR-576-5p水平的相关性 通过Pearson相关性分析,结直肠癌患者血清miR-212-5p与miR-576-5p表达水平之间存在显著的负相关(r=−0.598,P<0.05)。见图1。

2.4 血清miR-212-5p、miR-576-5p水平与结直肠癌患者临床病理特征的关系 以血清miR-212-5p、miR-576-5p表达水平的平均值为界,将结直肠癌患者分为miR-212-5p高表达组(n=54)和miR-212-5p低表达组(n=63)、miR-576-5p高表达组(n=61)和miR-576-5p低表达组(n=56)。miR-212-5p、miR-576-5p高表达组和低表达组在TNM分期、有无淋巴结转移方面差异有统计学意义(P<0.05)。见表4。

表1 引物序列

Tab.1 Primer sequences

基因名称	正向引物(5′→3′)	反向引物(5′→3′)
miR-212-5p	GCT TAC GCT TCG AGC CCA C	GAC ACC ACG GCC CAC TCT GCA
miR-576-5p	GCG CGA TTC TAA TTT CTC CAC	AGT GCA GGG TCC GAG GTA TT
U6	CTC GCT TCG GCA GCA CA	AAC GCT TCA CGA ATT TGC GT

表2 两组血清miR-212-5p、miR-576-5p表达比较 ($\bar{x}\pm s$)

Tab.2 Comparison of the expressions of serum miR-212-5p and miR-576-5p between two groups ($\bar{x}\pm s$)

组别	例数	miR-212-5p	miR-576-5p
对照组	50	1.02±0.24	1.00±0.23
观察组	117	0.76±0.21	1.37±0.31
t值		7.016	7.589
P值		<0.001	<0.001

表3 不同预后结直肠癌患者血清miR-212-5p、miR-576-5p表达比较 ($\bar{x}\pm s$)

Tab.3 Comparison of serum miR-212-5p and miR-576-5p expressions in colorectal cancer patients with different prognostic outcomes ($\bar{x}\pm s$)

组别	例数	miR-212-5p	miR-576-5p
生存组	91	0.82±0.21	1.28±0.26
死亡组	26	0.55±0.17	1.69±0.37
t值		6.011	6.413
P值		<0.001	<0.001

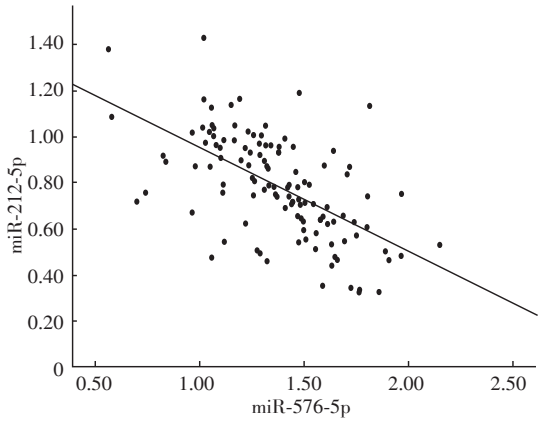

图1 结直肠癌患者血清miR-212-5p、miR-576-5p水平的相关性

Fig.1 Correlation of serum miR-212-5p and miR-576-5p levels in patients with colorectal cancer

表4　血清miR-212-5p、miR-576-5p水平与结直肠癌患者临床病理特征的关系　［例(%)］

Tab.4　Relationship between serum miR-212-5p and miR-576-5p levels and the clinicopathological characteristics of patients with colorectal cancer　［case(%)］

临床特征	例数	miR-212-5p		χ^2值	P值	miR-576-5p		χ^2值	P值
		高表达(n=54)	低表达(n=63)			高表达(n=61)	低表达(n=56)		
性别									
男	64	30(55.56)	34(53.97)	0.030	0.860	33(54.10)	31(55.36)	0.019	0.891
女	53	24(44.44)	29(46.03)			28(45.90)	25(44.64)		
年龄									
<60岁	67	30(55.56)	37(58.73)	0.120	0.729	35(57.38)	32(57.14)	0.001	0.980
≥60岁	50	24(44.44)	26(41.27)			26(42.62)	24(42.86)		
肿瘤位置									
结肠	73	33(61.11)	40(63.49)	0.070	0.791	38(62.30)	35(62.50)	0.001	0.982
直肠	44	21(38.89)	23(36.51)			23(37.70)	21(37.50)		
肿瘤直径									
<5 cm	61	29(53.70)	32(50.79)	0.099	0.753	31(50.82)	30(53.57)	0.089	0.766
≥5 cm	56	25(46.30)	31(49.21)			30(49.18)	26(46.43)		
TNM分期									
Ⅰ~Ⅱ期	53	19(35.19)	34(53.97)	4.140	0.042	35(57.38)	18(32.14)	7.503	0.006
Ⅲ~Ⅳ期	64	35(64.81)	29(46.03)			26(42.62)	38(67.86)		
分化程度									
低分化	39	17(31.48)	22(34.92)	0.155	0.694	20(32.79)	19(33.93)	0.017	0.896
中、高分化	78	37(68.52)	41(65.08)			41(67.21)	37(66.07)		
淋巴结转移									
有	31	9(16.67)	22(34.92)	4.975	0.026	11(18.03)	20(35.71)	4.687	0.030
无	86	45(83.33)	41(65.08)			50(81.97)	36(64.29)		

2.5　血清miR-212-5p和miR-576-5p水平对结直肠癌的早期诊断价值　以是否有结直肠癌(否=0,是=1)为状态变量,血清miR-212-5p和miR-576-5p水平为自变量,进行ROC曲线分析。结果显示,血清miR-212-5p和miR-576-5p单独及联合诊断结直肠癌的曲线下面积(area under curve, AUC)分别为0.764(95%*CI*: 0.692~0.826)、0.827(95% *CI*: 0.760~0.881)、0.907(95%*CI*: 0.853~0.947),且联合检测优于miR-212-5p和miR-576-5p二者单独检测($Z_{\text{二者联合 miR-212-5p}}$=3.902, $Z_{\text{二者联合-miR-576-5p}}$=3.170, P<0.05)。见表5、图2。

2.6　多因素Cox回归分析结直肠癌预后的影响因素　以结直肠癌患者3年内是否死亡为因变量,以TNM分期、淋巴结转移、miR-212-5p、miR-576-5p为自变量进行多因素Cox回归分析,结果显示,TNM分期Ⅲ~Ⅳ期、淋巴结转移、miR-576-5p升高是结直肠癌患者死亡的危险因素(P<0.05),miR-212-5p升高是结直肠癌患者死亡的保护因素(P<0.05)。见表6。

2.7　血清miR-212-5p和miR-576-5p水平对结直肠癌预后的预测效能　以结直肠癌患者预后生存情况

表5　血清miR-212-5p和miR-576-5p水平对结直肠癌的早期诊断价值

Tab.5　The early diagnostic value of serum miR-212-5p and miR-576-5p levels for colorectal cancer

项目	AUC	95%*CI*	敏感度(%)	特异度(%)	约登指数	截断值
miR-212-5p	0.764	0.692~0.826	88.03	56.00	0.440	0.92
miR-576-5p	0.827	0.760~0.881	72.65	82.00	0.547	1.19
联合检测	0.907	0.853~0.947	82.05	92.00	0.741	–

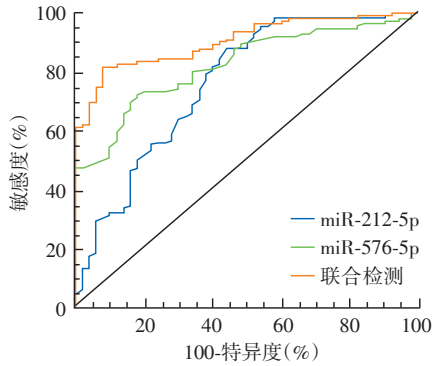

图2　血清miR-212-5p和miR-576-5p水平诊断结直肠癌的ROC曲线

Fig.2　ROC curves of serum miR-212-5p and miR-576-5p levels in the diagnosis of colorectal cancer

表6　多因素Cox回归分析结直肠癌预后的影响因素

Tab.6　Multivariate Cox regression analysis of the influencing factors of prognosis of colorectal cancer

因素	β	SE	Waldχ^2	P值	OR值	95%*CI*
TNM分期Ⅲ~Ⅳ期	0.516	0.241	4.592	0.032	1.676	1.045~2.688
淋巴结转移	0.768	0.357	4.631	0.031	2.156	1.071~4.340
miR-212-5p	−0.543	0.209	6.750	0.009	0.581	0.386~0.875
miR-576-5p	0.499	0.179	7.778	0.005	1.647	1.160~2.340

（生存=0，死亡=1）为状态变量，血清 miR-212-5p 和 miR-576-5p 水平为自变量，进行 ROC 曲线分析。结果显示，血清 miR-212-5p 和 miR-576-5p 单独及联合预测结直肠癌患者死亡的 AUC 分别为 0.861（95%*CI*：0.785~0.918）、0.720（95% *CI*：0.630~0.799）、0.937（95%*CI*：0.877~0.974），且联合检测优于 miR-212-5p 和 miR-576-5p 二者单独检测（$Z_{二者联合\ miR\text{-}212\text{-}5p}$=2.460，$Z_{二者联合\text{-}miR\text{-}576\text{-}5p}$=4.377，$P<0.05$）。见表 7、图 3。

表 7　血清 miR-212-5p 和 miR-576-5p 水平对结直肠癌预后的预测效能

Tab.7　The predictive efficacy of serum miR-212-5p and miR-576-5p levels for the prognosis of colorectal cancer

项目	AUC	95%*CI*	敏感度（%）	特异度（%）	约登指数	截断值
miR-212-5p	0.861	0.785~0.918	96.15	58.24	0.544	0.80
miR-576-5p	0.720	0.630~0.799	53.85	82.42	0.363	1.64
联合检测	0.937	0.877~0.974	88.46	93.41	0.819	–

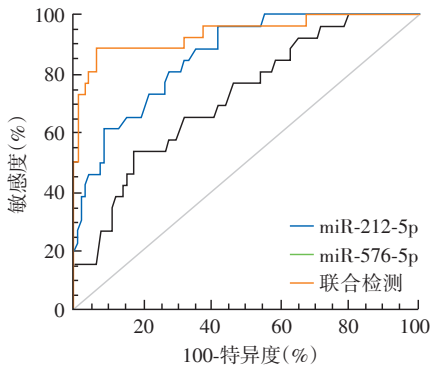

图 3　血清 miR-212-5p 和 miR-576-5p 水平预测结直肠癌预后的 ROC 曲线

Fig.3　ROC curves of serum miR-212-5p and miR-576-5p levels for predicting the prognosis of colorectal cancer

3　结　论

结直肠癌作为消化系统领域普遍存在的恶性肿瘤之一，其全球范围内的发病频率和致死率均呈现出上升趋势，且该疾病的发病年龄结构逐渐向年轻群体分布[12]。早期结直肠癌常缺乏显著的特异性症状，其疾病进程中的潜伏期可超过 10 年，使得疾病的早期识别与干预面临重大挑战[13]。结直肠癌的发生受表观遗传调控机制的作用，其中 miRNA 作为核心调控因子起着重要作用[14]。大量研究成果表明，miRNA 具备作为多种癌症及疾病诊断标志物的潜力[15]。

miRNA 能够作为肿瘤抑制因子或癌基因，参与调控一系列关键生物过程，包括细胞增殖、细胞凋亡以及化疗药物耐药性、血管生成等[16]。因此，miRNA 是结直肠癌早期诊断、预后评估和个性化治疗的极具潜力的生物标志物。miR-212-5p 作为 miR-212 家族的一员，已被证实在多种癌症中扮演肿瘤抑制因子的角色，其表达水平下调与肿瘤细胞增殖加速、侵袭性增强及转移能力提高等恶性行为密切相关[17]。研究表明，miR-212 通过靶向抑制神经纤毛蛋白-1（neuropilin-1，NRP1）的表达调节细胞免疫应答，并进一步诱导结直肠癌细胞死亡[18]。与上述报道相似，本研究中发现，观察组血清 miR-212-5p 表达水平低于对照组，死亡组血清 miR-212-5p 表达水平低于生存组，表明血清 miR-212-5p 低表达与结直肠癌病情进展具有一定关系。miR-212-5p 表达水平与患者 TNM 分期以及有无淋巴结转移密切相关，推测可能参与结直肠癌转移的发展进程，ROC 曲线进一步分析显示，血清 miR-212-5p 表达水平预测结直肠癌预后的 AUC 为 0.861，当血清 miR-212-5p 表达水平低于 0.80 时，提示结直肠癌预后不良的可能性较大，医师团队应及时调整治疗方案，降低预后不良，为防治病情恶化提供一定参考。

miR-576-5p 同样作为 miRNA 家族的一员，既往研究表明 miR-576-5p 具有一定的促癌作用[19]。Zhang 等[20]研究报道，在食管癌的病理进程中，miR-576-5p 的表达水平显著上升，可作为潜在的预后标志物评估食管癌患者的疾病进展。Luo 等[21]研究报道，在结直肠癌细胞中观察到 miR-576-5p 的高表达。与上述研究报道相似，本研究发现，与健康对照组相比，结直肠癌患者血清中 miR-576-5p 表达水平显著升高，与患者 TNM 分期以及有无淋巴结转移密切相关，与生存组相比，死亡组结直肠癌患者血清中 miR-576-5p 的表达水平更高。推测 miR-576-5p 水平参与结直肠癌病情进展，与患者预后不良具有一定关系。ROC 曲线进一步分析显示，血清 miR-576-5p 表达水平预测结直肠癌预后的 AUC 为 0.720，当血清 miR-576-5p 表达水平高于 1.64 时，提示结直肠癌预后不良的可能性较大，应提前调整方案，做好应对措施。

进一步分析显示，结直肠癌患者血清 miR-212-5p 与 miR-576-5p 表达水平呈负相关，且二者血清水平与患者 TNM 分期和有无淋巴结转移密切相关。TNM 分期是评估结直肠癌病情严重程度的关键指标[22]，而淋巴结转移则是患者预后不良的重要预测因素[23]。提示 miR-212-5p 和 miR-576-5p 可能参与结直肠癌的进展过程，并有望成为评估结直肠癌恶性程度和预测预后的新指标。ROC 曲线进一步发现，miR-212-5p 和 miR-576-5p 单独和联合检测均表现出较高的诊断

价值，且联合检测的AUC达到0.907，显著高于单独检测。此外，本研究还探讨了血清miR-212-5p和miR-576-5p在结直肠癌预后评估中的潜在价值。ROC曲线进一步证实miR-212-5p和miR-576-5p在预测结直肠癌患者预后中的作用，二者联合预测结直肠癌患者死亡的AUC达到0.937，显示出极高的预测效能。以上结果均表明血清miR-212-5p和miR-576-5p在结直肠癌的诊断和预测中发挥重要作用。

综上所述，结直肠癌患者血清中miR-212-5p的表达水平下降，而miR-576-5p的表达水平升高，为结直肠癌预后的影响因素，二者有望成为诊断结直肠癌发生和预测患者生存情况的有效指标。但本研究样本量相对有限且单一，且未深入探究其具体的分子机制。未来研究可进一步扩大样本量，并结合分子生物学实验和生物信息学分析，深入探讨miR-212-5p和miR-576-5p在结直肠癌发生发展中的作用机制及其作为生物标志物的潜在价值。

利益冲突 无

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收稿日期:2025-04-08 **修回日期**:2025-05-29 **编辑**:王宇