miR-106b-5p in stage II left-sided and right-sided colon cancer and its association with the prognostic characteristics of patients

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Abstract. MicroRNA (miR)-106b-5p is highly expressed in colon cancer; however, data on its expression levels in left-sided colon cancer (LCC) vs. right-sided colon cancer (RCC) is lacking. The present study aimed to assess the differences in miR-106b-5p expression in stage II LCC and RCC, as well as its relationship with patient prognosis. From August 2018 to February 2020, 40 specimens of primary stage II colon cancer were collected from Huizhou First Hospital (Huizhou, China), which included 20 cases of LCC and 20 cases of RCC. The miR-106b-5p expression levels in cancer tissues were compared with normal adjacent tissues, as well as between LCC and RCC tissues, and survival outcomes were assessed. miR-106b-5p expression was significantly higher in stage II LCC tissues compared with RCC tissues. However, no significant difference in 5-year survival was observed between the two groups. Notably, 5-year survival was significantly lower in the high miR-106b-5p expression group compared with the low expression group among patients with RCC. By contrast, there were no survival differences between the high and low miR-106b-5p expression groups in LCC. Multivariate analysis indicated that miR-106b-5p expression was an independent prognostic factor for patients with RCC. In conclusion, miR-106b-5p expression was significantly upregulated in colon cancer tissues, with higher expression levels demonstrated in LCC compared with RCC. High miR-106b-5p expression in RCC was identified as an independent prognostic factor, whilst its expression in LCC did not show a significant association with prognosis.

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Introduction

Colorectal cancer is the third most common cancer worldwide, with an estimated 1.93 million new cases in 2020, accounting for ~10% of all new cancer cases and can be classified into left-sided colon cancer (LCC) and right-sided colon cancer (RCC) based on its primary site (1,2). The clinical presentations of these two categories vary considerably. Patients with RCC are more likely to experience iron deficiency anemia due to occult blood loss, whilst common symptoms in those with LCC include hematochezia and alterations in bowel habits. From a molecular perspective, RCC and LCC represent distinct entities. RCC is associated with mutations in mismatch repair genes, KRAS and BRAF, as well as microRNA (miR)-31, whereas LCC is linked to chromosomal instability, p53, NRAS and several miRs, including miR-146a, miR-147b and miR-1288 (3).

The prognoses for LCC and RCC may differ, with variations also observed based on cancer stage. Epidemiological data from a study involving 77,978 patients with colon cancer revealed a significant difference in median survival: 78 months for RCC and 89 months for LCC (4). Warschkow *et al* (5) reported that RCC had better OS rates in both stage I and stage II, whilst stage III LCC and Rs exhibited similar prognoses. Qiu *et al* (6) reported that patients with RCC had a better prognosis than those with LCC in stage II. Furthermore, a study performed in China reported that the recurrence rate of RCC was higher than that of LCC disease, with patients with RCC facing worse prognoses compared with those with stage III LCC (7). However, there is currently no molecular marker that reliably indicates the prognostic differences between LCC and RCC.

miRs are small (20-22 nt) non-coding RNAs transcribed by RNA polymerase II, serving as important regulatory molecules of gene expression, typically inhibiting the translation of mRNAs (8,9). miRs have been identified as predictive and prognostic indicators for several cancers, including lung, liver, breast and colon cancers (10-13). Previous studies have reported that miRs can serve as predictive and prognostic molecular markers in stage II colon cancer (14). For instance, the expression of miR-31 has been reported to be higher in RCC and associated with an increased cancer-specific mortality rate (15). Omrane *et al* (16) reported that the expression

levels of miR-146a and miR-147b were markedly higher in LCC compared with RCC. Gopalan *et al* (17) reported that miR-1288 expression was elevated in LCC and rectal cancers compared with RCC. These findings suggest that miRs exhibit distinct expression patterns based on the location of colon cancer. Given that miRs are differentially expressed in LCC and RCC (18,19), further exploration of miRs as prognostic indicators for stage II colon cancer is warranted. Moreover, a study by Zhang *et al* (20) in an Asian population identified six miRs, including miR-106b-5p, as potentially reliable prognostic and predictive markers for disease recurrence in patients with stage II colon cancer. Therefore, the present study aimed to assess the differential expression of miR-106b-5p in stage II LCC and RCC and to assess its association with patient prognosis.

Materials and methods

Clinical data. All samples were obtained from 40 primary stage II colon cancer specimens, comprising 20 cases of left hemicolectomy and 20 cases of right hemicolectomy. These samples were surgically resected by gastrointestinal surgery at Huizhou First Hospital (Huizhou, China) between August 2018 and February 2020, with no preoperative radiotherapy, chemotherapy or other tumor-specific treatments. Each sample was confirmed by a pathologist post-surgery. All samples were staged according to the 8th edition of the American Joint Committee on Cancer staging criteria (21). Each sample consisted of one specimen of colon cancer and one specimen of normal adjacent colon tissue, collected from >5 cm away from the lesion. Specimens were collected aseptically in the operating room within 5 min of surgical resection, rapidly frozen in liquid nitrogen and stored at -80˚C. The present study was approved by the Medical Ethics Committee of Huizhou First Hospital (approval no. 201806).

Inclusion and exclusion criteria. The inclusion criteria were as follows: i) Diagnosis of primary stage II colon cancer; ii) no preoperative radiotherapy, chemotherapy or other tumor-targeted treatments; iii) surgical specimens obtained from gastrointestinal surgery; iv) all surgical specimens confirmed by pathology experts; v) all specimens clearly identified as either LCC or RCC; and vi) written informed consent provided. The exclusion criteria were as follows: i) Presence of other primary cancers, unless unrelated to colon cancer; ii) preoperative radiotherapy, chemotherapy or other tumor-targeted treatments administered; iii) specimens not confirmed by pathology experts; and iv) colon cancer diagnosed as stage I or other stages.

Reverse transcription-quantitative PCR. Total RNA was extracted from patient samples using TRIzol reagent (Thermo Fisher Scientific, Inc.). After extraction, RNA samples were treated with DNase I (Thermo Fisher Scientific, Inc.) to remove potential genomic DNA contamination and then RNA concentrations were measured using a spectrophotometer. Reverse transcription of RNA to cDNA was performed using the PrimeScript™ RT Reagent Kit (Takara Bio, Inc.), following the manufacturer's instructions. The temperature protocol consisted of the following steps: 37˚C for 15 min (reverse transcription), followed by 85˚C for 5 sec (inactivation of reverse transcriptase) and cooling to 4˚C. The cDNA was amplified using SYBR PrimeScript™ miRNA RT-PCR Kit (cat. no. RR716; Takara Bio, Inc.). The thermocycling protocol consisted of a total of 45 cycles, with denaturation at 95˚C for 10 sec, followed by annealing at 60˚C for 20 sec and extension at 72˚C for 20 sec. The relative expression was calculated with the $2^{-\Delta\Delta Cq}$ method (22), using U6 as an internal reference. The primers for miR-106b-5p used in the present study were designed based on methodologies outlined in previous studies (23,24). The primer sequences are as follows: miR-106b-5p (forward) 5'-TGCGGCAACACCAGTCGATGG-3' and (reverse) 5'-CCAGTGCAGGGTCCGAGGT-3'; and U6 (forward) 5'-CTCGCTTCGGCAGCACA-3' and (reverse) 5'-AACGCTTCACGAATTTGCGT-3'.

Table I. Clinical and demographic data of patients with colon cancer (n=40).

Item	Value
Sex	
Male	14 (35)
Female	26 (65)
Age, years	72.5±7.5
T stage	
T3	37 (92.5)
T4	3 (7.5)
miR-106b-5 expression	5.112±1.223
Bowel obstruction	
Yes	1 (2.5)
No	39 (97.5)
CEA, ng/ml	
>5	12 (30)
≤5	28 (70)
CA 19-9, U/ml	
>37	5 (12.5)
≤37	35 (87.5)
Differentiation	
Poor to undifferentiated	3 (7.5)
Well to moderate	37 (92.5)
Lymphovascular invasion	
Yes	3 (7.5)
No	37 (92.5)
Perineural invasion	
Yes	1 (2.5)
No	39 (97.5)
Lymphocyte infiltration	
Yes	8 (20)
No	32 (80)
Follow-up, months	46.93±17.45

Values are expressed as n (%) or the mean ± standard deviation. T stage, tumor stage; miR, microRNA; CEA, carcinoembryonic antigen; CA 19-9, carbohydrate antigen 19-9.

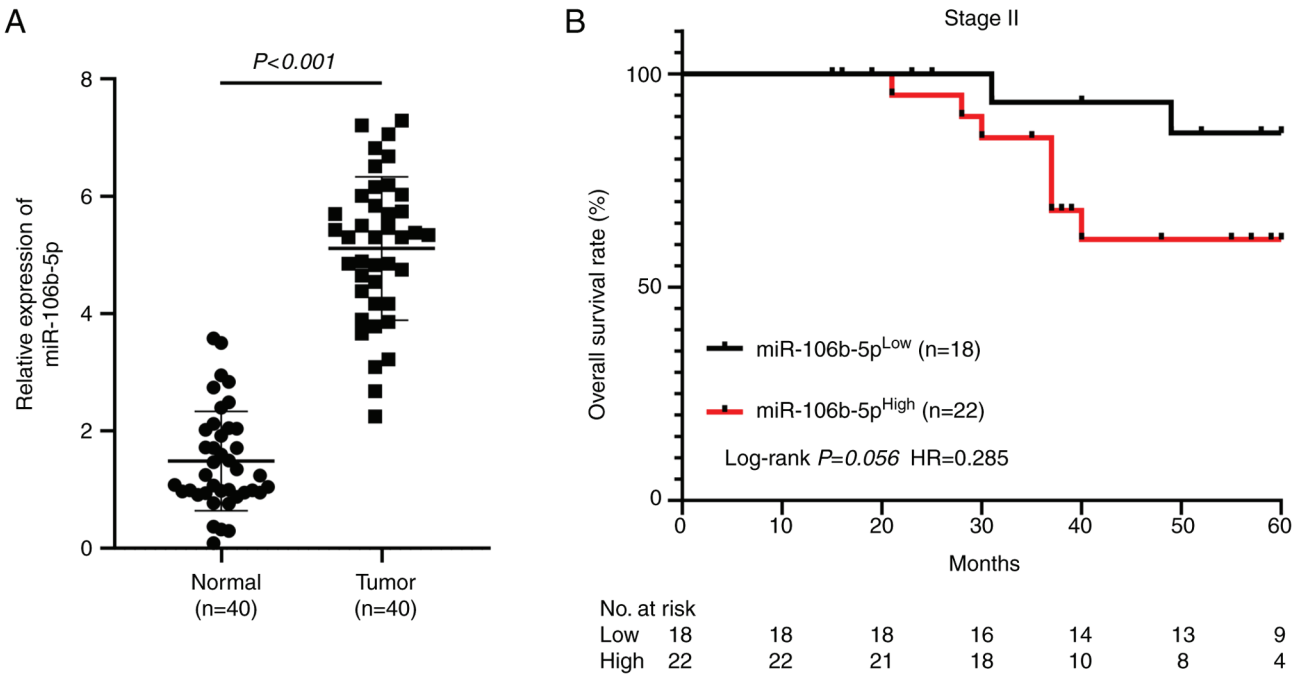

Figure 1. Expression of miR-106b-5p in patients with stage II colon cancer in relation to the 5-year survival rate. (A) Relative expression of miR-106b-5p in colon cancer tissues (Tumor) and adjacent normal tissues (Normal). (B) Comparison of the 5-year survival rate between patients with colon cancer with high and low miR-106b-5p expression levels. miR, microRNA; HR, hazard ratio.

Statistical analysis. The data were processed using SPSS 25 statistical software (IBM Corp.) and GraphPad 8.0 software (Dotmatics). Count data were compared using Fisher's exact test. Measurement data were compared using the paired t-test and are expressed as mean ± standard deviation. A Cox proportional risk regression model was used for the multivariate analysis of the effect on survival. Survival curves were plotted using the Kaplan-Meier method for survival analysis and the log-rank test was used for comparison of survival times. P<0.05 were considered to indicate a statistically significant difference.

Results

Relationship between miR-106b-5p expression and patient prognosis in stage II colon cancer. The cohort comprised 35% male and 65% female patients, with a mean age of 72.5 years. The majority of patients had T3 stage tumors (92.5%). The mean expression of miR-106b-5p was 5.112. Bowel obstruction was observed in 2.5% of patients. Elevated carcinoembryonic antigen (CEA) levels (>5 ng/ml) were noted in 30% of patients and carbohydrate antigen 19-9 (CA 19-9) levels were >37 U/ml in 12.5% of patients. Most tumors were well to moderately differentiated (92.5%). Lymphovascular invasion was present in 7.5% of patients and perineural invasion was observed in 2.5%. Lymphocyte infiltration, defined based on the presence of tumor-infiltrating lymphocytes observed in the tumor microenvironment (21,22), particularly in the stroma surrounding the tumor, was detected in 20% of patients. The mean follow-up period was 46.93 months. The clinical and demographic data of the patients in the present study are detailed in Table I. The expression of miR-106b-5p was significantly elevated in stage II colon cancer samples compared with that of adjacent normal tissue (5.09±0.58 vs. 1.46±0.53; P<0.001; Fig. 1A). Using the median expression level (5.30) of miR-106b-5p in all stage II colon cancer samples as a cut-off, patients were categorized into a high expression group (total, n=22; LCC, n=12; and RCC, n=10) and a low expression group (total, n=18; LCC, n=8; and RCC, n=10). The mean follow-up duration for all patients was 48.5 months (range, 15-73 months). The 5-year overall survival (OS) rate for the miR-106b-5p low expression group was 86.15%, which was notably higher than that of the high expression group at 61.2%, although this difference was not statistically significant (P=0.056; Fig. 1B). Univariate analysis of OS prognostic factors indicated that an age of >70 years, abnormal preoperative CEA levels and tumor stage were significantly associated with a worse OS (Table II). In the multivariate analysis, although age >70 years, elevated preoperative CEA levels (>5 ng/ml) and T3 tumor stage were significantly associated with OS in the univariate analysis, they did not retain statistical significance in the multivariate analysis. Specifically, patients aged ≤70 years had a hazard ratio (HR) of 0.619 (P=0.237) compared to those aged >70 years, with preoperative CEA levels ≤5 ng/ml serving as the reference group, while those with CEA levels >5 ng/ml had an HR of 1.922 (P=0.245). Additionally, the HR for T3 stage compared to T4 stage was 0.621 (P=0.659), which also did not show any statistical significance.

Prognosis of patients with LCC and RCC. No significant differences were observed between the clinical-pathological characteristics of patients in the RCC and LCC groups (Table III). However, the expression level of miR-106b-5p was notably higher in the left hemicolectomy samples compared with that of the right hemicolectomy samples (5.50±1.22 vs. 4.73±1.13; P=0.0454; Fig. 2A). Moreover, the 5-year survival

Table II. Univariate analysis and multivariate analysis of potential prognostic factors of patients with stage II colon cancer (n=40).

		Univariate analysis		Multivariate analysis	
Factor	n	5-year OS, %	P-value	HR (95% CI)	P-value
Age, years			0.001		0.237
≤70	17	93.75		0.619 (0.280-1.369)	
>70	23	52.33		1 (Reference)	
Sex			0.152		-
Male	26	64.86	-		
Female	14	85.12		-	
Bowel obstruction			0.138		-
Yes	1	0.00	-		
No	39	74.97		-	
Pre-op CEA, ng/ml			<0.001		0.245
≤5	28	84.40		1 (Reference)	
>5	12	46.62		1.922 (0.639-5.779)	
Pre-op CA 19-9, U/ml			0.055		-
≤37	35	75.06		-	
>37	5	53.33		-	
miR-106b-5p			0.056		-
<5.3	18	86.15			
≥5.3	22	61.20		-	
T stage			0.042		0.659
T3	37	76.54		0.621 (0.075-5.154)	
T4	3	33.33		1 (Reference)	
Differentiation			0.112		-
Well to moderate	37	74.70		-	
Poor to undifferentiated	3	50.00		-	
Lymphovascular invasion			0.935		-
Present	3	50.00			
Absent	37	73.86		-	
Perineural invasion			0.564		-
Present	1	100.00			
Absent	39	71.51		-	
Lymphocyte infiltration			0.613		-
Present	8	71.43		-	
Absent	32	74.21		-	
Mucinous component, %			-		-
≥50	0	-		-	
<50	40	-		-	

OS, overall survival; CEA, carcinoembryonic antigen; CA 19-9, carbohydrate antigen 19-9; miR, microRNA; T stage, tumor stage; HR, hazard ratio; CI, confidence interval.

rate in the RCC group was 75.03%, which was markedly greater than that of the LCC group at 70.56%, although the difference was not statistically significant (P=0.833; Fig. 2B).

Relationship between miR-106b-5p expression and patient prognosis in LCC and RCC. In RCC samples, the 5-year survival rate for the miR-106b-5p low expression group was 90%, significantly higher than the 52.5% observed in the high expression group (P=0.022; Fig. 3A). Univariate analysis of OS prognostic factors for RCC identified an age of >70 years, abnormal preoperative CA 19-9 levels and high miR-106b-5p expression as poor prognostic indicators for OS (Table SI).

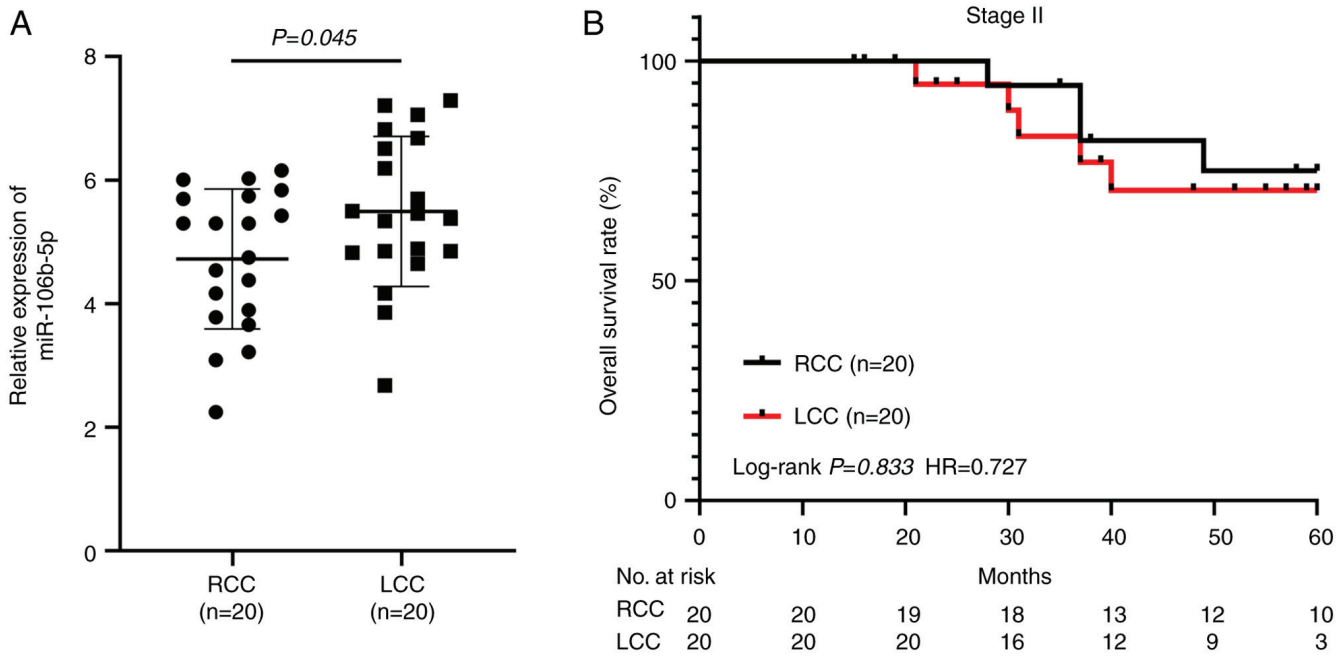

Figure 2. Expression of miR-106b-5p and 5-year survival in stage II LCC and RCC tissues. (A) Relative expression of miR-106b-5p in LCC and RCC tissues. (B) Comparison of the 5-year survival rate between LCC and RCC. miR, microRNA; HR, hazard ratio; LCC, left-sided colon cancer; RCC, right-sided colon cancer.

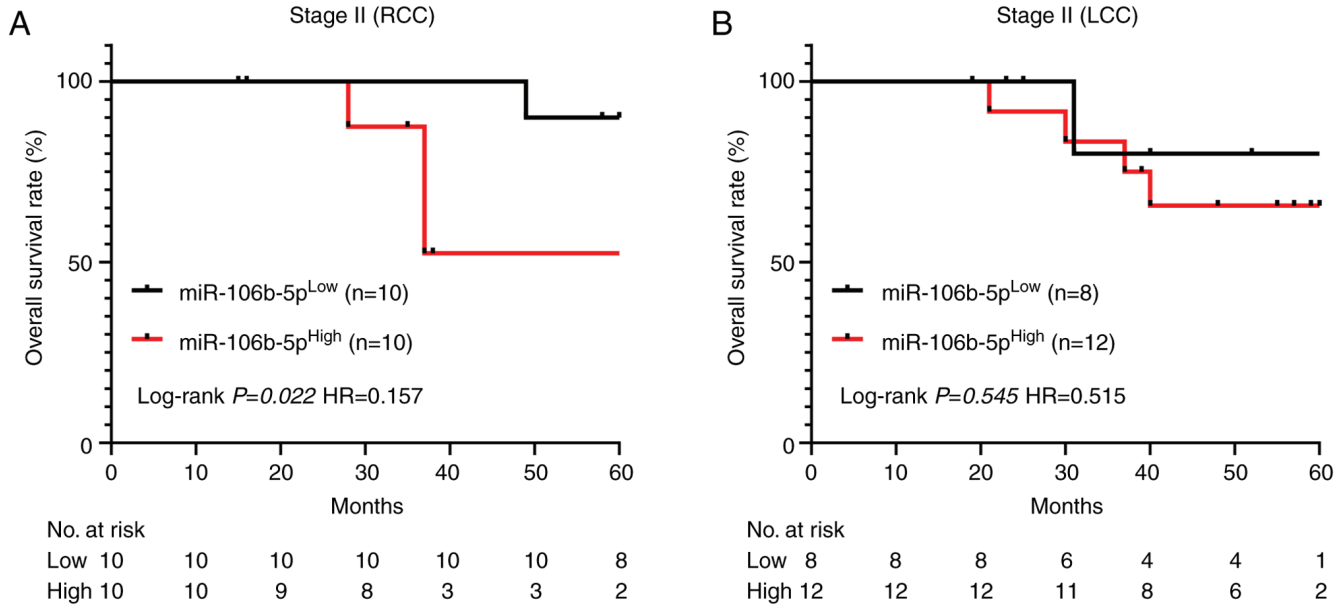

Figure 3. Expression levels of miR-106b-5p and their association with 5-year survival rates in colon cancer subtypes. Expression levels of miR-106b-5p in (A) RCC and (B) LCC in relation to the 5-year survival rate. miR, microRNA; HR, hazard ratio; LCC, left-sided colon cancer; RCC, right-sided colon cancer.

When these factors were incorporated into a Cox regression model and adjusted for multiple variables, miR-106b-5p expression emerged as an independent prognostic factor for patients in the RCC group (Table SI).

Furthermore, in LCC samples, the 5-year survival rate for the miR-106b-5p low expression group was 80%, which was notably higher than that of the high expression group at 65.63%; however, this difference was not statistically significant (P=0.545; Fig. 3B). Univariate analysis for LCC identified abnormal preoperative CEA levels as a poor prognostic factor for OS (Table SI).

Discussion

The present research demonstrated that miR-106b-5p expression was significantly upregulated in colon cancer tissues, with higher levels found in LCC compared with RCC. Additionally, it was revealed that high miR-106b-5p expression in RCC was an independent factor influencing patient prognosis, whilst its expression in LCC was not significantly associated with prognosis. The present study demonstrated that miR-106b-5p expression was notably elevated in colon

Table III. Clinicopathological features of patients with right- and left-sided colon cancer.

Factor	RCC (n=20)	LCC (n=20)	P-value
Age, years			0.749
≤70	8	9	
>70	12	11	
Sex			0.654
Male	13	13	
Female	7	7	
Bowel obstruction			0.311
Yes	0	1	
No	20	19	
Pre-op CEA, ng/ml			0.731
≤5	13	15	
>5	7	5	
Pre-op CA-19-9, U/ml			0.633
≤37	17	18	
>37	3	2	
T stage			0.231
T3	20	17	
T4	0	3	
Differentiation			0.231
Well to moderate	17	20	
Poor to undifferentiated	3	0	
Lymphovascular invasion			0.548
Present	2	1	
Absent	18	19	
Perineural invasion			0.311
Present	0	1	
Absent	20	19	
Lymphocyte infiltration			0.548
Present	4	4	
Absent	16	16	
Mucinous component, %			0.423
≥50	0	0	
<50	20	20	

RCC, right-sided colon cancer; LCC, left-sided colon cancer; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; T stage, tumor stage.

cancer tissues and could serve as an independent prognostic factor in RCC.

Several studies have reported that high miR-106b-5p expression is associated with numerous cancers, including cervical cancer (25), non-small cell lung cancer (26) and prostate cancer (27). In the present study, the results revealed that miR-106b-5p expression was significantly higher in colon cancer tissues compared with adjacent normal tissues, which is consistent with previous findings, suggesting that the expression level of miR-106b-5p may be increased in several cancers. However, it is uncertain whether the elevated miR-106b-5p levels in colorectal cancer tissue are associated with a worse prognosis. To address this, the present study analyzed the relationship between different miR-106b-5p expression levels and survival in patients with colon cancer. It was demonstrated that the 5-year OS rate of patients with colon cancer with high miR-106b-5p expression was significantly lower than that of patients with low miR-106b-5p expression. Similar results have been reported in several cancers. For instance, in hepatocellular carcinoma, higher expression of miR-106b-5p was associated with shorter survival rates and a worse prognosis (23). Furthermore, patients with breast cancer with elevated levels of miR-106b-5p also exhibited worse relapse-free survival and OS (28).

Conversely, the present study also demonstrated that low miR-106b-5p expression was associated with poor survival in patients with cancer. Zhuang *et al* (29) reported that low miR-106b-5p expression predicted poor survival in patients with colorectal cancer, particularly in combination with high metastasis associated lung adenocarcinoma transcript 1/SLAIN motif family member 2 expression. These inconsistent results could be due to the molecular and pathological differences between LCC and RCC. Without distinguishing between these differences, the conclusions may not be representative.

Studies have reported differences in molecular characteristics and prognosis between LCC and RCC (30-32). However, it is uncertain whether miR-106b-5p expression levels were similar in tissue samples from LCC and RCCs. Therefore, the present study further assessed miR-106b-5p expression levels between these two types of colon cancer tissues. The results indicated that miR-106b-5p mRNA levels were higher in LCC tissues than in RCC tissues. Moreover, as Warschkow *et al* (5) reported improved OS rates in patients with stage II RCC compared with LCC, we hypothesize that the expression level of miR-106b-5p may contribute to this observation. However, this conclusion is not entirely reliable, as the present study did not identify a significant difference in 5-year survival rates between LCC and RCCs. Although several studies have compared OS between LCC and RCC, a consensus has yet to be reached. A Surveillance, Epidemiology, and End Results study performed by Weiss *et al* (33) demonstrated no difference in OS between the right and left sides across all stages of colon cancer. By contrast, Benedix *et al* (34) reported that after adjusting for tumor stage, survival rates for RCC were notably lower than those for LCC. Similar results have been reported in several other studies (4,35-37). These findings suggest that reanalyzing the data after stratification may yield new insights.

Upon categorizing patients with stage II LCC and RCC based on the median expression levels of miR-106b-5p into high-expression and low-expression groups, the present study demonstrated that patients with high miR-106b-5p expression in RCC had a significantly lower 5-year survival rate. By contrast, the survival rate for the LCC high miR-106b-5p expression group was not statistically significant compared with that of the low-expression group. These findings indicate the necessity of separately comparing LCC and RCCs when analyzing potential molecular markers. Furthermore, high expression of miR-106b-5p in RCC is associated with an increased risk of death. In future clinical practice, it may be beneficial to analyze miR-106b-5p expression levels in tissue samples after surgery for RCC. If the expression level is high,

this may warrant closer follow-up to mitigate the risk of recurrence. However, it is important to note that whilst the present study defined an expression level of >5.3 as high, it did not assess whether this cutoff is applicable to patients from other centers. Further research is required in this regard.

Furthermore, whilst CEA and CA 19-9 are traditional tumor markers for colorectal cancer and have a prognostic value in certain patients, their sensitivity and specificity are limited, particularly in early-stage patients (38). This is a limitation and therefore, miR-106b-5p may be an emerging molecular marker that may offer potential advantages in supplementing existing prognostic models. Future research could integrate CEA, CA 19-9 and novel markers such as miR-106b-5p to further enhance the accuracy of prognostic assessments for patients with colorectal cancer.

The present study has several limitations. Regarding the differences in miR-106b-5p levels between LCC and RCC samples, although the present study did not observe a difference in 5-year OS rates, this does not imply that there are no differences in tumor characteristics. It is possible that the data in the present study were insufficient to detect such differences. Furthermore, as only patients with stage II colon cancer were included, it remains unclear whether the observed differences in miR-106b-5p levels and their predictive value for postoperative survival are also applicable to other stages. Additionally, the average follow-up period may be too short to draw definitive conclusions about long-term survival outcomes for a disease such as colorectal cancer, where late recurrence is common (39). Nevertheless, an average follow-up duration of ~4 years provides meaningful preliminary insights into the early prognostic value of miR-106b-5p in patients with colorectal cancer. Moreover, although several variables were controlled for in the multivariate analysis, there may still be unmeasured confounders (such as genetic variations, lifestyle factors or comorbidities) that could influence the expression of miR-106b-5p and prognosis. Lastly, the relatively small sample size of the present study, particularly the limited number of patients with LCC, may lead to insufficient statistical power to detect potential survival differences. However, it cannot be definitively concluded that even with a sufficient sample size, there would necessarily be differences between the high and low expression groups of miR-106b-5p in LCC, as this remains a speculation without data to support it.

In conclusion, the present study demonstrated that miR-106b-5p expression was significantly upregulated in colon cancer tissues from clinical samples. Additionally, miR-106b-5p expression was significantly higher in LCC compared with RCC. Furthermore, high miR-106b-5p expression in RCC emerged as an independent factor influencing patient prognosis, whilst no association was observed between miR-106b-5p expression and prognosis in LCC.

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Availability of data and material

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

SZ, WS and XY contributed to the conception and design of the study. YW and GZ performed the experiments, and collected and analyzed data. SZ, WS and XY wrote the manuscript. All authors have read and approved the final manuscript. SZ and WS confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of Huizhou First Hospital (Huizhou, China; approval no. 201806). Written informed consent was obtained from all the study subjects before enrollment.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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