Clinical role of miR-421 as a novel biomarker in diagnosis of gastric cancer patients
A meta-analysis

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Abstract

Background: Gastric cancer (GC) has been identified as one of the most common malignancies. It was found that microRNAs can be used as potential biomarkers for GC diagnosis. The aim of this study was to estimate the diagnostic value of 4 potential microRNAs in GC.

Methods: PubMed, Embase, Cochrane Library, and Web of Science were used to search published studies. The quality of the studies was scored with the Quality Assessment of Diagnostic Accuracy Studies. The pooled sensitivity and specificity, diagnostic odds ratio (DOR) and area under the curve (AUC) were calculated. The heterogeneity was evaluated using Cochrane Q statistics and the inconsistency index.

Results: A total of 22 studies reporting the diagnostic value of miR-21 (n = 9), miR-106 (n = 10), miR-421 (n = 5) and miR-223 (n = 3) were included. Quality Assessment of Diagnostic Accuracy Studies scores showed the high quality of the selected 22 articles. The random effects model was adopted by evaluating the heterogeneity between articles. The DOR, AUC, and Q value of miRNA-21 were 12.37 [95% confidence interval (CI): 5.36–28.54], 0.86 and 0.98, respectively. The DOR, AUC and Q value of miRNA-106 were 12.98 [95% CI: 7.34–23.61], 0.85 and 0.78, respectively. The DOR, AUC and Q value of miRNA-421 were 27.86 [95% CI: 6.04–128.48], 0.92 and 0.86, respectively. The DOR, AUC and Q value of miRNA-223 were 18.50 [95% CI: 7.80–43.86], 0.87 and 0.80, respectively. These results indicate that miRNA-421 has the highest diagnostic accuracy, followed by miR-223, miRNA-21, and miRNA-106 among the 4 microRNAs in GC.

Conclusions: miR-21, miR-106, miR-421, and miR-223 have good diagnostic efficacy, especially miR-421, could be used as auxiliary diagnostic indicator for GC.

Abbreviations: AUC = area under the curve, CI = confidence interval, DOR = diagnostic odds ratio, GC = gastric cancer, ROC = receiver operating characteristic.

Keywords: diagnostic value, gastric cancer, meta-analysis, microRNA

1. Introduction

Gastric cancer (GC) is one of the most common gastrointestinal malignant tumors that seriously harm human health. According to the latest statistics, GC is a leading cancer worldwide and is responsible for over 1,000,000 new cases and an estimated 769,000 deaths in 2020, making it the fifth most frequently...
diagnosed cancer and the third leading cause of cancer death.\(^1\)
In spite of the incidence and mortality of both males and females showing a downward trend,\(^2\) it could be concluded that the incidence of early GC is consistently increasing.\(^3,4\)
Therefore, accurate early diagnosis of GC is critical for early treatment and improved prognosis of GC patients. GC is commonly diagnosed by gastroscopy, surgical biopsy, and some noninvasive methods such as evolutionary endoscopy and positron emission tomography.\(^5\)
However, due to the invasiveness or high cost, these methods have not been widely used in the early diagnosis of GC. Thus, it is necessary to find biomarkers for the early diagnosis of GC. Traditional tumor biomarkers for GC, including cancer embryo antigen, pepsinogen, carbohydrate antigen 199, carbohydrate antigen 724 and gastrin-17, have been applied in clinical practice, but with insufficient sensitivity and specificity.\(^6,7\)
It is of great practical significance to search for suitable diagnostic markers for mass screening of GC.

MicroRNA is a class of short non-protein-coding RNAs with a length of 18 to 25 nucleotides that have been implicated in the regulation of gene post-transcriptional modification and almost all signaling pathways in cells.\(^8,9\)
Numerous studies demonstrate that microRNAs are dysregulated in various tumors and have a causal relationship with cell cycle, apoptosis and migration which depicts their potential as effective biomarkers of tumor diagnostic and prognostic.\(^10,11\)
They are stable in plasma or serum and are readily available, which is attractive for researchers. By observing the expression profile of microRNAs in different digestive cancer, it was found that microRNAs can be used as potential biomarkers for tumor diagnosis.\(^10\)
Thus, it is promising to explore the diagnostic value of microRNAs for GC.

At present, many microRNAs and their targets have been found to be closely related to the proliferation, invasion, metastasis and apoptosis of GC cells and the treatment and prognosis of GC. Studies have shown that miR-21 regulates the occurrence and development of various cancers, such as non-small cell lung cancer, GC, colorectal cancer and ovarian cancer.\(^12–15\)
Exosome miR-21–5P promotes peritoneal metastasis of GC through mesothelial-to-mesenchymal transition,\(^16\) so miR-21 can be used as a potential biomarker for predicting peritoneal recurrence of GC.\(^17\)
MiR-106 belongs to the miR-17 family, one of the most common studied onco-miRNA groups. In vivo and in vitro experiments showed that miR-106 promoted metastasis of early GC by targeting ALEX1. Comprehensive analysis identified miR-106 as a molecular marker for GC.\(^18\)
At present, the related studies of miR-421 mainly focus on gastrointestinal carcinomas and genital carcinomas. In gastrointestinal cancers, such as gastric cancer, esophageal cancer, colorectal cancer, biliary cancer and liver cancer, miR-421 acts as a carcinogen miRNA to promote cancer development.\(^19–21\)
In biliary tract cancer and liver cancer, miR-421 promoted cell proliferation and migration by down-regulating farnesoid X receptor.\(^22,23\)
The gene encoding miR-223 is located at q12 site of X chromosome, and miR-223 play a regulatory role as both tumor promoter and tumor suppressor. MiR-223 regulates cell differentiation, proliferation, apoptosis and metastasis as a tumor suppressor in leukemia, lymphoma, oral cancer, lung cancer and breast cancer.\(^24\)
MiR-223 was up-regulated in human gastric cancer tissue samples, FBXW7/hCdc4 (FBW7)\(^25\) and RhoB\(^26\) and Stathmin1\(^27\) as the target genes of miR-223 regulate the occurrence and development of GC and drug resistance. Macrophage-derived miR-223 transfer leads to adriamycin resistance in GC.\(^28\)
Therefore, we selected miR-21, miR-106, miR-421, and miR-223 up-regulated in GC and compared the diagnostic value of these 4 microRNAs in GC through meta-analysis.

2. Materials and methods

2.1. Search strategy

Keywords including
1. (gastric cancer [All Fields] OR gastric carcinoma [All Fields] OR stomach cancer [All Fields] OR stomach carcinoma [All Fields]),
2. (microRNA-21 [All Fields] OR miR-21 [All Fields] OR miRNA-21[All Fields] OR hsa-miR-21[All Fields]),
3. (microRNA-106 [All Fields] OR miR-106 [All Fields] OR miRNA-106 [All Fields] OR hsa-miR-106 [All Fields]),
4. (microRNA-421 [All Fields] OR miR-421 [All Fields] OR miRNA-421[All Fields] OR hsa-miR-421[All Fields]),
5. (microRNA-223 [All Fields] OR miR-223 [All Fields] OR miRNA-223[All Fields] OR hsa-miR-223 [All Fields] OR microRNA-223 [All Fields] OR hsa-miR-223 [All Fields] were searched on PubMed, Embase, Cochrane Library and Web of Science up to May of 2021.

The search strategy was (1) and (2), (1) and (3), (1) and (4), and (1) and (5). The language was limited to English, and the subject was limited to humans. We also searched the articles of reference to obtain additional studies. Finally, all literature identified according to the search strategy was independently evaluated by 2 researchers. If there was any disagreement, discussion was conducted, or a third researcher was consulted for a consensus. The search strategies are depicted in Figure 1.

2.2. Inclusion and exclusion criteria

The inclusion criteria were as follows:
1. the articles were published in English and full text was available;
2. the diagnosis of GC was made by histopathology;
3. the sample types included plasma, serum, blood and others;
4. patients with benign diseases or healthy people were selected as the control group; and
5. the studies had sensitivity, specificity or other data to calculate true positive, false positive, false negative and true negative.

The exclusion criteria were as follows:
1. unqualified data;
2. duplicate publications;
3. non-experimental studies, such as case reports, reviews and letters; and
4. no full text.

2.3. Study selection and data extraction

The screening was in strict accordance with the inclusion and exclusion criteria. Data for each study were retrieved independently by 2 reviewers and divergences were resolved by discussing with the third researcher. Characteristics of the studies included first author, publication year and country, and characteristics of the subjects included number of patients, age,
sample type, pathologic stage and detection methods. According to the numbers of experimental and control groups, sensitivity and specificity, we calculated the true positive, false positive, false negative and true negative. The main characteristics of the included studies are presented in Table 1.

2.4. Quality assessment

Quality assessment was performed according to Quality Assessment of Diagnostic Accuracy Studies-2. Two researchers assessed the quality of studies separately, and any objections

| First author, year | Country | Patients (Controls) | Mean or median age | Stage I, II% | Sample type | Detection methods | TP | FN | FP | TN |
|--------------------|---------|---------------------|--------------------|-------------|-------------|------------------|----|----|----|----|
| Cui L, 2013        | China   | 42 (99)             | 64.2               | NR          | Gastric juice | qRT-PCR           | 36 | 6  | 2  | 97 |
| Li BS, 2012        | China   | 70 (70)             | 54                 | 33          | Plasma       | qRT-PCR           | 52 | 18 | 17 | 53 |
| Wu J, 2015         | China   | 50 (50)             | NR                 | 40          | Serum        | qRT-PCR           | 44 | 6  | 10 | 40 |
| Liu HN, 2018       | China   | 80 (82)             | 65.1               | 47.5        | Serum        | qRT-PCR           | 62 | 18 | 47 | 35 |
| Zheng Y, 2011      | China   | 53 (20)             | 60                 | 30.2        | Blood        | qRT-PCR           | 44 | 9  | 4  | 16 |
| Wang B, 2012       | China   | 30 (39)             | 58                 | 36.7        | Serum        | qRT-PCR           | 17 | 13 | 2  | 37 |
| Shiotani A, 2013   | Japan   | 62 (70)             | 67.8               | 100         | Serum        | qRT-PCR           | 36 | 26 | 10 | 60 |
| Tsujiura M, 2010   | Japan   | 69 (30)             | NR                 | 73.9        | Plasma       | qRT-PCR           | 42 | 27 | 12 | 18 |
| Shen J, 2012       | China   | 29 (25)             | 54                 | NR          | Serum        | qRT-PCR           | 15 | 14 | 2  | 23 |
| Zhou H, 2010       | China   | 90 (27)             | 61.4               | NR          | Serum        | qRT-PCR           | 43 | 47 | 3  | 24 |
| Zeng Q, 2014       | China   | 40 (36)             | NR                 | 22.5        | Serum        | qRT-PCR           | 30 | 10 | 3  | 33 |
| Li F, 2017         | China   | 65 (65)             | 54.1               | 40          | Plasma       | qRT-PCR           | 56 | 9  | 5  | 60 |
| Hou X, 2015        | China   | 80 (60)             | 68                 | 56.3        | Plasma       | qRT-PCR           | 62 | 18 | 4  | 56 |
| Tsujiura M, 2010   | Japan   | 69 (30)             | NR                 | 73.9        | Plasma       | qRT-PCR           | 55 | 14 | 11 | 19 |
| Cai H, 2013        | China   | 90 (90)             | 46.2               | 38.9        | Plasma       | qRT-PCR           | 59 | 31 | 18 | 72 |
| Shiotani A, 2013   | Japan   | 62 (70)             | 67.8               | 100         | Serum        | qRT-PCR           | 47 | 15 | 34 | 36 |
| Cui L, 2013        | China   | 42 (99)             | 64.2               | NR          | Gastric juice | qRT-PCR           | 31 | 11 | 8  | 88 |
| Wang N, 2017       | China   | 110 (110)           | NR                 | 57.2        | Serum        | qRT-PCR           | 69 | 41 | 13 | 97 |
| Yuan R, 2017       | China   | 48 (22)             | 64                 | NR          | Serum        | qRT-PCR           | 37 | 11 | 8  | 14 |
| Zhou H, 2012       | China   | 40 (17)             | 64.9               | 52.5        | Mononuclear  | qRT-PCR           | 38 | 2  | 6  | 11 |
| Zhang X, 2012      | China   | 42 (47)             | 56.8               | NR          | Gastric juice | qRT-PCR           | 30 | 12 | 13 | 34 |
| Wu J, 2014         | China   | 90 (90)             | NR                 | 58.9        | Serum        | qRT-PCR           | 81 | 9  | 13 | 77 |
| Liu HN, 2018       | China   | 80 (82)             | 65.1               | 47.5        | Serum        | qRT-PCR           | 75 | 5  | 65 | 17 |
| Chen JL, 2019      | China   | 90 (45)             | NR                 | 27.6        | Plasma       | qRT-PCR           | 87 | 3  | 2  | 43 |
| Zhou XY, 2015      | China   | 50 (50)             | 57.8               | 38          | Plasma       | qRT-PCR           | 35 | 15 | 10 | 40 |
| Li BS, 2012        | China   | 70 (70)             | 54                 | 33          | Plasma       | qRT-PCR           | 59 | 11 | 8  | 62 |
| Wang H, 2014       | China   | 50 (47)             | NR                 | 62          | Serum        | qRT-PCR           | 41 | 9  | 10 | 37 |

FN = false negative, FP = false positive, NR = not report, TN = true negative, TP = true positive.
were resolved through discussion with the third investigator. The result is shown in Figure 2.

2.5. Statistical analysis

The data of the included studies were extracted and the diagnostic odds ratios (DOR) were combined according to the types of microRNA. The higher the DOR value, the better the diagnostic efficacy. The feasibility and accuracy of microRNA as diagnostic tools for GC was evaluated using receiver operating characteristic (ROC) curves and the area under the ROC curve (AUC). ROC curve was drawn according to sensitivity and specificity and the AUC of each microRNA was calculated respectively. The value of AUC ranged from 0.5 to 1.0, and the closer the value was to 1.0, the better the diagnostic accuracy was.

The Meta-Disc version 1.4 software package was used to perform statistical analysis. \( P \) value \(<.10 \) or \( I^2 \) value >50% indicate high heterogeneity. If moderate or high heterogeneity was calculated, the random-effects model was utilized to pool the results. Otherwise, the fixed-effects model was used.

3. Results

3.1. Included studies

The initial search identified 673 articles among which 246 duplicates and 156 nonexperimental studies were excluded. The left 271 potentially relevant studies were reviewed and for more detailed evaluation. After intensive reading, 247 articles were excluded as not mentioned miR-21, miR-106, miR-421, and miR-223 \((n = 97)\), diagnosis value \((n = 64)\) and GC \((n = 86)\), and additional 2 studies failed to publish detailed information (Fig. 1). Thus, a total of 22 full-text articles were included in this study.\(^{29-50}\)

3.2. Study characteristics and quality assessment

In these studies, all the GC patients were diagnosed based on histopathology. The control individuals were all from healthy volunteers who had never been diagnosed with a malignant tumor. Among them, 9 articles reported the diagnostic value of microRNA-21, including 485 GC patients and 485 healthy controls.\(^{29-37}\) The sources of miR-21 were plasma \((n = 2)\), serum \((n = 5)\), gastric juice \((n = 1)\), and blood \((n = 1)\) in these studies. Ten articles reported the diagnostic value of microRNA-106, including 696 GC patients and 609 healthy controls.\(^{29,35,36,38-44}\) The sources of miR-106 were plasma \((n = 5)\), serum \((n = 4)\), gastric juice \((n = 1)\) in these studies. Five studies reported the diagnostic value of microRNA-421, including 342 GC patients and 281 healthy controls.\(^{32,43-48}\) The sources of miR-421 were plasma \((n = 1)\), serum \((n = 2)\), gastric juice \((n = 1)\), and mononuclear cells \((n = 1)\) in these studies. And 3 studies reported the diagnostic value of microRNA-223, including 170 GC patients and 167 healthy controls.\(^{30,50,51}\) The sources of miR-223 were plasma \((n = 2)\) and serum \((n = 1)\) in these studies.

All of the included studies were from China and Japan. Detection methods of microRNAs expression were mostly reverse transcription PCR (RT-PCR). The characteristics of each included study and of the patients are described in detail in Table 1. And Quality Assessment of Diagnostic Accuracy Studies-2 results were shown that no low-quality studies were included in this meta-analysis (Fig. 2).
### 3.3. Data analysis

The random effects model was applied to evaluate the pooled analysis. The DOR, AUC and Q value of miRNA-21 were 12.37 (95% confidence interval [CI]: 5.36–28.54), 0.86 and 0.79, respectively (Fig. 3). The DOR, AUC and Q value of miRNA-106 were 12.98 [95% CI: 7.14–23.61], 0.85 and 0.78, respectively (Fig. 4). The DOR, AUC and Q value of miRNA-421 were 27.86 [95% CI: 6.04–128.48], 0.92 and...
0.86, respectively (Fig. 5). The DOR, AUC and Q value of miRNA-223 were 18.50 [95% CI: 7.80–43.86], 0.87 and 0.80, respectively (Fig. 6). These results indicate that miRNA-421 has the highest diagnostic accuracy, followed by miR-223, miRNA-21 and miRNA-106 among the 4 microRNAs in GC.

Figure 4. The DOR, AUC, and Q value of miR-106 in the diagnosis of GC.
4. Discussion

Early GC is easy to be ignored or mistaken for stomach disease since there are no obvious specific symptoms. However, early detection of GC is pivotal to improve the survival rate and prognosis of GC. Although endoscopy is a highly reliable method for the diagnosis of GC, it is unlikely to be widely used, especially in developing countries, due to the financial burden and fear of physical discomfort caused by endoscopy. To date, the widely used approach for early detection of GC is a number of serum biomarkers, such as cancer embryo antigen, carbohydrate antigen 199, and carbohydrate antigen 724, but their sensitivity and specificity are very low. Thus, a novel effective serum biomarker is urgently needed.

In recent years, aberrantly expressed microRNAs have gained widespread attention as potential biomarkers for early detection...
of GC.\textsuperscript{[52]} Firstly, microRNAs have relatively high stability and specificity in substantial post-transcriptional regulation and expression. Second, microRNAs are stable in tissues, cells and peripheral blood because they are short and resistant to degradation.\textsuperscript{[53]} Third, each microRNA is specifically expressed in tissue specimens and microRNAs have been shown to be differentially expressed in GC vs. normal tissues. Finally, altered expression of microRNAs in GC is involved in the tumorigenesis and cancer development.

Increasing evidences reported that miR-21, miR-106, miR-421, miR-34, miR-17, miR-25, and miR-133b are dysregulated in GC and could be used as potential diagnostic biomarkers.\textsuperscript{[31,41,48,54,55]} However, previous studies have the defects of a small number of included studies, inconsistent results and few types of microRNA. In GC cells, down-regulation of miR-21 inhibits cell proliferation and EMT, thereby inhibiting invasion and metastasis of tumor cells,\textsuperscript{[56,57]} while miR-106 has similar biological effects on GC, colorectal cancer and endometrial
MiR-421 and miR-223 regulates the apoptosis and invasion ability of GC cells by targeting Caspase-3 and Arid1a respectively. [61,62] These 4 miRNAs are also involved in regulating drug resistance of GC cells. MiR-21 regulates cisplatin resistance of GC cells through the PI3K/Akt/mTOR pathway. [63] MiR-421 was involved in regulating 5-fluorouracil and gemcitabine resistance in MGC-803 GC cell lines and pancreatic cancer cell lines. [64,65] The sensitivity of GC cells to cisplatin and trastuzumab was regulated by miR-223/ FBXW7 axis. [66,67] Therefore, future large-size study is needed to validate our findings.

Nevertheless, substantial heterogeneity existed in this study. That may cause by different types of samples (plasma, serum, gastric juice, cells), different portion of early stage, different source of samples and limited number of included studies. Another disadvantage of this study is the included studies mainly from China or Japan, indicating that publication bias existed. Therefore, future large-size study is needed to validate our finding.

In conclusion, despite the limitations mentioned above, the current evidence suggests that miR-21, miR-106, miR-421, and miR-223 have good diagnostic efficacy, especially miR-421, could assist in early diagnosis and mass screening of GC as a noninvasive indicator.

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