MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2020; 26: e923444
DOI: 10.12659/MSM.923444

Received: 2020.02.12
Accepted: 2020.03.16
Available online: 2020.04.02
Published: 2020.06.03

Circulating miR-19a-3p and miR-483-5p as Novel Diagnostic Biomarkers for the Early Diagnosis of Gastric Cancer

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Source of support: This work was supported by the Youth Research Fund of Beijing Shijitan Hospital of Capital Medical University [2018-q15] and the Beijing Municipal Science and Technology Project [D141100000414005]

Background: MicroRNAs (miRNAs) are attracting substantial interest as promising noninvasive biomarkers for gastric cancer (GC). Our study aimed to identify circulating miRNAs that are potential noninvasive markers for precancerous lesions and early gastric cancers (EGCs).

Material/Methods: Plasma specimens were obtained from 58 gastritis subjects, 54 patients with precancerous lesions, and 38 EGC patients for study.

Results: Significant differences in the plasma expression levels of miR-19a-3p, miR-22-3p, miR-146a-5p, and miR-483-5p (all $P<0.05$) were observed between EGC patients and gastritis subjects. Multivariable analysis showed that age (OR, 1.054; 95% CI, 1.006–1.104), miR-19a-3p expression (OR, 3.676; 95% CI, 1.914–7.061), and miR-483-5p expression (OR, 1.589; 95% CI, 1.242–2.033) were independently associated with EGCs and precancerous lesions. A combined diagnostic model incorporating these 3 variables for the prediction of EGCs and precancerous lesions was derived. The area under the receiver operating characteristic curve (AUC) of the model was 0.84; the sensitivity was 87.7% and the specificity was 62.8% at the cutoff value of –0.08.

Conclusions: Plasma miR-19a-3p and miR-483-5p are promising and powerful noninvasive markers for the early detection of GC. Patients are more willing to undergo noninvasive diagnostic procedures than gastroscopy for cancer screening, economizing limited medical resources.

MeSH Keywords: Biological Markers • MicroRNAs • Precancerous Conditions • Stomach Neoplasms

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/923444

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Background

Gastric cancer (GC) is the fifth most common cancer worldwide, based on global cancer statistics in 2018 [1,2]. In China, there were approximately 456 124 new cases and 390 182 GC-related deaths in 2018 [3]. The prognosis of GC is closely related to the timing of diagnosis and treatment. Due to the limited therapeutic methods [4], the 5-year survival rate of GC is 35.9% [5], but patients with early gastric cancer (EGC) have a 5-year survival rate of greater than 95% [6]. However, EGC is a clinically silent disease and lacks identifiable laboratory characteristics. Conventional serum tumor markers such as CEA, CA72-4, and CA19-9 are useful only for identifying cases of advanced GC and monitoring GC recurrence. Moreover, these serum markers lack sufficient sensitivity and specificity. Currently, endoscopy remains the standard diagnostic method in populations at high risk for GC. However, since endoscopy is invasive and medical resources are limited, developing noninvasive approaches for EGC diagnosis to stratify GC populations by risk and improve the suitability of endoscopy is imperative.

MicroRNAs (miRNAs) are 21–25 ribonucleotides long and posttranscriptionally regulate gene expression [7]. Circulating miRNAs are stable in plasma in AGO2-miRNA complexes, which are protected against the adverse effects of multiple freeze-thaw cycles and RNase degradation [8]. miRNAs play important roles in many biological fields and are often dysregulated in cancer [9]. Specific circulating miRNAs have been detected in many kinds of cancers, including colorectal, breast, and other cancers [10–12]. Collectively, these characteristics indicate that miRNAs can be biomarkers for the early detection of cancer.

To date, many circulating miRNAs have been found to be dysregulated in GC [13]. Some miRNAs, such as miR-214 and miR-940, were identified by quantitative real-time reverse transcription–polymerase chain reaction (qRT-PCR) [14,15]. However, these studies did not include EGC patients or patients with precancerous lesions, although an optimal noninvasive marker should be able to identify cancers in early or precancerous stages.

In order to identify high-risk populations of GC patients, this study, which included gastritis subjects, patients with EGC, and patients with precancerous lesions, aimed to select candidate plasma miRNAs for the early identification of EGCs and precancerous lesions.

Material and Methods

Clinical Specimens

This study included 150 plasma specimens obtained from gastritis subjects and consecutive patients with low-grade intraepithelial neoplasias (LGINs), high-grade intraepithelial neoplasias (HGINs), or EGCs at Peking Union Medical College Hospital (PUMCH), China, between March 2010 and December 2016. Blood samples (4 ml) were collected in EDTA tubes and immediately centrifuged at 3000 rpm at room temperature for 15 min to separate the plasma, which was stored at –80°C until use. All experiments were performed according to the relevant guidelines and regulations. All procedures involving humans in this study were performed in accordance with the ethical standards of the PUMCH Institutional Ethics Committee.

RNA extraction

Total RNA, including miRNA, was isolated with a miRNeasy Serum/Plasma Kit (Qiagen, Venlo, The Netherlands).

Plasma samples were defrosted on ice. Four hundred microliters of plasma were transferred into 2 clean tubes, and 5 volumes of QIAzol (Qiagen) were added, mixed by vortexing, and incubated at room temperature (23°C) for 5 min. One volume of chloroform was added, mixed by vortexing, and incubated at 23°C for 3 min. After centrifugation at 4°C and 12 000×g for 15 min, the supernatant was transferred to a clean tube, and 1.5 volumes of 100% ethanol were added. The sample was then transferred to a Qiagen RNeasy Mini Spin Column and centrifuged at 23°C and 13 000×g for 15 s, and the flow-through was discarded. These steps were repeated once. The isolated RNA was dissolved in 15 µl of RNase-free water. Subsequently, the RNA purity and concentration were measured with a NanoDrop ND-1000 spectrophotometer (NanoDrop, Wilmington, DE, USA).

miRNA validation by qRT-PCR

Seven differentially expressed miRNAs were selected from previous miRNA microarray analysis results and the miRCancer database for further validation by qRT-PCR assays. The selection criteria are described in the supplementary material. A TaqMan Advanced miRNA cDNA Synthesis Kit (Ambion, Wilmington, DE, USA) and TaqMan Fast Advanced Master Mix (Ambion) were used for reverse transcription. RT-PCR was performed using TaqMan Advanced miRNA Assays (Ambion) in a Mx3005P real-time PCR system (Stratagene, CA, USA). qRT-PCR was conducted with reaction volumes of 20 µl, comprising 10 µl of 2×Fast Advanced Master Mix, 1 µl of TaqMan Advanced MiRNA Assay Buffer (20×), and 9 µl of cDNA (diluted 40-fold). Reactions were carried out in 8-strip tubes (Axygen, USA) under the following cycling conditions: 50°C for 2 min, 95°C for 10 min, and 40 cycles at 95°C for 15 s and 40 cycles at 60°C for 1 min. miR-16-5p was used for normalization of miRNA expression levels. The selection of endogenous reference miRNAs is described in the supplementary material (Supplementary Figure 1). All qRT-PCRs were performed in triplicate. The relative expression levels of miRNAs were calculated using the $2^{-\Delta CT}$ method.

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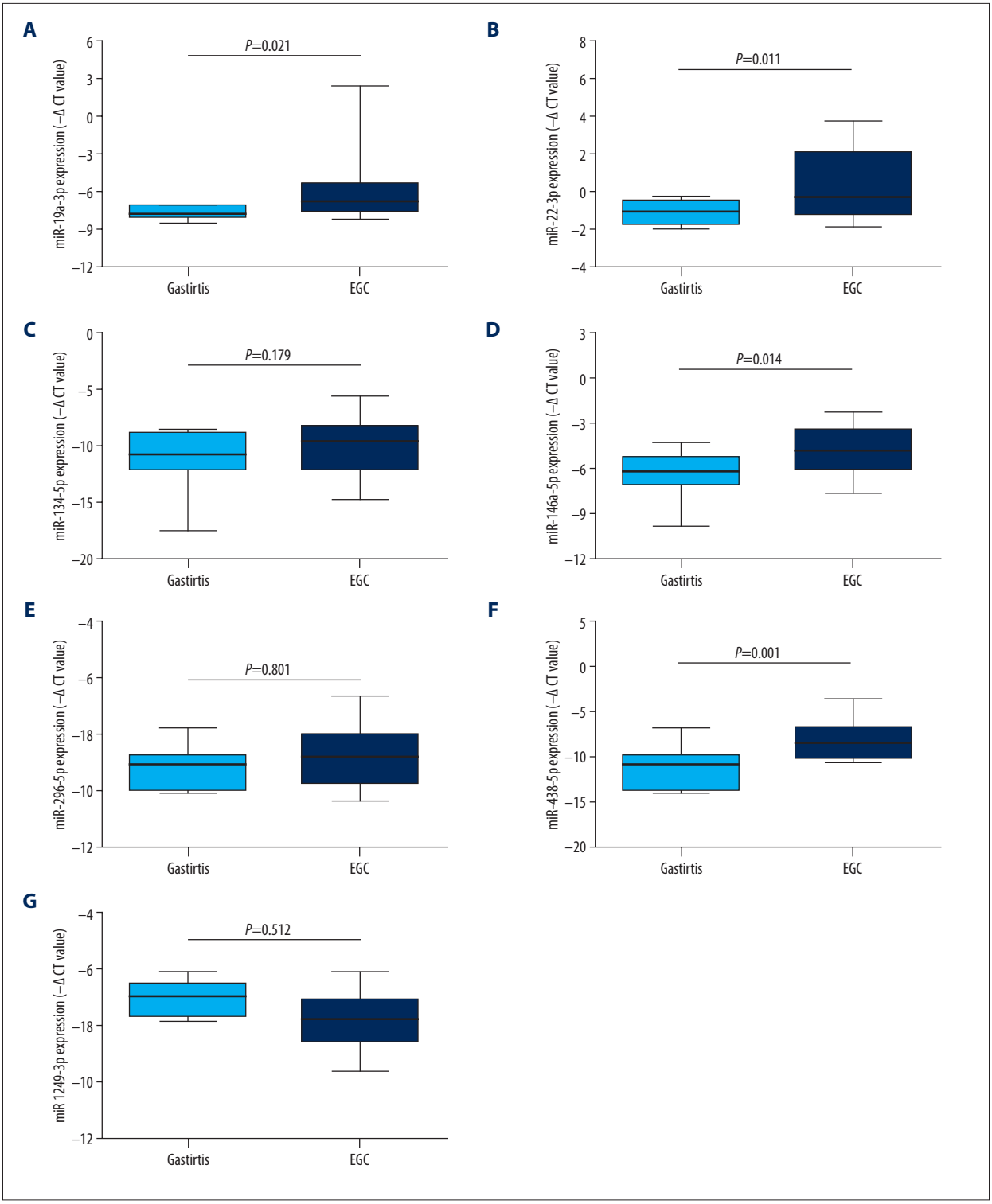

Figure 1. Differential expression levels of 7 miRNAs in the screening group (n=30). The box plots indicate the plasma miRNA expression levels in gastritis subjects (n=12) and patients with EGCs (n=18). The y-axes show the relative expression levels of miRNAs normalized to the expression level of the reference gene miR-16-5p. The expression levels of miR-19a-3p (**A**), miR-22-3p (**B**), miR-146a-5p (**D**), and miR-483-5p (**F**) in patients with EGCs were higher than those in subjects with gastritis. The expression levels of miR-134-5p (**C**), miR-296-5p (**E**), and miR-1249-3p (**G**) did not differ significantly between patients with EGC and subjects with gastritis.

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Table 1. Clinicopathological characteristics of all individuals by subgroup.

	Screening group (n=30)			Validation group (n=150)				
	Gastritis (n=12)	EGC (n=18)	*P* value	Gastritis (n=58)	LGIN (n=20)	HGIN (n=34)	EGC (n=38)	*P* value
Age (years)	55.7±10.8	59.6±10.0	0.305	57.8±9.9	61.9±8.4	62.0±8.1	61.2±9.2	0.095
Sex			0.694					0.342
Male	7	13		37	12	26	29	
Female	5	5		21	8	8	9	
Location								0.402
Upper		0			2	8	4	
Middle		7			4	7	12	
Lower		11			14	19	22	
Differentiation								
Well		5					12	
Moderate		7					12	
Poor		6					14	
Invasion depth								
Mucosa		8					18	
Submucosa		10					20	

LGIN – low-grade intraepithelial neoplasia; HGIN – high-grade intraepithelial neoplasia; EGC – early gastric cancer.

Statistical analysis

All data were analyzed with SPSS (version 21.0, IBM, USA) software and GraphPad Prism 7.0 (GraphPad Software, CA, USA). Differences between groups were analyzed with the independent samples *t* test for continuous variables or the χ^2 test for categorical variables.

Logistic regression analysis was used to generate a model for predicting EGC and precancerous lesions. Candidate predictors with $P<0.05$ in univariable analysis were included in the stepwise multivariable logistic regression analysis model ($P<0.05$). A combined diagnostic model was developed according to these independent factors, and each variable was weighted according to its regression coefficients. The areas under the receiver operating characteristic (ROC) curves (AUCs) were used to assess the diagnostic efficiency of the miRNAs and combined diagnostic model. For all analyses, $P<0.05$ was considered statistically significant.

Results

Characteristics of the subjects

A total of 150 patients were included in this study. The screening group comprised 12 gastritis subjects and 18 EGC patients. The age (55.7±10.8 *vs.* 59.6±10.0, $P=0.305$) and proportion of males (58.3% *vs.* 72.2%, $P=0.694$) were not significantly different. The validation group comprised 58 gastritis subjects, 20 LGIN patients, 34 HGIN patients, and 38 EGC patients. In this group, no significant differences were observed in age, sex, or lesion location ($P=0.095$, $P=0.342$, and $P=0.402$, respectively). The clinical characteristics of all patients are summarized in Table 1.

miRNA expression profiles in plasma samples

The expression levels of the 7 miRNAs associated with GC were compared between the 18 EGC patients and 12 gastritis subjects. The expression levels of miR-19a-3p, miR-22-3p, miR-146a-5p, and miR-483-5p in EGC patients were higher than those in gastritis subjects ($P<0.05$). The expression levels of miR-134-5p, miR-296-5p, and miR-1249-3p did not differ significantly between gastritis subjects and EGC patients (Figure 1).

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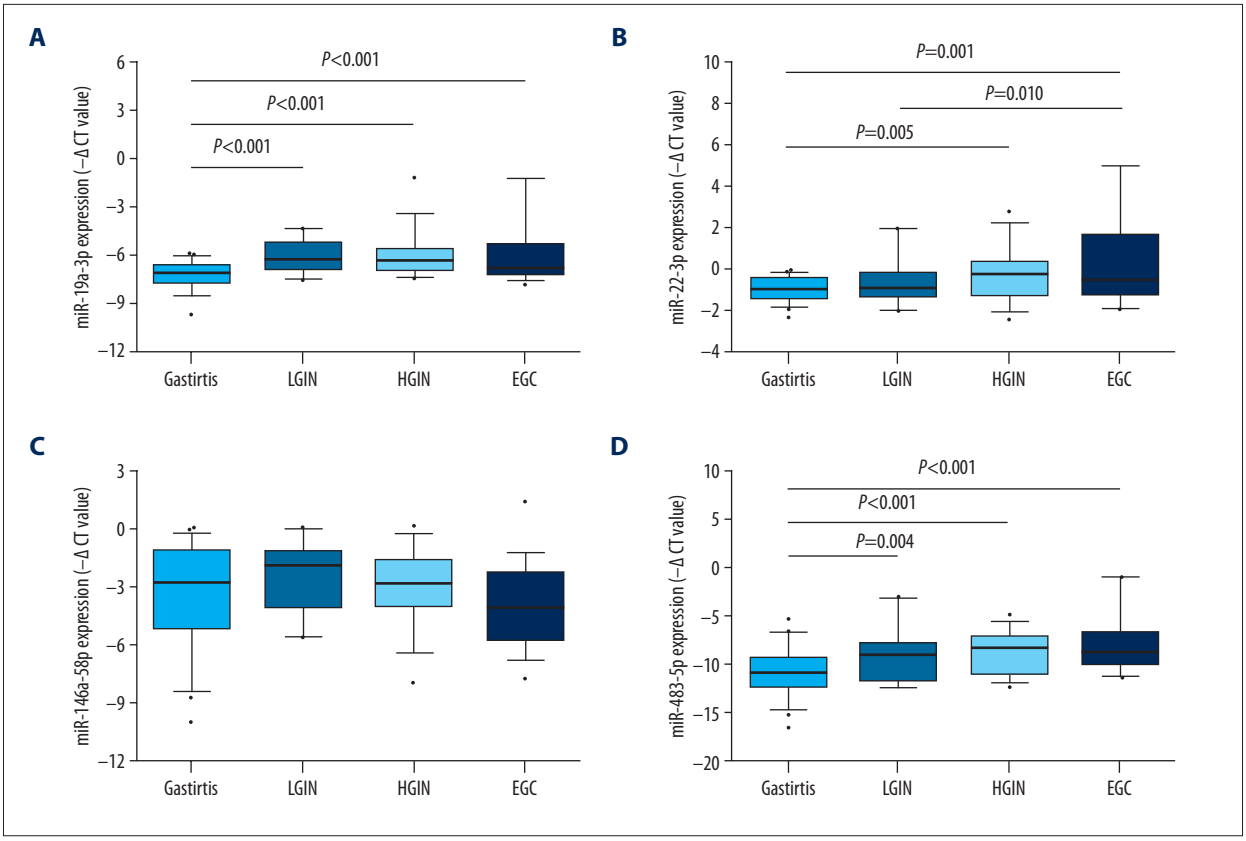

Figure 2. Plasma expression levels of 4 miRNAs in the validation group (n=150). The expression levels of miR-19a-3p (**A**) and miR-483-5p (**D**) in patients with EGCs and precancerous lesions (LGIN and HGIN) were significantly higher than those in gastritis subjects. The expression levels of miR-22-3p (**B**) in patients with EGCs and HGINs were significantly higher than those in subjects with gastritis. The miR-146a-5p expression levels (**C**) did not differ significantly between patients with EGCs and subjects with gastritis.

The power of the 4 differentially expressed miRNAs (miR-19a-3p, miR-22-3p, miR-146a-5p, and miR-483-5p) to distinguish EGC from gastritis was further assessed in the validation group by qRT-PCR. The expression levels of miR-19a-3p in patients with EGC and precancerous lesions (LGIN and HGIN) were significantly higher than those in gastritis subjects (EGC *vs.* gastritis, HGIN *vs.* gastritis and LGIN *vs.* gastritis – all $P<0.001$), as shown in Figure 2. Moreover, a significant difference among subgroups was also observed for the expression level of miR-483-5p ($P<0.001$ for EGC *vs.* gastritis and HGIN *vs.* gastritis, $P=0.004$ for LGIN *vs.* gastritis). The expression levels of miR-22-3p in patients with EGC and HGIN were significantly higher than those in gastritis subjects ($P=0.001$ and $P=0.005$, respectively). In the validation group, no significant difference was observed in the expression level of miR-146a-5p among the subgroups (all $P>0.05$).

Derivation of the combined diagnostic model to predict EGCs and precancerous lesions by differential miRNA expression

To distinguish EGC, HGIN, and LGIN patients from gastritis subjects, a diagnostic logistic regression analysis model combining the selected differentially expressed miRNAs was developed. The predictors were age, sex, and the 3 selected differentially expressed miRNAs (Table 2). Univariable analysis showed that age and the expression of miR-19a-3p, miR-22-3p, and miR-483-5p were significantly associated with EGCs and precancerous lesions. However, only age (OR, 1.054; 95% CI, 1.006–1.104), miR-19a-3p expression (OR, 3.676; 95% CI, 1.914–7.061), and miR-483-5p expression (OR, 1.589; 95% CI, 1.242–2.033) were independently associated with EGCs and precancerous lesions in multivariable analyses (Table 2). Based on the 3 regression coefficients, the following combined diagnostic model was derived:

$$Y1=10.799+0.052\ (\text{age})+1.302\ (\text{miR-19a-3p})+0.463\ (\text{miR-483-5p}).$$

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Table 2. Univariable and multivariable analyses of factors for predicting EGCs and precancerous lesions.

Predictor	Univariable analysis		Multivariable analysis		
	OR (95% CI)	*P* value	β coefficient	OR (95% CI)	*P* value
Age	1.047 (1.009, 1.087)	0.015	0.052	1.054 (1.006, 1.104)	0.028
Sex, male	0.657 (0.324, 1.331)	0.244			
miR-19a-3p	4.171 (2.351, 7.399)	<0.001	1.302	3.676 (1.914, 7.061)	<0.001
miR-22-3p	2.054 (1.349, 3.129)	0.001			
miR-483-5p	1.620 (1.328, 1.976)	<0.001	0.463	1.589 (1.242, 2.033)	<0.001

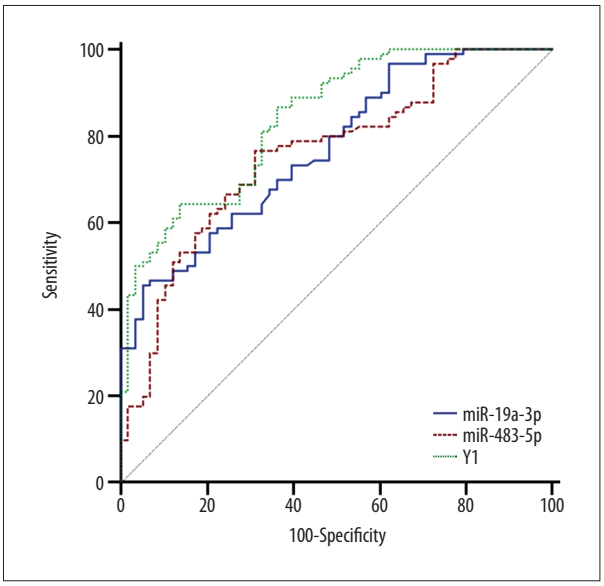

Figure 3. ROC curve analyses using serum miRNAs to distinguish patients with EGC or precancerous lesions from gastritis subjects. For distinguishing patients with EGCs or precancerous lesions from subjects with gastritis, the combined diagnostic model (Y1) yielded an AUC value of 0.840, with a sensitivity of 87.7% and specificity of 62.8% (cutoff value, –0.08). The AUC values of plasma miR-19a-3p and miR-483-5p expression were 0.770 and 0.758, respectively, for diagnosing EGC and precancerous lesions.

In addition, the diagnostic performance of miR-19a-3p, miR-483-5p, and the combined diagnostic model (Y1) was assessed by ROC curves, as shown in Figure 3. The AUC values for miR-19a-3p, miR-483-5p, and Y1 were 0.770 (95% CI, 0.694–0.835), 0.758 (95% CI, 0.681–0.825), and 0.840 (95% CI, 0.771–0.895), respectively. The ROC curves of the miRNAs and the Y1 model were compared using the DeLong method. The Y1 model showed significantly better performance for diagnosing EGCs and precancerous lesions than any single miRNA (Y1 *vs.* miR-19a-3p, *P*=0.014; Y1 *vs.* miR-483-5p, *P*=0.015). The accuracies of miR-19a-3p and miR-483-5p for predicting EGCs and precancerous lesions were statistically equivalent to each other (*P*=0.824). According to the highest Youden index, the cutoff value of Y1 model was 0.8. The sensitivity and specificity for EGCs and precancerous lesions were 64.4% (95% CI, 53.7–74.3%) and 86.2% (95% CI, 74.6–93.9%), respectively, at the cutoff value.

Discussion

Circulating miRNAs are promising, noninvasive biomarkers for cancer screening [16]. In this study, 7 miRNAs overexpressed in the plasma of EGC patients were selected from a previous study and further validated by qRT-PCR in 150 plasma samples from gastritis subjects and patients with LGIN, HGIN, or EGC. The qRT-PCR results indicated that the expression levels of miR-19a-3p and miR-483-5p were significantly higher in patients with EGC and precancerous lesions than in subjects with gastritis.

miRNA-19a-3p is located on chromosome 13q31.3 and has been reported to be overexpressed in various kinds of cancers, such as colorectal, pancreatic, and gallbladder cancers [17–19]. Previous studies have demonstrated that miR-19a-3p is involved in several cancer phenotypes, such as cancer growth, chemoresistance, and metastasis [20–23]. Bai et al. [20] demonstrated that miR-19a-3p promotes ovarian cancer growth through inhibition of IGFBP-3 expression. It has been reported that miR-19a-3p was overexpressed in hepatocellular carcinoma (HCC) and could promote the proliferation, metastasis, and sorafenib resistance of HCC through activating the PTEN/Akt pathway [21]. miR-19a-3p can regulate the FOXF2-mediated Wnt/β-catenin signaling pathway, thus affecting the epithelial-mesenchymal transition, proliferation, invasion, and migration of colorectal cancer cells [22]. Moreover, it has been documented that miRNA-19a regulates GC cell proliferation and migration by activating nuclear factor κ-B [23]. In this study, we found that circulating miRNA-19a-3p was highly expressed in patients with EGCs and precancerous lesions compared with subjects with gastritis. The plasma expression level of miR-19a-3p was significantly increased in LGINs and continued to increase gradually with progression.

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miR-483-5p is located on chromosome 11p15.5 in the intron of the IGF2 gene. The expression of miR-483 is upregulated in esophageal squamous cell cancer and is negatively correlated with overall survival [24]. The oncogenic and promoting metastasis role of miR-483-5p has been implicated in several cancers [25–27]. Agosta et al. [25] demonstrated that miR-483-5p promotes adrenocortical cancer cell migration and invasion by targeting NDRG2. Lu et al. [26] confirmed that miR-483-5p can promote migration and invasion of hepatocellular carcinoma cells by regulating ALCAM, which leads to intrahepatic metastasis and distant metastasis and, finally, postoperative short-term recurrence. Tian et al. [27] found that miR-483-5p was positively associated with advanced tumor stage and positive lymph node metastasis in nasopharyngeal carcinoma (NPC), whereas the overexpression of miR-483-5p decreases the radiosensitivity of NPC cells by targeting DAPK1. Although the oncogenic role of miR-483-5p is confirmed in several cancers, the effect of miR-483-5p in GC is still unknown. Our study showed that the AUC of miR-483-5p alone was 0.76 for diagnosing EGCs and precancerous lesions, suggesting that this miRNA may be a useful screening biomarker for EGCs and precancerous lesions.

Biomarker combinations can improve the diagnostic performance of a model for various cancers [28–30]. In this study, a predictive logistic regression analysis model called the Pre-Cancer Screening Model for diagnosing EGCs and precancerous lesions was developed. This screening model had an AUC of 0.84 for diagnosing GC and precancerous lesions.

Its sensitivity and specificity were 64.4% and 86.2%, respectively, at a cutoff point of 0.8 (according to highest Youden index). However, we needed fewer missed diagnosis, which means a low false-negative rate and high sensitivity, for the purpose of identifying high-risk populations of GC patients in the general population. Considering the sensitivity and specificity, we redefined the cutoff value as -0.08. The sensitivity and specificity of the model for EGCs and precancerous lesions were 87.7% and 62.8%, respectively, at a cutoff value of –0.08. Patients with a positive value (>–0.08 in the screening model) are considered high-risk populations of GC patients and are advised to undergo gastroscopy. However, to confirm the validity of this screening model, prospective validation studies including other tumors in multiple centers are urgently needed. A multicenter validation study is necessary before the Pre-Cancer Screening Model can be applied clinically.

Conclusions

This study showed that miR-19a-3p and miR-483-5p are powerful and promising circulating markers for the early diagnosis of GC. Moreover, we developed a new screening model for diagnosing EGCs and precancerous lesions. Patients are more willing to undergo noninvasive diagnostic methods than gastroscopy for cancer screening, economizing limited medical resources.

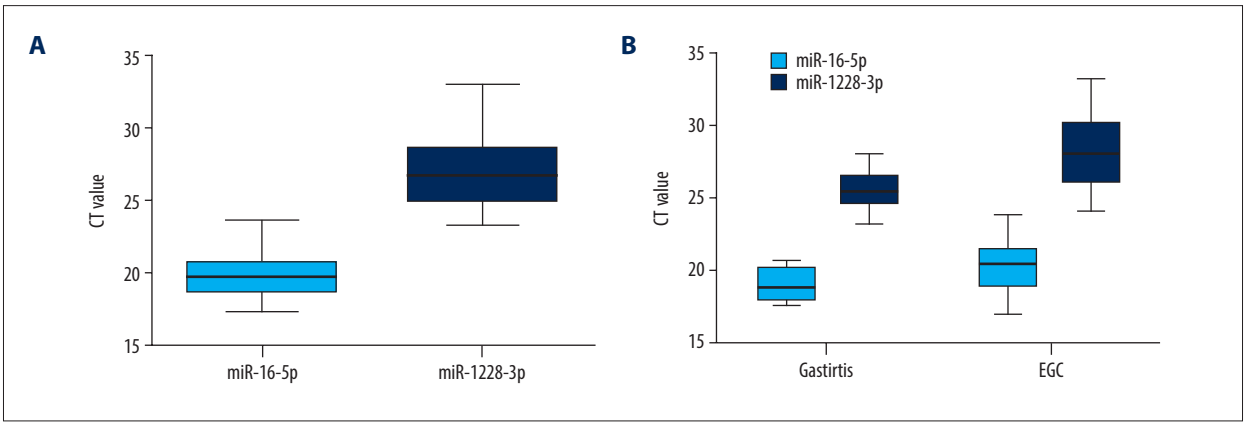
Acknowledgements

We would like to express our gratitude to Dr. Botao Zhang and Dr. Chengli Zhang for their excellent technical assistance.

Conflicts of interest

None.

Supplementary Data



Supplementary Figure 1. Results of endogenous reference gene selection by qRT-PCR. The variation degree of miR-1228-3p is higher than miR-16-5p (**A**). The expression levels of miR-1228-3p and miR-16-5p are not significantly different in EGCs and gastritis (**B**).

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References:

1. Ferlay J, Colombet M, Soerjomataram I et al: Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. Int J Cancer, 2019; 144: 1941–53
2. Bray F, Ferlay J, Soerjomataram I et al: Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. Cancer J Clin, 2018; 68: 394–424
3. Ferlay J, Ervik M, Lam F et al: Global cancer observatory: Cancer today. Lyon, France: International Agency for Research on Cancer, 2018
4. Tan Z: Recent advances in the surgical treatment of advanced gastric cancer: A review. Med Sci Monit, 2019; 25: 3537–41
5. Allemani C, Matsuda T, Di Carlo V et al: Global surveillance of trends in cancer survival 2000-14 (CONCORD-3): Analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. Lancet, 2018; 391: 1023–75
6. Tanabe S, Ishido K, Matsumoto T et al: Long-term outcomes of endoscopic submucosal dissection for early gastric cancer: A multicenter collaborative study. Gastric Cancer, 2017; 20: 45–52
7. Anfossi S, Babayan A, Pantel K, Calin GA: Clinical utility of circulating noncoding RNAs – an update. Nat Rev Clin Oncol, 2018; 15: 541–63
8. Mitchell PS, Parkin RK, Kroh EM et al: Circulating microRNAs as stable blood-based markers for cancer detection. Proc Natl Acad Sci USA, 2008; 105: 10513–18
9. Peng Y, Croce CM: The role of microRNAs in human cancer. Signal Transduct Target Ther, 2016; 1: 15004
10. Muhammad S, Tang Q, Wei L et al: miRNA-30d serves a critical function in colorectal cancer initiation, progression and invasion via directly targeting the GNA13 gene. Exp Ther Med, 2019; 17: 260–72
11. Orangi E, Motovali-Bashi M: Evaluation of miRNA-9 and miRNA-34a as potential biomarkers for diagnosis of breast cancer in Iranian women. Gene, 2019; 687: 272–79
12. Pan J, Zhou C, Zhao X et al: A two-miRNA signature (miR-33a-5p and miR-128-3p) in whole blood as potential biomarker for early diagnosis of lung cancer. Sci Rep, 2018; 8: 16699
13. Yang GD, Zhang YJ, Yang JY: Identification of potentially functional circRNA-miRNA-mRNA regulatory network in gastric carcinoma using bioinformatics analysis. Med Sci Monit, 2019; 25: 8777–96
14. Liu X, Kwong A, Sihoe A, Chu KM: Plasma miR-940 may serve as a novel biomarker for gastric cancer. Tumour Biol, 2016; 37: 3589–97
15. Zhang KC, Xi HQ, Cui JX et al: Hemolysis-free plasma miR-214 as novel biomarker of gastric cancer and is correlated with distant metastasis. Am J Cancer Res, 2015; 5: 821–29
16. Santangelo A, Tamanini A, Cabrini G, Dechecchi MC: Circulating microRNAs as emerging non-invasive biomarkers for gliomas. Ann Transl Med, 2017; 5: 277
17. Huang L, Wang X, Wen C et al: Hsa-miR-19a is associated with lymph metastasis and mediates the TNF-alpha induced epithelial-to-mesenchymal transition in colorectal cancer. Sci Rep, 2015; 5: 13350
18. Tan Y, Yin H, Zhang H et al: Sp1-driven up-regulation of miR-19a decreases RHOB and promotes pancreatic cancer. Oncotarget, 2015; 6: 17391–403
19. Li H, Jin Y, Hu Y et al: The PLGF/c-MYC/miR-19a axis promotes metastasis and stemness in gallbladder cancer. Cancer Sci, 2018; 109: 1532–44
20. Bai R, Cui Z, Ma Y et al: The NF-κB-modulated miR-19a-3p enhances malignancy of human ovarian cancer cells through inhibition of IGFBP-3 expression. Mol Carcinog, 2019; 58: 2254–65
21. Jiang XM, Yu XN, Liu TT et al: microRNA-19a-3p promotes tumor metastasis and chemoresistance through the PTEN/Akt pathway in hepatocellular carcinoma. Biomed Pharmacother, 2018; 105: 1147–54
22. Yu FB, Sheng J, Yu JM et al: MiR-19a-3p regulates the Forkhead box F2-mediated Wnt/β-catenin signaling pathway and affects the biological functions of colorectal cancer cells. World J Gastroenterol, 2020; 26: 627–44
23. Yang F, Wang H, Jiang Z et al: MicroRNA-19a mediates gastric carcinoma cell proliferation through the activation of nuclear factor-κB. Mol Med Rep, 2015; 12: 5780–86
24. Zhou Y, Hong L: Prediction value of miR-483 and miR-214 in prognosis and multidrug resistance of esophageal squamous cell carcinoma. Genet Test Mol Biomarkers, 2013; 17: 470–74
25. Agosta C, Laugier J, Guyon L et al: MiR-483-5p and miR-139-5p promote aggressiveness by targeting N-myc downstream-regulated gene family members in adrenocortical cancer. Int. J Cancer, 2018; 143: 944–57
26. Lu XY, Chen D, Gu XY et al: Predicting value of ALCAM as a target gene of microRNA-483-5p in patients with early recurrence in hepatocellular carcinoma. Front Pharmacol, 2017; 8: 973
27. Tian YH, Yan MH, Zheng JL et al: miR-483-5p decreases the radiosensitivity of nasopharyngeal carcinoma cells by targeting DAPK1. Lab Invest, 2019; 99: 602–11
28. Sun L, Tu H, Chen T et al: Three-dimensional combined biomarkers assay could improve diagnostic accuracy for gastric cancer. Sci Rep, 2017; 7: 11621
29. Shin VY, Ng EK, Chan VW et al: A three-miRNA signature as promising non-invasive diagnostic marker for gastric cancer. Mol Cancer, 2015; 14: 202
30. Alemar B, Izetti P, Gregorio C et al: miRNA-21 and miRNA-34a are potential minimally invasive biomarkers for the diagnosis of pancreatic ductal adenocarcinoma. Pancreas, 2016; 45: 84–92

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