Received: 25 February 2022 | Revised: 24 March 2022 | Accepted: 25 March 2022

DOI: 10.1002/jcla.24411

RESEARCH ARTICLE

WILEY

Diagnosis value of miR-181, miR-652, and CA72-4 for gastric cancer

Wenyan Tian | **Xueqin Pang** | **Fujuan Luan**

Department of Gastroenterology, First Affiliated Hospital of Soochow University, Suzhou, People's Republic of China

Correspondence
Fujuan Luan, Department of Gastroenterology, First Affiliated Hospital of Soochow University, 188 Shizi Road, Suzhou 215006, People's Republic of China.
Email: rfujian@163.com

Abstract

Purpose: To find a useful disease marker for early diagnosis of gastric cancer, we tried to explore the expression of serum miR-181, miR-652, and carbohydrate antigen 72-4 (CA72-4).

Patients and Methods: According to clinical pathologic stages, 112 patients with gastric cancer were divided into early gastric cancer group ($n = 60$) and advanced gastric cancer group ($n = 52$), stage I-II ($n = 65$), and stage III-IV ($n = 47$). Another 50 cases of gastric benign lesions and 40 healthy controls were also selected. Real-time quantitative PCR together with chemiluminescence were applied to detect expression levels. ROC curve was applied to judge their diagnostic efficiency. Pearson's correlation analysis was put into use to investigate the relevance of three indicators.

Results: Compared with benign lesions group and control group, significantly higher expression levels were found in patients of gastric cancer (all $p < 0.001$). Similarly, compared with early gastric cancer group, significantly higher expression levels were found in advanced gastric cancer group (all $p < 0.001$). The same result was also found in stage III-IV (all $p < 0.001$). The best cutoff values were 0.93, 2.38, and 16.94 U/ml, respectively. The area under the curve (0.917, 95%CI: 0.856–0.975) of the three combined diagnosis of early gastric cancer was the largest, and its sensitivity and specificity were 92.5% and 86.8%. And miR-181 and miR-652 were positively correlated with CA72-4 ($r = 0.772$, $p < 0.001$, $r = 0.853$, $p < 0.001$).

Conclusion: Serum miR-181, miR-652, and CA72-4 are closely linked to the occurrence and development of gastric cancer. Combination of three indicators has diagnostic value for early gastric cancer.

KEYWORDS
carbohydrate antigen 72-4, diagnostic value, gastric cancer, miR-181, miR-652

Wenyan Tian and Xueqin Pang contributed equally to this work.

1 | INTRODUCTION

Gastric cancer (GC) has the highest incidence rate in digestive tumors globally.[1] Due to lack of obvious clinical symptoms of GC in the early stage, too many patients are diagnosed at advanced-stage, resulting in poor prognosis and losing their lives.[2–4] Thus, diagnosis and treatment in early stage are crucial to improving life quality and reducing death rate.[5]

The etiology and pathogenesis of psoriasis vulgaris is complex, involving multiple factors such as heredity, immunity, infection, and environment.[6] miRNA is a small non-coding RNA, 18–25 nucleotides in length, it participates in the post-transcriptional regulation of target genes by shearing miRNA and inhibiting protein translation.[7] miRNA plays an important regulatory role in various physiologic processes in the organism.[8,9] It is becoming important targets in the diagnosis and treatment in cancers.[10] Researches have reported that miRNA may participate in the tumorigenesis and occurrence of gastrointestinal cancer.[11] For gastrointestinal cancer, recent insights have proved abnormal expression level in miR-181 and miR-652, as well as its role in the tumorigenesis and development of other cancers though adjusting several cellular signaling pathways.[12–14] Thus, miR-181 and miR-652 may have implications for gastrointestinal cancer. CA72-4 (carbohydrate antigen 72-4), a common available tumor marker, has been considered as an important and useful marker for diagnosis and prognosis of GC.[15,16] In this research, we analyzed the expression level of miR-181, miR-652, and CA72-4 in gastric diseases to evaluate the value for early diagnosis and prognosis of GC.

2 | MATERIAL AND METHODS

2.1 | Clinical specimens

112 patients with gastric cancer admitted to our hospital were selectively enrolled from January 2019 to October 2020, including 70 male and 42 female (median age, 58.6 years; range, 33~79 years). Inclusion criteria were as follows: (1) gastric adenocarcinoma confirmed histopathologically; (2) having not received radiotherapy, chemotherapy, immunotherapy, and surgical resection before test. Exclusion criteria were as follows: a history of other malignant cancers, pathological angiogenesis, immune system disease, and serious liver and kidney diseases. In addition, 50 patients with benign gastric diseases were recruited for the controls group, including 32 gastric ulcers and 18 gastric polyposis (33 male and 17 female). 40 healthy individuals were recruited for the control group (healthy controls) (25 male and 15 female). Based on the progress of gastric cancer and the clinical pathological stages, the patients were classified for two groups including early gastric cancer group and advanced gastric cancer group. The clinical tumor stage was determined on the basis of seventh edition of the TNM classification.[17] All patients signed written consent form and study protocol was approved by the Ethics Committee of First Affiliated Hospital of Soochow University.

2.2 | Quantitative real-time PCR

Two milliliters of peripheral blood was placed in tubes with no anticoagulant, and the serum was separated by centrifugation. RNA extraction was applied a standard liquid–liquid extraction protocol using TRIzol LS (Invitrogen, Life Sciences, Carlsbad, CA). cDNA synthesis was based on the TaqMan miRNA reverse transcription kit (Applied Biosystems, Life Sciences, Foster City, CA). The reaction system was 15 μl, which contained 5 μl of eluted plasma miRNA, 10 μl of master mix (3 μl of reverse transcription-specific primer, 1.5 μl of buffer, 4.16 μl of nuclease-free H2O, 1 μl of 50 U/ μl MultiScribe Reverse Transcriptase, 0.15 μl of 100 mmol/L dNTPs, 0.19 μl of 20 U/ μl RNase inhibitor). We used real-time PCR to calculate the miR-181 and miR-652 expression on ABI 7500. 20 μl reaction systems with iQ SYBR Premix Ex Taq Perfect Real Time was built. $2^{-\triangle\triangle Ct}$ formula was applied to calculate relative mRNA expression, and the U6 was applied as an endogenous control. Additionally, chemiluminescence method was used to quantitate CA72-4 level on Roche Electrochemical luminescence Immunoassay Analyzers.

2.3 | Survival analysis

Online tool Kaplan-Meier plotter (KM plotter, www.kmplot.com) can assess the impact of gastric (nasty 1440) cancer on survival rate. OC patients were divided into the expression and low expression group, according to the median expression level of specific genes. Kaplan–Meier was used to analyze the overall survival of patients with OC. Calculate and show the hazard ratio (HR) of the 95% confidence interval (CI).

2.4 | Statistical analysis

The SPSS 12.0 was applied for whole analysis, the measurement data was represented by (X ± S), and the comparison of the means of two independent samples was performed by *t* test. The counting data were expressed as percentage (%) and was performed by the χ^2 test. Pearson's correlation analysis was also applied. $p < 0.05$ indicated the difference was statistically significant. Bioinformatics analysis was based on common data base and published literatures.[18,19]

3 | RESULTS

3.1 | miR-181, miR-652, and CA72-4 expression

Compared with benign lesions group and control group, significantly higher expression levels were found in patients of gastric cancer (all $p < 0.001$) (Figure 1). Similarly, compared with early gastric cancer group, significantly higher expression levels were found in advanced gastric cancer group (all $p < 0.001$) (Figure 2). The serum miR-181 ($r = 0.772$, $p < 0.001$) and miR-652 ($r = 0.853$, $p < 0.001$)

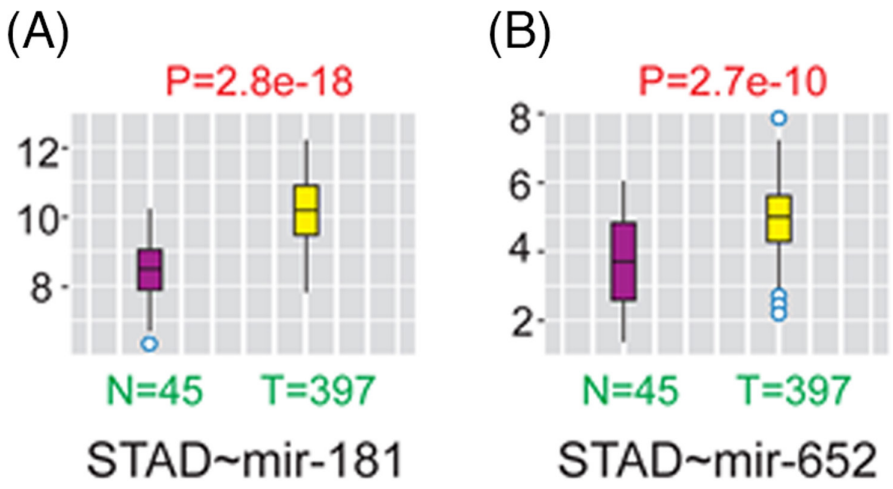

FIGURE 1 Expression level of miR-181 and miR-652 in normal tissue group and gastric cancer tissue group

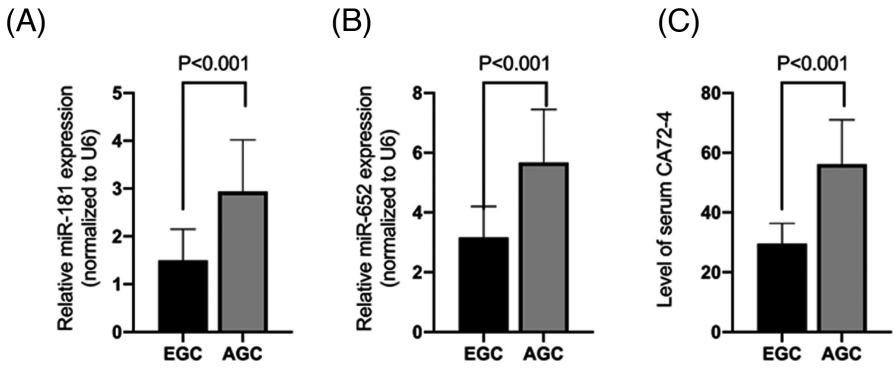

FIGURE 2 Expression level of miR-181, miR-652, and CA72-4 in early gastric cancer group and advanced gastric cancer group

was positively associated with CA72-4 in patients with gastric cancer (Figure 3). Compared with stage III~IV, significantly higher expression levels were found in stage III~IV (all $p < 0.001$) (Figure 4).

3.2 | The diagnostic value of serum miR-181, miR-652, and CA72-4 levels patients with early gastric cancer

AUC of miR-181, miR-652, and CA72-4 generated by ROC analysis was 0.820, 0.842 and 0.769. The cutoff points of above three indicators is 0.93, 2.38, 16.94 U/ml.

Moreover, AUC of combination of miR-181, miR-652, and CA72-4 is 0.917 (95% CI = 0.856 to 0.975, sensitivity = 92.5%, and specificity = 86.8%) (Figure 5 and Table 1).

3.3 | The prognostic value of serum miR-181 and miR-652 levels patients with gastric cancer

Two selected miRNAs, namely, miR-181 and miR-652, were significantly associated with the prognosis of patients (Figure 6). High expression of miR-181 in STAD patients was associated with poor OS (HR: 1.35; 95% CI: 0.99–1.84; $p = 0.045$). High expression of miR-652 in STAD patients was associated with poor OS (HR: 1.45; 95% CI: 1.03–2.04; $p = 0.034$).

4 | DISCUSSION

CA72-4, the most common serum tumor biomarker, was widely used in the diagnosis, metastasis monitoring, and prognosis judgment of gastric cancer.[20,21] Emoto et al.[22] reported that, CA72-4 is associated with advanced stages of gastrointestinal cancer and poor prognosis. Similarly, the serum level of CA72-4 can provide material circumstances about prognosis such as the extent of tumor invasion, metastases. However, CA72-4 has low sensitivity in the early diagnosis of GC, and the value of single index in the diagnosis of early gastric cancer is limited. Therefore, identification of biomarkers with higher sensitivity and combined markers would be of great value.

Numerous miRNAs in GC have been found to be upregulated including miR-15b, miR-16, miR-21, miR-23a, miR-27, miR-43c, miR-106a, miR-107, miR-130b, miR-150, and miR-223.[23–35] Meanwhile, various miRNAs in GC have been found to be downregulated including miR-9, miR-34b, miR-124a, miR-126, miR-129-2, miR-143, miR-145, miR-146a, miR-148b, miR-181c, miR-212, miR-218, miR-375, and miR-451.[36–52]

Although increasing studies have indicated that miRNAs play key roles in the progression of gastric cancer, the clear mechanism and functions of numerous miRNAs remains unknown. Therefore, the role and pathway of miRNAs in gastric cancer need to be further explored in future study. A majority of miRNAs were found be associated with cell proliferation and a small minority of miRNAs

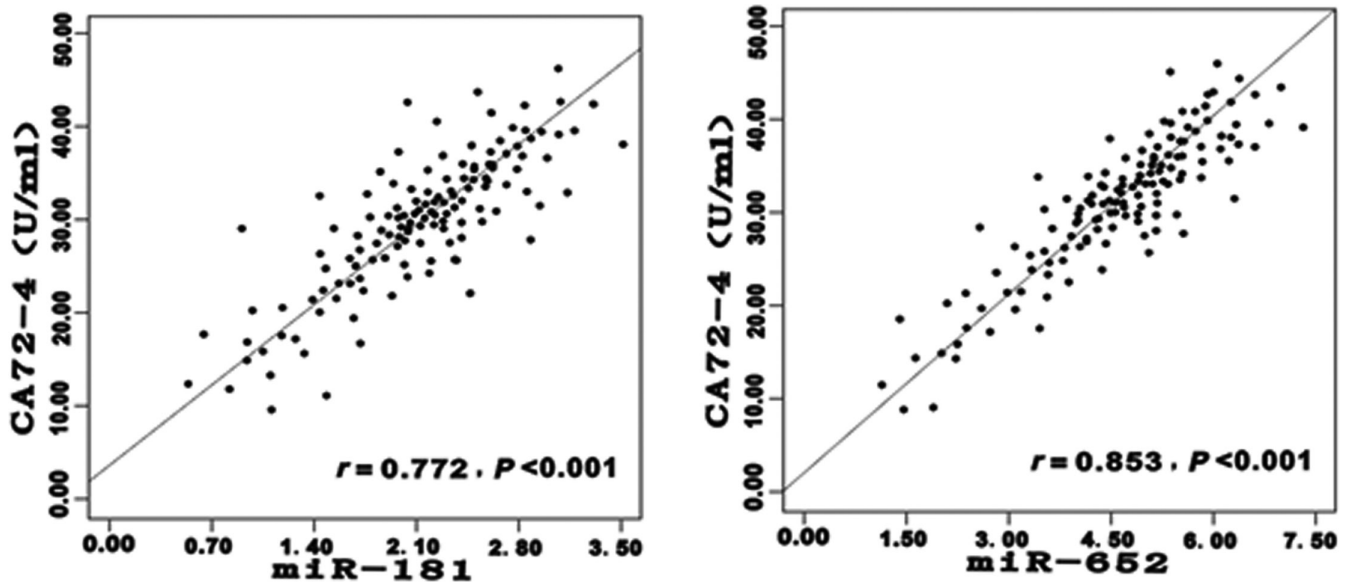

FIGURE 3 Correlation of serum miR-181 and miR-652 levels with CA72-4

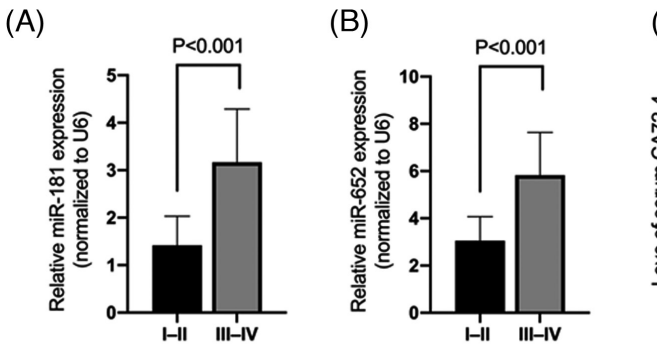

FIGURE 4 Expression level of miR-181, miR-652, and CA72-4 in stage I-II and stage III-IV

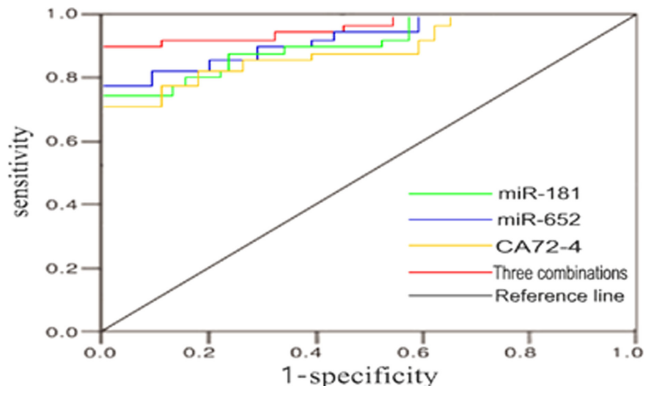

FIGURE 5 ROC curve of serum miR-181, miR-652, and CA72-4 in the diagnosis of early gastric cancer

were found be associated with cell survival, epigenetic regulation, cell cycle regulation and cell cycle arrest. miR-181 was considered to promote cell proliferation and inhibit apoptosis in gastric cancer and miR-652 was served as a prognostic biomarker in gastric cancer.[14,53] Furthermore, CA72-4 was considered highly specific to gastric cancer.[21] As far as we know, this is the first study that investigates the diagnosis of gastric cancer by combining three indicators.

In this research, our data indicated that serum miR-181, miR-652, and CA72-4 are closely linked to the occurrence and development of gastric cancer. Combination of three indicators has diagnostic value for early gastric cancer. Thus, miRNA could be biomarkers for GC to predict its diagnosis and prognosis. The expression level of miR-181 and miR-652 were in positive relation to serum CA72-4 level, suggesting the similar roles in gastric cancer. Moreover, the expression of miR-181, miR-652, and CA72-4 in advanced GC were significantly higher than in gastric benign disease cases and healthy group. Their expression level in III~IV stage GC were significantly higher than in I~II. All the evidence suggested that increased expression level of miR-181 and miR-652 in Patients were correlated to the progression of GC.

Multiple marker combination may contribute to improving the diagnostic accuracy of various diseases, including GC. The present study suggested that three indictors combined improved the diagnostic accuracy of GC. The diagnosis value of early gastric cancer was enhanced when combined with the conversed biomarker CA72-4, providing a new strategy for elucidating the mechanism underlying GC. N4-acetylcytidine (ac4C) has been subject to widespread attention as comprehensive modifications have been detected in mRNAs of human and yeast.[54] It contributes to

TABLE 1 Serum miR-181, miR-652, and CA72-4 cutoff points and the corresponding sensitivity and specificity for predicting EGC

Indicator	Cutoff point	AUC (95%CI)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	PLR	-LR
miR-181	0.93	0.820 (0.761~0.879)	83.6	78.5	80.7	81.5	3.888	0.209
miR-652	2.38	0.842 (0.783~0.902)	86.2	80.4	83.5	83.6	4.398	0.172
CA72-4	16.94 U/ml	0.796 (0.741~0.854)	80.4	73.5	76.2	77.8	3.034	0.267
Combinations	/	0.917 (0.856~0.975)	92.5	86.8	89.3	90.4	7.008	0.086

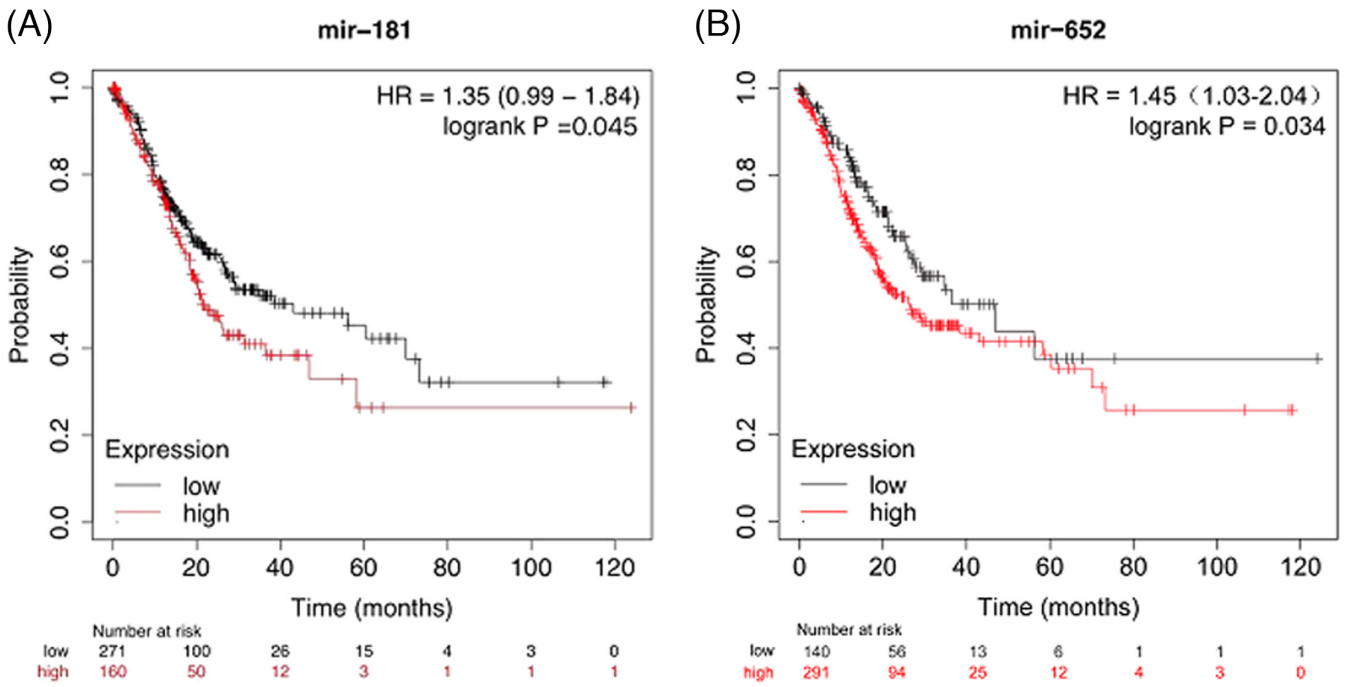

FIGURE 6 Relationship between miR-181, miR-652 expression and prognosis

accurately reading codons in the process of translation and improving translational efficiency.[54] Furthermore, there is a direct correlation between ac4C and occurrence, development, progression of number diseases.[54] This may be an interesting and meaningful research topic to investigate the relationship between ac4C and miRNA expression.

5 | CONCLUSIONS

In summary, serum miR-181, miR-652, and CA72-4 were significantly associated with the progression and stage of gastric cancer. Combination of miR-181, miR-652, and CA72-4 had the greater diagnostic value for early diagnosis of GC.

ACKNOWLEDGMENTS

We sincerely thank some students for helping us in data collection and collation.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

AUTHOR CONTRIBUTIONS

Fujuan Luan conceived study design; Xueqin Pang conceived the content concept; Wenyan Tian and Xueqin Pang performed the data collection, extraction, and analyzed the data. Wenyan Tian interpreted and reviewed the data and drafts. Fujuan Luan reviewed the final draft. All authors were involved in literature search, writing the paper and had final approval of the submitted and published versions.

DATA AVAILABILITY STATEMENT

All the data generated or analyzed during this study are included in this published article.

ORCID

Fujuan Luan https://orcid.org/0000-0003-2944-9824

REFERENCES

1. Sun X, Zhang K, Li D. Prognostic potential of miR-21-3p in gastric cancer. *J BUON*. 2020;25(6):2678-2682.
2. Strong VE. Progress in gastric cancer. *Updates Surg*. 2018;70(2):157-159.

3. Jia X, Wen Z, Sun Q. Apatinib suppresses the proliferation and apoptosis of gastric cancer cells via the PI3K/Akt signaling pathway. *J BUON*. 2019;24(5):1985-1991.
4. Tekesin K, Emin Gunes M, Tural D. Clinicopathological characteristics, prognosis and survival outcome of gastric cancer in young patients: a large cohort retrospective study. *J BUON*. 2019;24(2):672-678.
5. Zhou G, Yang J. Correlations of gastrointestinal hormones with inflammation and intestinal flora in patients with gastric cancer. *J BUON*. 2019;24(4):1595-1600.
6. Trowbridge RM, Pittelkow MR. Epigenetics in the pathogenesis and pathophysiology of psoriasis vulgaris. *J Drugs Dermatol*. 2014;13(2):111-118.
7. Ruksha TG, Komina AV, Palkina NV. MicroRNA in skin diseases. *Eur J Dermatol*. 2017;27(4):343-352.
8. Tang L, He S, Zhu Y, et al. Downregulated miR-187 contributes to the keratinocytes hyperproliferation in psoriasis. *J Cell Physiol*. 2019;234(4):3661-3674.
9. Qiao M, Ding J, Yan J, Li R, Jiao J, Sun Q. Circular RNA expression profile and analysis of their potential function in psoriasis. *Cell Physiol Biochem*. 2018;50(1):15-27.
10. Luo X, Burwinkel B, Tao S, Brenner H. MicroRNA signatures: novel biomarker for colorectal cancer? *Cancer Epidemiol Biomarkers Prev*. 2011;20(7):1272-1286.
11. Mishra P, Singh D, Ganju L, Kumar B. MicroRNA in gastrointestinal cell signalling. *Inflammopharmacology*. 2018;26(1):1-14.
12. Peng W, Si S, Zhang Q, et al. Long non-coding RNA MEG3 functions as a competing endogenous RNA to regulate gastric cancer progression. *J Exp Clin Cancer Res*. 2015;34(1):79.
13. Yu J, Qi J, Sun X, et al. MicroRNA-181a promotes cell proliferation and inhibits apoptosis in gastric cancer by targeting RASSF1A. *Oncol Rep*. 2018;40(4):1959-1970.
14. Li J, Zou X. MiR-652 serves as a prognostic biomarker in gastric cancer and promotes tumor proliferation, migration, and invasion via targeting RORA. *Cancer Biomark*. 2019;26(3):323-331.
15. Yang A-P, Liu J, Lei H-Y, Zhang Q-W, Zhao L, Yang G-H. CA72-4 combined with CEA, CA125 and CAI9-9 improves the sensitivity for the early diagnosis of gastric cancer. *Clin Chim Acta*. 2014;437:183-186.
16. Chen C, Chen Q, Zhao Q, Liu M, Guo J. Value of combined detection of serum CEA, CA72-4, CA19-9, CA15-3 and CA12-5 in the diagnosis of gastric cancer. *Ann Clin Lab Sci*. 2017;47(3):260-263.
17. Jung H, Lee HH, Song KY, Jeon HM, Park CH. Validation of the seventh edition of the American Joint Committee on Cancer TNM staging system for gastric cancer. *Cancer*. 2011;117(11):2371-2378.
18. Xie J, Li H, Chen L, et al. A novel pyroptosis-related lncRNA signature for predicting the prognosis of skin cutaneous melanoma. *Int J Gen Med*. 2021;14:6517-6527.
19. Qiu Y, Li H, Xie J, Qiao X, Wu J. Identification of ABCC5 among ATP-binding cassette transporter family as a new biomarker for hepatocellular carcinoma based on bioinformatics analysis. *Int J Gen Med*. 2021;14:7235-7246.
20. Peng W, Zhou Z, Zhong Y, et al. Plasma activity of thioredoxin reductase as a novel biomarker in gastric cancer. *Sci Rep*. 2019;9(1):19084.
21. Hamazoe R, Maeta M, Matsui T, Shibata S, Shiota S, Kaibara N. CA72-4 compared with carcinoembryonic antigen as a tumour marker for gastric cancer. *Eur J Cancer*. 1992;28A(8-9):1351-1354.
22. Emoto S, Ishigami H, Yamashita H, Yamaguchi H, Kaisaki S, Kitayama J. Clinical significance of CA125 and CA72-4 in gastric cancer with peritoneal dissemination. *Gastric Cancer*. 2012;15(2):154-161.
23. Xiao B, Guo J, Miao Y, et al. Detection of miR-106a in gastric carcinoma and its clinical significance. *Clin Chim Acta*. 2009;400(1-2):97-102.
24. Cimmino A, Calin GA, Fabbri M. miR-15 and miR-16 induce apoptosis by targeting BCL2. *Proc Natl Acad Sci U S A*. 2005;102(39):13944-13949.
25. Zhang BG, Li JF, Yu BQ, Zhu ZG, Liu BY, Yan M. microRNA-21 promotes tumor proliferation and invasion in gastric cancer by targeting PTEN. *Oncol Rep*. 2012;27(4):1019-1026.
26. Motoyama K, Inoue H, Mimori K. Clinicopathological and prognostic significance of PDCD4 and microRNA-21 in human gastric cancer. *Int J Oncol*. 2010;36(5):1089-1095.
27. Liu X, Ru J, Zhang J, et al. miR-23a targets interferon regulatory factor 1 and modulates cellular proliferation and paclitaxel-induced apoptosis in gastric adenocarcinoma cells. *PLoS One*. 2013;8(6):e64707.
28. Liu T, Tang H, Lang Y, Liu M, Li X. MicroRNA-27a functions as an oncogene in gastric adenocarcinoma by targeting prohibitin. *Cancer Lett*. 2009;273(2):233-242.
29. Guo X, Jing C, Li L, et al. Down-regulation of VEZT gene expression in human gastric cancer involves promoter methylation and miR-43c. *Biochem Biophys Res Commun*. 2011;404(2):622-627.
30. Petrocca F, Visone R, Onelli MR. E2F1-regulated microRNAs impair TGFbeta-dependent cell-cycle arrest and apoptosis in gastric cancer. *Cancer Cell*. 2008;13(3):272-286.
31. Kim Y-K, Yu J, Han TS, et al. Functional links between clustered microRNAs: suppression of cell-cycle inhibitors by microRNA clusters in gastric cancer. *Nucleic Acids Res*. 2009;37(5):1672-1681.
32. Li X, Zhang Y, Shi Y, et al. MicroRNA-107, an oncogene microRNA that regulates tumour invasion and metastasis by targeting DICER1 in gastric cancer. *J Cell Mol Med*. 2011;15(9):1887-1895.
33. Lai KW, Koh KX, Loh M, et al. MicroRNA-130b regulates the tumour suppressor RUNX3 in gastric cancer. *Eur J Cancer*. 2010;46(8):1456-1463.
34. Wu Q, Jin H, Yang Z, et al. MiR-150 promotes gastric cancer proliferation by negatively regulating the pro-apoptotic gene EGR2. *Biochem Biophys Res Commun*. 2010;392(3):340-345.
35. Li X, Zhang Y, Zhang H, et al. miRNA-223 promotes gastric cancer invasion and metastasis by targeting tumor suppressor EPB41L3. *Mol Cancer Res*. 2011;9(7):824-833.
36. Gao C, Zhang Z, Liu W. Reduced microRNA-218 expression is associated with high nuclear factor kappa B activation in gastric cancer. *Cancer*. 2010;116(1):41-49.
37. Wada R, Akiyama Y, Hashimoto Y, Fukamachi H, Yuasa Y. miR-212 is downregulated and suppresses methyl-CpG-binding protein MeCP2 in human gastric cancer. *Int J Cancer*. 2010;127(5):1106-1114.
38. Hashimoto Y, Akiyama Y, Otsubo T, Shimada S, Yuasa Y. Involvement of epigenetically silenced microRNA-181c in gastric carcinogenesis. *Carcinogenesis*. 2010;31(5):777-784.
39. Takagi T, Iio A, Nakagawa Y, Naoe T, Tanigawa N, Akao Y. Decreased expression of microRNA-143 and -145 in human gastric cancers. *Oncology*. 2009;77(1):12-21.
40. Wan HY, Guo LM, Liu T. Regulation of the transcription factor NF-kappaB1 by microRNA-9 in human gastric adenocarcinoma. *Mol Cancer*. 2010;9:16.
41. Rotkrua P, Akiyama Y, Hashimoto Y, Otsubo T, Yuasa Y. MiR-9 downregulates CDX2 expression in gastric cancer cells. *Int J Cancer*. 2011;129(11):2611-2620.
42. Ji Q, Hao X, Meng Y, et al. Restoration of tumor suppressor miR-34 inhibits human p53-mutant gastric cancer tumorspheres. *BMC Cancer*. 2008;8:266.
43. Pei L, Xia JZ, Huang HY. Role of miR-124a methylation in patients with gastric cancer. *Zhonghua Wei Chang Wai Ke Za Zhi*. 2011;14(2):136-139.
44. Feng R, Chen X, Yu Y, et al. miR-126 functions as a tumour suppressor in human gastric cancer. *Cancer Lett*. 2010;298(1):50-63.

45. Shen R, Pan S, Qi S, Lin X, Cheng S. Epigenetic repression of microRNA-129-2 leads to overexpression of SOX4 in gastric cancer. *Biochem Biophys Res Commun*. 2010;394(4):1047-1052.
46. Kogo R, Mimori K, Tanaka F, Komune S, Mori M. Clinical significance of miR-146a in gastric cancer cases. *Clin Cancer Res*. 2011;17(13):4277-4284.
47. Song Y-X, Yue Z-Y, Wang Z-N, et al. MicroRNA-148b is frequently down-regulated in gastric cancer and acts as a tumor suppressor by inhibiting cell proliferation. *Mol Cancer*. 2011;10:1.
48. Shinozaki A, Sakatani T, Ushiku T, et al. Downregulation of microRNA-200 in EBV-associated gastric carcinoma. *Cancer Res*. 2010;70(11):4719-4727.
49. Tie J, Pan Y, Zhao L, et al. MiR-218 inhibits invasion and metastasis of gastric cancer by targeting the Robo1 receptor. *PLoS Genet*. 2010;6(3):e1000879.
50. Tsukamoto Y, Nakada C, Noguchi T. MicroRNA-375 is downregulated in gastric carcinomas and regulates cell survival by targeting PDK1 and 14-3-3zeta. *Cancer Res*. 2010;70(6):2339-2349.
51. Ding L, Xu Y, Zhang W, et al. MiR-375 frequently downregulated in gastric cancer inhibits cell proliferation by targeting JAK2. *Cell Res*. 2010;20(7):784-793.
52. Bandres E, Bitarte N, Arias F, et al. microRNA-451 regulates macrophage migration inhibitory factor production and proliferation of gastrointestinal cancer cells. *Clin Cancer Res*. 2009;15(7):2281-2290.
53. Ge S, Zhang H, Deng T. MiR-181a, a new regulator of TGF-beta signaling, can promote cell migration and proliferation in gastric cancer. *Invest New Drugs*. 2019;37(5):923-934.
54. Jin G, Xu M, Zou M, Duan S. The processing, gene regulation, biological functions, and clinical relevance of N4-acetylcytidine on RNA: a systematic review. *Mol Ther Nucleic Acids*. 2020;20:13-24.

How to cite this article: Tian W, Pang X, Luan F. Diagnosis value of miR-181, miR-652, and CA72-4 for gastric cancer. *J Clin Lab Anal*. 2022;36:e24411. doi:10.1002/jcla.24411