

# Diagnostic Value of Circulating Nucleic Acids in Gastric Cancer: A Systematic Review

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## ABSTRACT

**Background:** At present, the diagnosis of gastric cancer lacks sufficient biomarkers. In this review, we will identify and discuss the value of circulating free nucleic acids in the diagnosis of gastric cancer, in order to find a way to sort out the diagnostic markers for gastric cancer.

**Methods:** A systematic search was performed on PubMed using the following keywords: (gastric cancer) and (blood or plasma or serum) and (biomarker) and (DNA or RNA or cfDNA or cell-free DNA or RNA or CTC). and the supplementary materials were added from Embase The Science Citation Index and The Cochrane. All the studies contain biomarkers based on CTCs, DNAs, RNAs were reviewed and of which include sensitivity, specificity, and/or AUC/ROC values were further discussed.

**Results:** 458 studies were searched and 87 contained biomarkers. Of these, 32 were prognostic, 12 were DNA, and 43 were RNA. Finally, 28 studies with complete data were included. The sensitivity and specificity ranged at 38.60%-95.50% and 44.30%-100%. The number of patients varied from 11 to 200, and the media is 60. Additionally, 6 studies included independent validation cohort, and the media sensitivity and specificity were 83.95% and 80.35% respectively.

**Conclusion:** Although the sensitivity and specificity of biomarkers in current research are still insufficient, they also show great potential value. Therefore, biomarkers with higher sensitivity and specificity require further exploration.

**Keywords:** Gastric cancer; Circulating nucleic acids; Biomarker; Diagnosis

## BACKGROUND

Gastric cancer has become the fifth common cancer disease and the third cause of cancer induced death in the world, with 1,033,701 new cases and 782,685 deaths in 2018 [1]. However, it is mainly distributed in East Asia, especially China [2]. Usually the early gastric cancer has no remarkable symptoms and it is often found to be a period of progress, therefore only a few patients were cured. There are still no relevant biomarkers for gastric cancer. According to the existing prognosis-related factors, most of them are age, gender, pathological type, and so on [3]. Currently, gastric cancer is diagnosed depending on gastroscopic biopsy as the gold standard.

Liquid biopsy is a major breakthrough in cancer research, especially with circulating blood. It provides a new perspective for noninvasive monitoring of tumors. Since Ashworth first reported cells found in the blood of tumor-dead patients similar to tumor cells, a large number of studies on circulating tumor cells in various tumors have emerged. With the development of next-generation sequencing technology, more and more researches are focused on nucleic acids based on circulating tumor cells. Nowadays, the detection of circulating tumor cells and circulating free nucleic acids have been proved having important clinical significance in the field of tumor diagnosis [4-6].

In this review, in order to provide some clues for finding diagnostic markers of gastric cancer, we mainly focus on the

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diagnostic value of circulating nucleic acids in gastric cancer, including RNA and DNA. To our knowledge, this is the first systematic review to discuss the diagnostic value of circulating nucleic acids in gastric cancer.

## INTRODUCTION

Four types of RNA have been found to be important for tumors, including miRNA, circRNA, lncRNA and mRNA. In addition, circulating cell-free DNA has also proven to be of value in the early diagnosis and prognosis of many tumors.

miRNA is a type of non-coding RNA, and its biological role is mainly in regulating gene expression [7,8] found that miRNAs in the circulatory system are relatively stable and have anti-ribonuclease properties. Therefore, it can be stored at room temperature for a long time and can be detected after repeated freeze-thaw cycles. There have been reported a large number of studies on the role of microRNAs in tumor growth, development, and metastasis [9].

circRNA is a special type of RNA, which was originally thought to be the result of mis-splicing during gene expression, but more and more studies have proved its role in tumor pathogenesis and progression [7,10]. Studies have found that low expression of circRNA in esophageal and colorectal cancer can inhibit tumor development [7,11,12]. In gastric cancer, some studies have found that the level of circRNA in tumor tissues has also increased, but there are still few studies.

lncRNA is a type of non-coding RNA with gene regulation effect over 200 nucleotides in length [13]. It can usually be detected in body fluids such as blood and urine of tumor patients. Studies have found that it has good diagnostic value in prostate cancer and esophageal cancer, and therefore has potential as a diagnostic marker [14,15].

As an intermediate product in gene expression, mRNA is detected and confirmed to play an important role in the blood of various tumor patients [16,17,18]. However, there is insufficient evidence as a diagnostic biomarker.

In 1948, Mandel first detected cell free DNA (cf-DNA) in human blood. In blood sample, cf-DNA is mainly derived from apoptotic nucleated cells. Apoptosis results in small, uniform DNA fragments, typically less than 180 bp in length, 3.6-5.0 ng / ml in normal human blood, and even more than 10 times in tumor patients [19]. As a branch of cf-DNA, circulating tumor DNA (ct-DNA) derived from tumor cells is one of the most extensive and in-depth research directions in the clinical management of tumor. Especially in evaluating the early detection and prognosis.

## METHODS

### Search strategy

A systemic review of the literature was performed using PubMed on 20 March 2019 with the following keywords/MeSH words: (gastric cancer) and (blood or plasma or serum) and (biomarker) and (DNA or RNA or cf-DNA or cell-free DNA or RNA or

CTC). The supplementary materials were added from Embase The science citation index and The Cochrane on 21 March.

### Inclusion and exclusion criterion

The inclusion criteria includes: (1) all gastric cancer; (2) circulating nucleic acids (DNA and RNA) based on blood; (3) diagnostic biomarkers. While the exclusion criteria contains: (1) abstracts, reviews, comments, and letters; (2) duplicate studies; (3) proteins and tissues; (4) biomarkers for prognosis and treatment response; (5) incomplete data.

### Data extraction and quality assessment

All the articles were filtered three times by three independent authors, and then the suitable studies were extracted by the corresponding author. According to the inclusion and exclusion criteria, the data about patients and control, type of biomarker, sensitivity, specificity, AUC were summarized by the first author. Afterwards the other author revised to confirm data was accurate.

## RESULTS

### Characteristic of studies

The inclusive flowchart is shown in Figure 1. A total of 449 studies were identified in the systematic database search. 94 studies were retrieved after assessment through titles and abstracts. Then 66 studies were excluded due to being unrelated with diagnosis or lacking of statistics. Finally, twenty-eight studies were included, among which, fourteen for miRNA, three for circRNA, six for lncRNA, one for mRNA, one for combination of miRNA and lncRNA, three for ct-DNA. A summary of the included studies is shown in Table 1 [20-47].

We can find that in general, circulating nucleic acids show a sensitivity and specificity ranging from 38.60% to 95.50% and 44.30% to 100.00% in the diagnosis of gastric cancer. A total of 11-200 patients were included in the study, with a median of 60. In addition, six studies included independent validation cohorts (Table 2) with median sensitivity and specificity of 83.95% and 80.35%, respectively.

### miRNA biomarkers

A total of 14 miRNA studies have demonstrated their value in the diagnosis of gastric cancer. Its sensitivity ranges from 65.40% to 94.29%, with a median of 82.55% specificity ranges from 44.29% to 100.00%, with a median of 79.40%. Twelve studies were performed on a single miRNA and two were performed on a combined miRNA. Six of these studies have a validation cohort.

In the study of Liu et al. [31] the level of miR-940 was reduced using a sample of 5 patients, and subsequently, a controlled study using 80 patients confirmed that the AUC reached 0.966, which is the highest in the current study. In the joint test, we found that its diagnostic value is more obvious than the single test. Zhao et al. [45] established the value of miR-21, miR-93, miR-106a, and miR-106b through a cohort of 147 people, and then verified the results using a cohort of 28 people. The

sensitivity and specificity of the combination were improved compared with the four when independent, with an AUC of 0.887 when combined. Also, Shin et al. [36] Found 6 high levels of miRNAs in a control study of 123 gastric cancer patients and healthy people: miR-18a, miR-140-5p, miR-199a-3p, miR-627, miR-629 and miR-652. A 15-patient verification cohort was then used to find a combination of miR-627, miR-629, and miR-652, with sensitivity and specificity of 86.70% and 85.50%, respectively.

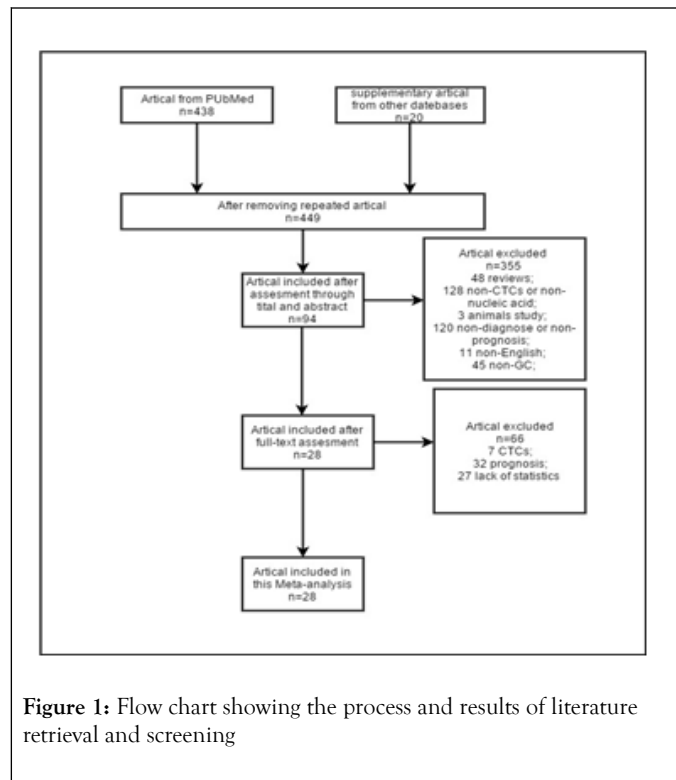


Figure 1: Flow chart showing the process and results of literature retrieval and screening

### circRNA biomarkers

There are three circRNA-related studies, the most valuable of which is Sunet et al. [38] Their research showed that the sensitivity and specificity of hsa\_circ\_0000520 as a diagnostic marker for gastric cancer reached 82.35% and 84.44%, respectively. But the biggest problem is that their sample size is too small.

### LncRNA biomarkers

A total of 6 studies have demonstrated the potential value of LncRNA in the diagnosis of gastric cancer. Five of them are for single LncRNA and one is for combined detection. The overall sensitivity of LncRNA is between 68.00%-89.20%, with a median of 81.91%; the overall specificity is between 56.67% -89.00%, and the median is 81.95%.

Studied from Hashad et al. [24] and Zhou et al. [46] revealed the value of LncRNA-H19. The former used 32 patients and controls with sensitivity and specificity lower than 70.00%, while the latter sample expanded to 70 cases In comparison, they all exceeded 70.00%. In the study of Zhang et al. [44] the combination of five lncRNAs (TINCR, CCAT2, AOC4P, BANCR and LINC00857) was found to have an AUC of 0.910 in the diagnosis of gastric cancer. In the second part, the combined test of the five also has some value in differential diagnosis. The AUCs that distinguish gastric cancer from precancerous lesions and gastric stromal tumors are 0.820 (95% CI: 0.710–0.920) and 0.800 (95% CI: 0.680–0.910).

Table 1: Basic information for the 28 studies included.

NO	Authors	Cancer type	Patients	Controls	Fluid	Method	Biomarkers	Sensitivity	Specificity	AUC	AUC 95% CI	Validation
<b>miRNA</b>												
1	Zhao et al. [45]	all GC	11 GC	17 normal	plasma	ddPCR	combination of miR-21, miR-93, miR-106a, miR-106b	84.80%	79.20%	0.887	0.83 - 0.943	YES
2	Li et al.[28]	all GC	65 GC	65 normal	plasma	qRT-PCR	miR 106b	86.20%	92.30%	0.898	0.839-0.958	NO
							miR 25	87.60%	76.90%	0.817	0.738-0.897	NO
							miR 93	81.50%	73.80%	0.756	0.665-0.846	NO
3	Qiu et al. [34]	all GC	200 GC	200 normal	plasma	qRT-PCR	miR-26a	83.60%	81.50%	0.882	0.847-0.916	YES

4	Liu et al. [31]	all GC	80 GC	70 normal	plasma	qRT-PCR	miR-940	81.25%	98.57%	0.966	0.940-0.992	YES
5	Wu et al. [42]	all GC	90 GC	90 normal	Serum	qRT-PCR	miR-421	90%	85.70%	0.779	0.691-0.898	NO
6	Wu et al. [43]	all GC	50 GC	50 normal	Serum	qRT-PCR	miR-21	88.40%	79.60%	0.912	0.869-0.968	NO
7	Tsujiura M et al.[39]	all GC	104 GC	65 normal	plasma	qRT-PCR	miR-18a	84.60%	69.20%	0.806		NO
8	Shin VY et al.[36]	all GC	15 GC	15 normal	plasma	qRT-PCR	combination of miR-627, miR-629, miR-652	86.70%	85.50%	0.941		YES
9	Wang et al. [41]	all GC	50 GC	47 normal	Serum	qRT-PCR	miR-223	81%	78%	0.85	0.780-0.930	NO
							miR-16	79%	78%	0.9	0.840-0.960	NO
							miR-100	71%	58%	0.71	0.610-0.820	NO
10	Su et al. [37]	all GC	82 GC	65 normal	plasma	qRT-PCR	miR-18a	80.50%	84.60%	0.907	0.860-0.953	NO
11	Peng et al. [33]	all GC	57 GC	58 normal	Serum	qRT-PCR	miR-191	70.20%	99.90%	0.849	0.780-0.920	NO
12	Li et al.[29]	all GC	180 GC	80 normal	plasma	qRT-PCR	miRNA-199a-3p	80%	74%	0.837		YES
20 precancerous lesions												
13	Valladares-Ayerbes M et al.[40]	all GC	52 GC	15 normal	blood	qRT-PCR	miR-200c	65.40%	100%	0.715	0.597-0.833	NO
14	Li et al.[30]	all GC	60 GC	60 normal	plasma	qRT-PCR	miR-223	84.29%	88.57%	0.909	0.860-0.958	YES
<b>circRNA</b>												
15	Huang et al.[25]	all GC	60 GC	60 normal	plasma	qRT-PCR	hsa_circ_0000745	85.50%	45%	0.683		NO
16	Chen et al. [20]	all GC	104 GC	104 normal	plasma	qRT-PCR	hsa_circ_0000190	41.40%	87.50%	0.6		NO
17	Sun et al. [38]	all GC	45 GC	17 normal	plasma	qRT-PCR	hsa_circ_0000520	82.35%	84.44%	0.897		NO
<b>LncRNA</b>												
18	Zong et al. [47]	all GC	110 GC	44 benign lesions	serum	RTEQ-PCR	lncRNA CTC497E21.4	81.82%	75%	0.848	0.794-0.901	NO

19	Zhang et al. [44]	all GC	162 GC	110 normal	plasma	qRT-PCR	five lncRNA-based panel	82%	87%	0.91	0.880-0.950	NO
				28 precancerous lesions					89%	0.82	0.710-0.920	NO
				21 GIST					86%	0.8	0.680-0.910	NO
20	Jin et al. [26]	all GC	100 GC	110 normal	Serum	qRT-PCR	lncRNA HULC	82%	83.60%	0.888	0.843-0.934	NO
21	Hashad al.[24]	all GC	32 GC	30 normal	plasma	qRT-PCR	LncRNA-H19	68.75%	56.67%	0.724		NO
22	Zhou et al. [46]	all GC	70 GC	70 normal	plasma	qRT-PCR	LncRNA-H19	82.90%	72.90%	0.838		NO
23	Gao et al. [22]	all GC	20 GC	20 normal	plasma	qRT-PCR	lncRNA-UCA1	89.20%	80.30%	0.928	0.888-0.968	NO
<b>miRNA and LncRNA</b>												
24	Ghaedi et al.[23]	all GC	62 GC	40 normal	plasma	qRT-PCR	combination of H19, MEG3 and miR-675-5p	89%	85%	0.927	0.850-0.960	NO
<b>mRNA</b>												
25	Kang et al. [27]	all GC	118 GC	40 CAG / 58 normal	plasma	qRT-PCR	cell-free hTERT mRNA	66%	87%	0.891		NO
<b>DNA</b>												
26	Chen et al. [21]	all GC	104 GC	20 normal	plasma	MSP	Zic1 promoter methylation	60.60%	61.40%	0.61		NO
				50 GIN								
27	Sakakura et al.[35]	all GC	65 GC	50 normal	Serum	RTQ-MSP	RUNX3 methylation	95.50%	62.50%	0.865		NO
28	Park et al. [32]	all GC	57 GC	39 normal	plasma	qRT-PCR	MYC/GAPDH ratio	38.60%	100%	0.816	0.732-0.899	NO

Table 2: Basic information on 6 studies in the validation cohort.

Study details			Discovery cohort					Validation cohort						
Author	Cancer type	Biomarkers	P	C	Sensitivity	Specificity	AUC	AUC	P	C	Sensitivity	Specificity	AUC	AUC
							C	95% CI			C	95% CI	C	95% CI
Zhao et al.[45]	all GC	combination of miR-21, miR-106a, miR-106b	10	4				Not given	11	17	84.80%	79.20%	0.8	0.830 - 0.943
Qiu et al. [34]	all GC	miR-26a	80	8				Not given	20	20	83.60%	81.50%	0.8	0.847-0.916

Liu et al. [31]	all GC	miR-940	30	3	60.00%	96.67%	0.8	Not given	80	70	81.25%	98.57%	0.9	0.940-0.992
Shin et al. [36]	all GC	combination of miR-627, miR-629, miR-652	50	5				Not given	15	15	86.70%	85.50%	0.9	Not given
Li et al. [29]	all GC	MiRNA-199a-3p	30	3				Not given	18	10	80.00%	74.00%	0.8	Not given
Li et al. [30]	all GC	miR-223	10	1	87.50%			Not given	60	60	84.29%	88.57%	0.9	0.860-0.958
		miR-21			100.00%			Not given			74.29%	75.71%	0.7	0.721-0.868
		miR-218			87.50%			Not given			94.29%	44.29%	0.7	0.663-0.824

### mRNA biomarkers

There is only one study of mRNA. Kang's et al. [27] found that the level of free hTERT mRNA was significantly increased in gastric cancer patients in a study of 118 patients with gastric cancer, 40 patients with chronic gastritis and 58 healthy controls ( $P < 0.05$ ). In the value of distinguishing gastric cancer patients, its sensitivity and specificity reach 66.00% and 87.00%, respectively, compared with CA19-9, CEA are significantly improved, so it may have important value in the diagnosis of gastric cancer.

### Associated RNA biomarkers

Ghaedi et al. [23] found that LncRNA-H19, MEG3 levels were statistically different in 60 patients and 40 matched control groups ( $P < 0.01$ ), and then they detected the associated miRNA and found that miR-141-3p levels were also significantly reduced ( $P < 0.05$ ). Since then, the researchers have combined the three and found that they have a sensitivity of 88.87% and a specificity of 85.00% in distinguishing gastric cancer from controls, with an AUC of 0.927 (95% CI: 0.850-0.960). Therefore, the combination of these three may have some potential value for the diagnosis of gastric cancer. However, this study uses relevant RNA detection. If miRNA and LncRNA that are not very relevant can be used, then more research is still needed on whether the same results will be produced.

### DNA biomarkers

There were 3 DNA studies, 2 of which were methylation of genes. In these studies, we found that the sensitivity and specificity have 'seesaw'-like results. That is one high and another low. Park et al. [32] used the ratio of MYC / GAPDH and found that its specificity can reach 100.00%, but unfortunately its sensitivity is only 38.60%.

### DISCUSSION

There is currently no ideal biomarker in the diagnosis of gastric cancer. Although in this review we found 28 studies with potential, none of the studies were randomized controlled trials

and their AUC values were the best. Therefore, the risk of bias increases. However, this is also an inevitable stage of early exploration.

In this review, various RNA and DNA molecules are reported. We found some common targets, including miR-21, miR-93, miR-106, and LncRNA-H19. These targets have shown some value in both individual and combined detection. A new point is circRNA, which has been demonstrated by a total of 3 studies. Although the results are not very satisfactory, it also provides a new direction for gastric cancer diagnostic targets.

In this review we found that 20 studies extracted samples from plasma, while only 7 were extracted from serum, and 1 was extracted from whole blood. Although the concentration of nucleic acid in the serum is higher its advantages are greatly diminished due to the worse storage conditions of the serum. For whole blood, there are more interference factors and higher technical requirements, so its disadvantage is relatively obvious [48].

Because miRNA has a small molecular weight and is relatively stable, it is more accurate in detection. The number of studies included in the article is also the most, and the potential of miRNA is also confirmed from the side. miR-21, miR-93, and miR-106 have been reported in different studies, but the results have significant differences. In the study of Zhao et al. [45] although the three were jointly tested, the results were still not ideal. From the validation queue, we can see that the joint detection results may be more stable. But unfortunately there is insufficient evidence for the detection of the combination, so whether the detection of the combination can provide better diagnostic value needs our further research.

From the study of miRNA combined with LncRNA, [23] we can see that the related miRNA and LncRNA have similar results in the diagnosis of gastric cancer, so the combined detection of these two has a certain feasibility to improve the value of detection. For both of them showing a certain value alone but not strongly related to each other, whether the combination still has sufficient value needs to be further explored.

Interestingly, we found that the circulating cell-free DNA has a "seesaw" effect as described above when used as a detection marker in gastric cancer. This may be due to the relatively poor stability of the DNA molecules, which can easily lead to loss during sample extraction. Therefore, its value as a diagnostic marker deserves further discussion.

As a diagnostic biomarker, another important factor is the differentiation from other diseases. Only one study has performed this step. In this study we found that the sensitivity and specificity of using a panel from five lncRNAs to identify gastric cancer and precancerous lesions were 68.00% and 89.00%, while for gastro intestinal stromal tumors were 68.00% and 86.00% [44].

Another note worthy result is that in the study by Zhang et al. [44] they found that the level of lncRNA diagnosed and detected before surgery was significantly reduced at 14 days after surgery ( $P=0.016$ ). This may suggest that we can use this as a follow-up indicator of tumor progression for patients with high expression levels before surgery.

## CONCLUSION

Although we saw many hopeful nucleic acid biomarkers in this review, these studies still have certain shortcomings, so we need more research to find more satisfactory nucleic acid biomarkers.

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