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REVIEW

Gastric Juice microRNAs in Gastric Cancer: What is the Evidence?

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ABSTRACT

Background: *So far, combining gastroscopy with biopsy remains the gold-standard for screening gastric cancer. Recently, the study of circulating microRNAs (miRNAs or miRs) has yielded valuable insights into gastric cancer prognosis. However, because these molecules are common to multiple cancer types, their clinical applicability remains uncertain.*

Materials and methods: *We investigated the pertinent literature dealing with gastric juice microRNAs in gastric cancer patients. Only five original articles have investigated the feasibility of using gastric juice miRNAs as potential biomarkers to assist in screening for gastric cancer.*

Results: *Gastric juice microRNAs proved correlated with high reliability, high sensitivity, high specificity and relative stability.*

Conclusion: *MicroRNAs found in gastric juice may offer a promising alternative approach for gastric cancer screening without the need for biopsy. More studies are needed to reach safe conclusions. However, it seems that this novel potential biomarkers' testing is reliable and reproducible.*

Keywords: gastric cancer, gastric juice, microRNAs, novel biomarkers, screening.

INTRODUCTION

Gastric cancer (GC) represents a significant global health concern. It is characterized by high mortality primarily resulting from delayed diagnosis and the limited effectiveness of available treatment options (1-3). It remains the fifth most common cancer worldwide, with an incidence approaching 4.8% in both sexes, and it represents the fifth cause of cancer-related death. Urgent demand exists for useful and feasible biomarkers that can identify high-risk individuals for GC and support endoscopic diagnosis (4). These biomarkers would enable accurate prediction of treatment response and prognosis in GC patients, facilitating the development of personalized, effective therapeutic approaches. Upper gastrointestinal tract endoscopy with biopsy remains the gold standard for GC detection. However, this method is invasive and costly, often causing discomfort and anxiety for patients.

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Moreover, individuals without symptoms typically do not undergo endoscopic evaluation. Thus, simple, cost-effective and non-invasive methods are urgently required for GC detection (3, 5).

Because non-endoscopic screening methods for GC – such as measuring tumor markers in serum or gastric juice (GJ), including carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19.9) and cancer antigen 72-4 (CA72.4) – have shown limited sensitivity and specificity, research has shifted focus toward a different group of molecules known as microRNAs (miRNAs or miRs) (1, 6).

First described in 1993 (7), microRNAs (miRNAs or miRs) are non-coding RNA molecules, containing approximately 19-24 nucleotides, that control gene expression in eukaryotes (including humans, animals and plants) at the post-transcriptional level. Although miRNAs do not code for proteins, by interrupting cellular signaling pathways, they can function as oncogenes (oncogenic miRs or oncomiRs) or tumor suppressors (tumor-suppressor miRs) by affecting the cell cycle in GC cells (5, 8, 9). By binding completely or partially to the 3′-untranslated regions (3′-UTRs) of target mRNAs, miRNAs induce mRNA degradation or inhibit translation, thereby negatively regulating the expression of their target genes (9). These molecules are often found to be abnormally expressed in cancerous tissues. Tumor cells can release miRNAs into biological fluids via exosomes or microvesicles, which protect them from RNase-mediated degradation; such miRNAs have been detected in serum, plasma, urine, tears and GJ. Growing evidence suggests that miRNAs hold potential as biomarkers for various cancer types (5).

In this review, we present a comprehensive overview of the recent advances and challenges in the use of miRNAs in the GJ and emphasize their emerging significance as novel and promising potential biomarkers for GC. ❑

MATERIALS AND METHODS

This review synthesizes the current literature on GJ miRNAs as novel biomarkers in GC. The literature research was conducted using the PubMed database up to December 3, 2025. The search terms were “gastric juice” and “microRNAs”. A total of 35 articles were initially retrieved. Thirteen of them were excluded based on their title or abstract due to lack of relevance,

TABLE 1. Summary of original studies investigating miRNAs in gastric juice

Author	Year of publication	Type of study	Number of patients	miRNA	Methodology	Levels compared to controls	Outcomes	OCEBM level of evidence
Cui *et al* (12)	2013	Clinical, observational, case–control study	141	miR-21 miR-106a	RT-qPCR	↓	- Higher sensitivity and specificity of miR-21 - The level of miR-21 in the intestinal type was higher than that in the diffuse or mixed types - No significant association with tumor sites - Combined use of gastric juice miR-21, miR-106a and CEA revealed remarkably better results - Statistically significant correlation with the stage of GC	Level 3
Zhang *et al* (10)	2012	Clinical observational case–control study	141	miR-421	RT-qPCR	↓	- Statistically significant outcome - No correlation with main clinicopathological factors - Better results than CEA	Level 3
Yu *et al* (13)	2013	Clinical observational case–control study	141	miR-129-1/2	RT-qPCR	↓	- Statistically significant outcome (AUC up to 0.656)	Level 3
Shao *et al* (11)	2016	Clinical observational study	203	miR-133a	RT-qPCR	↓	- High operability, high reliability, high sensitivity, high specificity and relative stability	Level 3
Birsan *et al* (15)	2025	Prospective observational clinical study	38	miR-129	RT-qPCR	↓	- MiR-129 downregulation correlates with tumor stage (T2 → T3 → T4) - Diagnostic accuracy: ROC AUC = 0.75 - Reduced miR-129 aligns with vascular and cognitive impairment/neuroimaging abnormalities	Level 3
Kagota *et al* (14)	2019	Case series	4	miRLET7A1-5p miR16-5p miR103a-3p miR191-5p miR423-5p	RT-qPCR	NA	- These microRNAs were present in EVs from GJ of GC patients	Level 4-5

RT-qPCR=reverse transcriptase-quantitative polymerase chain reaction; GJ=gastric juice; CEA=carcinoembryonic antigen; GC=gastric cancer; ROC=receiver operating characteristic; AUC=area under the curve; NA=not available; EVs=extracellular vesicles.

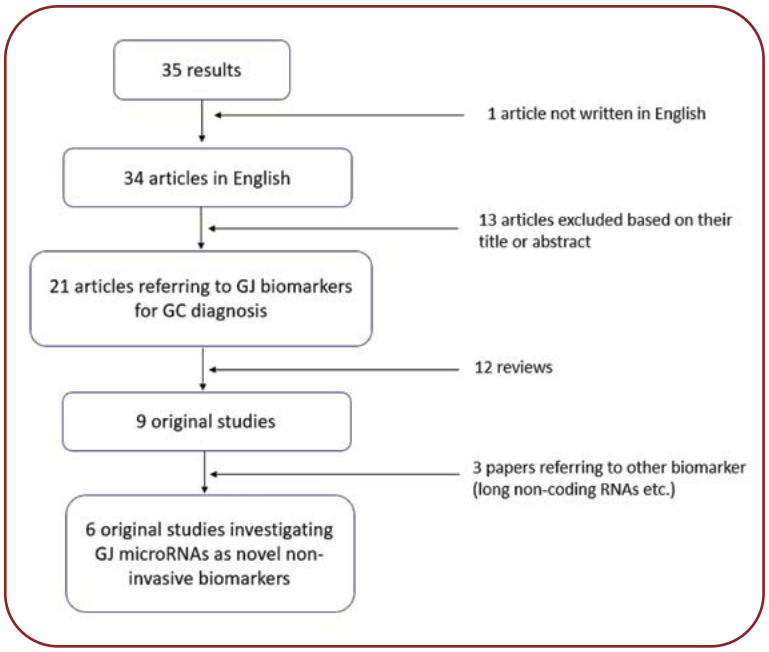

FIGURE 1. Study flowchart

12 were review articles, three referred to long non-coding RNAs or other biomarkers and one article was not written in English. Six original articles involving adult patients with GC were ultimately included (Figure 1). All studies investigated whether GJ miRNAs could represent reliable novel non-invasive biomarkers for early GC detection, staging and prognosis. The level of evidence was categorized using the Oxford Centre for Evidence-Based Medicine (OCEBM) criteria (Table 1). ❑

RESULTS

Despite growing interest, investigations in this area remain relatively poor. Only five original studies have investigated the feasibility of using GJ miRNAs as potential biomarkers to assist in screening for GC.

In 2012, the first analysis of a miRNA in GJ came to light. A study conducted by Zhang *et al* on a cohort including 141 patients demonstrated that miR-421 levels in GJ were significantly lower in GC subjects compared to those with benign gastric diseases ($p < 0.001$). This marker effectively differentiated GC from benign cases, showing a sensitivity of 71.4% and a specificity of 71.7%. Notably, similar positive rates were observed in both early and advanced GC. No correlation with tumor size, Lauren's classification and Borrmann's classification was detected. Neither statistically significant result came out after analyzing CEA levels in serum and GJ (10). In a similar study, Shao *et al* analyzed GJ samples from 204 participants, including 62 patients diagnosed with GC. They observed that miR-133a expression was downregulated, consistent with previous findings. Moreover, a Pearson's correlation analysis revealed a strong positive correlation ($p < 0.0001$) between miR-133a expression levels in GC tissues and GJ. These results suggest that miR-133a in GJ may potentially serve as a promising GC diagnostic biomarker (11).

A quite similar clinical observational case–control study investigated the role of GJ miR-21 and GJ miR-106a as reliable GC biomarkers. Cui *et al* observed that GJ miR-21 exhibited higher sensitivity and specificity compared to miR-106a and carcinoembryonic antigen (CEA). Downregulation of both miR-21 and miR-106a in GJ was a more sensitive biomarker than CEA for detecting GC. Notably, miR-21 levels were higher in the intestinal type than in the diffuse or mixed types, while miR-106a levels showed no significant variation among the three Lauren classifications. No significant association was found between miR-21 or miR-106a expression and tumor location. However, the combined analysis of GJ miR-21, miR-106a and CEA yielded markedly improved diagnostic performance. The sensitivity and specificity of miR-21 (85.7% and 97.8%, respectively) surpassed those of miR-106a (73.8% and 89.3%, respectively). Furthermore, miR-21 and miR-106a levels in GJ were significantly correlated with the clinical stage of GC (12). Yu *et al* analyzing miR-129-1/2 levels in GC patients underlined the tissue specificity of GJ, too (13). In 2019, Kagota *et al* noticed that specific miRNAs (miRLET7A1-5p, miR16-5p, miR103a-3p, miR191-5p, miR423-5p) were expressed in GJ extracellular vesicles of GC patients (14).

In a recent prospective observational case–control analysis published in 2025, Birsan *et al* found that miR-129 levels were significantly lower in cancer patients compared with controls and decreased progressively with advancing tumor stage. Reduced miR-129 levels were associated to vascular and cognitive impairment/neuroimaging abnormalities too. Diagnostic performance was moderate (AUC 0.75), suggesting miR-129 may have potential as a minimally invasive ad-

junct biomarker, although findings remain preliminary due to the small sample size (15). ❑

DISCUSSION

Upper gastrointestinal endoscopy combined with multiple biopsies remains the current gold-standard method for GC screening and clinical diagnosis. Although tumor markers have not been proven to be useful in diagnosis or screening, they constitute valuable tools for detecting recurrence following systemic or surgical therapy (8).

Over the past few decades, the quest for an ideal GC biomarker has continued. While many researchers have focused on analyzing blood samples, others have turned their attention to a different biological fluid: the GJ. They propose that GJ may serve as an excellent non-invasive low-cost source of GC biomarkers (2), since these molecules are secreted directly by the tumor and are not eliminated by the liver (16).

Thousands of human miRNAs have been identified within the last 20 years. The majority of human genes are directly regulated by miRNAs. These molecules are crucial in controlling nearly all biological processes, including the development and progression of cancer. Biofluid miRNAs, or circulating miRNAs, are a class of microRNAs that remain stable within body fluids (17). Tumor cells release these molecules into circulation through specific secretion pathways. Among them, exosome-encapsulated miRNAs have been the most extensively studied. Interestingly, the quantity of miRNAs secreted *via* exosomes does not always correspond to the total miRNA content within them, suggesting that miRNAs are selectively packaged into these vesicles. Nevertheless, the precise mechanisms governing this selective secretion process are still unclear (5).

Both tissue-derived and circulating (biofluid) miRNAs exhibit abnormal expression patterns in numerous diseases, particularly in cancers. In tumor tissues, miRNA expression levels are associated with tumor characteristics such as stage, size, invasiveness and metastatic potential, making them promising markers for early cancer detection. However, miRNAs from tumor tissues are not ideal for clinical diagnostic use, since acquiring tissue samples requires an invasive procedure (5). Novel non-invasive and cost-effective tests are considered necessary in everyday practice (3).

Gastric juice is a digestive secretion produced in the stomach and serves as the primary barrier between the gastrointestinal tract and ingested pathogens. It mainly consists of hydrochloric acid (HCl), lipase and pepsin. The strongly acidic pH of GJ results from HCl secreted by parietal cells, while its corrosive nature is neutralized by mucins – glycoproteins secreted by mucous cells. GJ samples can be collected using a gastric aspirator suction device during oesophagogastroduodenoscopy (OGD), enabling aspiration of GJ without contamination from other digestive organs. Once collected, the samples can be processed or stored at −80 °C for subsequent analyses. In recent years, GJ has attracted growing attention for its potential to serve as a valuable source of biomarkers associated with GC. Because it is produced at the site where GC develops, it is reasonable to assume that GJ contains a higher concentration of tumor-derived substances compared to other body fluids (1, 18).

Although miRNAs show considerable potential as biomarkers for GC, several challenges must be addressed before they can be implemented in clinical practice. The first challenge lies in validating their diagnostic utility. The reliability of miRNAs as indicators for GC diagnosis, prognosis, and therapeutic response needs confirmation through larger multicenter studies, as most current research is limited by single-center designs and small sample sizes. The second challenge concerns the sensitivity and specificity of miRNAs for GC. Identifying highly sensitive miRNAs suitable for use as biomarkers remains difficult due to the intrinsic heterogeneity of GC. Only a few miRNAs have demonstrated sufficient sensitivity for clinical use. Likewise, the specificity of miRNAs poses a problem, given their widespread involvement in multiple cancer types (5). For instance, elevated miR-21 expression is associated with poor prognosis not only in GC (19) but also in hepatocellular (20) and breast cancers (21). The third challenge pertains to the methodology of miRNA detection. Various biological specimens – including tissue, plasma, serum, urine and GJ – are used for GC-related miRNA analysis. Each specimen type requires standardized protocols for collection, pre-analytical processing and analysis to ensure consistency and clinical applicability. Finally, the fourth

challenge involves deepening our understanding of miRNA function and mechanisms. Given that a single miRNA can regulate multiple genes and, conversely, a single gene can be targeted by several miRNAs, these molecules form complex regulatory networks. Therefore, comprehensive studies on the functional roles and molecular mechanisms of miRNAs in GC are essential to advance their translation into clinical practice (5). ❑

MicroRNAs remain intact within gastric environment; therefore, the analysis of gastric fluid provides the opportunity to repeat testing and obtain reliable results. Thus, they may serve as reliable biomarkers for the prediction, early diagnosis, staging and prognosis of GC. Additional research on these and other related molecules is necessary to enhance the diagnostic accuracy and reliability of liquid biopsy. ❑

CONCLUSIONS

Liquid biopsy constitutes a highly promising approach in the era of precision medicine.

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