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ORIGINAL ARTICLE

A systematic review of microRNAs as potential biomarkers for diagnosis and prognosis of gastric cancer

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Abstract

Gastric cancer (GC) is the third leading cause of global cancer morbidity and mortality. One of the significant challenges in GC treatment is that most GC patients are diagnosed with advanced-stage disease due to the lack of suitable biomarkers. Recent studies have shown that microRNAs (miRNAs) can acts as a potential biomarker in GC diagnosis and prognosis. I performed a systematic review of published miRNA studies in GC, which includes the miRNA expression profiles between GC tissues and normal tissues and also miRNA studies to evaluate their potential value in the diagnosis and prognosis of GC. Among the studies, upregulation of miR-21, miR-106b, miR-25, miR-214, miR-18a, miR-191, and miR-93 and downregulation of miR-375, miR-148a, miR-92, miR-155, and miR-564 were observed in GC tissues. In evaluating of diagnosis value of miRNAs, the study was performed on a combined miRNA include miR-21, miR-93, miR-106a, and miR-106b indicated the panel of these miRNAs have the highest AUC 0.887 to discriminate GC patients from healthy. Also, miR-940 with a sensitivity of 81.25% and specificity of 98.57% may be used for diagnostic biomarkers for GC. Finally, the pooled prognostic result of miR-21 for hazard ratios (HR) was 1.260 (95% CI 0.370–4.330, $P < 0.001$), showing that miR-21 could predict poor survival in GC patients. This systematic review can confirm that we need to find a miRNA or a panel of miRNAs with high sensitivity and specificity for further exploration to investigate a better diagnostic or therapeutic tool for personalized management of GC patients.

Keywords Gastric cancer · MicroRNAs · Biomarker · Diagnosis · Prognosis

Introduction

Gastric cancer (GC) remains one of the most lethal digestive malignancies and is the fourth most common cancer, with an estimated 989,600 new cases and 738,000 deaths globally in 2008 (Jemal et al. 2011; Torre et al. 2015). GC has no remarkable symptoms, and it is usually found in the advanced stage; therefore, only a few patients were cured. Due to the lack of sensitivity and specificity, the classical biomarkers such as carcinoembryonic antigen (CEA) and carbohydrate antigen 19.9 (CA19.9) cannot be used as a potential biomarker to diagnose or prognosis of GC (Zhang et al. 2012; Cui et al. 2013; Jiexia et al. 2013; Yu et al. 2013; Shao et al. 2016).

In recent years, an increasing number of non-coding RNAs (ncRNAs) containing microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) have been proven to have great potential clinical value in GC. Recent studies have indicated the pivotal role of miRNAs in regulating biological processes such as proliferation, cellular differentiation, apoptosis, and gene regulation (Alvarez-Garcia and Miska 2005; Esquela-Kerscher and Slack 2006). Moreover, miRNAs are dysregulated in many cancers, and miRNA expression profiling has shown that specific miRNAs are associated with cancer development and progression.

Several studies indicated the several aspects of miRNAs interacting with multiple target genes and pathways, making them a potential biomarker for clinical diagnostics. Moreover, miRNAs could maintain its stability in plasma, urine, and saliva (Mitchell et al. 2008). Also, the classifications of miRNAs can investigate tissue

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source in the cancers of uncertain primaries. Additionally, dysregulation of miRNAs could be observed during the sequential cancer pattern, including the early stage, during progression, and after metastasis. Thus, miRNAs may act as favorable clinical biomarkers for distinguishing tumors and selection of therapeutic approach.

Several studies have been conducted to find a biomarker by identifying the differential expression of miRNAs between GC and normal samples (Guo et al. 2009; Tchernitsa et al. 2010; Ueda et al. 2010; Oh et al. 2011; Saito et al. 2013). Therefore, they are good candidates for diagnostic, prognostic, and predictive biomarkers (Iorio and Croce 2012).

In this study, I conducted a systematic review to identify the differential expression of miRNAs consistently reported in GC to find the miRNAs that could act as a potential biomarker in GC diagnosis and prognosis.

Materials and methods

Search strategy

I searched in the PubMed online database for published articles up to September 1, 2020, with the following keywords: microRNA," "miRNA," "gastric cancer," "expression profiling," "prognosis," "diagnosis," "biomarker," and "survival." The data were then extracted from the selected studies and input into tables that contain different characteristics of interest.

Selection criteria

The inclusion criteria were as follows: (1) studies had to be miRNA profiling studies in GC patients and reported on dysregulated miRNAs; (2) studies that investigated the diagnosis value of miRNAs to discriminate GC patients from normal; (3) studies that investigated the association between miRNAs expression and survival outcome and that provided a hazard ratio (HR) and a 95% confidence interval (CI), while the exclusion criteria were as follows: (1) non-English and non-human subject studies; (2) abstracts, reviews, comments, and letters; (3) studies with incomplete or insufficient data.

Data extraction

All the articles were filtered three times, and then the suitable studies were extracted. According to the inclusion and exclusion criteria, the data about GC patients, total samples used for the study on diagnosis value of miRNAs in serum or plasma and platform used in these studies, fold change of statistically differentially expressed miRNAs in GC tissues have been provided. The list of upregulated and downregulated miRNAs was summarized in (Tables 1 and 2).

Ranking of miRNA

In this study, I used the vote-counting strategy-based method developed by Griffith and Chan (Griffith et al. 2006; Chan et al. 2008) to rank miRNAs as potential molecular markers. MiRNAs were ranked based on criteria as (1) the number of

Table 1 The list of differentially expressed miRNAs in GC/normal tissues

miRNAs	Dysregulation	No. of tissue sample (cancer/normal)	Fold change	Median fold change	References
miR-21	Upregulated	721	1.49–10.44	4.05	Li et al. (2012); Zheng et al. (2012); Wang et al. (2014); Wu et al. (2015b)
miR-223	Upregulated	350	2.13–4.90	3.13	Li et al. (2012)
miR-375	Downregulated	608	0.15–0.37	0.27	Ding et al. (2010); Tsukamoto et al. (2010); Ueda et al. (2010)
miR-564	Downregulated	204	-	-	Kim et al. (2011)
miR-155	Downregulated	169	0.36–0.66	0.42	Yao et al. (2009); Li et al. (2011)
miR-18a	Upregulated	602	1.70–10.66	2.27	Tsukamoto et al. (2010); Ueda et al. (2010); Tsujiura et al. (2015)
miR-106a	Upregulated	574	1.52–9.02	2.80	Yao et al. (2009); Tsukamoto et al. (2010); Ueda et al. (2010)
miR-214	Upregulated	165	2.11–2.85	2.48	Tchernitsa et al. (2010); Oh et al.(2011)
miR-93	Upregulated	568	1.49–8.27	2.40	Tchernitsa et al. (2010); Kim et al. (2011); Li et al. (2011)
miR-148a	Downregulated	596	0.19–0.47	0.23	Tchernitsa et al. (2010); Tsukamoto et al. (2010); Ueda et al. (2010)
miR-25	Upregulated	629	1.26–5.57	2.55	Ding et al. (2010); Tchernitsa et al. (2010); Tsukamoto et al. (2010); Ueda et al. (2010)
miR-92	Downregulated	629	1.39–5.24	2.80	Ueda et al. (2010)
miR-106b	Upregulated	574	1.60–4.30	2.00	Yao et al. (2009); Ding et al. (2010); Tchernitsa et al. (2010); Tsukamoto et al. (2010); Ueda et al. (2010); Kim et al. (2011)
miR-191	Upregulated	546	1.27–1.30	1.285	Volinia et al. (2006); Ueda et al. (2010)

Table 2 Summary of miRNAs used as diagnosis biomarkers of GC

miRNAs	Samples	Patients	Controls (normal)	Methods	Sensitivity	Specificity	AUC	AUC 95% CI	Ref
miR-106b	Plasma	65	65	qRT-PCR	86.20	92.30	0.898	0.839–0.958	Li et al. (2012)
miR-18a	Plasma	104	65	qRT-PCR	84.60%	69.20%	0.806	-	Tsujiura et al. (2015)
miR-25	Plasma	65	65	qRT-PCR	87.60%	76.90%	0.817	0.738–0.897	Li et al. (2012; Kong et al. (2019)
miR-223	Serum	50	47	qRT-PCR	81%	78%	0.85	0.780–0.930	Wang et al. (2014)
miR-421	Serum	90	90	qRT-PCR	90%	85.70%	0.779	0.691–0.898	Wu et al. (2015b)
miR-93	Plasma	65	65	qRT-PCR	81.50%	73.80%	0.756	0.665–0.846	Li et al. (2012); Guan et al. (2017)
Combination of miR-21, miR-93, miR-106a, miR-106b	Plasma	11	17	ddPCR	84.80%	79.20%	0.887	0.83–0.943	Zhao et al. (2018)
miR-100	Serum	50	47	qRT-PCR	71%	58%	0.71	0.610–0.820	Wang et al. (2014)
miR-200c	blood	52	15	qRT-PCR	65.40%	100%	0.715	0.597–0.833	Valladares-Ayerbes et al. (2012), Chang et al. (2015)
miR-940	Plasma	80	70	qRT-PCR	81.25%	98.57%	0.966	0.940–0.992	Cui et al. (2011)

studies in agreement, reporting miRNA deregulation with statistical significance, as well as the direction of deregulation (upregulated or downregulated), (2) the miRNA frequency was reported in the studies, and (3) the mean fold change (FC) of each miRNA reported by the studies in agreement.

Results

A total of 320 studies were identified from PubMed using my search strategy. A total of 183 studies were retrieved after screening the titles and abstracts, including irrelevant studies, reviews, and studies that are not a human or English study. Finally, I found that 105 articles lacked sufficient data or were not relevant to diagnoses or prognoses. Therefore, 32 studies, including 14 miRNAs studies for analysis of differential expression of miRNAs in GC tissues, 10 for evaluating the diagnostic value of miRNA expression in plasma or serum to discriminate GC patients from healthy, and 8 for predictive analysis of miRNAs, were included in the analysis. A flow diagram of the study selection process is presented in Fig. 1.

Dysregulation of miRNAs in GC tissues

Among differentially expressed miRNAs, the upregulation of miR-21 was reported in four studies, followed by upregulation of miR-106b, miR-25, and miR-214 in six, six, and two studies, respectively. Moreover, the downregulation of miR-375 and miR-148a and upregulation of miR-18a and miR-93 were reported in three studies, followed by two downregulated miRNAs including miR-155 and miR-564 in two and one studies, respectively. I have also summarized miRNAs that were upregulated and downregulated (Table 1).

Diagnostic value of miRNAs in GC

A total of 8 miRNA studies have indicated their potential value in the diagnosis of GC. Its sensitivity ranges from 65.40 to 90%, and specificity ranges from 58 to 100.00%. Among them, nine studies were performed on a single miRNA, and one was performed on a combined miRNA include miR-21, miR-93, miR-106a, and miR-106b; the list of these studies is summarized in Table 2. The sensitivity of one miRNA was higher than 90%, and the specificity of the three miRNAs was higher than 90%. The highest sensitivity was 90% for miR-421 (Wu et al. 2015a), while the highest specificity was 100% for miR-200c (Valladares-Ayerbes et al. 2012). In the study of Liu et al. (2016), the expression 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 research that was conducted by Zhao et al. (2018), they determined the diagnostic value of a panel of miRNAs include miR-21, miR-93, miR-106a, and miR-106b, and they verified the sensitivity and specificity of the combination were improved compared with the four when independent, with an AUC of 0.887 when combined.

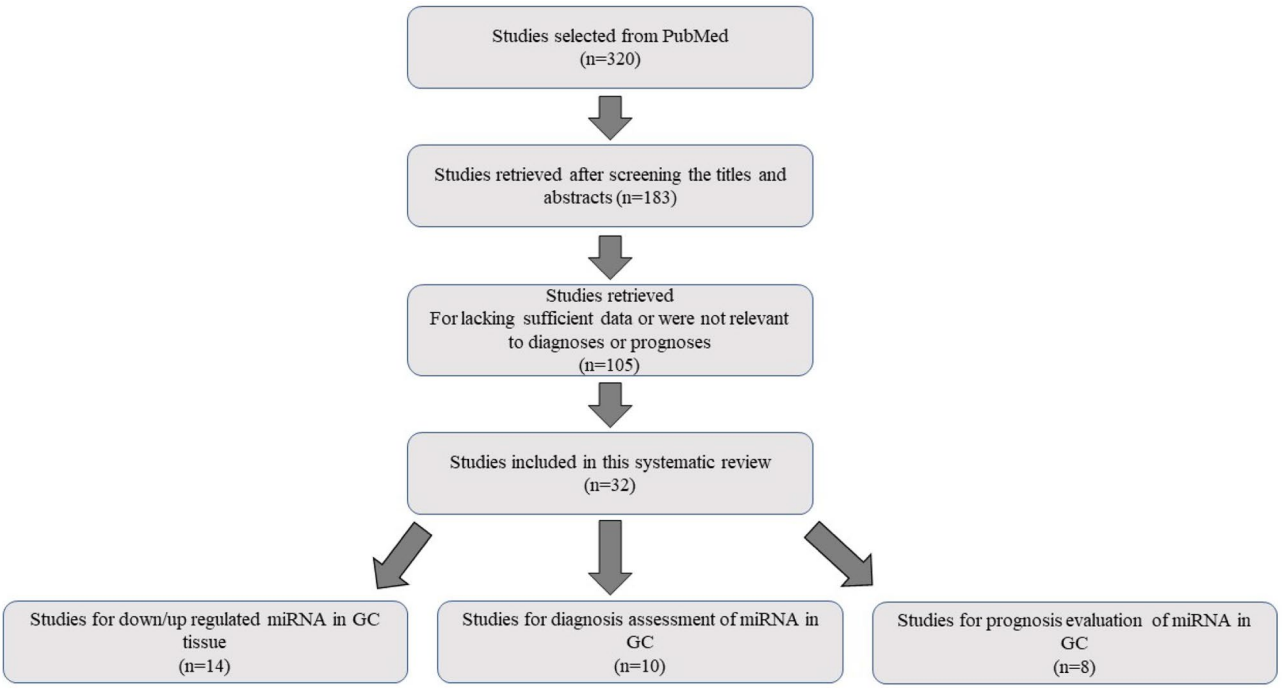

Fig. 1 Flow diagram of the study selection

MiRNAs act as a prognosis biomarker in GC

In this study, I used the hazard ratios (HRs) or relative risks (RRs) for each miRNA. The pooled results indicated that miR-21 were significant prognostic biomarkers for GC patients (HR = 1.260, 95% CI 0.370–4.330, $P < 0.001$). Also, the HR of miR-148 was statistically significant, with a value of 3.076 (95% CI 1.216–8.776; $P < 0.017$). The significant HR value of two miRNAs includes miR-200c and miR-204, which were found with the HR value of 2.240 (95% CI 1.091–4.614; $P = 0.028$) and HR value of 3.900 (95% CI 1.300–11.800; $P = 0.017$), respectively. Additionally, in the list of studies summarized in Table 3, the association between miRNA expression and RR was observed. The highest RR value was for miR-15a with an RR of 1.950, these studies followed by the RR value for miR-125a-3p, miR-106b, and miR-20a, which includes RR = 1.800, 1.600, and 1.110, respectively.

Discussion

In the translational aspect of using miRNAs in cancer, there has been an evolution from profiling altered miRNA expressions in cancers to clinical trials with miRNAs as therapy in the last decade. Recent studies have shown that its promise with miRNA replacement therapy in pre-clinical and clinical pilot studies and its potential use in personalized medicine. These studies have also explored a range of applications from diagnostics, prognostics, disease surveillance to primary therapy, or a tool to sensitize patients to treatment modalities such as chemotherapy and radiotherapy. Advancements in delivering miRNAs, from viral vectors and liposomal delivery to nanoparticle-based, have led to several pre-clinical and clinical applications for miRNA cancer therapeutics (Kwok et al. 2017).

Table 3 The list of miRNAs could act as prognosis biomarker in GC

miRNAs	HR/RR	95% CI	*P* value	References
miR-125a-3p	RR = 1.800	1.160–2.870	0.008	Zheng et al. (2012)
miR-15a	RR = 1.950	0.470–9.130	0.357	Cui et al. (2011)
miR-148	HR = 3.076	1.216–8.776	0.017	Wang et al. (2012)
miR-200c	HR = 2.240	1.091–4.614	0.028	Yang et al. (2014)
miR-21	HR = 1.260	0.370–4.330	< 0.001	Shin et al. (2014)
miR-106b	RR = 1.600	0.210–14.390	0.643	Cui et al. (2011)
miR-20a	RR = 1.110	0.200–7.140	0.014	Tsujiura et al. (2014)
miR-204	HR = 3.900	1.300–11.800	0.017	Naito et al. (2014)

In this systematic review, I conducted a systematic search to retrieve data from studies that explored aberrantly expressed miRNAs as candidate biomarkers for GC diagnosis and prognosis, using either tissue samples or blood samples. With regard to tissue-diagnostic miRNAs, I identified eight consistently upregulated miRNAs (miR-21, miR-223, miR-18a, miR-214, miR-93, miR-191, miR-25, miR-106b) and five miRNAs consistently downregulated (miR-375, miR-564, miR-155, miR-148a, miR-92) (Table 1). MiR-21 was most consistently upregulated, with a differential expression reported among four studies and a median fold change of 4.05. However, miR-21 is vastly cited across the literature for this upregulation in GC. I found only these four studies matching the inclusion criteria that had reported significant upregulation of miR-21.

Furthermore, the upregulation of miR-21 significantly promoted cell proliferation. It revealed a higher proportion of cells at the S phase, and the knockdown of miR-21 expression resulted in a cell-cycle arrest at the G2/M phase and inhibited cell proliferation (Zhong et al. 2012). Additionally, Zhang et al. (2012), De Val and Black (2009), and Yamanaka et al. (2012) demonstrated that miR-21, as an oncomir, contributes to GC progression by inhibiting apoptosis and elevating cell proliferation by targeting the tumor suppressor gene RECK. Moreover, the highest fold change for downregulated miRNAs was found for miR-92 with a median fold change of 2.80. Additionally, in this systematic review, ten diagnostic and eight prognostic studies were included to study whether miRNAs are useful biomarkers for GC. The data showed that specific miRNAs could be used (with moderate sensitivity and specificity) in the diagnosis of GC. The study's result related to miR-940 showed that the sensitivity and specificity were 81.25% and 98.57%, respectively (Liu et al. 2016), which indicate the potential act of this miRNA as a biomarker in GC diagnosis. Also, a recent study has shown the dysregulation of miR-940 in stage IV of GC patients, and CD276 as a target gene of this miRNA played a significant role in promoting migration and invasion of GC cells (Liu et al. 2016). Also, miR-940 has been proven to promote tumor cell invasion and metastasis with the aid of interacting with ZNF24 in GC (Liu et al. 2015), and plasma miR-940 decreased during gastric carcinogenesis. This miRNA might be applied as a novel biomarker for the diagnosis of GC.

Moreover, the combined diagnostic AUC, sensitivity, and specificity of miR-21, miR-93, miR-106a, and miR-106b in plasma were 0.887, 84.80%, and 79.20%, respectively, for discriminating GC cases. With this combination, the diagnostic efficiency for the early-stage gastric non-cardia adenocarcinoma (GNCA) increased significantly (Zhu et al. 2014). As supporting evidence, a recent study that analyzed the expression level of miR-21, miR-93, miR-106a, and miR-106b in GC samples using ddPCR, the results have shown the association between the increased levels of these miRNAs with advanced TNM stage (Tchernitsa et al. 2010; Shiotani et al. 2013). Due to the overexpression of miR-25, miR-93, and miR-106b in GC stem cells, the functional analysis of these miRNAs might also be essential for GCs diagnosis (Yu et al. 2014). A previous study verified that upregulation of miR-25 could induce cell apoptosis via targeting gene BIM. MiR-106b and miR-93 abrogate TGFβ prompted apoptosis in GC cells by targeting the expression of BIM, encoding the pro-apoptotic protein BCL2-like 11, thereby preventing apoptosis and leads to tumor progression. Also, recent studies indicated that the differential expression of miR-335 had been used as a signature for GC diagnosis, and the expression level of this miRNA is correlated significantly with LNM, distant metastasis, and TNM stage (Li et al. 2011; Ahadi and Safavi 2019). In the next step, I listed the studies on miRNAs potential to act as a prognosis biomarker using HRs and RRs to determine each miRNA overall prognostic performance. The analysis indicated a closer relationship between miR-204 expression and poor survival in GC patients (HR = 3.900, 95% CI 1.300–11.800), and this miRNA can be applied to monitor the therapeutic effects. The upregulation of miR-204 is related to GC cell invasion and epithelial-mesenchymal transition (EMT) by targeting SIRT-1 at the post-transcriptional level. Thus, miR-204 is believed to play a crucial role in regulating the metastasis of GC. Therefore, miR-204 can increase GC cells responsiveness to 5-fluorouracil and oxaliplatin treatment by targeting Bcl-2, indicating that miR-204 might be a therapeutic target for improving GC prognosis (Canu 2012). The results also revealed that miR-15a yielded worse overall survival in GC (RR = 1.950, 95% CI 0.470–9.130). The downregulation of miR-15a induces cell proliferation, EMT, migration, and invasion by Twist1 and YAP1 as the target genes (Wang et al. 2017).

In conclusion, from this systematic review study, I identified that miR-940 and the combination of miR-21, miR-93, miR-106a, and miR-106b with the highest AUC in discriminating of GC patient could act as a diagnostic biomarker, and miR-204 and miR-15a with the highest HR and RR are closely associated to poor survival in GC which can be determined as a prognosis biomarker for further assessment. The study found several promising miRNAs that had been consistently reported. However, more investigations are needed for the clinical studies focusing on these miRNAs to understand these miRNAs potential roles in GC. One of the significant factors limiting the use of miRNAs as a diagnostic tool in clinical settings is associated with the fact that frequently reported miRNA biomarkers are detected in patients with different tumor types. Moreover, other limitations of using miRNAs as a diagnostic biomarker include the range of concentrations in body fluids and modulation

depending on various parameters (age, gender, health/disease) that are not yet clearly established (Gillespie et al. 2019). In the future, a miRNA or a miRNA signature should be a better diagnostic or therapeutic tool than a single gene. Ultimately, the personalized management, diagnosis, and prognosis of the disorder can be finished using a panel of miRNAs (Ahadi 2020).

Compliance with ethical standards

Conflict of interest The author declares that there is no conflict of interest.

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