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REVIEW

MicroRNAs as non-invasive diagnostic biomarkers for gastric cancer: Current insights and future perspectives

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Abstract

Non-invasive diagnostic biomarkers may contribute to an early identification of gastric cancer (GC) and improve the clinical management. Unfortunately, no sensitive and specific screening biomarkers are available yet and the currently available approaches are limited by the nature of the disease. GC is a heterogenic disease with various distinct genetic and epigenetic events that occur during the multifactorial cascade of carcinogenesis. MicroRNAs (miRNAs) are commonly deregulated in gastric mucosa during the *Helicobacter pylori* infection and in stepwise manner from chronic gastritis, through preneoplastic conditions such as atrophic gastritis and intestinal metaplasia, to early dysplasia and invasive cancer. Identification of miRNAs in blood in 2008 led to a great interest on miRNA-based diagnostic, prognostic biomarkers in GC. In this review, we provide the most recent systematic review on the existing studies related to miRNAs as diagnostic biomarkers for GC. Here, we systematically evaluate 75 studies related to differential expression of circulating miRNAs in GC patients and provide novel view on various heterogenic aspects of the existing data and summarize the methodological differences. Finally, we highlight several important aspects crucial to improve the future translational and clinical research in the field.

Key words: MicroRNA; Biomarkers; Screening; Stomach; Gastric cancer; Systematic review; Blood; Serum; Plasma

Core tip: Over the past years, large amount of data to microRNAs (miRNAs) in gastric cancer (GC) has been

published. We aimed to provide the critical, first of its kind in depth overview of existing studies to the miRNAs diagnostic biomarkers in GC. For this, we systematically reviewed published literature and identified 75 studies related specifically to microRNAs as blood-related non-invasive diagnostic biomarker in GC. This work provides a critical compendium to 106 studied microRNAs and summarizes the technical and methodological differences in reported studies. Furthermore, we highlight several aspects that need careful attention in future studies.

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INTRODUCTION

Gastric cancer (GC) is a deadly disease with a great challenge in clinical management despite of a steady decline of the cancer incidence[1,2]. Despite of increasing understanding of genetic and epigenetic cancer events, the absence of non-invasive methods or biomarkers for early identification of GC is one of the biggest difficulties in GC. With an ongoing technical revolution, there is a great hope to find an appropriate way to solve this limitation. Non-coding RNAs (ncRNAs) and specifically microRNAs (miRNAs) have entered the "cancer-arena" for now more than 10 years ago[3] and much research has been done over the past decade. For several years we performed systematic analysis and reviewed the role of miRNAs in GC and potential of miRNAs as a biomarker in gastrointestinal cancers[4,5]. Since then, huge amount of data has been gained, making impossible to keep an overview of existing research. In this work, we performed a systematic search and reviewed published papers related to miRNAs as non-invasive biomarkers in GC. Because of the overwhelming amount of published data, we focused solely on miRNAs as non-invasive diagnostic biomarkers in GC and excluded the data to functional alterations, prognostic and predictive role. In the first part, we will briefly review the specific and unique issues related to GC crucial for understanding the disease, provide the compiling data showing the current stand of the research and highlight the need for the future development and new directions in the field.

GC - HETEROGENIC DISEASE

GC is a multifactorial heterogenic disease with unique cascade of genetic and epigenetic events leading to the cancer. There are multiple factors that, in more or less fashion, responsible for the clinical and biologically-relevant tumor heterogeneity, which may substantially impact an identification of potential diagnostic biomarkers. Those factors include geographical differences in prevalence of the risk factors, genetic background of the population, environmental factors and probably nutrition. For instance, the prevalence of GC in Asian countries and Russia is higher than in United States, Canada and northern Europe. Interestingly, geographical differences correlate with anatomical localization of primary gastric tumors. Tumors in corpus-distal subtype are predominant in Asian countries and junctional-proximal subtype in Europe. Among the most important etiological factors that may influence the tumor biology at least during the process of carcinogenesis is the *Helicobacter pylori* (*H. pylori)* infection, which is now acknowledged as an infectious disease with all the consequences of prevention and treatment[6]. For in depth review of the role of *H. pylori* in GC development, we refer to several recent publications[7,8]. Briefly, *H. pylori* is a chronic infectious diseases that causes almost always an active chronic inflammation of the gastric mucosa[6]. The persistent chronic inflammation of gastric mucosa causes different range of molecular alterations with increasing loss and accumulation of changes that leads to the phase of atrophic gastritis (AG) with intestinal metaplasie (IM) and dysplasia, which may further progress to GC and is known as Correa's cascade[9]. AG and IM are well acknowledged preneoplastic stages of GC with an increased GC risk[10]. Close endoscopic follow up of patients with preneoplastic conditions and lesions is recommended[11]. The risk of *H. pylori*-related GC development may be associated with severity of mucosal inflammation and be partially dependent on bacterial virulence factors such as cytotoxin-associated gene A (CagA) and vacuolating cytotoxin A (VacA)[12]. We and others have recently shown that VacA is probably one of the most important bacterial factors that correlate with mucosa inflammation[13] and is strongly associated with anti-CagA-IgG production[14]. *H. pylori* eradication is suggested as the most effective way in GC reduction in high-prevalence regions[15]; however, its value is beneficial mainly for primary and secondary GC prevention without strong diagnostic value in GC screening.

Historically, GC is divided based on the Lauren's classification into 2 histologic subtypes: intestinal and diffuse[16]. Lauren's classification is of the remarkable value in treatment decisions and has prognostic and predictive value. With an advance of high throughput technologies, the value of Lauren's classification has been questioned. The landmark work from The Cancer Genome Atlas (TCGA) has provided a new molecular classification subdividing GC in chromosomal instable (CIN), genomically stable (GS), microsatellite instable (MSI) and Epstein-Barr-Virus positive (EBV) tumor groups[17]. GS group shows relatively strong overlap with Lauren's diffuse type tumors. Hence, one of the main advantages of TCGA molecular classification may be in further subdivision of intestinal subtype of GC tumors in CIN, MSI and EBV. Those tumor subtypes carry not only unique molecular patterns relevant for understanding

the etiology but have potential predictive value for implementation of individualized novel therapeutic strategies.

CURRENTLY AVAILABLE BIOMARKERS FOR GC

To date, different molecules have been analyzed as potential biomarkers in patients with GC; however, as of 2018, there are no single blood-based biomarker that have sufficient sensitivity or specificity for implementation in GC screening routinely[8]. Several well-known antigens including carcinoembryonic antigen (CEA), cancer antigen 19-9 (CA19-9) and cancer antigen 72-4 (CA72-4) have been investigated in relation to GC[18]. Although the concentration of those antigens may be increased in some GC patients, the overall sensitivity of individual or combined CEA, CA19-9 and CA72-4 levels remains of insufficient discriminative power necessary for GC screening[18]. Besides typical "tumor-based" biomarkers, an effort has been made to establish a "functional" test for gastric mucosa also called "serological biopsy"[15]. Pepsinogen Ⅰ and Ⅱ (PGⅠ and PGⅡ) concentration correlate with AG, which is the preneoplastic condition of intestinal type of GC is intestinal type of GC, and is frequently used in Asian countries. In Europe the PGI and PGⅡ panels is expanded by the use of Gastrin-17 (G17). G17 is produced by the G-cells and stimulates the hydrochloric acid and pepsinogen production and therefore is part of the same physiological cascade as PGI. Unfortunately, the use of G17 is hampered by the stability of the peptide and the net benefit in addition to PGI and Ⅱ is a matter of ongoing research[19]. According to the recent systemic reviews and meta-analysis the sensitivity for AG identification is up to 70%[20,21]. Thus, PGI and PGⅡ may be helpful for serological identification of patients with probability of AG in regions with limited resources and availability of endoscopy. However, upper GI endoscopy with careful assessment of the gastric mucosa and targeted biopsies remains the gold-standard for GC screening and identification of patients at risk. One's upper GI endoscopy is performed, there is no additional diagnostic benefit of PGI/PGⅡ/G17 for instance in GC screening or risk assessment[22].

MiRNAs have gathered a lot of scientific attention during the past 10 years. As we have mentioned above, miRNAs are unique subgroup of ncRNAs with crucial role in multiple biological processes. MiRNAs are involved in regulation of different molecular pathways including cell differentiation, cell cycle progression or apoptosis through post-transcriptional regulation of gene expression[23]. Deregulation of miRNAs can influence carcinogenesis through mRNA targets encoding tumor suppressor genes or oncogenes[24]. Due to its unique biogenesis, miRNAs have several features that make them an attractive group of molecules in biomarker research field. MiRNAs are very stable and are easily and reproducibly retrieved from different biological material including tissues, blood, feces, saliva, ascites and even paraffin embedded blocks[25-32]. Due to those properties, miRNAs carry a huge potential as biomarkers and have been recently extensively explored in GC. For detailed information we kindly refer to our recent reviews[4,5].

MIRNA ALTERATIONS IN GC AND FUNCTIONAL ROLE

Multiple studies have demonstrated the differential expression of miRNAs in GC tissues and its functional role in GC has been suggested[4]. It is believed that miRNA alterations appear early in the cascade of the preneoplastic events. For instance, differential expression of miRNAs is identified in subjects with *H. pylori* infection and expression of miR-155 and miR-223 showed gradual increase in correlation to Correa's cascade both in antrum and corpus mucosa[25]. TCGA group has shown that different molecular subtypes of GC have unique miRNA expression profiles[17], which is in support of several other profiling studies[26,33]. Understanding of the mechanisms of miRNA expression such as CpG island promoter methylation, provides valuable information for biomarker research. For example, miR-137 was implicated in GI cancers showing differential methylation in colorectal cancer (CRC) and GC patients, although the magnitude of changes was superior in CRC[34]. MiR-29c expression is reduced early in gastric carcinogenesis and has been suggested as a diagnostic and therapeutic biomarker for patients with GC[35]. The interplay of the two transcription factors HNF4γ and NR2F2 and their coordinated regulation by miR-30 and miR-194, respectively, may represent a miRNA related network responsible for expression regulation of intestinal transcripts in the development of intestinal metaplasia[36].

Another growing field of miRNA research in GC is related to the analysis of single nucleotide polymorphisms (SNPs) in miRNA genes. Variation in miRNA-sequences may lead to the expression differences and modify regulatory function of miRNAs[37,38]. To date, both gene sequences encoding precursor miRNAs[39,40] as well as variations in miRNA binding regions of target genes[41] have been extensively explored in cancer studies. The most investigated SNPs in GC are related to miR-27a, miR-146a, miR-421, miR-449a; miR-196a-2, miR-492 and miR-608[42]. Although some associations between the risk of GC development and miRNA-related SNPs have been suggested, none of the identified associations is ready to be applied in clinical settings in particular in GC screening.

MIRNAS AS BIOMARKERS

Having shown the miRNA changes in tumor tissues, multiple research groups simultaneously evaluated the potential of miRNAs as non-invasive biomarkers in various specimens. Three publications related to large B-cell lymphoma, prostate and lung cancer appeared in 2008

strongly suggesting miRNAs as potential biomarkers for cancer[43–45]. This knowledge has been further extended to systematic analysis in feces in CRC[28], pancreatic cancer[29], and other diseases and specimens. Recently, it has been shown that miRNAs can be reproducibly measured in peritoneal fluid and ascites from cancer patients with peritoneal carcinomatosis and ascites[31,46]. It seems that basically any kind of body fluids (breast milk, urine, synovial fluids *etc*.) have measurable expression of miRNAs, which may potentially reflect a normal condition or be associated with pathophysiological alterations and therefore used as a biomarkers[5]. With existence of the overwhelming data to miRNAs in GC, we provide in the next chapter the most comprehensive summary of the exiting published data to miRNAs as non-invasive diagnostic biomarkers in GC.

METHODS AND LITERATURE SEARCH

To identify all available papers, we performed a systematic search with following steps: (1) Identify papers in MEDLINE/PUBMED using following criteria: gastric cancer, stomach cancer, microRNA, miRNA, biomarkers, plasma, serum, blood (until 30th November 2017); (2) We further screened all available abstracts manually one by one and excluded following papers: reviews, duplicates, retracted work, paper primarily related to miRNAs in tissues, *in vitro* or as prognostic or predictive biomarkers, papers without confirmed GC at the time point of the analysis or missing control group for direct comparison; (3) in January 2018 we updated the list including the papers published in December 2017 by applying more stringed criteria: diagnostic biomarkers, GC, plasma, serum. Overall, we obtained 75 original papers analyzing the expression of miRNAs in blood/serum/plasma between GC patients and controls. Among those, 18 papers refer to profiling of circulating miRNAs in GC compared to controls. Seventy-four full text papers and 1 abstract were systematically reviewed and the data were entered into the database. GraphPad Prism 7 (La Jolla, CA, United States) was used to create the figures.

MIRNA AS DIAGNOSTIC BIOMARKERS IN GC: TIMELINE AND PUBLICATION TRENDS

The first data to potential of miRNAs as diagnostic biomarkers in GC appeared in 2010 only two years after the first reports to detection of circulating miRNAs. We identified 75 publications from 2010 to 2017 where miRNA expression was studied in blood of GC patients and controls independently to the primary aim of the study. Over the period of 8 years, as shown in the Figure 1, we observed an increasing number of publication per year with maximum of 21 papers published in 2015 suggesting an increasing interest to the topic during the last years. To access the regional differences, we evaluated the origin of the used specimens as a surrogate. Majority of GC specimens and according published papers originate from China (55/75 or 73.3%) followed by Japan, Taiwan, Korea and others, further suggesting the regional difference in priority of the research topic and potential clinical relevance (Figure 1B).

SCIENTIFIC EVIDENCE AND REPORTING QUALITY

As next, we aimed to systematically assess the reporting quality and translational potential of the published work. For this, we created 4 internal quality measures: (1) how many samples from GC patients was used; (2) is TNM-Stage reported; (3) is Lauren's classification reported; and (4) proportion of patients with TNM Ⅰ/Ⅱ in total amount of GC tumors. Figure 1C shows the number of GC samples used among the 75 published papers. The median number included in the study was 57 (range 3-285) and total 5699 specimens were analyzed. Among those, 5 reports included over 200 samples each with highest number of included samples published by Qiu *et al*[47].

As we have shown in the introduction part, the Lauren's classification is among the most valuable tools to assess the histological subtype, which further correlates with molecular subtype[17]. Unfortunately, the data to Lauren's classification were available only for 16% (12/74) of the studies. TNM staging was used as another reporting quality surrogate as it correlated with prognosis and potential biomarkers need to be able to identify early cancers. Interestingly, TNM staging was reported only in 69% (51/74) of studies, which may substantially limit the quality assessment of the published work (Figure 1D). Among the studies with reported TNM staging, the proportion of GC with relatively early stages (TNM Ⅰ/Ⅱ) was quite heterogenic between the studies (Figure 1E). Only two studies focused solely on samples from GC patients with TNM stage Ⅰ and Ⅱ, while 68.8% (35/51) of studies had more than 50% of samples from patients with metastatic GC (lymph node or distant metastases).

TECHNICAL DIFFERENCES AMONG THE STUDIES

Among the identified papers, 38 papers studied the expression of miRNAs in plasma, 32 studies in serum, 3 studies in blood and only 2 reports for peripheral blood mononuclear cell (PBMC) (Figure 2). For miRNA extraction, the mirVana, Trizol and miRNeasy were the most frequently used kits. There were substantial differences between the methods for detection/analysis. SYBR Green-based method was applied in 57% (42/74) more frequently used as TaqMan-based method (Figure 2C).

As next, we focused on the data to internal normalization of circulating miRNAs (Figure 2D). In several previous publications, RNU6b has been clearly criticized for unsuitability for normalization of blood samples as it shows different biogenesis, stability and may not reflect biogenesis of miRNAs[5]. Nevertheless, almost

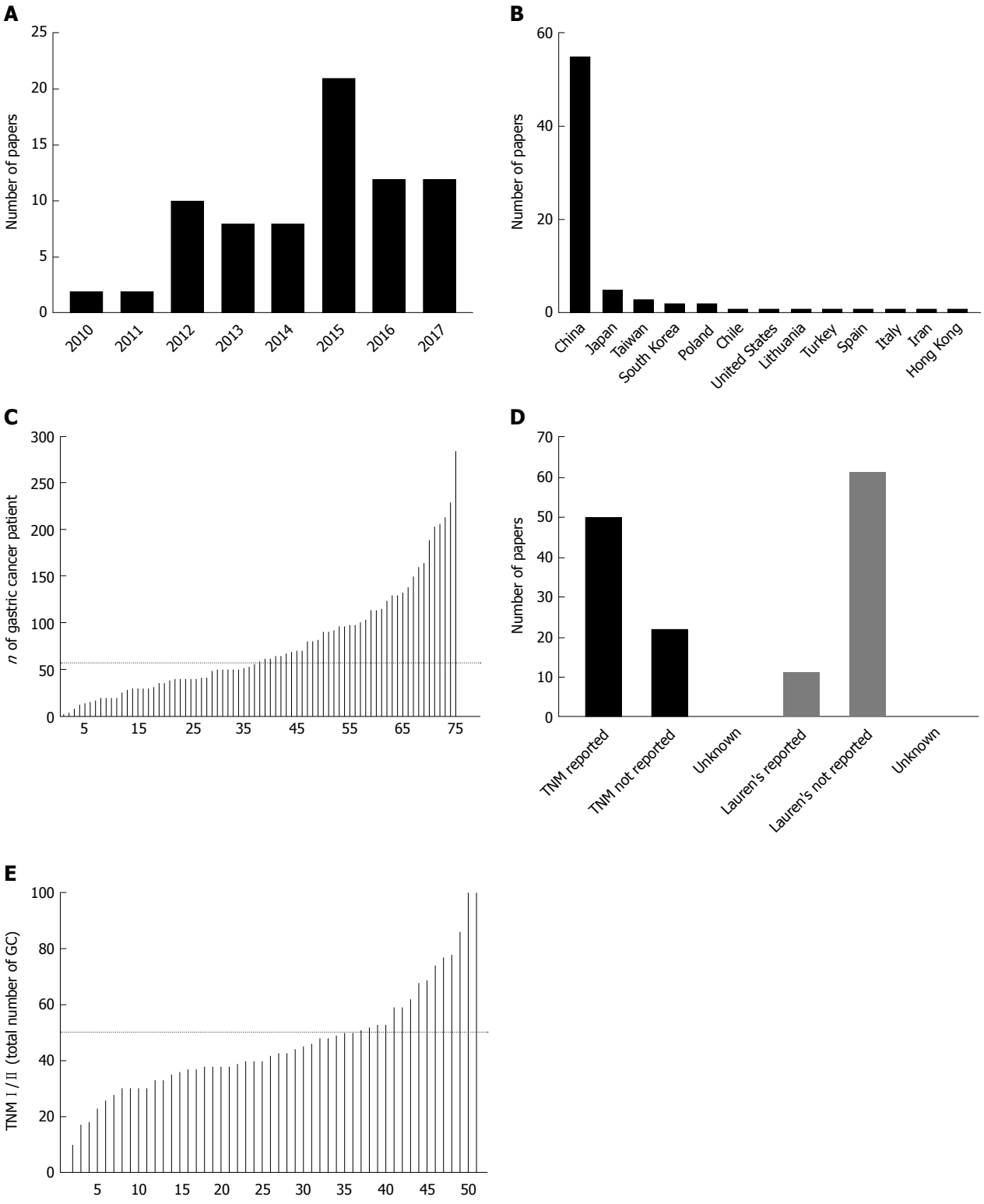

Figure 1 Characteristics of the studies to microRNAs as diagnostic biomarkers in gastric cancer. In total we have identified 75 studies. A: Time trends in number of published papers starting 2010 to 2017. B: Number of papers dependent on the origin of GC tumor specimens studied. C: Total number of specimens per publication/analysis from GC patients studied. D: Number of papers reporting or not reporting TNM staging or Lauren´s classification. E: Proportion of patients with early (TNM stage Ⅰ and Ⅱ) to total number of GC specimen's studied. GC: Gastric cancer.

60% of studies used the RNU6b-method for internal normalization of blood specimens. In similar fashion, 15% of papers applied miR-16-based method (alone or in combination with other methods), although an increasing evidence suggests that miR-16-based method may not be the best way for normalization of circulating miRNAs. Spiked-in-based method (most frequently cel-miR-39) is still considered as the most appropriate currently available methods for miRNAs normalization in blood and was used in up to 26% of studies, even though, it may

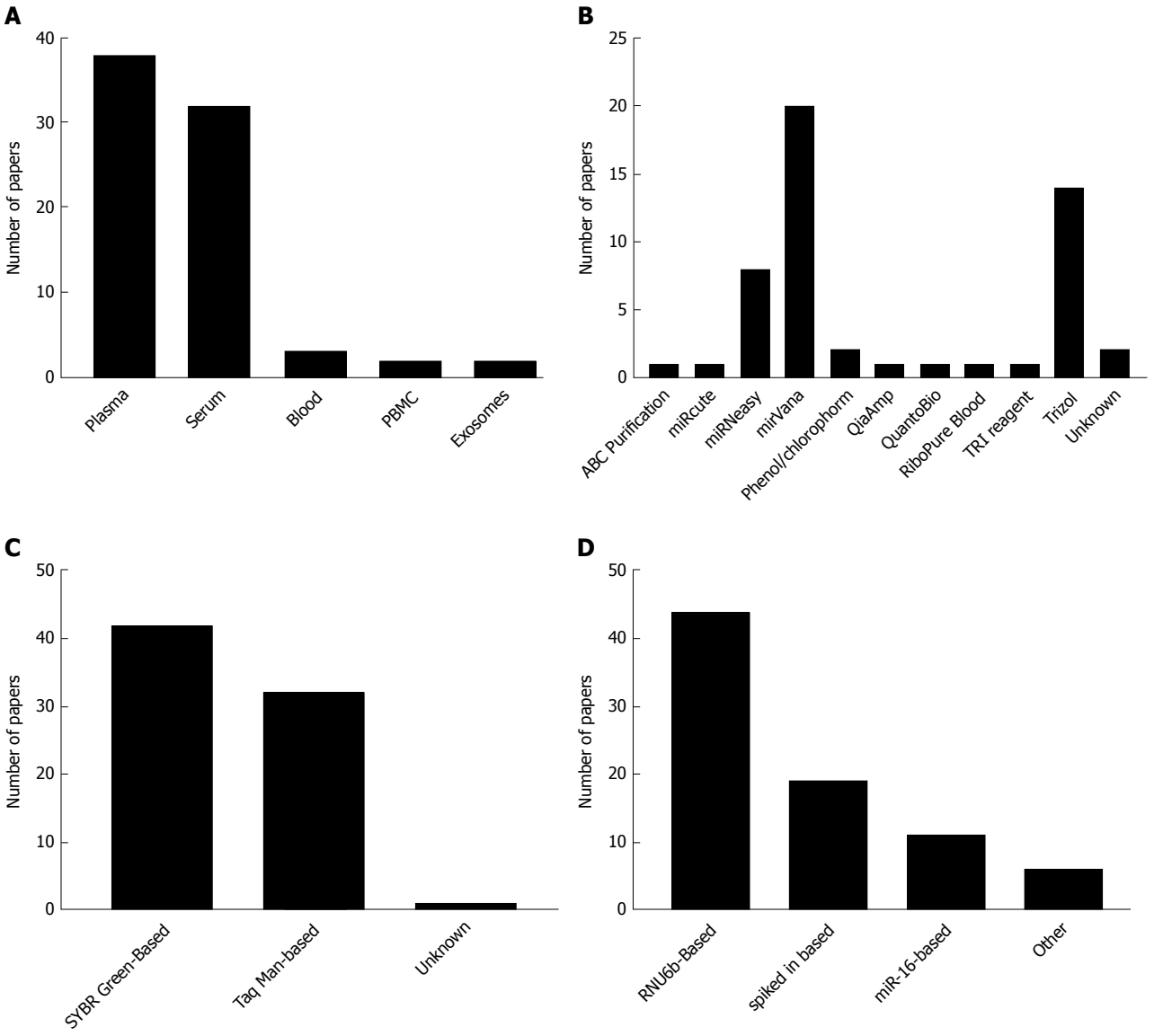

Figure 2 Characteristics of the studies to microRNAs as non-invasive diagnostic biomarkers in gastric cancer based on technical characteristics. A: Number of studies based on the used blood specimens. B: Number of papers using various extraction kits. C: Number of papers with various method for miRNA analysis. D: Number of studies using different normalization methods for miRNA analysis. Since several studies used one or several methods, the total number may exceed 75.

probably not be the perfect long-term solution for miRNA normalization.

Challenges with normalization of circulating miRNAs may probably be the most disappointing issue related to this topic. Several papers deal with the normalization issues and compare several methods, most frequently miR-16 and RNU6b. For instance, Song *et al*[48] studied the expression of several miRNAs in blood and showed that there is quite a large degree of variation among miRNAs. In particular, the expression of miR-21 was higher in stage Ⅳ GC patients; however, only if the samples were normalized to miR-16, miR-93 or miR-16 and miR-93 together. This was not the case if normalization was done based on the volume[48]. Interestingly, both miR-16 and miR-93 showed substantial variation and lower expression in healthy controls arguing against it usefulness as a normalizer. Peng *et al*[49] studied the expression of miR-191 and miR-425 in serum of 57 GC patients. No difference was found if the authors used RNU6b, while miR-16-based normalization led to significantly higher values of miR-191. In another study, Shiotani *et al*[50] also compared different normalization methods in GC samples from GC patients after endoscopic submucosal dissection. The authors conclude that only normalization to miR-16, but not RNU6b, led to the higher expression of miR-106b and let-7. According to our search (Table 1)[26,47,48,51-120], there are 3 reports to differential expression of miR-16 in GC with 399 studies samples[51-53]. Two reports show up- and one report downregulation of miR-16 in plasma and sera samples, further questioning the usefulness of miR-16 for normalization of circulating miRNAs.

The approach of miR-16-based normalization may be also called as a "proportional normalization" as rather the proportion between certain miRNAs (in comparison to miR-16) and not the absolute value of studied

Table 1 Differentially expressed circulating microRNAs in gastric cancer

microRNA	Changes in GC	Changes in GC tissue	Controls (*n*)	GC (*n*)	TNM reported	ROC	Validation	Source (PI/BI/Se)	qPCR	Normalization (qPCR)	Ref.
let-7a	↓	↓	30	69	Yes		Yes	Plasma	TaqMan	RNU6b	[56]
	↓	↓	45	80	Yes			Serum	SYBR	RNU6b	[57]
	↔		30	30	Yes			Plasma	TaqMan	RNU6b	[58]
let-7c	↔		202	214	No			Serum	SYBR	standard curve	[59]
let-7e	↑		82	82	No	0.7	Yes	Serum	TaqMan	cel-miR-39	[60]
let-7f	↔		30	30	Yes			Plasma	TaqMan	RNU6b	[58]
	↑		202	214	No			Serum	SYBR	standard curve	[59]
let-7g	↔		30	30	No			Serum	SYBR	miR-16	[61]
let-7i	↑		202	214	No			Serum	SYBR	standard curve	[59]
miR-1	↑		127	164	Yes			Serum	TaqMan	volume	[62]
	↔		30	30	No			Plasma	SYBR	cel-miR-39	[63]
miR-100	↑		47	50	Yes	0.71		Serum	TaqMan	RNU6b	[52]
miR-103	↑		14	17	No			Plasma	SYBR	Sp6	[64]
	↔		50	50	No	0.548		Plasma	SYBR	cel-miR-39	[65]
miR-106a	↑		30	69	Yes		Yes	Plasma	TaqMan	RNU6b	[56]
	↑		27	41	No	0.684		PBMC	SYBR	RNU6b	[66]
	↔		30	30	No			Plasma	SYBR	cel-miR-39	[63]
	↑	↑	22	48	NA			Serum	NA	NA	[67]
	↑	↑	20	20	Yes		Yes	Serum	TaqMan	cel-miR-39 miR-191-5p	[68]
	↑		130	130	No	0.786	Yes	Serum+ Exosomes	TaqMan	cel-miR-39	[69]
miR-106b	↑	↑	30	69	Yes	0.721	Yes	Plasma	TaqMan	RNU6b	[56]
	↑		90	90	Yes	0.773	Yes	Plasma	SYBR	cel-miR-39	[63]
	↑		15	31	Yes			Serum	TaqMan	cel-miR-39	[70]
	↑	↑	20	20	Yes			Plasma	TaqMan	cel-miR-39 RNU6b	[71]
	↓		36	40	Yes	0.856		Serum	SYBR	QuantoEC	[72]
	↑		65	65	Yes	0.898		Plasma	TaqMan	RNU6b	[73]
miR-107	↑	↑	36	36	No	0.63		Serum	SYBR	5srRNA	[74]
	↑		14	14	Yes			Serum	TaqMan	RNU6b	[75]
	↔		50	50	No	0.563		Plasma	SYBR	cel-miR-39	[65]
miR-10b-5p	↑	↑	167	203	Yes	0.627	Yes	Serum+ Exosomes	SYBR	cel-miR-39 miR-16	[76]
miR-122	↔		36	96	Yes			Plasma	SYBR	ath-miR-159a	[77]
miR-1233	↓		3	3	No			Plasma	SYBR	RNU6b	[78]
miR-130a	↑	↑	41	41	No	0.905		Serum	SYBR	RNU6B	[79]
	↑	↑	20	20	Yes		Yes	Serum	TaqMan	cel-miR-39 miR-191-5p	[68]
miR-132-3p	↑	↑	167	203	Yes	0.652	Yes	Serum+ Exosomes	SYBR	cel-miR-39 miR-16	[76]
miR-139	↓	↑	18	25	No	0.940		Plasma	SYBR	RNU6b	[80]
miR-140-5p	↑		50	50	Yes			Plasma	SYBR	RNU6B	[81]
miR-141	↓		3	3	No			Plasma	SYBR	RNU6b	[78]
	↓		14	17	No			Plasma	SYBR	Sp6	[64]
miR-142-3p	↓		285	285	Yes	0.839	Yes	Plasma	TaqMan	cel-miR-39	[47]
miR-143-3p	↔		73	206	Yes		Yes	Serum	SYBR	RNU6b	[82]
miR-144	↓	↓	40	96	Yes	0.821		Serum	SYBR	RNU6b	[83]
miR-146a	↔		15	31	Yes			Serum	TaqMan	cel-miR-39	[70]
	↔		73	206	Yes		Yes	Serum	SYBR	RNU6b	[82]
	↑	↔	20	20	Yes		Yes	Serum	TaqMan	cel-miR-39 miR-191-5p	[68]
miR-146b	↑	↔	20	20	Yes		Yes	Serum	TaqMan	cel-miR-39 miR-191-5p	[68]
miR-148a	↔		15	31	Yes			Serum	TaqMan	cel-miR-39	[70]
	↓		285	285	Yes	0.842	Yes	Plasma	TaqMan	cel-miR-39	[47]
	↓	↓	39	38	Yes	0.349		Plasma	TaqMan	miR-16-5p	[26]
miR-151-5p	↑		130	230	Yes	0.625	Yes	Plasma	TaqMan	RNU6b	[58]
miR-155	↑		20	30	No		Yes	Plasma	TaqMan	RNU6b	[84]
	↔		15	15	No			Plasma	TaqMan	RNU6b	[85]
miR-15b-5p	↑	↑	100	100	No			Plasma	SYBR	RNU6b	[86]
miR-16	↑		106	160	Yes	0.768-0.925	Yes	Plasma	TaqMan	cel-miR-39	[51]
	↑		47	50	Yes	0.90		Serum	TaqMan	RNU6b	[52]
	↓		129	189	Yes	0.772	Yes	Plasma	TaqMan	cel-miR-39 miR-16-5p	[53]

miR-17	↑		27	41	No	0.743		PBMC	SYBR	RNU6b	[66]
	↓		36	40	Yes	0.879		Serum	SYBR	QuantoEC	[72]
	↑		30	69	Yes		Yes	Plasma	TaqMan	RNU6b	[56]
	↔		30	30	No			Plasma	SYBR	cel-miR-39	[63]
	↔		20	20	No			Serum+ Exosomes	TaqMan	cel-miR-39	[69]
miR-181a	↑	↑	18	25	No	0.882		Plasma	SYBR	RNU6b	[80]
miR-181b	↓		89	92	Yes		Yes	Serum	SYBR	miR-16	[61]
miR-181c	↑	↑	60	30	No			Plasma	SYBR	RNU6b	[87]
miR-185	↑	↑	109	133	Yes	0.65	Yes	Plasma	SYBR	cel-miR-39 RNU6b	[88]
	↑	↔	167	203	Yes	0.637	Yes	Serum+ Exosomes	SYBR	cel-miR-39 miR-16	[76]
miR-187-3p	↑		61	61	Yes		Yes	Serum	SYBR	RNU6b	[89]
miR-18a	↑		50	50	Yes			Plasma	SYBR	RNU6B	[81]
	↑	↑	65	104	Yes	0.805		Plasma	TaqMan	RNU6b	[90]
miR-191	↑		82	82	No	0.63	Yes	Serum	TaqMan	cel-miR-39	[60]
	↑		58	57	Yes	0.849		Serum	TaqMan	miR-16	[49]
miR-192	↔		36	96	Yes			Plasma	SYBR	ath-miR-159a	[77]
miR-194	↑		3	3	No			Plasma	SYBR	RNU6b	[78]
	↔		50	50	No	0.512		Plasma	SYBR	cel-miR-39	[65]
miR-195	↓		285	285	Yes	0.765	Yes	Plasma	TaqMan	cel-miR-39	[47]
	↓	↓	36	62	Yes		Yes	Serum	SYBR	RNU6b	[91]
	↓		190	20	No			Plasma	(TaqMan)	global mean	[92]
	↑	↔	167	203	Yes	0.683	Yes	Serum+ Exosomes	SYBR	cel-miR-39 miR-16	[76]
mir-196a	↓	↑	14	17	No			Plasma	SYBR	Sp6	[64]
	↑	↑	126	98	Yes	0.864		Plasma	SYBR	miR-16	[93]
miR-196b	↑	↑	126	98	Yes	0.811		Plasma	SYBR	miR-16	[93]
miR-198	↔		30	30	Yes			Plasma	TaqMan	RNU6b	[58]
miR-199a-3p	↑		70	80	Yes	0.818	Yes	Plasma	TaqMan	RNU6b	[94]
	↑		130	230	Yes	0.837	Yes	Plasma	TaqMan	RNU6b	[58]
	↑		50	50	Yes			Plasma	SYBR	RNU6B	[81]
miR-19a	↑	↑	20	20	Yes		Yes	Serum	TaqMan	cel-miR-39 miR-191-5p	[68]
miR-19b	↑	↔	20	20	Yes		Yes	Serum	TaqMan	cel-miR-39 miR-191-5p	[68]
	↑		3	3	No			Plasma	SYBR	RNU6b	[78]
	↓		129	189	Yes	0.749	Yes	Plasma	TaqMan	cel-miR-39, miR-16-5p	[53]
	↑		130	130	No	0.769	Yes	Serum+ Exosomes	TaqMan	cel-miR-39	[69]
miR-200b	↓		14	17	no			Plasma	SYBR	Sp6	[64]
miR-200c	↑		15	52	Yes	0.715		Blood	SYBR	RNU6b 5SrRNA	[95]
	↑		100	98	Yes			Serum	SYBR	RNU6b	[96]
miR-203	↓		89	92	Yes		Yes	Serum	SYBR	miR-16	[61]
	↓		22	130	Yes	0.707	Yes	Serum	TaqMan	cel-miR-39	[97]
miR-204	↓		40	115	Yes		Yes	Serum	SYBR	RNU6b	[98]
miR-206	↓		150	150	Yes	0.89		Serum	TaqMan	cel-miR-39	[99]
miR-20a	↑		127	164	Yes			Serum	TaqMan	volume	[62]
	↑		90	90	Yes	0.859	Yes	Plasma	SYBR	cel-miR-39	[63]
	↑	↑	30	30	No			Plasma	SYBR	RNU6b	[100]
	↑	↑	109	133	Yes	0.67	Yes	Plasma	SYBR	cel-miR-39 RNU6b	[88]
	↑	↑	28	28	No			Plasma	SYBR	RNU6b	[101]
	↑	↔	167	203	Yes	0.637	Yes	Serum+ Exosomes	SYBR	cel-miR-39 miR-16	[76]
	↑		12	12	No			Serum	SYBR	cel-miR-39	[102]
miR-21	↑		30	69	Yes		Yes	Plasma	TaqMan	RNU6b	[56]
	↑		20	53	Yes	0.853		Blood	SYBR	RNU6b	[103]
	↑		70	70	Yes	0.794	Yes	Plasma	TaqMan	cel-miR-39	[104]
	↑		39	30	Yes	0.81		Serum	SYBR	miR-16	[105]
	↑		20	40	Yes			Serum	All-in-one	Volume miR-16, miR-93	[48]
	↔		90	90	Yes			Plasma	SYBR	cel-miR-39	[63]
	↔		15	31	Yes			Serum	TaqMan	cel-miR-39	[70]
	↔		15	15	No			Plasma	TaqMan	RNU6b	[85]
	↑		50	50	Yes	0.912		Serum	SYBR	RNU6b	[106]
	↑		50	50	Yes	0.898		PBMC	SYBR	RNU6b	[106]
	↑	↑	14	17	No			Plasma	SYBR	Sp6	[64]
	↑		89	92	Yes		Yes	Serum	SYBR	miR-16	[61]
	↑	↑	20	20	Yes		Yes	Serum	TaqMan	cel-miR-39 miR-191-5p	[68]

miR-210	↑	↑	109	133	Yes	0.75	Yes	Plasma	SYBR	cel-miR-39 RNU6b	[88]
miR-212	↑	↔	20	20	Yes		Yes	Serum	TaqMan	cel-miR-39 miR-191-5p	[68]
miR-218	↓		70	70	Yes	0.743	Yes	Plasma	TaqMan	cel-miR-39	[104]
	↓		56	68	Yes			Serum	SYBR	cel-miR-39	[107]
miR-220	↑	↔	20	20	Yes		Yes	Serum	TaqMan	cel-miR-39 miR-191-5p	[68]
miR-221	↑		82	82	No	0.7	Yes	Serum	TaqMan	cel-miR-39	[60]
	↑		90	90	Yes	0.796	Yes	Plasma	SYBR	cel-miR-39	[63]
	↑		14	17	No			Plasma	SYBR	Sp6	[64]
miR-222	↑		82	82	No	0.65	Yes	Serum	TaqMan	cel-miR-39	[60]
	↑		56	114	Yes	0.85		Plasma	TaqMan	RNU6b	[108]
miR-223	↑		70	70	Yes	0.91	Yes	Plasma	TaqMan	cel-miR-39	[104]
	↑		15	31	Yes			Serum	TaqMan	cel-miR-39	[70]
	↑		47	50	Yes	0.85		Serum	TaqMan	RNU6b	[52]
	↑	↑	50	50	Yes	0.81		Plasma	SYBR	RNU6b	[109]
	↑		3	3	No			Plasma	SYBR	RNU6b	[78]
	↑	↑	20	20	Yes		Yes	Serum	TaqMan	cel-miR-39 miR-191-5p	[68]
	↑	↑	20	15	Yes			Plasma	NCode	cel-miR-39/-54/-238; miR-16	[110]
	↑	↑	39	38	Yes	0.671		Plasma	TaqMan	miR-16-5p	[26]
miR-23a	↑		14	17	No			Plasma	SYBR	Sp6	[64]
miR-23b	↑		50	138	Yes	0.80		Plasma	SYBR	RNU6b	[111]
miR-25	↔		10	10	No			Plasma	TaqMan	cel-miR-39	[104]
	↑		106	160	Yes	0.694-0.925	Yes	Plasma	TaqMan	cel-miR-39	[51]
	↑	↑	20	20	Yes			Plasma	TaqMan	cel-miR-39; RNU6b	[71]
	↑	↑	109	133	Yes	0.65	Yes	Plasma	SYBR	cel-miR-39; RNU6b	[88]
	↔	↑	70	70	Yes			Plasma	TaqMan	RNU6B	[112]
	↑		14	14	Yes			Serum	TaqMan	RNU6b	[75]
	↑		65	65	Yes	0.817		Plasma	TaqMan	RNU6b	[73]
miR-26a	↓		285	285	Yes	0.882	Yes	Plasma	TaqMan	cel-miR-39	[47]
miR-26b	↔		30	30	Yes			Plasma	TaqMan	RNU6b	[58]
miR-27a	↑		127	164	Yes			Serum	TaqMan	volume	[62]
	↑		82	82	No	0.67	Yes	Serum	TaqMan	cel-miR-39	[60]
	↔		30	30	No			Plasma	SYBR	cel-miR-39	[63]
	↔		15	31	Yes			Serum	TaqMan	cel-miR-39	[70]
	↑	↑	35	35	Yes	0.70	Yes	Plasma	TaqMan	RNU6b	[85]
miR-27b	↑		82	82	No	0.66	Yes	Serum	TaqMan	cel-miR-39	[60]
miR-296	↑	↔	20	20	Yes		Yes	Serum	TaqMan	cel-miR-39; miR-191-5p	[68]
	↑	↑	167	203	Yes	0.652	Yes	Serum+ Exosomes	SYBR	cel-miR-39 miR-16	[76]
miR-30a-5p	↔		20	20	No			Serum+ Exosomes	TaqMan	cel-miR-39	[69]
miR-30c	↑	↔	20	20	Yes		Yes	Serum	TaqMan	cel-miR-39; miR-191-5p	[68]
miR-31	↓		89	92	Yes		Yes	Serum	SYBR	miR-16	[61]
miR-32	↑	↑	40	40	No			Plasma	SYBR	RNU6b	[113]
miR-323-3p	↑	↔	20	20	Yes		Yes	Serum	TaqMan	cel-miR-39; miR-191-5p	[68]
miR-331	↑	↑	20	20	Yes		Yes	Serum	TaqMan	cel-miR-39; miR-191-5p	[68]
miR-335	↓	↓	7	4	No			Plasma	TaqMan	RNU6b	[114]
miR-34	↔		30	30	No			Plasma	SYBR	cel-miR-39	[63]
miR-346	↓		14	17	No			Plasma	SYBR	Sp6	[64]
miR-34a	↑		127	164	Yes			Serum	TaqMan	volume	[62]
miR-365	↑	↔	20	20	Yes		Yes	Serum	TaqMan	cel-miR-39; miR-191-5p	[68]
miR-370	↑	↑	12	40	Yes	0.79		Plasma	TaqMan	miR-16	[115]
miR-371-5p	↑		61	61	Yes		Yes	Serum	SYBR	RNU6b	[89]
miR-374	↑	↑	20	20	Yes		Yes	Serum	TaqMan	cel-miR-39; miR-191-5p	[68]
miR-375	↓	↓	20	20	No	0.835		serum	TaqMan	RNU6b	[116]
	↓	↓	39	38	Yes	0.32		Plasma	TaqMan	miR-16-5p	[26]
miR-376a	↔	↑	108	65	Yes			Plasma	TaqMan	RNU6B	[117]
miR-376c	↑		82	82	No	0.71	Yes	Serum	TaqMan	cel-miR-39	[60]
	↔		30	30	No			Plasma	SYBR	cel-miR-39	[63]
	↑	↑	108	65	Yes	0.77		Plasma	TaqMan	RNU6B	[117]

miR-378	↑	↓	61	61	Yes	0.861	Yes	Serum	SYBR	RNU6b	[89]
	↔		30	30	No			plasma	SYBR	cel-miR-39	[63]
	↓		14	17	No			Plasma	SYBR	Sp6	[64]
miR-421	↑		17	40	Yes	0.773		PBMC	SYBR	RNU6b	[118]
	↑		50	50	No		Yes	Serum (?)	SYBR	RNU6b	[119]
	↑		90	90	No	0.779		Serum	SYBR	RNU6b	[120]
	↑		90	90	No	0.821		PBMC	SYBR	RNU6b	[120]
miR-423-5p	↑		127	164	Yes			Serum	TaqMan	volume	[62]
	↔		30	30	No			Plasma	SYBR	cel-miR-39	[63]
miR-425	↔		58	57	Yes			Serum	TaqMan	miR-16	[49]
miR-433	↔		15	31	Yes			Serum	TaqMan	cel-miR-39	[70]
	↑	↔	20	20	Yes		Yes	Serum	TaqMan	cel-miR-39; miR-191-5p	[68]
miR-451	↑	↓	30	56	Yes	0.96	Yes	Plasma	TaqMan	RNU6b	[54]
	↔		90	90	Yes			Plasma	SYBR	cel-miR-39	[63]
	↑	↔	20	20	Yes		Yes	Serum	TaqMan	cel-miR-39; miR-191-5p	[68]
	↑		106	160	Yes	0.790-0.850	Yes	Plasma	TaqMan	cel-miR-39	[51]
	↔		73	206	Yes		Yes	Serum	SYBR	RNU6b	[82]
miR-484	↓	↓	14	17	No			Plasma	SYBR	Sp6	[64]
miR-486	↑	↓	30	56	Yes	0.92	Yes	Plasma	TaqMan	RNU6b	[54]
	↔		30	30	No			Plasma	SYBR	cel-miR-39	[63]
	↑		106	160	Yes	0.779-0.863	Yes	Plasma	TaqMan	cel-miR-39	[51]
	↓		14	17	No			Plasma	SYBR	Sp6	[64]
miR-501-3p	↔		73	206	Yes		Yes	Serum	SYBR	RNU6b	[82]
miR-518d	↑	↔	20	20	Yes		Yes	Serum	TaqMan	cel-miR-39; miR-191-5p	[68]
miR-518f	↑	↔	20	20	Yes		Yes	Serum	TaqMan	cel-miR-39; miR-191-5p	[68]
miR-627	↑	↑	111	123	Yes	0.937	Yes	Plasma	SYBR	RNU6B	[81]
miR-629	↑	↑	111	123	Yes	0.912	Yes	Plasma	SYBR	RNU6B	[81]
miR-652	↑	↑	111	123	Yes	0.918	Yes	Plasma	SYBR	RNU6B	[81]
miR-720	↔		30	30	Yes			Plasma	TaqMan	RNU6b	[58]
miR-744	↑		82	82	No	0.74	Yes	Serum	TaqMan	cel-miR-39	[60]
	↔		30	30	No			Plasma	SYBR	cel-miR-39	[63]
miR-92a	↑		106	160	Yes	0.732-0.913	Yes	Plasma	TaqMan	cel-miR-39	[51]
	↓		89	92	Yes		Yes	Serum	SYBR	miR-16	[61]
miR-92b	↑	↑	109	133	Yes	0.69	Yes	Plasma	SYBR	cel-miR-39; RNU6b	[88]
miR-93	↑	↑	20	20	Yes			Plasma	TaqMan	cel-miR-39; RNU6b	[71]
	↑		65	65	Yes	0.756		Plasma	TaqMan	RNU6b	[73]
miR-940	↓	↓	105	115	Yes	0.96	Yes	Plasma	SYBR	miR-16	[55]

GC: Gastric cancer; phen/chlor: Phenol-chloroform method; SYBR: SYBR Green; NA: Non available.

miRNAs is used. This has been implemented by multiple studies and has been shown of potential diagnostic benefit independently to its scientific objectivity and validity. For instance, we analyzed miRNAs expression in ascites and showed that miR-21 was upregulated in patients with peritoneal carcinomatosis compared to control group[31]. However, also patients with peritonitis demonstrated similar increase as patients with peritoneal carcinomatosis. To overcome this limitation, we used the proportion of miR-21 (cancer-associated) and miR-223 (inflammation-associated) to differentiate the groups[31]. For miR-16, the very high values of miR-16 in erythrocytes strongly suggest that other factors such as tumor anemia or hemolysis may have an additional impact on the results. Nevertheless, this does not necessarily mean that miR-16 is not suitable, but rather that we need to know the influential factors and to know exact biogenesis of miR-16 in circulation. Further studies are needed to provide the comprehensive view on patients-related factors.

An alternative normalization way has been proposed where multiple miRNAs can be used simultaneously. For instance, miRCURY LNA Universal RT microRNA PCR System offers internal standard including miR-103a-3p, miR-191-5p, miR-423-3p and -5p and miR-451. However, we strongly doubt the usefulness of this method, as every single of those selected miRNAs have been reported as deregulated in cancer and in particular GC (Table 1). Furthermore, miR-451 is highly dependent on hemolysis and may provide some unexpected bias in analysis. Thus, in similar way as addressed for miR-16, additional studies are needed to confirm the usefulness, biological suitability and stability of the methods.

DIFFERENTIALLY EXPRESSED CIRCULATING MIRNAS IN GC PATIENTS

In the Table 1, we have summarized the miRNAs that have been analyzed for the differential expression between GC patients and controls. According to our search, we identified 106 miRNAs that were studied in different studies. Among those, 13 miRNAs such as let-

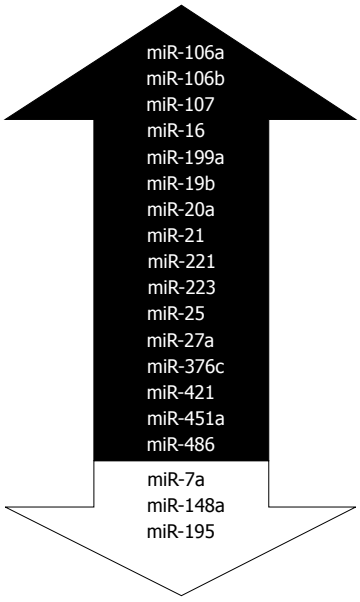

Figure 3 Schematic presentation of most frequently deregulated microRNAs in gastric cancer. Selection was made using following criteria: at least 3 reports with at least 2 reports with either up or downregulation.

7c, let-7g, miR-143-3p, miR-122, miR-192, miR-198 etc. showed no significant changes. As shown in in Table 1, multiple miRNAs have conflicting results showing differential expression in one cohort while no changes found in another. In the Figure 3 we summarize the most frequently deregulated miRNAs. Those were selected using two criteria: (1) at least 3 publications and (2) at least two with reproducible report on increased or decreased expression. Among the most consistent miRNAs are the miR-20a, miR-223 and miR-421. Among the most studied is the miR-21 with total 13 reports. Summarizing the data to miR-21 expression, three reports showed no differences while 10 reports show an upregulation of miR-21 both in sera and in plasma of GC patients. As shown in the Table 1, multiple groups used samples from independent cohorts to confirm the results, which substantially contributes to the quality of the reports.

To estimate the diagnostic potential of miRNAs as biomarkers in GC, multiple studies provided receiver operator curves (ROC) values. For instance, Konishi *et al*[54] reported the diagnostic accuracy for miR-451 reaching 0.96 with calculated sensitivity of 96% and specificity of 100%. Liu *et al*[55] studied miR-940 and reported the ROC value of 0.96 although with slightly lower sensitivity 81.2% and specificity 98.6%. Although those results are striking, we need to keep in mind that validation of the results from independent groups or cohorts in prospective studies are still to come. We believe that the data from our summary table will be helpful for the future search, validation and discussion of the results.

PROFILING OF CIRCULATING MIRNAS IN GC PATIENTS

It is well known that the most promising way to identify the potential biomarkers is the unbiased profiling of the samples. This approach was applied in the pivotal work by Chen *et al*[45] in 2008 in lung cancers, where the authors used multiple pooled samples for profiling and performed independent validation using qPCR. As shown in the Table 2[47,51,53-55,58,60,62,64,68,76,78,81,82,88,92,121], this approach was very intensively used for miRNA-profiling in GC patients. Among the total eighteen miRNA-profiling studies, 50% (9/18) reported the use of the pooled samples. Majority of studies used single technical pooled profiling from 5-40 samples for GC and controls. Although, this may be an appropriate way for proof-of-principle studies, it has several limitations where inappropriate changes of miRNAs in few subjects may create very strong deviation and bias and therefore independent validation is mandatory. Among the 18 profiling studies (Table 2), 11 reports studied miRNA in plasma, 6 in sera and 1 in blood samples. From the technical perspective there was substantial variation in use of extraction kits and profiling platforms used for analysis. Similar to the overall data in total cohort (Table 1), researches from China with 12 profiling studies provided the most overwhelming data. Remaining work comes from Poland, Japan, Turkey, Hong-Kong and United States. The first studies tend to use relatively small number of samples while more recent studies provide increasing number of samples and include an impressive number of samples for validation analysis as well[68,76].

FUTURE PERSPECTIVES AND CONCLUDING REMARKS

In this review, we systematically summarized and analyzed the existing data to miRNAs as non-invasive biomarkers for GC. There is no doubt that further studies with an improved study design will follow and it is a matter of time until the miRNA-based biomarkers will enter the clinical studies either in oncologic patients or patients with other diseases. However, following our critical review of the existing papers we would like to provide several cautionary notes for improvement.

Quality of reports

The era of proof-of-principle studies in GC has passed and with 75 published data it is time to improve the quality of the work. There are several ways that may be considered: (1) description of patient's cohort including Lauren's Classification, TNM staging and precise number of patients is necessary; (2) reporting of the methodological steps (extraction kits, measurements, reproducibility, validation *etc*.) need to be carefully reviewed and reported; (3) for primary research an independent cohort of samples need to be included; and (4) reporting of ROC/AUC values, sensitivity and specificity are currently used in quite biased way in proportion of GC patients to controls mostly in 1:1; however, in real-life settings the proportion will be at least 100-1000:1. Unless the prospective study is done it is clear that the real-life settings are not possible to achieve and additional effort is needed to increase the number of

Table 2 Profiling of circulating microRNAs in gastric cancer

Ref.	Year	Source	Extraction Kit	Platform	Sample Origin	GC (number of technical runs)	Controls (number of technical runs)	pooled samples	GC (number of pooled samples)	Controls (number of pooled samples)
Liu *et al*[62]	2011	Serum	phen/chlor	Solexa	China	1	1	Yes	20	20
Song *et al*[60]	2012	Serum	miRNeasy	qPCR-array	China	1	1	Yes	14	14
Liu *et al*[89]	2012	Serum	mirVana	Agilent	China	7	10	No		
Konishi *et al*[54]	2012	Plasma	mirVana	microarray	Japan	3	3	No		
Gorur *et al*[92]	2013	Plasma	high-pure miRNA Isolation	TaqMan Array	Turkey	1	1	Yes	20	190
Shah *et al*[121]	2013	Blood	miRNeasy	Geniom Biochip	Poland	1	1	Yes	8	19
Li *et al*[58]	2013	Plasma	mirVana	Agilent	China	20	20	No		
Zhu *et al*[51]	2014	Plasma	miRNeasy	TaqMan Array	China	1	1	Yes	40	40
Zhang *et al*[53]	2015	Plasma	mirVana	Agilent	China	16	18	No		
Zhou *et al*[88]	2015	Plasma	mirVana	Exiqon	China	3	1	Yes	30	10
Shin *et al*[81]	2015	Plasma	Trizol miRNeasy	miRCURY LNA	China	5	5	No		
Zhang *et al*[78]	2015	Plasma	mirVana	Agilent	China	3	3	No		
Liu *et al*[55]	2016	Plasma	miRNeasy	miRCURY LNA	Hong-Kong	5	5	No		
Qiu *et al*[47]	2016	Plasma	miRNeasy	Agilent	China	1	1	Yes	5	5
Treece *et al*[64]	2016	Plasma	miRCURY	GastroGenus miR Panel	United States	17	14	No		
Jiang *et al*[82]	2017	Serum	unknown	miSeq	China	2	1	Yes	20	10
Huang *et al*[76]	2017	Serum	mirVana	Exiqon	China	3	1	Yes	30	10
Sierzega *et al*[68]	2017	Serum	miRNA ABC Purification	TaqMan Array	Poland	20	20	No		

GC: Gastric cancer; phen/chlor: Phenol-chloroform method.

control sample.

Technical comparison between the studies

In the present review of the studies, there is a substantial technical heterogeneity among the studies: various extraction kits, qPCR methods and most importantly normalization. We have just recently published our data showing the differences between various extraction kits and miRNA expression in ascites[31]. Those results need to be taking to account and an independent validation of the primary samples will be needed. As we have recently reviewed[5], use of serum and plasma will probably have an independent effect on recovery and stability of miRNAs. Besides, contamination with various parts of circulating cells (erythrocytes, thrombocytes) may also provide an additional bias and caution in interpreting of miRNA data is necessary. As reviewed above, one of the larges differences among the studies is related to the choice of reference genes for normalization of miRNAs. Here we would like to caution the use of RNU6b for normalization of miRNAs and also probably reduce the use of miR-16 for normalization of circulating miRNAs unless additional studies provide the evidence for the objectivity of measurements.

High-risk patients

Taking to account the unique biology of GC, further focus should be made to identify the high-risk patients with the highest risk of GC development. For instance, patients with moderate to severe AG or IM are at increased risk for development of intestinal type of GC. Here, much more effort needs to be done to characterize the miRNA changes not only in GC but also in patients with preneoplastic conditions or lesions. It would be extremely interesting to know the cascade of changes in miRNA expression in subjects with hereditary diffuse GC.

GC-heterogenic disease

In currently available studies, all GC subtypes are pooled together and most effort is made to identify "all fits one" biomarkers for GC. This is definitely the most desirable way, where all GC patients could be diagnosed with the same biomarkers; however, we need also keep in mind that GC is a heterogenic disease with unique molecular alterations[17]. Since GC shows subtype-unique miRNA alterations, it may be very likely that circulating miRNAs, at least partly, may behave differently between intestinal and diffuse types of GC. With the knowledge of TCGA molecular classification, it would also very exciting to see if different molecular subtypes have characteristic circulating miRNA expression pattern.

Beyond miRNAs: Value of isomiR's in GC

High throughput genomic data sequencing showed that conventional miRNAs may differ both in length of the molecule and its' sequence[122,123]. These variant miRNA-sequences are now being referred to as isoforms of miRNAs or isomiR's. Up to date, the role of these molecules in GC remains largely unexplored. Nevertheless, increasing number of studies point out important deregulation patterns of isomiR's in cancer. For instance, in a recent study, we identified 219 deregulated isomiR'

s between gastrointestinal stromal tissue and tumor adjacent tissues[124]. To our knowledge, the only study that investigated isomiR's in GC found that certain isomiR-types preferentially occur in normal gastric tissue but other types prefer GC tissue[122]. Although these data may be available, no published data is available to isomiR's changes in blood samples of GC patients and may be focus of future studies.

Circulating tumor cells and miRNA analysis

As discussed in above, multiple studies have shown that circulating miRNAs may serve as diagnostic biomarkers for GC; however, the origin of these molecules is not fully clear. Using profiling data from sera and tumor tissues, Sierzega *et al*[68] identified differences in expression pattern in GC patients; however, miRNA expression data analysis did not support the conclusion that circulating miRNA originate primarily from the tumor tissue. Hence, it remain open if exosomal miRNAs or even certain blood-cells-related miRNAs may be more promising to study[27]. Furthermore, flow-cytometry or microfluidic-based single-cell or cell-type specific sequencing analysis may provide more specific transcription patterns with higher diagnostic and prognostic value[125]. Therefore, additional studies employing single-cell based analysis from blood samples of GC patients are needed in order to identify more sensitive and specific biomarkers.

CONCLUSION

During the past 7 years, large amount of data has been gathered to support the need for intensive research on miRNA-based biomarkers in GC. In this review, we systematically summarized the data to miRNAs as non-invasive diagnostic biomarkers in GC. Meticulous analysis of the published work revealed relatively high level of heterogeneity not only in methodological and technical aspects, but also in reporting quality of the studies. At present, no miRNA-based biomarkers are ready to be implemented for GC-screening other than in research studies; however, the provided data clearly highlight the potential of miRNAs as diagnostic biomarkers and also highlight the need for the further improvement. We hope that this first of its kind comprehensive review with critical points may lead to a "next wave" of "second generation" comprehensive studies that take into account not only technical aspects of miRNA research but also unique aspects of GC biology.

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