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REVIEW

Emerging circulating MiRNAs and LncRNAs in upper gastrointestinal cancers

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ABSTRACT

Introduction: Circulating non-coding RNAs (ncRNAs) possess high stability in circulation, making them capable of being utilized in the diagnosis, prognosis, and treatment of upper gastrointestinal (GI) tract cancers.

Areas covered: Herein, the potential clinical application of emerging circulating miRNAs and lncRNAs in upper GI cancers are comprehensively reviewed.

Expert opinion: For esophageal cancer (EC), the circulating miRNAs, miR-21, miR-223, and miR-375 have been validated as promising diagnostic biomarkers in a meta-analysis. For gastric cancer (GC), miR-17, miR-18a, miR-21, miR-25, miR-223, miR-451, and lncRNA-H19 have been reported in several studies and are likely to be promising biomarkers. Unlike EC, many circulating lncRNAs have been newly reported for GC and each is often limited to one study. They show excellent or outstanding discrimination performance, such as XIST, LOC100506474, UCA1, LINC00467, ZNFX1-AS1, HULC, AA174084, CEBPA-AS1, MIAT, PCSK2-2:1, HOTTIP, H19 (AUCs 0.8 to 0.9), and particularly CUDR, LSINCT-5, PTENP1, HOTAIR, and LncRNA-GC1 (AUCs > 0.9). Most importantly, using a group of ncRNAs as a diagnostic panel would give a more promising diagnostic or prognostic performance. However, different clinical trials and large, multi-center cohorts as well as comprehensive meta-analyses should also be conducted to validate and use emerging circulating ncRNAs as the indicators of GI cancers.

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1. Introduction

Cancers are the most relevant issue of public health worldwide. Gastrointestinal (GI) cancers, with a high mortality worldwide, are amongst the most popular causes of cancer-related deaths. Upper GI cancers include esophageal and gastric cancers (EC and GC). EC is the eighth most common malignant tumor and the sixth major cause of cancer-related deaths throughout the world. The incidence of EC is different in various geographical locations, and esophageal squamous cell carcinoma (ESCC) is considered the most popular type of EC, which causes over 400,000 deaths every year [1,2]. GC is a prevalent disorder in the digestive system; it is the fifth pervasive type of cancer (6.8%) worldwide, and the third cause of cancer mortality (8.8%). In spite of the decrease in its occurrence in some parts of the world, GC is still a crucial clinical challenge as most patients are diagnosed at advanced stages, with poor prognosis and restricted treatment choices [2].

GI cancers have been identified as major cancer types associated with major health complications. Therefore, accurate and novel biomarkers, applying less invasive approaches, are needed to enhance the detection of GI cancers. Less than 2% of the human genome encodes proteins, which are about 19,000 to 21,000 protein-coding genes. Most genomes are non-protein-coding, and about 60 to 70% of the human transcriptome is made of non-coding RNAs (ncRNAs). ncRNAs consist of long non-coding RNAs (lncRNAs), piwi-interacting RNAs (piRNAs), microRNAs (miRNAs), and transfer RNAs (tRNAs), which possess no capacity to encode proteins [3]. Research shows that these ncRNAs manifest high stability in circulation. Circulating biomarkers are considerably effective in clinical applications including disease diagnostics, therapeutic effect monitoring, and recurrence prediction in patients with cancer [3]. MiRNAs and lncRNAs have been widely studied in the last years. These ncRNAs can be found in plasma or serum samples; they may potentially function as circulating biomarkers for prognosis, diagnosis, and chemosensitivity in different cancer types [3,4]. Aberrant expression of many ncRNAs in a variety of human cancers shows a potential role of ncRNAs in tumor initiation, progression, and metastasis [5–7]. Endogenous miRNAs are non-coding, single-stranded, and small RNAs (21–22 nucleotides), regulating gene expression through integrating into RISC – an RNA-induced silencing complex. Following they preferentially bind to specific sequences at the 3′-UTR of their target mRNAs, suppressing translation or inducing degradation of mRNA [8].

Among numerous types of miRNAs, two cancer-related miRNAs, miR-34 and miR-21, are often deregulated in GICs tissues. Tumor-suppressive miR-34 is down-regulated and oncogenic miR-21 is up-regulated by epigenetic and genetic alterations, and by an inflammatory microenvironment in human GI cancers [6,7]. LncRNAs (ncRNAs longer than 200 nucleotides) are emerging elements that are crucial in cancer

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progression and development. They are also involved in numerous developmental and biological processes like X–inactivation (lyonization), cell pluripotency induction, or gene imprinting. RNA silencing is the sequence-specific regulation of gene expression via double-stranded RNAs. LncRNAs contribute to each stage of the carcinogenesis/tumor progression via affecting the key pathways of cancer-related signal transduction like mTOR, WNT/β-catenin, EGFR, PI3K/Akt, NOTCH, and TP53 [9–11]. Many ncRNAs have been found to affect the gene expression rates through changing the chromatin, transcription, and post-transcriptional processing [12]. LncRNAs like miRNAs can act as oncogenes or tumor-suppressors, and are capable of regulating proliferation, angiogenesis, and invasion or metastasis of cancer cells. While lncRNAs are up- or down-regulated in cancers, most of them are up-regulated in normal tissues regarding their canonical expression [13]. The only ncRNA translated into a molecular diagnostic test is PCA3, approved by the Food and Drug Administration (FDA) [14]. Circulating miRNAs and lncRNAs possess the essential conditions that are measured as biomarkers in many types of cancers, repeatedly and noninvasively, to distinguish patients from healthy individuals. Herein, we summarized the origins of circulating ncRNAs and assessed the current molecular biomarkers which can be considered as noninvasive biomarkers for the diagnosis, prognosis, and treatment of upper GI cancers. Finally, we focused on current therapeutic strategies targeting ncRNAs and their delivery systems.

2. The origin of circulating ncRNAs

There are numerous hypotheses which take the circulating ncRNAs into account in various body fluids, like blood, plasma or serum [15]. These involve the passive release of ncRNAs from broken cells after tissue damage, cell necrosis or apoptosis, chronic inflammation, and from the cells with a short half-life (e.g., platelets). Cell fragments are transported in apoptotic bodies from dying cells when apoptosis happens, which are engulfed through neighboring living cells via phosphatidylserine signaling [16]. Particular miRNAs increase in blood after hepatobiliary injury or myocardial infarction [17]. Although an alternative hypothesis is not exclusive mutually, membrane-bound vesicles including microvesicles and exosomes are the main origins of circulating ncRNAs [18]. The ncRNAs can take part in modulating cellular functions, like hematopoiesis, angiogenesis, exocytosis, and tumorigenesis when these vesicles are received by the recipient cells [18]. RNA binding proteins (RBPs) or lipidproteins including nucleophosmin, HDL, or Argonaute proteins are able to modulate the gene expression. RBPs along with miRNAs might be effective in protecting miRNAs from degradation. RBPs are involved in many parts of mRNA maturation process, like pre-mRNA splicing and transport of mRNA, localization, and translation [19]. These circulating miRNAs have the ability to enter the recipient cells and reduce the protein levels of the target genes. The highest number of circulating miRNAs is assumed to result from cell-oriented vesicles, which has been challenged in two different studies indicating that the higher than 90% of the miRNAs within the blood have no membrane and are related to Argonaute proteins [20]. Several released miRNAs cannot be found within the parental cells [21]. Another assumption states that a large number of circulating miRNAs possibly result from the blood cells and other body parts, thus cancer-related circulating miRNAs are likely to originate from immunocytes in the microenvironment of the tumors or from other responses mediated by the affected system or organ [22]. A large number of research has shown a similar course regarding the change among circulating ncRNAs and tissue ncRNAs. Therefore, determining the association among circulating ncRNAs and tissue ncRNAs would help us to understand the origin of circulating ncRNAs. However, it is not yet clear whether tumor-associated circulating ncRNAs result from tumor cell death and lysis or are released through tumor cells (Figure 1).

3. Circulating ncRNAs in EC

3.1. Circulating miRNAs in EC diagnosis

Sensitive biomarkers are required for the early EC detection to decrease the high death rate of the disease. There is limited evidence regarding the importance of circulating miRNAs within the blood as a forecasting biomarker for EC. In a meta-analysis study, miR-21 and miR 223 were markedly overexpressed, while the expression level of miR 375 was decreased in esophageal squamous cell carcinoma (ESCC) patients compared to healthy individuals. The areas under the curves (AUCs) were 0.80, 0.73, and 0.69 for miR-21, miR-223, and miR-375, respectively. The AUCs increased when discriminating between patients with early ESCC in stage 0-I and the noninvasive carcinoma stage Tis-T1 from controls. Thus, it was proposed that plasma miR-21, miR-223, and miR-375 may serve as diagnostic biomarkers in patients with ESCC, especially early ESCC in stages 0-I and Tis-T1 [23]. Three types of miRNA (miR-21/miR-25/miR-145) in serum were assumed as potential biomarkers for ESCC. Furthermore, the expression level of miR-145 in serum was up-regulated, compared with the downregulation reported in previous studies in ESCC tissues and cells [24]. MiR-21, miR-184, and miR-221 are proven as oncogenic miRNAs and miR-375 as a tumor suppressive miRNA, revealing that the miR-21 to miR-375 ratio in plasma can be applied in the diagnosis of squamous cell carcinoma (SCC) [25]. MiR-10a, miR-100, miR-223, miR-148b, miR-133a, miR-22, and miR-127-3p were also indicated as a diagnostic index. These miRNAs, individually or in combination, had great diagnostic capacity [26]. The profiles of miR-25-3p, miR-100-5p, miR-151a-3p, and miR-375 possibly act as serum biomarkers to diagnose EC patients, and circulating miRNA profile might be beneficial in clinical applications for early diagnosis or response of treatment in EC patients [27]. Huang et al. found that exosomal miR-20b-5p, miR-192-5p, miR-28-3p, miR-223-3p, and miR-296-5p were overexpressed significantly in patients with ESCC. The 5-miRNA signature diagnostic value was validated through an external cohort [28]. The expression level of miR-718 in plasma is also down-regulated in individuals with ESCC. The plasma miR-718 can function as a diagnostic marker for ESCC detection [29].

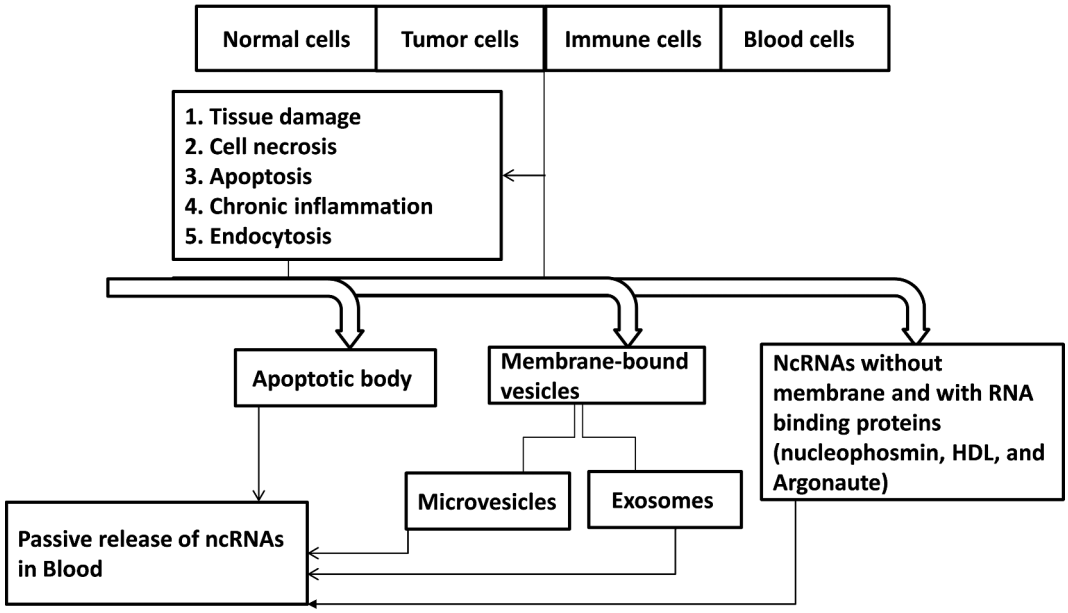

Figure 1. The origin of circulating ncRNAs and several manners of them encapsulation.

Sixty-two miRNAs were prioritized differentially and expressed among responders and non-responders to neoadjuvant chemotherapy (NAC); of 62 miRNAs, miR-193b-5p, miR-873-3p, and miR-23a-5p were highly expressed in non-responders. As indicated by qPCR analysis, the serum expression levels of miR-193b-5p and miR-873-3p were significantly higher in non-responders between three chosen miRNAs. Niwa et al. generated 2-miR-model (miR-873-3p and miR-193b-5p), 2-miR + lymphatic invasion (ly) model, and 3-miR-model, obtaining better area under the ROC curves compared to single miRNAs as 2-miR-model, 0.70, 3-miR-model, 0.70, and 2-miR + ly, 0.73. The detective power of the combined model was compared: 2-miR + ly for discrimination of non-responders to NAC to other pre-treatment clinical characteristics. So, 2-miR + ly model was better compared to serum SCC antigen with high significance and to ly and clinical T stage with slight significance. MiR-652 and miR-660 expression levels significantly rose in SCC patients, compared to healthy individuals (Table 1) [30].

3.2. Circulating miRNAs in EC diagnosis and prognosis

miR-9 within plasma were remarkably up-regulated for individuals with ESCC than healthy individuals. High concentrations of plasma miR-9 were associated with large tumor size, lymph node metastasis, deep local invasion, poor tumor differentiation, and poor survival. Multivariate survival analysis proved plasma miR-9 as an independent ESCC prognostic factor. It was up-regulated in ESCC and may function as a novel prognostic and diagnostic biomarker [52]. MiR-367 is up-regulated aberrantly in ESCC patients' serum and tumors, while it is down-regulated in ESCC patients after being treated with chemotherapy and esophagostomy. MiR-367 is a potential ESCC biomarker and may function as an oncogene in the regulation of ESCC development [53]. The abnormal expression for serum miRNA-1246 has been reported as a prognostic factor of ESCC. Both miR-1246real and miR-1246pred were independent predictors of overall survival. MiR-1246pred generated by radiogenomics was similar to miR-1246real in predicting ESCC prognosis (Table 1) [54].

3.3. Circulating lncRNAs in EC diagnosis

The serum HOTAIR expression level was significantly higher in ESCC patients compared to healthy people (AUC 0.793). Serum HOTAIR might act as a biomarker for ESCC diagnosis [55]. It is approved that the increased levels of CFLAR-AS1, Linc00152, and POU3F3 might be promising biomarkers for predicting the early progress with the AUCs of 0.651, 0.698, and 0.584, respectively. The three circulating lncRNAs might function as promising biomarkers for the prediction of the early incidence of ESCC. The plasma levels of POU3F3, SPRY4-IT1, and HNF1A-AS1 were remarkably greater in individuals with ESCC than healthy ones. POU3F3 rendered the best diagnostic performance for detecting ESCC with an AUC of 0.842; sensitivity of 72.8%, and specificity of 89.4% [56,57].

Exosomal ZFAS1 was also up-regulated and miR-124 was down-regulated in ESCC tissues that enhanced the proliferation, migration and invasion of ESCC cells and stopped their apoptosis through up-regulating the STAT3 and down-regulating the miR-124, leading to the tumorigenesis of ESCC [58]. Exosomal PCAT1 has been shown to contribute to various human cancers such as ESCC. PCAT1 expression level was greatly up-regulated in ESCC tissues and cell lines. PCAT1 knockdown hindered the ESCC cell growth, while its overexpression revealed the opposite impact *in vitro* and *in vivo*. PCAT1 knockdown arrested the cell cycle at G2/M phase, decreased the cyclin B1 and CDC2 expression, and made cells more sensitive to paclitaxel. Moreover, PCAT1 might bind to miR-326, which is a tumor suppressor in various human cancers. Rescue investigations showed that an

Table 1. The circulating ncRNAs features effective in diagnosis and/or prognosis of EC.

NcRNAs	No. Cases, Controls	Expression change, Source	Sensitivity, Specificity – AUC	Type of biomarker	References
MiRNA					
miR-10a	290, 140	Up-regulated, Serum	81.2%, 80.0% – 0.886	Diagnostic	[26]
miR-22		Up-regulated, Serum	88.6%, 86.0% – 0.949	Diagnostic	
miR-100		Up-regulated, Serum	63.8%, 81.0% – 0.817	Diagnostic	
miR-148b		Up-regulated, Serum	66.4%, 87.0% – 0.855	Diagnostic	
miR-223		Up-regulated, Serum	83.2%, 83.0% – 0.911	Diagnostic	
miR-133a		Up-regulated, Serum	65.1%, 83.0% – 0.830	Diagnostic	
miR-127-3p		Up-regulated, Serum	78.5%, 87.0% – 0.899 AUC for panel = 0.929	Diagnostic	
miR-25-3p, miR-151a-3p	10, 11	Up-regulated, Serum	NR	Diagnostic	[27]
miR-100-5p, miR-375		Down-regulated, Serum	NR	Diagnostic	
miR-223, miR-375	194, 94	Down-regulated, Serum	NR – 0.734 and 0.720, respectively	Prognostic	[31]
miR-21, miR-375	126, 86	Up-regulated, Serum	NR – 0.796 and 0.712, respectively AUC = 0.832 for both miR-21/miR-375	Diagnostic	[32]
miR-21	33, 32	Up-regulated, Serum	71%, 96.9% – 0.88	Diagnostic	[24]
miR 25		Up-regulated, Serum	71%, 68.8% – 0.72	Diagnostic	
miR-145		Up-regulated, Serum	90.3%, 68.8% – 0.83	Diagnostic	
miR-367	35, 35	Down-regulated, Serum	NR	Diagnostic	[33]
miR-200 c	64, 64	Up-regulated, Serum	NR	Prognostic	[34]
miRNA-718	120,51	Down-regulated, Plasma	69.2%, 66.7% – 0.715	Diagnostic	[29]
miR-1246	92, 92	Up-regulated, Serum	71.2%, 73.9% – 0.754	Prognostic	[54]
miR-146a	154, 154	Down-regulated, Serum	85.7%, 68.6% – 0.863 (discovery group), 82.1%, 83.3% – 0.891 (validation group)	Diagnostic; Prognostic	[35]
miR-21	Meta-analysis	Up-regulated, Plasma	74%, 78% – 0.80	Diagnostic	[23]
miR-223		Up-regulated, Plasma	68%, 68% – 0.73	Diagnostic	
miR-375		Down-regulated, Plasma	78%, 59% – 0.69	Diagnostic	
miR-31	121, 121	Up-regulated, Serum	86.7%, 84.3% – 0.902 (discovery group), 0.888 (validation group)	Diagnostic; Prognostic	[36]
miR-1322	120, 120	Up-regulated, Serum	81.7%, 82.5% – 0.847 (discovery group), 0.845 (validation group)	Diagnostic	[37]
miR-1246	10, 46	Up-regulated, Serum	71.3%, 73.9% – 0.754	Diagnostic; Prognostic	[38]
miR-16, miR-21	38, 19	Up-regulated, Plasma	NR – 0.643 and 0.690, respectively.	Diagnostic; Prognostic	[39]
miR-185		Up-regulated, Plasma	NR – 0.697	Diagnostic	
miR-375		Up-regulated, Plasma	NR – 0.921	Diagnostic	
miR-155	60, 60	Down-regulated, Plasma	NR – 0.66	Diagnostic	[40]
miR-218	106, 60	Down-regulated, Serum	71.7%, 76.7% – 0.833	Diagnostic	[41]
miR-20a	70, 40	Up-regulated, Plasma	64.3%, 75.0% – 0.767	Diagnostic	[42]
let-7a		Down-regulated, Plasma	74.3%, 85.0% – 0.829	Diagnostic	
miR-18a	106, 54	Up-regulated, Plasma	86.8%, 100% – 0.944	Diagnostic	[43]
miR-107	14, 17	Down-regulated, Serum	NR – 0.713	Diagnostic	[44]
miR-613	75, 75	Down-regulated, Serum	81.3%, 62.7% – 0.767	Diagnostic; Prognostic	[45]
miR-365	69, 14	Up-regulated, Serum	80.5%, 86.7% – 0.831	Diagnostic	[46]
miR-129		Up-regulated, Serum	78.8%, 73.3% – 0.792	Prognostic	
miR-10b	50, 50	Down-regulated, Serum	76%, 84% – 0.85	Predictive Biomarker	[47]
miR-29 c		Down-regulated, Serum	68%, 68% – 0.72	Predictive Biomarker	
miR-205		Down-regulated, Serum	70%, 64% – 0.72	Predictive Biomarker	
miR-10b	29, 16	Down-regulated, Plasma	NA	Diagnostic	[48]
miR-25, miR-100, miR193-3p, miR-194, miR-223, miR-337-5p and miR-483-5p	63, 63	Up-regulated, Serum	81%, 81% – 0.83 for panel	Diagnostic; Prognostic	[49]
miR-9	131, 131	Up-regulated, Plasma	85.5%, 98.5% – 0.913	Diagnostic; Prognostic	[52]
miR 23a-5p, miR-193b-5p, miR-873-3p	100, 100	Up-regulated, Serum	NR – 0.58, 0.61, and 0.68, respectively	NR	[30]
miR-331–3p	32, 40	Down-regulated, Serum	NR	Predictive Biomarker	[50]

(*Continued*)

Table 1. (Continued).

NcRNAs	No. Cases, Controls	Expression change, Source	Sensitivity, Specificity – AUC	Type of biomarker	References
miR-20b-5p, miR-28-3p, miR-192-5p, miR-223-3p, miR-296-5p	32, 32	Up-regulated, Serum-Exosomes	NR – 0.731, 0.656, 0.662, 0.736, and 0.689, respectively (0.741 for panel)	Diagnostic	[28]
RNU6-1/miR16-5p, miR-25-3p/miR-320a, let-7e-5p/miR-15b-5p, miR30a-5p/miR-324-5p, miR-17-5p/miR-194-5p	18, 29	Dys-regulated, Serum-Exosomes	NR – 0.99	Diagnostic	[51]
LncRNA					
Linc00152, CFLAR-AS1, POU3F3	82, 210	Up-regulated, Plasma	NR – 0.698, 0.651, and 0.584, respectively	Predictive Biomarker	[56]
HOTAIR	42, 20	Up-regulated, Serum	56.0%, 90.0% – 0.793	Diagnostic	[55]
SPRY4-IT1, HNF1A-AS1, POU3F3	147, 147	Up-regulated, Plasma	72.8%, 89.4% for POU3F3; Levels of HNF1A-AS1 and SPRY4-IT1 in plasma were less sensitive (32.7% and 48.2%, respectively), AUC = 0.800, 0.781, and 0.842, respectively	Diagnostic	[57]
PCAT1	39, 39	Up-regulated, Serum-Exosomes	NR	NR	[59]
ZFAS1	136, 136	Up-regulated, Serum-Exosomes	NR	NR	[58]

enforced miR-326 expression decreased the promotive impact of PCAT1 on ESCC cell growth (Table 1) [59].

4. Circulating ncRNAs in GC

4.1. Circulating miRNAs in GC diagnosis

The expression levels of miR-21 and miR-222 were remarkably greater in plasma of the patients with GC compared to healthy individuals. The specificity and sensitivity in plasma and for miR-21 were72.2% and 86.7% and for miR-222 were 56.2% and 62.5%, respectively. According to bioinformatics analysis, most target miR-21 and miR-222 genes affect signaling pathways related to cancer including tumor initiation and progression. The expression levels of miR-21 and miR-223 increased in GC tissues, which was in accordance with their circulating expression levels. The miR-21 and miR-223 expression levels in the plasma were meaningfully greater in patients with GC compared to the healthy controls, while miR-218 was lower significantly. The miR-21, miR-223, and miR-218 combination gave 0.9531 AUC with 84.29% sensitivity and 92.86% specificity in differentiating patients with GC from healthy individuals. Using a single miRNA as a biomarker in the plasma for detecting GC yielded 84.29% and 74.29% sensitivity values, 88.57% and 75.71% specificity values, and 0.9089 and 0.7944 AUC values for miR-223 and miR-21, respectively [60].

The serum expression levels of miR-223, miR-16, and miR-100 were remarkably increased in the individuals with GC than the healthy ones, and AUC was obtained as 0.85, 0.90, and 0.71 for miR-223, miR-16, and miR-100, respectively in the diagnosis of GC. The miR-223 specificity and sensitivity were 78% and 81%, respectively. MiR-16 had a sensitivity and specificity of 79% and 78%, respectively while the highest sensitivity and specificity of miR-100 were equal to 0.71 and 0.58, respectively, showing that serum miR-16, miR-223, and miR-100 may act as biomarker candidates for the diagnosis of GC [61]. MiR-199a, miR19a, miR-18a, miR-21, miR-92a, and miR-421 were selected to validate their diagnostic effectiveness. Of them, five microRNAs in patients with GC had significantly different expressions. The miR-92a and miR-19a combination had the largest AUC at 0.850 with 91.3% sensitivity and 61.0% specificity. The analysis of GC/MS carried out a great diagnostic value, and the AUC became 1.0 [62]. In a large sample set, Wu et al. validated the high diagnostic performance of serum miR-421 with 95.5% maximal sensitivity, 89.1% maximal specificity, and 0.821 maximal AUC. The miR-421 expression level in tissues of GC was up-regulated, consistent with the levels of circulation [63]. Sierzega et al. found that 20 miRNAs in GC patients' serum represented the higher expression levels compared to the controls. Nevertheless, only seven molecules were highly expressed in primary tumors (miR-130a, miR-19a, miR-331, miR-106a, miR-223, miR-21, and miR-374). Furthermore, miR-331 and miR-21 expressions were considerably higher in the peripheral circulation in comparison with tumor-draining veins of the portal system (Table 2) [64].

The serum miR-17 expression level was decreased significantly in benign gastric disease and GC patients compared to healthy individuals. The AUC was 0.879 for serum miR-17 to distinguish patients with GC from healthy controls, with 90.6% sensitivity and 57.5% specificity. To distinguish controls from benign gastric disease patients, the AUC, specificity, and sensitivity of serum miR-17 were 0.725, 81.2%, and 62.9%, respectively [99]. Cai et al. found that plasma miR-20a, miR-106b, and miR-221 could act as noninvasive biomarkers for the detection of GC with the AUCs of 0.8593, 0.7733, and 0.7960, respectively [100]. The serum miR-196a was down-regulated significantly in patients with post-operative GC compared to patients with pre-operative GC; the serum miR-196a expression level was increased significantly when patients experienced a recurrence [101]. Su et al. validated the plasma miR-18a diagnostic value for GC diagnosis and showed the AUC, sensitivity, and specificity values of 0.907, 80.5%, and 84.6%, respectively, for distinguishing GC patients from healthy individuals. STAT3 was indicated as the miR-18a target to enhance its onco-miRNA activity in GC. The plasma/serum miR-18a, in addition to GC, showed potential as a next-generation

Table 2. The circulating miRNAs features effective in diagnosis and/or prognosis of GC.

miRNAs	No. Cases, Controls	Expression change, Source	Sensitivity, Specificity – AUC	Type of biomarker	References
miR-1, miR-20a, miR-27a, miR-34a, miR-423-5p	164, 127	Up-regulated, Serum	80%, 81% – 0.879, for panel	Diagnostic	[65]
miR-15b-5p	100, 100	Up-regulated, Plasma	NR	Diagnostic	[66]
miR-223	50, 47	Up-regulated, Serum	81%, 79% – 0.85	Diagnostic	[61]
miR-16		Up-regulated, Serum	71%, 78% – 0.9	Diagnostic	
miR-100		Up-regulated, Serum	78%, 58% – 0.71	Diagnostic	
miR-518 f, miR-130a, miR-212, miR-220, miR-433, miR-518d, miR-331, miR-19a, miR-365, miR-374, miR-296, miR-323-3p, miR-21, miR-146b, miR-146a, miR-106a, miR-223, miR-19b, miR-451, miR-30 c	20, 20	Up-regulated, Serum	NR	NR	[64]
miR-23a, miR-103, miR-221a	17, 14	Up-regulated, Plasma	NR	Diagnostic	[67]
miR-378, miR −346, miR −486-5p, miR −200b, miR −196a, miR −141, miR-484	17, 14	Down-regulated, Plasma	NR	Diagnostic	
miR-23b	138, 50	Up-regulated, Plasma	71.0%, 74.0% – 0.80	Prognostic	[68]
miR-26a	285, 285	Down-regulated, Plasma	83.6%, 81.5% – 0.882	Diagnostic	[69]
miR-142-3p		Down-regulated, Plasma	74.4%, 84.1% – 0.839	Diagnostic	
miR-148a		Down-regulated, Plasma	75.4%, 83.1% – 0.842	Diagnostic	
miR-195		Down-regulated, Plasma	69.2%, 75.4% – 0.765	Diagnostic	
miR-221, miR-744, and miR-376 c	82, 82	Up-regulated, Serum	NR – 0.70, 0.74, and 0.71, respectively	Diagnostic	[106]
miR-31, miR-181b, miR-203, miR-21, miR-92a	92, 89	Down-regulated, Serum	90%, 96% – 0.933 (Training set), 85.5%, 98.3% – 0.919 (Validation set)	Diagnostic	[70]
miR-25	184,78	Up-regulated, Serum	69.4%, 84.6% – 0.768	Diagnostic; Prognostic	[107]
miR-32	40, 40	Up-regulated, Plasma	NR	Diagnostic	[71]
miR-17	40,36	Down-regulated, Serum	80.6%, 87.5% – 0.879	Diagnostic	[99]
miR-106b		Down-regulated, Serum	75.0%, 92.5% – 0.856 83.3%, 87.5% – 0.913 for panel	Diagnostic	
miR-106a,	90, 27	Up-regulated Whole blood	48.15%,51.85% – 0.684	Diagnostic	[72]
miR-17		Up-regulated Whole blood	90.24%, 92.68% – 0.74 62.96%, 80.49% – 0.741 for panel	Diagnostic	
miR-16, miR-25, miR-92a, miR-451, miR-486-5p	106, 160	Up-regulated, Plasma	84.1%, 90.8% – 0.89 for panel	Diagnostic	[73]
miR-223	60, 60	Up-regulated, Plasma	84.29%, 88.57% – 0.908	Diagnostic	[60]
miR-21		Up-regulated, Plasma	74.29%,75.71% – 0.794	Diagnostic	
		Up-regulated, Plasma	84.29%, 92.86% – 0.953 for panel		
miR-218		Down-regulated, Plasma	94.29%, 44.29% – 0.7432	Diagnostic	
miR −106b-25	20, 20	Up-regulated, Plasma	NR	Diagnostic	[74]
miR-107	36, 36	Up-regulated, Serum	NR – 0.63	Diagnostic	[75]
miR10b-5p, miR132-3p, miR185-5p, miR195-5p, miR20a3p, miR296-5p	203, 167	Up-regulated, Serum	NR – 0.627, 0.652, 0.637, 0.683, 0.637, and 0.652, respectively (0.703 for panel)	Diagnostic	[76]
miR-223, miR-19b-2, miR-194, miR-141, miR-1233)	3, 3	Down-regulated, Plasma	NR	Diagnostic	[77]
miR-130a	41, 41	Up-regulated, Serum	NR – 0.905	Diagnostic	[78]
miR-21	25, 18	Upregulated, Whole blood	96.80%, 95.10% – 0.993	Diagnostic	[79]
miR-196a-1		Up-regulated, Whole blood	94.30%, 82.90% – 0.948	Diagnostic	

(*Continued*)

Table 2. (Continued).

miRNAs	No. Cases, Controls	Expression change, Source	Sensitivity, Specificity – AUC	Type of biomarker	References
miR-146b		Up-regulated, Whole blood	91.11%, 78.05% – 0.935	Diagnostic	
miR-17		Up-regulated, Whole blood	77.46%, 90.24% – 0.909	Diagnostic	
miR-181a-1		Up-regulated, Whole blood	82.86%, 87.80% – 0.931	Diagnostic	
miR-1-2		Down-regulated, Whole blood	78%, 84.40% – 0.903	Diagnostic	
miR-139		Down-regulated, Whole blood	87.80%, 84.80% – 0.930	Diagnostic	
miR-133b		Down-regulated, Whole blood	85.36%, 84.1% – 0.909	Diagnostic	
miR-133a-2		Down-regulated, Whole blood	76.75%, 92.68% – 0.905	Diagnostic	
miR-144	96, 40	Down-regulated, Serum	71.5%, 83.6% – 0.821	Diagnostic; Prognostic	[80]
miR-181 c	30, 60	Up-regulated, Plasma	NR	Diagnostic	[81]
miR-378	61, 61	Up-regulated, Serum	87.5%,70.73% – 0.861	Diagnostic	[103]
miR-371-5p		Up-regulated, Serum	75%, 63.41% – 0.715	Diagnostic	
miR-187-3p		Up-regulated, Serum	82.5%, 60.98% – 0.704	Diagnostic	
miR-18a	82, 65	Up-regulated, Plasma	80.5%, 84.6% – 0.907	Diagnostic	[102]
miR-18a	104, 65	Up-regulated, Plasma	84.6%, 69.2% – 0.805	Diagnostic	[82]
miR-18a	235, 136 (meta-analysis)	Up-regulated, Plasma	76%, 73% – 0.82	Diagnostic	[83]
miR-191	57, 58	Up-regulated, Serum	70.2%, 99.9% – 0.849	Diagnostic	[84]
miR-106b	60, 60	Up-regulated, Plasma	NR – 0.773	Diagnostic	[100]
miR-20a		Up-regulated, Plasma	NR – 0.859	Diagnostic	
miR-221		Up-regulated, Plasma	NR – 0.796	Diagnostic	
miR-122	36, 36	Down-regulated, Serum	NR – 0.815	Diagnostic	[85]
miR-192		Up-regulated, Serum	NR – 0.818	Diagnostic	
miR-195-5p	20, 190	Down-regulated, Plasma	NR	Diagnostic	[104]
miR-196a	20, 80	Up-regulated, Serum	NR	Diagnostic	[101]
miR-199a-3p	80, 70	Up-regulated, Plasma	74%, 75% – 0.818	Diagnostic	[86]
miR-200 c	52, 15	Up-regulated, Whole blood	65.4%, 100% – 0.715	Diagnostic; Prognostic	[108]
miR-204	115, 40	Down-regulated, Serum	NR	Prognostic	[87]
miR-206	150, 150	Down-regulated, Serum	78%, 86% – 0.89	Diagnostic; Prognostic	[88]
miR-222	30, 30	Up-regulated, Plasma	62.5%, 56.2% – 0.747	Diagnostic	[89]
miR-21		Up-regulated, Plasma	86.7%, 72.2% – 0.893	Diagnostic	
miR-375	20, 20	Up-regulated, Serum	80%, 85% – 0.835	Diagnostic	[90]
miR-335	4, 7	Down-regulated, Plasma	NR	NA	[91]
miR-370	40, 12	Up-regulated, Plasma	67%, 74% – 0.79	Diagnostic	[92]
miR-421	40, 17	Up-regulated, Whole blood	94.1%, 62.5% – 0.773	Diagnostic	[93]
miR-421	90,90	Up-regulated, Serum	95.5%, 89.1% – 0.821	Diagnostic	[63]
miR-451	56, 30	Up-regulated, Plasma	96%, 100% – 0.96	Diagnostic	[94]
miR-486		Up-regulated, Plasma	86%, 97% – 0.92	Diagnostic	

(*Continued*)

Table 2. (Continued).

miRNAs	No. Cases, Controls	Expression change, Source	Sensitivity, Specificity – AUC	Type of biomarker	References
miR-627, miR-629, miR-652	123, 111	Up-regulated, Plasma	86.7%, 85.5% – 0.941 for panel	Diagnostic	[95]
miR-940	115, 105	Down-regulated, Plasma	60%, 96.6% – 0.96	Diagnostic	[96]
miR-1246	82, 117	Up-regulated, Serum-Exosomes	82.3%, 86% – 0.911	Diagnostic	[97]
miR-185, miR-20a, miR-210, miR-25, miR-92b	133, 109	Up-regulated, Plasma-Exosomes	65%, 80% – 0.77 for panel	Diagnostic	[98]

biomarker in screening other cancer types, including EC (AUC 0.944) [102].

MiR-378 was a potential biomarker for the detection of GC with 87.5% sensitivity, 70.73% specificity, and 0.861 AUC. The expression levels of serum miR-378 did not significantly alter between the different stages of TNM. However, the miR-378 expression level in tissues of GC was down-regulated compared to normal tissues, showing that miR-378 may act as a tumor suppressor miRNA in GC [103]. Serum miR-106b rendered 0.856 AUC, 75.0% sensitivity, and 92.5% specificity for distinguishing GC patients from healthy individuals; 0.700 AUC, 87.2% sensitivity, and 45.0% specificity for distinguishing GC patients from benign gastric disease patients; and 0.739 AUC, 75.0% sensitivity, and 68.7% specificity for distinguishing patients with benign gastric disease from healthy individuals. It has also been shown that miR-106b is up-regulated in tissues of GC to act as an oncogene through targeting E2F5, PTEN, p21, and p57 [99]. The plasma miR-195-5 was shown to be significantly down-regulated, with more than 13-fold changes in expression in patients with GC compared to the control group, indicating its potential as a biomarker for GC diagnosis [104]. In addition, the serum levels of miR-148a, miR-146a, and miR-21 expression were associated with the pN stage of GC. A three-miRNA combination could be a biomarker candidate for differentiating GC patients' LN metastasis from LN-negative GC patients with 0.764 AUC [105]. Song et al. performed a multi-stage, case-control research on two large cohorts to study the potential application of serum miRNAs in the detection of GC. It was revealed that the miR-376 c, miR-221, and miR-744 combination was an effective biomarker for the diagnosis of GC with 82.4% sensitivity and 58.8% specificity. For early detection of GC, the three-miRNA panel revealed a good diagnostic value with 73.3% sensitivity. The three-miRNA panel could concurrently distinguish dysplasia from control individuals with 56.5% sensitivity and 47.8% specificity (Table 2) [106].

4.2. Circulating miRNAs in GC diagnosis and prognosis

The miR-25 level rose considerably in cancer patients' serum samples; cancer patients were detected with sensitivity of 67.3 to 69.4% and specificity of 80.4% to 81.0% through using this test. The high level of serum miR-25 was related to the lymph node metastasis, invasion depth, and the disease stage. For overall survival (OS), miR-25 was an independent prognostic factor. The high level of serum miR-25 was related to poor prognosis in subgroups of patients stratified by the depth of invasion, tumor size, and lymph node metastasis. Therefore, the miR-25 serum levels could enhance the screening of GC, and act as the superior prognostic and diagnostic GC marker [107]. MiR-200 c manifested the most expression level of all cluster members of miR-200 in the OE-19 and MKN-45 GC cell lines. A large diagnostic value for circulating miR-200 c was detected, with 0.715 AUC, 65.4% sensitivity, and 100% specificity, revealing that miR-200 c can be a new biomarker for GC diagnosis. The increased expression level of circulating miR-200 c was revealed as an independent prognostic factor for OS and progression free survival in GC patients [108]. In a meta-analysis study, the potential role of miR-21 for digestive system cancer was also assessed by enrolling 1248 cases and 716 controls. For diagnostic meta-analysis, the pooled sensitivity and specificity were 0.76 and 0.84, respectively; AUC was 0.87. For prognostic meta-analysis, the pooled HR of the increased miR-21 expression rate in circulation was 1.94, which likely predicts poorer survival. The increased expression of miR-21 was associated with worse OS in the Asian population (HR = 2.41; Table 2) [109].

4.3. Circulating lncRNAs in GC diagnosis

Liu et al. proved that three lncRNAs, AC100830.4, CTC-501O10.1, and RP11-210K20.5, were up-regulated in GC patients' plasma with the AUCs of 0.724, 0.730, and 0.737, respectively. The AUC resulted from the combination of the three lncRNAs was 0.764 [110]. Recently, a study showed that the expression of serum exosomal lnc-GNAQ-6:1 was significantly lower in the GC patients. AUC was 0.732, which was higher than the diagnostic accuracy of CA72–4, CA 19–9, and CEA. Therefore, GNAQ-6:1 might be assessed in larger studies as a new diagnostic GC biomarker [111]. Yörüker et al. assessed the prognostic and diagnostic values of circulating H19 in GC. The higher circulating H19 levels were detected in patients with GC compared to control ones. H19 was identified as a potential diagnostic marker in GC [112]. The HOTAIR plasma level was significantly greater in patients with GC compared to healthy participants. The plasma HOTAIR was able to detect GC with sensitivity of 88% and specificity of 84%. Moreover, the increased expression of HOTAIR was correlated with higher grades, advanced stages of tumor, and metastasis. Thus, the plasma HOTAIR can act as a potential noninvasive biomarker for GC diagnosis [113].

Li et al., assessed the expression rate of circulating LINC00152 in plasma specimens. They stated that the expression rates of plasma LINC00152 were remarkably greater in individuals with GC than the normal ones and it showed its capability as a favorable noninvasive biomarker in the detection of GC, with an AUC of 0.657, the sensitivity of 48.1%, and specificity of 85.2%, respectively [114]. The relative expressions of HULC and ZNFX1 AS1 were further examined in the plasma. The HULC and ZNFX1 AS1 levels in the pre-operative patients' plasma were significantly higher compared to those in the GIST (gastrointestinal stromal tumors) patients' plasma, gastritis/peptic ulcer patients' plasma, and control subjects' plasma, whereas no significant difference was found among these groups. The AUCs for HULC and ZNFX1 AS1 were 0.65 and 0.85, respectively [115].

The rate of CEBPA-AS1 was remarkably elevated in tissues and plasma exosomes in the individuals with GC. Stability assays revealed that the highest amount of the exosomal plasma CEBPA-AS1 was covered in exosomes, making it not to be depreciated by RNases. The AUC of CEBPA-AS1 was equal to 0.824. Exosomes with CEBPA-AS1 released by GC cells can enhance the cell proliferation, stop apoptosis, and stimulate the progression of the GC, showing that CEBPA-AS1 contributes to cell-to-cell interaction related to the formation of GC. The exosomal CEBPA-AS1 can be a favorable novel biomarker for clinical diagnosis of GC [116]. The expression rate of exosomal Lnc RNA PCSK2-2:1 was remarkably down-regulated in the serum exosomes of individuals with GC. Also, there was a correlation between the expression rate of lncRNA PCSK2-2:1 with the venous invasion, tumor size, and tumor stage. The AUC of lncRNA PCSK2-2:1 was equal to 0.896. Sensitivity and specificity for the diagnosis of GC were equal to 84 and 86.5%, respectively. So, it might play an important role in GC progression and act as a biomarker in the diagnosis of GC (Table 3) [117].

4.4. Circulating lncRNAs in GC diagnosis and prognosis

Four lncRNAs, namely XIST, UCA1, LOC100506474, and LINC00467 were dis-regulated significantly in the serum samples, and a panel was made by multivariate logistic regression model with 0.88 AUC on a validation cohort. For TNM stages I, II, and III, the corresponding AUCs of the panel were, 0.78, 0.85, and 0.93, respectively. LOC100506474 and XIST were independently correlated with GC tumor recurrence. These lncRNA panels could notably predict and provide prognostic data for GC and identify LOC100506474 and XIST as potential biomarkers presenting information on the GC recurrence risk [124]. Jin et al. showed that a high level of serum HULC was associated with *H. pylori* infection, tumor size, lymph node metastasis, distant metastasis, and tumor-node-metastasis stage. AUC was 0.88 for HULC, greater than that for CA72-4 (0.514) and CEA (0.694). Their study revealed that HULC is a promising predictor for the prognosis of GC. It was also proved that the circulating HULC can provide a novel serum tumor marker for early GC diagnosis, prognosis, and monitoring progression [125]. Dong et al. showed that LSINCT-5, CUDR, and PTENP1 in serum specimens were highly down-regulated among individuals with GC than the healthy ones. All of them showed the highest prognosis potential in differentiating the patients from healthy ones, with an AUC of 0.92, the sensitivity of 74.1% and specificity of 100%. The three-lncRNA panel determined a powerful diagnostic value for early diagnosis of GC, with 0.832 AUC, 77.8% sensitivity, and 97.0% specificity. Additionally, the three serum lncRNAs were adequately specific and sensitive to discriminate benign peptic ulcerations from patients with GC, with 0.902 AUC, 91.7% sensitivity, and 83.3% specificity, showing that the three-lncRNA serum signature might be a promising biomarker candidate for the detection of GC. This study found that a decreased level of expression of the three-lncRNA panel predicted increased survival rates in GC patients, showing that these three lncRNAs can predict the GC patients' prognosis. CUDR (termed also UCA1), however, was overexpressed in tissues of GC and gastric juice, implying its potential as an onco-lncRNA and a diagnostic biomarker in GC. Moreover, LSINCT-5 is up-regulated in GC tissues and indicates oncogenic activity to improve cellular proliferation. The LSINCT-5 overexpression predicts GC patients' negative prognosis. The LSINCT-5 and CUDR expression levels in GC tissues were not consistent with their circulating levels which needs to be validated by further reliable investigations [126]. Patients with GC were more susceptible to GC with an increased expression level of the serum exosomal MIAT. In addition, serum levels in the post-treatment blood sample were significantly reduced compared to pre-treatment samples, while significantly increased in cases where recurrence occurred. The up-regulation of the exosomal MIAT was significantly associated with shorter survival and worse clinical variables. In addition, MIAT was recognized as an independent prognostic factor for GC [127].

Zhao et al. indicated that expression rates of the exosomal HOTTIP were typically up-regulated among individuals with GC compared to healthy ones and there was a significant association between its expression rates and invasion depth and TNM stage. The AUC was equal to 0.827 for the exosomal HOTTIP that showed greater detective ability compared to CEA, CA 19–9 and CA72–4 (AUCs 0.653, 0.685, and 0.639, respectively). It found a significant association of the increased exosomal HOTTIP levels with poor OS, suggesting that the exosomal HOTTIP may be a potential diagnostic and prognostic biomarker for GC [128]. Recently, Guo et al. conducted a multi-phase study of circulating exosomal lncRNA-GC1, including patients with GC (n = 522), patients with precancerous gastric lesions (n = 85), and healthy donors (HDs; n = 219). In the test phase, lncRNA-GC1 achieved better diagnostic performance than the standard biomarkers CEA, CA72-4 and CA19-9 in discriminating GC patients from HDs. In the verification phase, lncRNA-GC1 maintained its diagnostic efficiency in discriminating GC patients from those with precancerous gastric lesions as well as HDs. LncRNA-GC1 showed a higher AUC (Test + Verification phases, early GC vs. HD; AUC 0.886, sensitivity 87.21%, specificity 87.10%) compared to CEA (AUC 0.6168, sensitivity 63.47%, specificity 53.46%), CA72-4 (AUC 0.6216, sensitivity 76.26%, specificity 48.39%) and CA19-9 (AUC 0.5497, sensitivity 52.05%, specificity 50.23%) for differentiating early GC patients from HDs, especially early GC patients with negative status of standard biomarkers (Test + Verification phases, early GC (negative) vs. HD; AUC 0.9023, sensitivity 91.78%, specificity 85.16%). In addition, circulating exosomal lncRNA-GC1 levels were significantly associated with early-to-advanced GC (Table 3) [129].

Table 3. The circulating lncRNAs features effective in diagnosis and/or prognosis of GC.

LncRNAs	No. Cases, Controls	Expression change, Source	Sensitivity, Specificity – AUC	Type of biomarker	References
XIST, LOC100506474, UCA1, LINC00467	230, 230	Up-regulated, Serum Down-regulated	83.95%, 81.01% – 0.886, for panel	Diagnostic; Prognostic	[124]
HULC	50, 50	Up-regulated, Plasma	58%, 80% – 0.65	Diagnostic	[115]
ZNFX1-AS1		Up-regulated, Plasma	84%, 68% – 0.85	Diagnostic	
HULC	100,110	Up-regulated, Serum	82%, 83.6% – 0.888	Diagnostic; Prognostic	[125]
AA174084	335, 130	Up-regulated, Plasma	46%, 93% – 0.848	Diagnostic	[118]
FER1L4	83, 83	Down-regulated, Plasma	67.2%, 80.3% – 0.778	Prognostic	[119]
LINC00152	79, 81	Up-regulated, Plasma	48.1%, 85.2% – 0.657	Diagnostic	[114]
CUDR, LSINCT-5, PTENP1	73, 86	Down-regulated, Serum	Sensitivity: 74.1% of CUDR + LSINCT-5 + PTENP1 for GC detection, 77.8% of CUDR + LSINCT-5 + PTENP1 for early GC detection Specificity: 100% of CUDR + LSINCT-5 + PTENP1 for GC detection, 97.0% of CUDR + LSINCT-5 + PTENP1 for early GC detection AUC: 0.92 of CUDR + LSINCT-5 + PTENP1 for GC detection, 0.832 of CUDR + LSINCT-5 + PTENP1 for early GC detection	Diagnostic; Prognostic	[126]
CTC-501O10.1	50, 50	Up-regulated, Plasma	90%, 51% – 0.724	Diagnostic	[110]
AC100830.4		Up-regulated, Plasma	84%, 58% – 0.730	Diagnostic	
RP11-210K20.5		Up-regulated, Plasma	89%, 55% – 0.737	Diagnostic	
			99%, 49% – 0.764, for panel		
HOTAIR	50, 50	Up-regulation, Plasma	88%, 84% – 0.944	Diagnostic	[113]
PCGEM1	317, 100	Up-regulation, Plasma	72.9%, 88.9% – 0.750	Diagnostic; Prognostic	[120]
RNAs PANDAR, FOXD2-AS1, SMARCC2	109,106	Up-regulation, Plasma	NR – 0.767, 0.700, and 0.748, respectively (0.839 for panel)	Diagnostic	[121]
H19	43, 34	Up-regulated, Plasma	74%, 58% – 0.64	Diagnostic	[4]
H19	40,42	Up-regulated, Plasma	87.2%, 38.1% – 0.643	Diagnostic	[112]
H19	32,30	Up-regulated, Plasma	68.75%, 56.67% – 0.724 (positive predictive value (PPV) 62.86% and negative predictive value (NPV) 62.96%)	Diagnostic	[122]
H19	81,78	Up-regulated, Serum-Exosomes	of 74.36%, 83.95% – 0.849	Diagnostic; Prognostic	[123]
GNAQ-6:1	27, 43	Down-regulated, Serum-Exosomes	83.7%, 55.6% – 0.736	Diagnostic	[111]
CEBPA-AS1	80, 281	Up-regulation, Plasma-Exosomes	87.9%, 78.8% – 0.824	Diagnostic	[116]
MIAT	50, 48	Up-regulated, Serum-Exosomes	NR – 0.892	Diagnostic; Prognostic	[127]
PCSK2-2:1	29, 63	Down-regulated, Serum-Exosomes	84%, 86.5% – 0.896	Diagnostic	[117]
HOTTIP	120, 126	Up-regulated, Serum-Exosomes	69.8%, 85% – 0.827	Diagnostic; Prognostic	[128]
LncRNA-GC1	522, 219	Up-regulation, Plasma-Exosomes	91.78%, 85.16% – 0.902 Test + Verification phases, early GC (negative): GC patients with negative status of CEA, CA72-4 and CA19-9 standard biomarkers	Diagnostic; Prognostic	[129]

5. Potential clinical application of miRNAs and lncRNAs in guiding treatment decisions

The role of ncRNAs in the diagnosis and prognosis of upper GI cancers was completely discussed before. But about treatment, many studies have been done. Dys-regulation in the expression of some miRNAs and lncRNAs can cause chemoresistance and radioresistance in patients with cancer. They can affect the efficacy of anti-cancer drugs. This can cause an increase or decrease in the side effects of drugs. In some studies, it has been shown that ncRNAs can be used as a target for treatment and can be useful for targeted therapy [130–133]. More interestingly, both miR-130a-3p, miR-148a-3p increased the sensitivity of EC cells toward chemotherapeutic

drugs such as cisplatin and 5-fluorouracil. In fact, the miRNA modulation in both directions led to similar effects on tumor biology and chemotherapy response (Table 4) [134].

6. Quantification of circulating ncRNAs

RT-qPCR is a well-established method used to detect non-coding RNAs. However, using RT-qPCR we just detect the known and annotated ncRNAs, while microarray and RNA-seq are high-throughput techniques showing unknown and also novel ncRNAs. Microarray platforms can detect thousands of non-coding RNAs in one assay. Therefore, this method is less expensive than RT-qPCR and can find many ncRNAs as a biomarker. However, this technique has a lower specificity in comparison to amplification-based methods. Microarray is an on-chip method showing some background signals and cross-hybridization. Therefore, the number of detected circulating ncRNAs as compared with tissue-derived ncRNAs is reduced significantly. In contrast, RNA-seq is a newly grown high-throughput technique. It has a strong potential for whole-genome transcriptome profiling, thus identify a larger number of novel circulating ncRNAs in one assay. Despite its many advantages, some weaknesses have been identified. In next-generation sequencing-based techniques, bioinformatics analysis pipeline is required, so this technique is not highly user friendly. Also, RNA-seq is currently expensive and it cannot be used frequently. Moreover, according to standard protocols of RNA-seq, a large amount of RNA is required for one assay and this requirement is difficult to reach for circulating ncRNA because of the lower amount of these RNAs naturally [153].

7. Therapeutic strategies for targeting ncRNAs focusing on novel delivery systems

Numerous preclinical studies have investigated anti-cancer strategies to target ncRNAs. Therapeutic targeting approaches are necessary for precision medicine. Inhibition therapy of miRNA is applied to hinder the expression of oncomiRs which are often highly expressed in human cancers and reestablish the tumor-suppressor genes' normal expression. The miRNA inhibition therapy involves these agents: locked nucleic acid (LNA) anti-miRs, antisense anti-miR oligonucleotides (AMOs), miRNA sponges, antagomiRs, and small molecule inhibitors of miRNAs (SMIRs). AMOs are single-stranded, modified antisense oligonucleotides (17–22 nucleotides) which are complementary to a miRNA [154]. LNA anti-miRs show a modified antisense anti-miR oligonucleotide. LNA-modified oligonucleotides represent a greater thermal stability/aqueous solubility and increased metabolic stability for delivery *in vivo*, as well as affinity for their target molecules of miRNA. LNAs and AMOs are the most popular types of antisense oligonucleotides. Anti-miRNAs are antisense oligonucleotides, chemically changed to increase their binding affinity to the target miRNA. LNA is an altered oligonucleotide with a therapeutic capability with elevated affinity, low toxicity, and high specificity and stability *in vivo* [155,156].

Multiple approaches can be considered to target lncRNAs: i) antisense oligonucleotides (ASOs) with chemical modifications can be applied to focus on the RNA for degradation through an RNase H-dependent mechanism; ii) post-transcriptional degradation pathways of RNA can remove pathogenic RNAs. This can be obtained via the application of siRNAs to invoke

Table 4. Potential clinical application of ncRNAs in guiding treatment decisions.

NcRNAs	Expression change	Effect on treatment	References
MiRNA			
Esophagus cancer			
miR-338-5p	Up-regulated	Enhanced the radiosensitivity of ESCC by inducing apoptosis in tumor cells	[132]
miR-200 c	Up-regulated	Enhanced the radiosensitivity of ESCC by inducing cell cycle arrest in tumor cells	[133]
miR-29 c, miR-125a-5p, and miR-1	Up-regulated	Enhanced ESCC cell sensitivity for anti-cancer drugs such as 5-fluorouracil, cisplatin, and gefitinib, respectively.	[135–137]
miR-130a-3p, miR-148a-3p	Both, up- and down-regulated	Increased the sensitivity of ESCC cells toward chemotherapeutic drugs, cisplatin and 5-fluorouracil; MiRNA modulation in both directions led to similar effects on chemotherapy response.	[134]
Gastric cancer			
miR-21, miR-106a	Up-regulated	Increased cisplatin resistance of GC cells	[138]
miR-195, miR-378	Up-regulated	Enhanced 5-azacytidine resistance	[139]
miR-449	Up-regulated	Increased sensitivity toward cisplatin	[140]
miR-508-5p	Up-regulated	Increased sensitivity toward vincristine or doxorubicin	[141]
miR-451	Up-regulated	Increased sensitivity of cancer cells toward radiotherapy by down-regulating macrophage migration inhibitory factor (MIF)	[142]
miR-27a	Down-regulated	Increased doxorubicin sensitivity	[143]
LncRNA			
Esophagus cancer			
LINC00473, FAM201A, LINC00657	Down-regulated	Impaired the effect of radiotherapy by acting as sponges for miRNAs	[130,131,144]
TUSC7	Up-regulated	Suppressed cisplatin and 5-fluorouracil resistance in ESCC cells by inhibiting miR-224	[145]
LINC01419	Down-regulated	Decreased the sensitivity of ESCC cells to 5-fluorouracil	[146]
PART1	Up-regulated	Induced gefitinib-resistant ESCC cells	[147]
Gastric cancer			
PVT1	Up-regulated	Enhanced 5-fluorouracil resistance of GC cells by activating BCL2	[148]
D63785	Down-regulated	Increased GC cells sensitivity to doxorubicin	[149]
MRUL	Up-regulated	Induced multidrug-resistant GC cell lines, including SGC7901/ADR and SGC7901/VCR	[150]
SNHG5	Up-regulated	Increased cisplatin resistance of GC cells	[151]
HOTTIP	Up-regulated	Enhanced cisplatin resistance of GC cells	[152]

a Dicer-/Argonaute-dependent cleavage pathway; iii) lncRNA genes' modulation via steric blockade of the promoter or through genome-editing methods. One can also obtain loss of function through creating steric prevention of RNA-protein interactions or inhibition of secondary structure formation. ASOs or RNA binding small molecules can be applied in this case [157]. MALAT1 ASOs may prevent the cancer cell metastasis and the tumor burden in mice [158]. Nano-particulate spherical nucleic acids are also capable of regulating lncRNAs for the knockdown of nuclear-retained metastasis related to lung adenocarcinoma transcript 1 (Malat1) using liposomal spherical nucleic acid constructs [159]. Having polyarginine peptide (R11) PEG, coated cross-linked poly (ethyleneimine) nanoparticles have been studied for the site-specific delivery of miRNA-145 to prostate cancer cells [160]. Li et al. synthesized gold nanoparticle based 2′ -o-methyl modified DNA probes to diagnose and hinder miRNA-21 for theranostics of breast cancer. The antimiR-21 probes were introduced successfully into cancer cells and knocked down miRNA-21 to prevent its function, inhibiting growth and killing apoptotic cells [161]. It was shown the superior pre-miR-145 transfer to breast and prostate cancer cell lines via developed thiolated gold NPs (miRNA–AuNPs) [162]. Manifesting interesting outcomes in the carcinoma cell line of the human and murine peritoneal macrophages, siRNA loaded chitosan nanoparticles expressed EGFP (endogenous enhanced green fluorescent protein). Nasal delivery of complexes showed an effective silencing of the targeted genes in transgenic EGFP mouse bronchiole epithelial cells. Developing a prosperous therapeutic system is a challenging and emerging area required to indicate the best delivery method for ncRNA molecules. Therefore, further explorations are required to solve problems related to *in vivo* ncRNAs' delivery, specifically emphasizing cellular uptake, stability, and site-specific delivery [163].

Several miRNA-based delivery systems have been developed and employed to achieve desired influences in application. Local treatment or intravenous injection has been introduced as the major administration method for miRNA delivery *in vivo* [164]. Viral and non-viral vectors have shortcomings, such as low oligonucleotide-loading capacity and immunogenicity. Evidence shows that viral vectors could transfer antagonists or miRNA mimics into tumor cells effectively. The non-viral strategy includes inorganic nano-particles and polymer-based and lipid-based strategies [165]. The first replacement therapy of miRNA was done in 2013 using MRX34 – a liposome-formulated miR-34 mimic – for metastatic liver cancer. There are many issues which are unsolved, like the off-target effects, optimal delivery system, long-time safety, and low bioavailability. Hence, many studies around the world have tried to overcome the so-called challenges and gain a specific, safe, and effective miRNA delivery [166].

Different lipid-based vesicles such as liposomes, microemulsions, and lipid nanoparticles (LNPs) have been examined for ncRNAs targeted delivery. Liposomes have attracted higher attention among the so-called nano-carrier systems [167]. OligofectamineTM, TransIT® 2020, and Lipofectamine® 2000 are cationic liposomes which can transport nucleic acids such as DNA, oligonucleotides, plasmid DNA, and siRNA [168]. LNPs, like liposomes, protect oligonucleotides from degradation by nucleases, raise cellular uptake, avoid renal clearance, and enhance endosomal escape [169]. Numerous LNP RNAi drugs have passed the pre-clinical assessment and have been included in clinical trials. One example is the LNP drug ALN-VSP, a lipid delivery system constructed by Alnylam Pharmaceuticals, which was examined in phase-I clinical trial to treat advanced solid tumors. LNPs are considered the most efficient formulations in delivering oligonucleotides for ncRNA treatment [170]. Exosomes can also deliver their content into the destinate cell, like tumor cells. They can cause cancer progression, proliferation, metastasis, and also drug-resistance by delivering some type of ncRNAs like miRNAs. It is shown that cancer-derived exosomes can induce immunosuppression response in the tumor microenvironment, and through spreading to other cells and tissues can form a pre-metastatic niche for metastasis. Based on the natural delivery capability of exosomes, they can be used as delivery vehicles in cancer treatment. Exosomes are biocompatible and biodegradable particles, and because of that, they have lower immunogenicity and toxicity. The size of exosomes is small and they can pass through the blood-brain barrier. They are also stable in body fluid. The interesting criteria for exosomes is that the adherence and internalization of exosomes within tumor cells is 10-times greater than liposomes with smaller size. So this criterion makes them more specific for cancer targeting. They accumulate in tumor tissues, thus increasing their drug delivery efficiency. Exosomes can be designed to present tumor-targeting proteins, peptides to enhance drug delivery efficiency. Moreover, the lipid bilayer membrane of exosomes makes them a favorable vehicle for drug delivery, because this membrane is like a protective shelter. The best exosome-based cancer therapy is targeting cancer stem cells. Exosomes derived from macrophage can also be used to transfer miRNA as inhibitors to GC cells. This miRNA decreases migration and induces apoptosis. Taken together, exosomes can carry many various molecules like ncRNAs as a suitable vehicle to modulate cancer behavior. Besides, many studies showed the exosome's potentials for carrying the drugs and also some types of ncRNA to inhibit tumor growth, proliferation, and metastasis [171,172].

8. Conclusion

Any research study about prevention and treatment of cancer is crucial because of widespread problems of cancer, and ncRNAs are potential biomarker candidates. In recent decades, miRNAs and lncRNAs have been the broadly explored ncRNAs. Different clinical trials are ongoing for using ncRNAs as indicators of cancers. Thus, an urgent research is required on the biomarkers which can detect these cancers in their initial stages in a simple, fast, and sensitive way. Discovering circulating ncRNAs has rendered a new perception of the basic mechanisms underlying oncogenesis and has brought about interesting diagnostic and prognostic approaches. They possess high stability in blood, making them capable of being utilized in diagnosis and/or prognosis as noninvasive biomarkers. In addition, very specific expression patterns of lncRNAs indicate that their expression signatures can be successfully used for accurate diagnosis and classification. Nevertheless,

several challenges must be resolved to construct them for clinical usages. Further studies may involve a high number of patients and controls, or meta-analytical investigations which would possibly confirm the biomarkeric strength of these molecules. In addition to the imminent use of circulating ncRNAs for diagnosis and/or prognosis, understanding the mechanisms by which miRNAs/lncRNAs function would allow targeting them for therapy. Several miRNAs and lncRNAs have induced disease resistance to current standard chemotherapy and radiotherapy for EC and GC, which have the potential to translate into clinical practice.

9. Expert opinion

Many studies state that circulating ncRNAs may act as a minimally invasive diagnostic and prognostic biomarker for detecting different kinds of cancer. A perfect biomarker is expected to have a high sensitivity, specificity, and predictive power. NcRNAs have some intrinsic features which make them promising as biomarkers. In this regard, circulating ncRNAs have general features that discriminate normal individuals from patients, including high circulation stability, easy collection via a noninvasive method, and reflecting progression of the disease. Circulating RNA level can be simply quantified through quantitative RT-PCR or high throughput assays like NanoString or miRNA microarrays. Many ncRNAs show cell and/or tissue/tumor specific expression, causing them to be attractive candidates for therapeutic purposes. Although ncRNAs have the required specificity to pathology to be adequate biomarkers, their quantification and extraction are the challenging limitations. A complete perception of factors that influence measurement of ncRNAs contributes to establishment of a popular admissible method for collecting, storing, and processing samples as well as measuring ncRNAs. Shortcomings of quantitative real-time polymerase chain reaction, like normalization and primer design, may greatly affect the results of biomarker investigations. Moreover, the transcripts' low abundance in body fluids prevents the determination of quality and quantity of isolated RNAs. New efficient methods are needed to purify fragmented free-circulating RNA and exosomal RNA from variable volumes of plasma or serum. We can therefore isolate all circulating RNA sizes regardless of the size or GC content, without bias. Moreover, new commercial kits for quantifying RNA from liquid biopsies that are expected to yield RNA at a lower pg per µL are broadly admitted.

For EC, the circulating miRNAs, miR-21, miR-223, and miR-375 have been validated as promising diagnostic biomarkers in a meta-analysis. For GC, miR-17, miR-18a, miR-21, miR-25, miR-223, miR-451, and lncRNA-H19 have been reported in several studies ($n \geq 3$) and are likely to be promising biomarkers (no meta-analysis was found except for miR-18a). Unlike EC, many circulating lncRNAs have been newly reported for GC and each is often limited to one study. They often show excellent or outstanding discrimination performance, such as XIST, LOC100506474, UCA1, LINC00467, ZNFX1-AS1, HULC, AA174084, CEBPA-AS1, MIAT, PCSK2-2:1, HOTTIP, H19 (AUCs 0.8 to 0.9), and particularly CUDR, LSINCT-5, PTENP1, HOTAIR, and LncRNA-GC1 (AUCs > 0.9). This is a prominent assumption considering that most lncRNAs have not been characterized functionally and could solely represent nonspecific transcriptional noise, which is neither functional nor capable of acting as a biomarker. Research studies with small sample size do not have statistical strength. Hence, different clinical trials and large multi-center cohorts are required for reliably validating emerging circulating ncRNA biomarkers. As consensus methods have been determined and involved for profiling circulating ncRNA, interpretation and comparison of various study results are possible to find ncRNAs which can be considered as novel sensitive and specific cancer biomarkers. Although a single circulating ncRNA molecule may have an acceptable AUC, sensitivity, and specificity for the diagnosis and/or prognosis of GI cancers, when combined with other molecules in the form of a panel, the overall accuracy can increase significantly. Hence, most importantly, using a group of ncRNA molecules as a diagnostic panel would give a more promising diagnostic or prognostic performance.

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