

Review article

Biomarkers of gastric cancer: current advancement

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ABSTRACT

Gastric cancer (GC) is one of the most prevalent malignant types worldwide, especially in East Asia. Due to its frequently advanced stage at diagnosis, the mortality from GC is high and the prognosis is still unsatisfactory. Thus, early detection using effective screening approaches is vital to decrease the morbidity and mortality of GC. Interestingly, biomarkers can be used for diagnosis, prediction of sensitivity to treatment, and prognosis in GC. The potential biomarkers detectable in liquid biopsies such as circulating tumor cells (CTCs), long non-coding RNAs (lncRNAs), cell-free DNA (cfDNA), microRNAs, and exosomes reveal numerous information regarding the early prediction and the outcomes for GC patients. Additionally, using the novel serum biomarkers has opened up new opportunities for diagnosing and monitoring patients with GC. This review mainly summarizes the novel progress and approaches in GC biomarkers, which could be potentially used for early diagnosis and therapy monitoring. Meanwhile, we also discussed the advantages, disadvantages, and future perspectives of GC biomarkers.

1. Introduction

Gastric cancer (GC) is one of the most prevalent malignant types worldwide, especially in East Asia. GC is the 5th most common neoplasm and the 3rd most deadly cancer, with an estimated 784,000 deaths in 2018 [1]. In recent years, endoscopic resection for early-stage, D2 lymphadenectomy for non-early operable cases, and chemotherapy or targeted therapies in advanced GC have been widely used in clinics, which can make significant improvements in the prognosis of GC [2]. Due to its frequently advanced stage at diagnosis, the mortality from GC is high and the prognosis is still unsatisfactory. Recent studies have found that the morbidity and mortality of GC is increasingly rising [3]. Thus, the early detection using effective screening approaches is vital to decrease the morbidity and mortality of GC. Undoubtedly, selecting appropriate biomarkers will play an important role in the early diagnose and treatment of GC.

Biomarkers are characteristics that are objectively measured and evaluated as an indicator of normal biologic process, pathogenic processes, or pharmacological response to a therapeutic intervention [4]. With advantages such as repeatability and minimal invasion [5], it is no wonder that the field of biomarkers of GC has received tremendous

attention. Recent studies have reported some biomarkers of GC related DNA, RNA and exosomes. Development of these biomarkers in GC is expected to greatly contribute to the progress of cancer, selection of appropriate therapeutic strategies and efficient follow-up programs [4].

GC is a heterogeneous disease which can exhibit different phenotypes and molecular profiles [6]. Currently, some advancements of biomarkers for the early diagnosis of GC have offered benefits; however, useful diagnostic biomarkers for early diagnosis of GC remain limited. Therefore, it is necessary to review GC associated biomarkers comprehensively, with the hope of identifying new predictive biomarkers for the purpose of achieving personalized treatment in clinics.

The data of the current review were mainly gathered from the previous studies published in PubMed and Web of Science in the past five years. Gastric cancer and biomarkers were the key words utilized for searching.

This review mainly summarizes the new advancement and clinical prospects of GC biomarkers, providing helpful information on the early diagnosis and therapy in GC care. The review has focused on GC biomarkers, relating to liquid biopsies such as circulating tumor cells (CTCs), long non-coding RNAs (lncRNAs), cell-free DNA (cfDNA), MicroRNAs, and exosomes. Moreover, the utilization of serum biomarkers has emerged as a new diagnosis option for the early and fast detection of GC.

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2. Liquid biopsies

Liquid biopsies have emerged as a new noninvasive method by using body fluid to provide early tumor detection, assess prognosis, monitor tumor burden, and predict therapeutic resistance, quantify minimal residual disease, and perform real-time cancer management in GC patients [7, 8]. Originally, the term liquid biopsies had been assigned only to the investigation of circulating tumor cells in the blood of patients with cancer, but it has now been extended primarily to include the analysis of circulating tumor DNA (ctDNA) and circulating non-coding RNAs (ncRNAs) [9].

ctDNA is usually only a small portion of circulating free DNA and has recently emerged to predict recurrence or relapse in several cancer types [10]. Cell-free DNA (cfDNA) is a widely used noninvasive biomarker for diagnosis and prognosis of multiple disease states [11]. Nowadays, liquid biopsies consist of different biological sources such as circulating tumor microemboli (CTM), exosomes and tumor-educated platelets (TEPs) [12, 13]. Among the nonmetastatic patients, some patients with higher postoperative cfDNA are more likely to recurrent [14, 15]. Interestingly, a year before the radiologically detectable disease progressed, researchers could detect cfDNA in plasma [10]. Notably, the detection of CTCs shows a significantly inferior effect than those with a smaller number of CTCs in all stages [16, 17]. Moreover, there is evidence that detectable CTM is an independent prognostic factor for shorter overall survival (OS) [18]. Among the potential biomarkers detectable in liquid biopsies, microRNAs are gaining more and more attention, since they are easily detectable, quite stable in biological fluids, and show high sensitivity [19]. Additionally, increasing studies suggest that exosomes have shown a great promise to serve as novel biomarkers in liquid biopsies [20].

In summary, compared with conventional biopsies, liquid biopsies have better prospects in repeatable sampling, real-time monitoring, and precision medicine. However, further improving the technology to realize its transformation to clinical practice is still hopeful but challenging.

2.1. Circulating tumor cells (CTCs)

CTCs are cells released from solid tumors or metastases into the peripheral blood circulation, which can be considered as an essential reason for postoperative recurrence and distant metastasis in patients with malignant tumors [21]. Moreover, CTCs may also play a vital role in monitoring GC dissemination and guiding the treatment of GC patients with recurrence and metastasis [21]. CTCs can exhibit specific molecular characteristics of the primary tumor, which are very promising for cancer screening [22]. Unfortunately, most CTCs cannot survive in the harsh environment of the vasculature, but several mechanisms are able to protect CTCs from the hostile environment [23]. Associated with increased mortality [24], these cells undergo epithelial-to-mesenchymal transition (EMT) by up or down-regulating some surface molecules to reduce cell-to-cell adhesions, increase plasticity, and migrate to the secondary site. Current technology makes it possible for CTCs to use an antibody to bind to the specific protein markers, which are not expressed on blood cells, for the purpose of separating the masses of blood cells [24]. In recent years, CTCs have provided the opportunity to improve sensitivity. However, because CTCs are rare in the circulatory system and have higher heterogeneity, it is more challenging to meet specificity and sensitivity in GC [24]. The following will list some of the latest research results in recent years.

For the diagnostic and prognostic value of CTCs, many experiments have been conducted to identify the correlation between the CTCs of GC patients and early diagnosis, staging, and lymphovascular invasion, but these conclusions are controversial [25, 26, 27, 28]. CTCs may be related to the high tumor heterogeneity, the insufficient number of patients, and different detection methods. At present, the only CTCs detection technology approved by the U.S. Food and Drug Administration (USFDA) and

widely used in clinical practice is the CellSearch™ system [29]. There are two main technical methods for the enrichment and detection of CTCs [30]. One uses the physical properties to separate CTCs from background cells, such as size, density, electric properties [31, 32, 33, 34], and the other is based on antigen-antibody reactions of specific molecules on the surface of CTCs [35]. Pernot et al. have studied the clinical value of CTC count using the CellSearch system in advanced gastric and orogastric junction adenocarcinoma (GOA). They aim to identify whether CTCs can become dynamic biomarkers in monitoring tumor burden and therapeutic effects and establish an optimal threshold [36]. In this study, 106 patients with untreated advanced GOA were included, and they detected CTCs (cytokeratins 8, 18, 19 positives, EpCAM (epithelial cell adhesion molecule) positive, CD45 negative) count in the peripheral blood on day 0 and day 28. They found that $CTCs \geq 2$ were the optimal threshold. At D0, for patients with CTCs between 0-1 and ≥ 2 , their median OS was 16.9 months and 11.1 months ($HR = 1.85$, $p = 0.01$, 95%CI). And median progression-free survival (PFS) was 7.6 months and 5.6 months ($HR = 1.59$, $p = 0.03$, 95%CI). At D28, their median OS was 17.9 months and 5.4 months ($HR = 3.13$, $p = 0.004$, 95%CI). And median PFS was 8.3 months and 2.9 months ($HR = 4.79$, $p = 0.0001$, 95%CI). In conclusion, $CTCs \geq 2$ are correlated with a shorter OS and PFS at D0 and D28 GC patients [36]. Notably, the number of CTCs seems to be a dynamic biomarker in advanced GC and GOA patients to help judge prognosis and treatment efficacy. In addition to CTCs count, its molecular map can also be used in early diagnosis and disease monitoring. A prospective study has evaluated the role of N-cadherin as a mesenchymal marker for CTCs through EMT, and they detect that N-cadherin could be expressed in the CTCs of 90% of patients. All 10 patients who had postoperative recurrence showed N-cadherin positive. Therefore, they concluded that N-cadherin might be a valuable tool to detect CTCs for GC patients [37]. More interestingly, Abdallah et al. have analyzed CTCs for GC patients and their expression of HER2 (human epidermal growth factor receptor-2) and plakoglobin before and after neoadjuvant. They found that HER2 in CTCs showed higher positivity compared with primary tumors. A significant CTC count drop was seen in CTC-positive cases compared to CTC-HER2-negative cases [38]. Furthermore, an ongoing phase II trial (NCT04168931 GASTHER2) is conducted to evaluate whether the addition of trastuzumab to standard treatment is effective in patients with HER2-positive expression in CTCs and HER2-negative GC patients [8]. Thus, CTCs appear to be a promising tool in understanding the behavior of GC and treatment efficacy. Yuichiro Miki et al. have concluded that circulating EpCAM-CEA (carcinoembryonic antigen)+ tumor cells may be a prognostic biomarker in patients with GC [39]. In addition, some scholars have noted that the only CellSearch system approved by the FDA based on EpCAM expression for clinical use is at risk of ignoring the most invasive CTCs subsets through EMT, which may underestimate the actual total CTCs number in the bloodstream. They established a method using a label-free inertial microfluidics approach (LFIMA) with next-generation sequencing (NGS) to capture CTCs effectively and detect genetic alterations [40].

Many researchers have come to the same conclusion that CTCs positivity was associated with poor outcomes. Therefore, the major challenge in clinical application is their precise detection and enrichment. Current methods to separate CTCs from background cells include antigen-antibody response, physical properties such as the sizes, densities, and electrical characteristics of cancer cells and blood cells [30, 41, 42, 43, 44]. However, CTCs are highly heterogeneous, and it doesn't remain easy to detect a wide range of markers by current technologies. Hence, it is essential to research the mechanism of tumorigenesis and progression and develop better technologies.

2.2. Long non-coding RNAs (lncRNAs)

lncRNAs are transcripts of longer than 200 nucleotides with no protein-coding function, which participate in physiological and pathological processes [45, 46, 47]. Zhang et al. have conducted a study to

evaluate the functional significance of small nucleolar RNA host gene 17(SNHG17). The results showed that the level of SNHG17 is upregulated in GC patients than healthy controls with a moderate accuracy for diagnosis of GC (area under the receiver operating characteristic curve (AUC) = 0.748; 95% CI, 0.666–0.830), and a high level of SNHG17 promotes cell proliferation, invasion, and migration and inhibited apoptosis [48]. In another study, Xian et al. have observed that the levels of the lncRNAs HULC and ZNF1-AS1 in preoperative patients' plasma were significantly higher than those detected in the other three no-malignant groups ($P < 0.01$), the AUC values are 0.65 and 0.85. It is suggested that circulating HULC and ZNF1-AS1 may serve as potential biomarkers for the diagnosis and prognosis of GC [49]. Similarly, Feng et al. have demonstrated that lncRNA β -1,3-galactosyltransferase 5-AS1(B3GALT5-AS1) level was markedly higher in GC patients than that in ordinary people ($P < 0.001$), with the AUC value is 0.816 (95% confidence interval, 0.758–0.874; $P = 0.03$), which indicates B3GALT5-AS1 may be a potential tool for distinguishing GC patients from healthy people [50]. Zhang et al. have demonstrated that a novel lncRNA HOXC-AS3 may play an essential role in tumorigenesis and migration [51]. A subsequent study found that the expression level of lncRNAs human ovarian cancer-specific transcript 2 (HOST2) in GC tissues was significantly higher than that in adjacent normal tissues by qRT-PCR ($P < 0.01$), and the same result was found in distant and close metastasis ($P < 0.01$), which are considered strongly connected with GC progression [52]. Moreover, Han et al. have identified that lncRNA X-inactive-specific transcript (XIST) is overexpressed in GC patients via qRT-PCR and relates to poor outcome and drug resistance by sponging miR-let-7b [53]. In vitro, Zhang et al. have concluded that the increased expression of lncRNA FTX could promote cell proliferation by binding miR-215-3p and reducing cell distribution in the G1-S phase [54]. In addition, Ren et al. have confirmed that lncRNA DDX11 antisense RNA 1 (DDX11-AS1) was upregulated in advanced GC tissues by acting as competing endogenous RNAs (ceRNA) for miR-873-5p to upregulate signal peptidase complex 18(SPC18) expression [55]. Another study found that lncRNA LINC01234 was also higher in GC samples than adjacent normal tissues, and 17 associations including 2 transcription

factors (TFs) (ELK1 and ZNF664) and 17 RNA binding protein (RBP) interactions were identified to be co-expressed [56]. As for the GC cells, Xin et al. have reported that upregulated lncRNA ABHD11 antisense RNA 1 (ABHD11-AS1) was closely associated with unfavorable prognosis by negatively regulating miR-361-3p in GC cells [57]. Interestingly, a preliminary study suggested that GC patients with high lncRNA ARAP1 antisense RNA 1 (ARAP1-AS1) expressions exhibited shorter OS and DFS and was distinctly associated with TNM stage ($p = 0.010$) and lymphatic metastasis ($p = 0.007$) [58]. According to another trial, LUCAT1 was confirmed to be highly expressed in GC tissues by down-regulating miR-134-5p/lncRNA YWHAZ axis, which led to shorter OS and DFS periods [59]. Moreover, Zhang et al. have verified that although there was no correlation between the OS and lncRNA colorectal neoplasia differentially expressed (CRNDE) expression in patients with GC, a decrease in its expression was significantly related to drug resistance, suggesting that CRNDE may act as a potential prognostic and therapeutic biomarker against chemoresistance in GC [60]. Besides, a study by Zhou and others researchers has shown that over-expression of lncRNA BCAR4 in GC tissues could activate the mitogen-activated protein kinase (MAPK)/extracellular-signal-regulated kinase (ERK) signaling pathways, which plays an essential role in promoting GC cell proliferation and inhibiting apoptosis [61], as is shown in Table 1.

Although a large number of studies on lncRNAs profiles are underway, lncRNAs have the potential to be a key biomarker in carcinogenesis, metastasis, and prognosis of GC. In addition, its expression levels and complex signal pathways are used to predict the biological behavior of GC cells, including proliferation, invasion, metastasis, and drug resistance. As a result, lncRNAs are expected to become a powerful tool for precise treatment, but the comprehensive mechanism is still unclear. Furthermore, the current measurement is challenging because of its abundance, ease of degradation, and instability.

2.3. Cell-free DNA (cfDNA)

CfDNA is cell-free extracellular DNA released from normal cells and cancerous cells, presenting in the blood (the plasma or the serum) and

Table 1. Expression level and functional role of lncRNAs correlated with the outcomes of gastric cancer (GC).

lncRNAs	Pattern	Signaling Pathway	Functional Role	Number of Cases	Correlation with Outcome
HOXC-AS3 [51]	Up	Binding to YBX1	Regulate cell proliferation and migration.	-	Over expression of HOXC-AS3 predict a poor prognosis in GC.
HOST2 [52]	Up	Unclear	Promote invasion and migration ability of GC cells.	72 GC patients (43 males and 29 females)	Enhance proliferation and metastasis in GC.
XIST [53]	Up	Unclear	Promote GC cells proliferation.	60 gastric adenocarcinoma tumor samples and matched healthy adjacent tissues	Higher XIST expression relates to poor prognosis and contributes to drug resistance.
FTX [54]	Up	FTX-miR 2153p-SI-VA1 regulatory axis	Reduce the expression of SIVA1 and promote the proliferation of GC cells by competitive binding to miR 215-3p during the occurrence of GC.	71 GC tissue samples	High FTX expression had poorer OS.
DDX11-AS1 [55]	Up	Serve as an oncogene by sponging miR- 873-5p and promoting SPC18 expression	Promote TNM stage and lymph node metastasis.	72 pairs of tumor specimens and adjacent non-tumor tissues from GC patients	Poorer outcome.
LINC01234 [56]	Up	Unclear	It is involved in the cell cycle, mismatch repair, and B-cell receptor signaling pathway.	83 pairs of cancerous and adjacent normal tissues	LINC01234 may be a diagnostic marker in GC patients.
ABHD11-AS1 [57]	Up	Down-regulating miR-361-3p/PDPK1 and activating PI3K/AKT signaling	Facilitate cell proliferation, tumor growth, and apoptosis.	41 pairs of cancerous and adjacent normal tissues	ABHD11-AS1 predicts dismal prognosis with upregulated expression in GC.
ARAP1-AS1 [58]	Up	Unclear	Promote tumor progression and metastasis.	157 GC patients (88 males and 69 females)	ARAP1-AS1 upregulation may be an unfavorable prognostic factor in GC patients.
LUCAT1 [59]	Up	By regulating the miR-134-5p/YWHAZ axis	Promote tumor proliferation and invasion.	98 pairs of paracancerous tissues and adjacent carcinoma tissues	High LUCAT1 expression is correlated with shorter OS and PFS.
BCAR4 [61]	Up	Unclear	Accelerate cell proliferation and suppress cell apoptosis.	45 pairs of cancerous and adjacent normal tissues	BCAR4 has the potential to be a marker for predicting the poor outcome of GC.

other body fluids of animals and human [62]. The value in monitoring the progression and prognosis of GC using DNA methylation has been evaluated in previous research. Previous studies demonstrated that aberrant DNA methylation might become a marker of diagnosis, prognosis, chemotherapy sensitivity for GC patients. In terms of prediction, Pimson et al. have found that aberrant methylation of PCDH10 and RASSF1A genes in blood samples is associated with poorer clinical outcomes in GC [63]. In early detection of GC, Lin et al. have measured that the methylation rate of ZIC1, HOXD10, and RUNX3 significantly increased in the progression of gastric carcinogenesis, and the combined assays of detecting plasma improved methylation sensitivity and specificity [64]. Furthermore, a validation study using the methylation-specific PCR method collected plasma samples from confirmed GC patients and healthy controls to investigate the methylation status of four tumor suppressor genes-P16, RASSF1A, RPRM, and RUNX3. They described that these four genes were markedly higher than the controls ($P < 0.001$). The AUC value of RPRM and RUNX3 is 0.70 versus 0.77 ($P < 0.001$). Combined RPRM and RUNX3 show a higher AUC value of 0.88. Thus, combined detection of plasma RPRM, RUNX3 methylation could be a valuable method for early diagnosis [65]. Subsequent study has performed genome-scale cfDNA methylation analysis using the methylated CpG tandem amplification and sequencing (MCTA-Seq) in patients with GC. Their data showed that these biomarkers, such as DOCK10, CABIN1, and KCNQ5, were particular substances for detecting GC in the blood, and MCTA-Seq has a high value in distinguishing early-stage of GC, colorectal cancer, and hepatocellular carcinoma [66]. However, further research on aberrant DNA methylation should be conducted [67]. Recently, Li et al. have identified that 5-Hydroxymethylcytosine (5hmC) biomarkers can distinguish cancer patients from healthy individuals with high sensitivity and specificity for colorectal cancer and GC using robust and highly efficient methods profiling-based approach to map 5hmC in plasma cfDNA samples from patients with cancer [68]. Moreover, previous studies have shown that quantitative determination of cfDNA has diagnostic and prognostic value for multiple tumors [69, 70]. On this basis, some scholars have further studied the significance of the ratio of single-stranded DNA (ssDNA) to double-stranded DNA (dsDNA) in circulating cfDNA for GC diagnosis. Their research has clarified that the ratio of ssDNA to dsDNA from GC patients was significantly lower than that of healthy individuals ($P < 0.0001$), and this ratio had distinctly higher diagnostic specificity and sensitivity than the level of ssDNA or dsDNA alone, which the AUC of this ratio was 0.930 (95%CI: 0.889–0.960) with a sensitivity of 83.96% and a specificity of 94.07%, but the study has some defects, such as insufficient sample size, single tumor type and small ratio fluctuation range [71]. Besides, cfDNA has been proved to serve as a prognostic marker and molecular target in drug resistance [72]. In addition, a study conducted among GC patients treated with PD-1 antibody immunotherapy has shown that decreasing cfDNA is correlated with high responsiveness to immunotherapy. Mutation status of TGFBR2, RHOA, and PREX2 in baseline cfDNA may influence the PFS of immunotherapy [73].

2.4. MicroRNAs

Among the potential biomarkers which are detectable in liquid biopsies, microRNAs (miRNAs) are gaining more and more attention, since they are easily detectable, quite stable in biological fluids, and they also show high sensitivity [19]. MicroRNA is an endogenous RNA with approximately 22 nucleotides. MicroRNA has the characteristics of resistance to RNase degradation and high stability in biological samples [74], which has become a hot spot in molecular research. It directly binds to the complementary sequence of the 3'-UTR of the targeted mRNAs to regulate the translational inhibition of the target mRNAs [75]. Previous studies have shown that microRNAs are related to cell proliferation, differentiation, migration, and invasion [76]. Kong et al. investigate the association between serum miR-25 level and diagnostic prediction. The results show that miR-25 improves GC screening with sensitivity and

Table 2. Expression pattern and functional role of microRNAs in GC.

Type	Expression Pattern	Functional Role	Ref.
miR-1-3p	Low	Low miR-1-3p expression is correlated with a worse prognosis.	[81]
miR-217	Low	MiR-217 inhibits invasion, metastasis, and EMT through targeting PTPN14.	[82]
miR-34a	Low	Low expression of miR-34a can promote the progression of gastric cancer and reduce the prognosis of patients.	[83]
miR-501-5p	High	Upregulation of miRNA-501-5p promotes cell proliferation and migration through down regulating LPAR1 expression.	[84]
miR-665	Low	MiR-665 overexpression inhibits cell growth, invasion, and EMT of GC.	[84]
miR-760	Low	MiR-760 inhibits cell viability, migration, invasion and promotes cell apoptosis through negatively regulating BST2.	[86]
miR-532	High	MiR-532 overexpression promotes gastric cell migration and invasion through inhibiting NKD1 and activating Wnt/ β -catenin pathway.	[87]
miR-125a-5p	Low	MicroRNA-125a-5p/insulin-like growth factor 2 messenger RNA-binding protein 3 axis contributes to the oncogenesis of advanced gastric cancer.	[88]
miRNA-1324	Low	MiRNA-1324 may function as a tumor suppressor gene by inhibiting MECP2 expression.	[89]
miR-376a	Low	The low expression of miR-376a is distinctly associated with tumorigenesis and poor prognosis.	[90]
miR-216b	Low	The downregulation of miR-216b may promote the progression of GC via inhibiting CCTN2.	[91]
miR-10b	High	Increasing miR-10b-5p is correlated with worse clinical outcomes.	[92]
miR-625-3p	Low	MicroRNA-625-3p might inhibit the malignant progression of GCA by regulating EZH2.	[93]

specificity [77]. For early detection of GC, Yu et al. found that miR-200 family members increased in early GC [78]. Zhu et al. demonstrated that some miRNAs (miR-425-5p, miR-1180-3p, miR-122-5p, miR-24-3p, miR4632-5p) in circulating plasma discriminated early-stage patients from trophic gastritis patients [79]. In terms of prognosis, Guo et al. studied the relationship between miR-3923 expression levels and clinical characteristics of GC, and their results clarified that high expression explains the poor prognosis [80]. Moreover, Chen et al. have assessed that high lipopolysaccharide-induced tumor necrosis factor- α factor (LITAF) expression resulting from low miR-1-3p expression is a biomarker for poor prognosis or therapeutic targets in GC [81]. Similarly, MiR-217 inhibits the expression of tyrosine-protein phosphatase non-receptor type 14 (PTPN14) by directly targeting its 3'-UTR, and the low expression is associated with a poor prognosis of GC [82]. Moreover, a meta-analysis concluded that a low expression of miRNA-34a in GC tissues suggests a poor development of tumors [83]. Additionally, Ma et al. have demonstrated that miRNA-501-5p might be a novel effective biomarker in diagnosing, prognosis, and treating GC. They discovered miRNA-501-5p could negatively regulate lysophosphatidic acid receptor 1 (LPAR1) [84]. Concerning carcinogenesis, Zhang et al. studied the roles of the miR-665/protein phosphatase 2A regulatory subunit B55 α (PPP2R2A) axis in GC. They found that miR-665 level was dramatically reduced in GC tissues, promoting GC cell proliferation and invasion and EMT [85]. Another study measured the expression level of miR-760 in GC tissues and found its expression decreased in GC, which plays a role in inhibiting tumorigenesis by down-regulating bone marrow stromal antigen 2 (BST2) [86]. More interestingly, in a preliminary observational study, there were 14 upregulated miRNAs and 8 downregulated miRNAs by comparing GC tissues with normal tissues. Four miRNAs (miR-31-3p up, miR-6736-3p up, miR-3065-5p down, and miR-3921 down) may be

Table 3. Expression level and functional role of serum biomarkers in GC.

Protein	Expression	Samples	Functional Role
IFNGR1, Notch-3, TNFRSF19L, GHR, SLAMF8, FR-beta, Integrity alpha 5 [108]	Up	15 patients diagnosed with stage IA (T1N0M0) and 10 controls	IFNGR1-A, key molecule of the IFN- γ signaling pathway is associated with early GC. Notch-3-a tumor suppressor. TNFRSF19L-Involved in EMT. GHR-A member of class I cytokine receptor family is correlated with proliferation and differentiation. SLAMF8-A regulator of development and function of many immune cells. FR-beta-A member of folate receptor. Integrity alpha 5-A promoter to cell adhesion, differentiation, migration, proliferation and cell survival.
SOX3 [109]	Up	60 GC patients and 60 healthy controls	A transcription factor can promote cell invasion and migration through MMP9 in GC.
SPRR2A [110]	Up	200 GC patients and 290 non-GC patients	A promoter can induce occurrence and metastasis of GC.
GKN1 [111]	Down	500 GC patients and 200 healthy controls	A tumor suppressor by regulating cell proliferation and differentiation in GC.
IL-6, IL-10, IL-1 β , IFN- γ [112]	Up	162 GC patients and 201 healthy controls	Cytokine characterized by tumor-promoting and anti-tumor activities.
19 serum proteins [113]	Up	100 GC patients and 50 controls	The combination of 19 serum proteins (CEACAM5, CA9, MSLN, CCL20, SCF, TGF- α , MMP-1, MMP-10, IGF1, CDCP1, PPIA, DDAH-1, HMOX-1, FLI1, IL-7, ZBTB-17, APBB1IP, KAZALD-1, and ADAMTS-15) can distinguish GC patients from healthy controls, especially for patients in the early stage and high microsatellite instability.
IL-26 [114]	Up	302 patients of GC and 100 with benign stomach diseases	An inflammatory factor may promote progression and immune escape of GC.
FGA, AHSG, APOA-I [115]	Up	32 pairs of pre- and postoperative GC patients and 30 healthy individuals	Potential biomarkers may be involved in tumorigenesis and reflect tumor burden in GC.
NSE [116]	Up	219 patients and gastric adenocarcinoma and 298 healthy controls	NSE may serve as a diagnostic and prognostic indicator of gastric adenocarcinoma, tumor monitoring and precise treatment.
IL-17 [117]	Up	76 GC patients and 30 healthy controls	IL-17 may have good value in the diagnosis of GC through activating some cancer pathways such as Src/PI3K/Akt/nuclear factor- κ B(NF κ B), MAPK, Stat 3 and COX-2, but its role in prognosis is unclear.
LMX1A [118]	Down	127 patients diagnosed with GC and 58 patients with benign gastric	A tumor suppressor implicated in the development and progression of GC, which has the potential to become

Table 3 (continued)

Protein	Expression	Samples	Functional Role
		diseases, and 69 healthy controls	a promising candidate for early detection of GC.
ANOS1 [119]	Up	301 GC patients and 66 healthy controls	ANOS1 may be a valuable tool for the diagnosis of GC.
CXCL13 and PECAM-1 [120]	Up	98 GC patients and 60 healthy controls	The measurement of serum CXCL13 and PECAM-1 may be of good value for the diagnosis and prognosis of elderly GC patients.
MIC-1 [121]	Up	55 GC patients and 52 healthy controls	High level of MIC-1 indicates high potential invasion, which has the potential to distinguish gastric and non-gastric patients, it may be used as an independent risk factor for early GC.

involved in gastric carcinogenesis. However, its small sample size (only ten samples) could not determine molecular mechanisms [87], as is shown in Table 2.

At present, there are still countless researches on microRNA, as shown in Table 2 [88, 89, 90, 91, 92, 93]. Another emerging research area of miRNAs is the single nucleotide polymorphism (SNPs) in the miRNA gene. Song et al. have investigated the genotype and allele frequencies of four SNPs in miRNA machinery genes (GEMIN4, DROSHA, DICER, and AGO1) in GC patients and healthy controls in the Chinese Han population. And they found there was a notable correlation between rs3742330 (DICER) and rs7813 (GEMIN4) and the susceptibility of GC, DICER, GEMIN4, and advanced stage of GC, GEMIN4, AGO1, and lymphatic metastasis of GC [94]. Besides, the presence of the SNP in miR-627 rs2620381 may be involved in the pathogenesis of GC [95].

miRNAs may be a group of new, noninvasive biomarkers of GC with sensitivity and specificity. However, there are still some limitations in the current research. First, the sample size is small, leading to quite a bias in experimental results. Secondly, due to the characterization of high heterogeneity in GC, whether circulating miRNAs can indicate cancer type and information of biological behavior of the primary tumor is unclear. The value of early diagnosis and prognosis of GC needs further investigation. Thirdly, a miRNA may have multiple target mRNAs and signaling pathways. And the complex molecular mechanism remains unclear. Fourthly, there is no uniform standard for miRNAs extraction, measurement, and verification. Applying miRNAs from the laboratory to clinical transformation is a promising direction.

2.5. Exosomes

Exosomes are vesicles secreted by almost all types of cells and filled with various biomolecules. They can mediate cell-to-cell communication by transferring specific biomolecules under physiological and pathological conditions [96, 97] and survive in body fluids without degradation due to lipid bilayer structure [98, 99, 100]. Increasing studies suggest that exosomes have a great promise to serve as novel biomarkers in liquid biopsies. Additionally, the potential of exosome serving as diagnostic and prognostic biomarkers has been investigated in a variety of cancers [20]. Related studies have shown that exosomes are closely correlated with GC tumorigenesis, metastasis, angiogenesis, immune evasion and drug resistance [101]. Besides, contents in exosomes including exosomal proteins, miRNAs, lncRNAs and circular RNAs promote tumor growth and progression [101]. Wei et al have identified that serum exosomal transfer of miR-15b-3p can enhance GC cells development via inhibiting the DYNLT1/Caspase-3/Caspase-9 signaling pathway, the expression of exo-miR-15b-3p was found to be upregulated with the AUC being 0.820. It may serve as a potential diagnosis and prognosis biomarker in GC

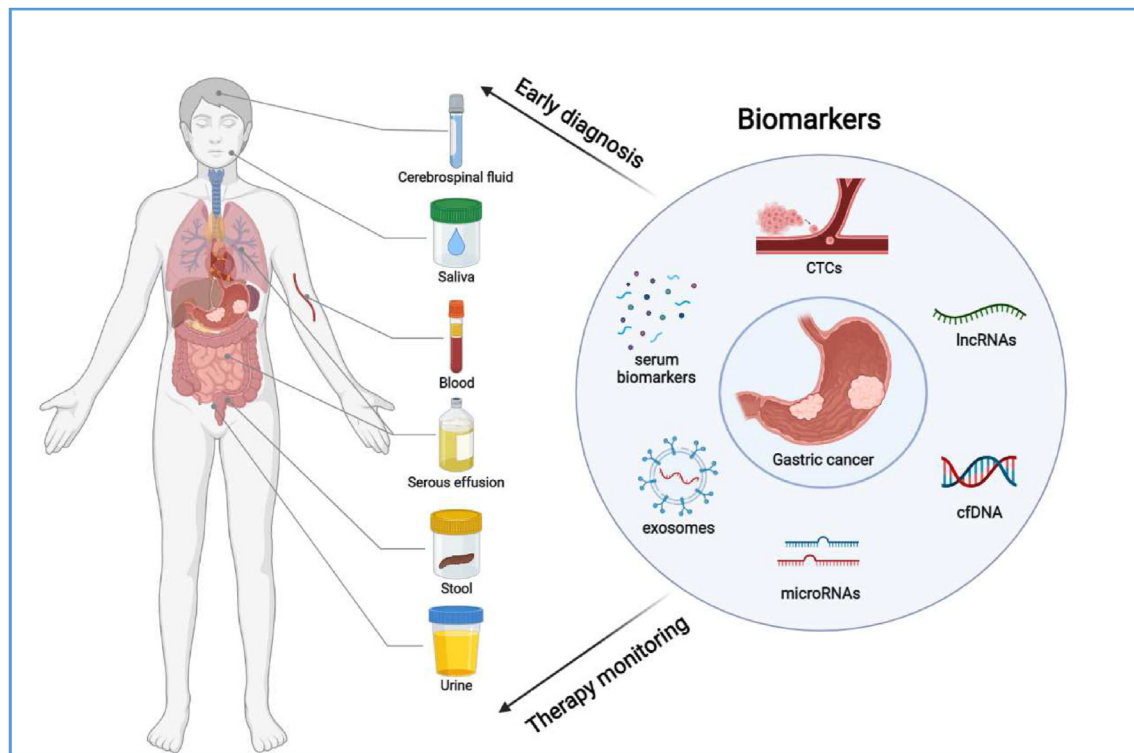


Figure 1. Scheme of biomarkers associated with gastric cancer.

[102]. A recent study found that exosomal circSHKBP1 is upregulated in GC patients and promote GC cell proliferation, migration and invasion serving as a sponge of miR-582-3p to upregulate Hu-antigen R (HUR) and vascular endothelial growth factor (VEGF) and inhibit heat shock protein 90 (HSP90) degradation. Liquid biopsy targeting serum exosomal circSHKBP1 may have value in diagnosis and prognosis in GC [103]. Another research has shown that exosome-delivered miR-135b contributes greatly to enhancing angiogenesis in GC by suppressing the expression of FOXO1 protein [104]. A study conducted by Wang et al has found that a paclitaxel-resistant gastric cancer cell line can induce chemoresistance in paclitaxel-sensitive cells by exosomal delivery of miR-155-5p. Their results suggest that targeting miR-155-5p may be a promising therapy for overcoming chemoresistance in GC [105]. Taken together, Exosomes and contents may become biomarkers in terms of diagnosis and prognosis for GC.

3. Serum biomarkers

At present, the development of molecular markers for the detection of advanced GC has achieved some progress, such as CEA, CA19-9, CA72-4, CA125. They have been clinically used for diagnosis, prognosis, and monitoring cancer burden [106, 107]. However, due to its unsatisfactory specificity and sensitivity, it is necessary to determine novel biomarkers [4]. Wu et al. collected serum samples from stage IA GC patients and healthy controls using antibody microarray technology. They found that 11 cytokines (IFNGR1, Notch-3, TNFRSF19L, GHR, SLAMF8, FR-beta, Integrin alpha 5, Galectin-8, EphA1, Epregrulin and FGF-12) were elevated, indicating that they may be novel serum biomarkers of GC [108]. Moreover, Shen et al. demonstrated that the high level of SOX3 negatively correlates with the prognosis of GC [109]. Xu et al. found that the expression of SPRR2A in GC patients was significantly increased, and the marked decrease can be seen after surgery [110]. Regarding diagnosis, Yoon et al. described that the serum GKN1 protein might act as an effective biomarker for early diagnosis of GC and differentiate GC patients from non-gastric cancers [111]. Similarly, a controlled study conducted by Norma et al. showed that the increased levels of IL-6, IFN- γ ,

and IL-10 might help discriminate GC patients in the early stages for healthy individuals [112]. To date, there are still many studies on serum biomarkers, as shown in Table 3 [113,114,115,116,117,118,119,120, 121].

4. Conclusion

GC shows high levels of heterogeneity and lacks early symptoms. Hence, the early and fast diagnosis of GC is very important for good outcomes. Nowadays, the utilization of biomarkers has emerged as a new diagnosis option for the early and fast detection of GC. It has been reported that GC biomarkers show the excellent prospects in detecting early tumor, evaluating prognosis, monitoring tumor burden, predicting drug resistance, and providing up-to-date information on the therapies. Liquid biopsies, a noninvasive technique, are expected to achieve repeated sampling, real-time monitoring, and precise treatment by detecting circulating tumor markers in body fluids. Broadly, the potential biomarkers detectable in liquid biopsies such as CTCs, IncRNAs, cfDNA, microRNAs and exosomes suggest numerous information in terms of the early prediction and the outcomes for GC patients. Additionally, the use of the novel serum biomarkers such as IFNGR1, Notch-3, TNFRSF19L, GHR, SLAMF8, FR-beta, Integrin alpha 5, Galectin-8, EphA1, Epregrulin and FGF-12 SOX3, SPRR2A, and GKN1 have opened up new opportunity for diagnosis and monitoring patients with GC. As a result, the present review gives an overview of the wide range of novel biomarkers in the early diagnosis and therapy monitoring of GC (Figure 1). Novel biomarkers will highlight the rapidly evolving field of research in GC, promising improved treatment stratification and identification of molecular targets for individualized treatment in GC.

5. Future perspectives

Regarding the diagnosis of GC, the current gold standard is still endoscopic pathological biopsy. However, endoscopy is an invasive technique with uncommon but serious side effects and a relatively high cost. Therefore, the advantages of GC molecular markers, such as no

invasion, high reproducibility, and easy access to materials, still have broad prospects in clinics, but the disadvantages of GC biomarkers lie in insufficient sensitivity and specificity. Thus, the diagnosis of GC needs to focus on improving its sensitivity and specificity. For one thing, an in-depth study of the molecular mechanism of tumor occurrence and progression is the key to solving this problem. In addition, another method is to further investigate the accuracy of diagnosis and prognosis by combining different GC markers and pathology. Finally, it is necessary to perform a technological platform in large, well-characterized cohorts of patients and controls to select the biomarkers with highest clinical relevance.

The exploration of precise biomarker closely related to GC development can also be applied to diagnosis and therapy. In the future, this review will help to identify the robust biomarkers in clinical care of GC patients for ultimating prevention and treatment of GC.

Declarations

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

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Data availability statement

Data will be made available on request.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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