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Review

Exosomal Functional Cargoes from Liquid Biopsy of Gastric Cancer: A Systematic Review of Studies With Potential Clinical Relevance

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Abstract. *Background/Aim: Liquid biopsy (LB) is a promising non-invasive tool to detect cancer. Over the last few years, exosomes recruited from LB have attracted the attention of researchers for their involvement in cancer. We focused on the role of LB exosomes in gastric cancer (GC). Materials and Methods: We investigated the world literature on exosome-encapsulated functional biomarkers (non-coding RNAs and DNAs) taken from GC patients' LBs. Only the studies exploring serum, intraperitoneal fluid or gastric lavage were included. Results: As of 2022, fifty articles with an overall count of 3552 GC patients were investigated. Given the statistically significant associations with the clinicopathological categories of tumor depth, lymph node metastasis, staging class and tumor size, most exosome-mediated microRNAs, long non-coding RNAs and circular RNAs proved to exert a potentially important bioclinical role in terms of diagnosis, screening, prognosis and therapeutic targets. Conclusion: In the future, resorting to exosomal biomarkers taken from LB of affected patients could revolutionize the non-invasive fight against GC.*

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Comparing the 2018 GLOBOCAN estimates of cancer incidence and mortality produced by the International Agency for Research on Cancer with the latter version edited in 2020, stomach cancer fell from fourth to fifth place of the most common types of cancer (but with increasing number of new cases from 1,033,101 to 1,089,103) and from the third place in 2018 to the fourth leading cause of global cancer deaths (causing 768,793 *vs*. 782,685 fatalities in 2018) (1, 2). Such epidemiologic ameliorations, although apparently minimal, are clinically of paramount importance, coming from decades of innumerable, sustained, and commendable efforts provided by the worldwide scientific community on all levels of research. Development of more precise systems of classification and prevention, innovative theories on metastatic routes, stronger indications to the type and timing of a multidisciplinary therapy strategy and standardization of surgical procedures (diagnosis, screening, therapy, and prognosis), in fact, have expanded the knowledge armamentarium and improved the survival chances (3-11). However, as of today, since most diagnoses are obtained at advanced stages, no standardized methods of non-invasive screening (alternative to gastroscopy) exist and its complex pathobiology is still far from being understood; gastric cancer (GC) keeps on being a fearsome disease with an ominous prognosis especially in the Western world. In fact, most GC cases continue to be detected at advanced phases of the disease when the prognosis is dismal (five-year survival rate of 10%) and the treatment options are limited (12). Although interesting, in terms of detection (especially for the early stages), the results of analyses of biomarkers taken from the sera of GC patients were of low specificity and sensitivity (this is particularly true for traditional markers such as pepsinogen, carcinoembryonic

antigen and several carbohydrate antigens such as CA 19-9, Ca 72-4, Ca 125, Ca 24-2 and Ca 50), provisional (necessitating further corroboration by trial studies) or with limited applications (several circulating GC biomarkers are susceptible to endogenous degradation) (13-16). Such observations prompted researchers to look for novel and effective biological markers, generically termed as functional biomarkers, able to convey or regulate genetic information such as micro RNAs (miRNAs or miRs), long non-coding RNAs (lncRNAs), circular non-coding RNAs (circRNAs), or even DNAs (17-19). For the purposes of noninvasive recruitment useful to methods of screening, prognosis and prediction, the concept of liquid biopsy of GC was expanded. Therefore, in addition to plasma, ascites, or peritoneal lavage fluid (PLF), gastric juice (GJ) or lavage (GL) of patients became the new compartments to investigate as sources of traditional or new biomarkers (20). Intragastric fluid in particular, due to its closer vicinity with GC and for bypassing the metabolic functions of the liver, attracted the attention of scientific community because it is thought to be more specific than serum in view of its high levels of exfoliated malignant cells and tumor products (21-25). A further evolution in this field of research was the discovery that in body fluids, such cell-free (or circulating tumor) markers exist in at least three forms: unbound (single or double stranded nucleic acids), bound (assembled in lipoprotein macromolecules such as virtosomes and NETosis) and encapsulated (in extracellular vesicles such as exosomes, microvesicles and apoptotic bodies) (26, 27). The study of genetic contents enclosed in exosomes derived from GC and taken from liquid biopsy represents a particular field of interest that begun only a few years ago but with already important and promising results. Herein, we offer a review on the clinical significance and possible implications of exosome-encapsulated functional biomarkers described so far by the world literature in the extracellular fluid compartments of GC patients.

Materials and Methods

We investigated the world literature written in the English language dealing with the exosome-encapsulated nucleic acids related to GC found in the liquid biopsy of affected patients. We consulted PubMed, Scopus, Science Direct, ResearchGate, Publons, Academia and Google Scholar as the main search engines. We used the following key-words and key-expressions: exosomal (exosome or exosomic) DNA gastric cancer, exosomal miRNAs gastric cancer, exosomal lncRNAs gastric cancer, exosomal circRNAs gastric cancer, exosomes gastric cancer, serum exosomes gastric cancer, plasma exosomes gastric cancer, exosomes peritoneal lavage fluid, exosomes ascites, exosomes gastric juice, exosomes gastric lavage and exosomes gastric wash. Only prospective or retrospective works have been included but, in order to better assess the real clinical impact of exosomal molecular biomarkers, the following categories of articles were excluded from this review: studies on non-human subjects; studies not focused on at least one liquid biopsy (biological fluids: blood, peritoneal lavage, gastric juice/lavage); studies fully devoid of patients'clinical features; studies dealing with exosomes derived from cultured cells only; past studies on the same markers (being analyzed more recently by updated researches); commentaries, editorials and letters to the editor. To improve the reporting quality of our systematic review, we resorted to a flow diagram following the PRISMA 2020 Explanation and Elaboration Document (28).

Results

The process and results of article selection for our systematic review were reproduced with a work flowchart according to the PRISMA 2020 V2 indications (Figure 1). After digging into the literature, the following findings were excluded from inclusion: 52 studies because they were conducted on cell lines only, fully *in vitro* or not including liquid biopsies (for example: only stomach tissues), 19 reviews, 2 letters to the editor and 7 former studies on exosomal biomarkers (we preferred to include more recent original reports). We thereby selected 50 studies dealing with functional contents encapsulated into exosomes derived from GC and isolated from liquid biopsy in GC patients. Almost the totality of the enrolled studies had a prospective nature; 37 works had an *in vitro* experimental part as well. As of 2022, no meta-analysis of studies on exosomal cargoes taken from liquid biopsy of GC exists. Twenty studies were on exosomal microribonucleic acids EmiRs (Table I) (29-48). Thirteen articles were on exosomal long non-coding ribonucleic acids ElncRNAs (Table II) (49-61). Fourteen studies were on exosomal circular ribonucleic acids EcircRNAs (Table III and Table IV) (61-74). Table V reviews the current publications on exosomal deoxyribonucleic acids EDNAs (76-78). Our review included 27 EmiRs (Table I and Table IV), 13 ElncRNAs (Table II), 14 EcircRNAs (Table III and Table IV) and 4 genomic EDNAs (Table V). Altogether, 3552 GC patients had been investigated with liquid biopsy (1,458 for EmiRs, 1,398 for ElncRNAs, 596 for EcircRNAs, 100 for EDNAs) (Table I, Table II, Table III, Table IV and Table V). Liquid biopsy mostly involved patients' sera (40 studies), followed by intragastric (GJ/GL) (6 studies) and intraperitoneal (PLF/ascites) (3 studies) compartments. Of the 2,999 GC patients investigated with liquid biopsy from serum (85.4% of total patients), 1239 were studied for EmiRs (41%), 1398 for lncRNAs (47%) and 362 for EcircRNAs (12%). Interestingly, all works on EDNAs investigated GJ samples (Table V). Esosomal cargoes were more frequently associated with an oncogenic rather than antioncogenic role: in fact, 12 out of 19 EmiR studies, 11 of 13 ElncRNAs papers and 9 out of 14 EcircRNAs publications dealt with oncogenic biomarkers. Conversely, studies on EDNAs focused more on tumor suppressor genes (Table V). When available, the pathologic pathways associated with each nucleic acid has been reported (Table I,

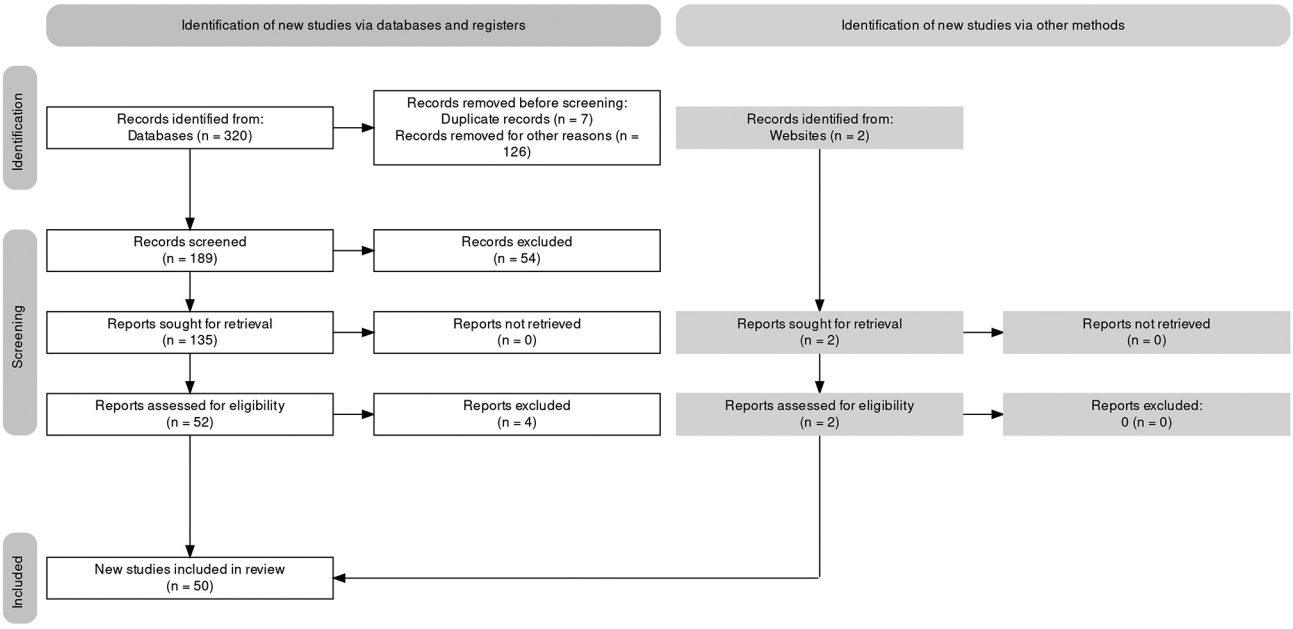

Figure 1. *Flowchart of the study according to the PRISMA 2020 V2 indications.*

Table II, Table III, Table IV and Table V). Associations between the up- or down-regulated expression of exosomal functional biomarkers and traditional clinicopathologic features of GC patients were clearly reported in 38 studies (76%). Staging class was the clinical parameter more often investigated (28 studies) and its association was statistically significant in 27 articles (96% of cases). Other relevant correlations were those with tumor depth (demonstrated in 9 out of 10 investigating studies, 90%), lymph node metastasis (13 of 14 exploring studies, 93%) and tumor size category (8 of 9 exploring studies, 89%). Most markers were also useful to diagnosis, screening and detection of recurrences and metastases with or without the combination of traditional soluble tumor antigens (Table I, Table II, Table III, Table IV and Table V). Moreover, in terms of survival, some exosomal nucleic acids resulted statistically significant independent factors of poor prognosis (32, 35, 38, 46, 47, 60, 62, 63, 65, 72). At last, some of these were identified as potential targets of therapy for their clinical role of chemosensitivity and chemoresistance (40, 51, 52, 68, 70) or the promotion effect on tumor microenvironment (19).

Discussion

Multicellular organisms can communicate either extra- or intra-cellularly, through direct interactions between cell surfaces (cell-cell contact) or transfer of functional molecules scavenged and secreted into extracellular vesicles (EVs) (79). EVs are small, spherical, membranous structures which can be divided into three subgroups based on differences in biosynthesis and size: membrane-shedding EVs (also known as microparticles or microvesicles) (size of 50-3,000 nm), apoptosis-derived EVs (apoptotic bodies, 800-5,000 nm) and endosomal system-derived EVs (exosomes) which have the smallest diameter (40-100 nm) (79). The stability of the phospholipid bilayer of exosomes is a very important feature because, by conferring resistance to enzymatic degradation by RNase, it permits the preservation of such EVs in extracellular space and body fluids (blood, urine, saliva, breast milk, tears, cerebrospinal fluid, cervicovaginal lavage fluid, ascites and PLF, GJ and GL) for long periods of time as well as a safe long-distance conveyance of their content (29, 79). As observed in our review, exosomes contain several types of functional molecules such as mRNAs, DNAs and non-coding RNAs (miRNAs, lncRNAs, circRNAs) besides lipids, enzymes and proteins (Table I, Table II, Table III, Table IV and Table V) (29-78). Exosome-mediated intercellular communication can take place in four possible manners: stimulation after direct binding of EVs with cell surface ligands, release of receptors, deliver of functional proteins (pattern of particular importance in case of bacterial or viral infectious diseases) and transferal of genetic information (79). The latter has been the subject of this review. Through integration of oncoregulatory factors transported by tumor-derived exosomes (TEX), in fact, cancer cells can promote neoplastic initiation and progression by affecting proliferation, phenotype, functions and homeostasis of recipient cells (Table I, Table II, Table

Table I. *Literature on exosomal microRNAs in liquid biopsy (serum or peritoneal lavage fluid), stomach tissue and cell lines from gastric cancer patients.*

Ref	Study type	Biomarker name	GC/Control Patients	Role	Serum expression*	Other fluid expression*	Pathologic associations	Mechanisms	Potential utility for GC
30	R	miR-19b-3p, miR-106a-5p	130/130	O	Higher (p<0.0001)	Not studied	N (p<0.01), Stage (p<0.05)	Not declared	Diagnostic biomarkers
31	P, iv	miR-21, miR-1225-5p	24/0	O	Not studied	PLG (higher: p=0.015)	T4 (p=0.027, p=0.008)	p, PM (axis not studied)	Prognostic PM biomarkers
32	R	miR-29 family	85 (33 PM+/ 52PM-)	TS	Not studied	PLG for miR-29 family (lower: p<0.001)	miR-29b-3p: bad OS (p=0.014), miR-29 fam: bad RFS (p≤0.038)	c, p, recurrence, and PM (axis not studied)	Prognostic PM biomarker; gene therapy
33	P	miR-552-5p	30/15	O	Higher (p<0.05)	iv (higher: p<0.05)	T (p≤0.004), N (p≤0.011), Stage (p≤0.01)	c, mi, EMT (*via* PTEN-TOB1axis), antiapoptosis (*via* caspase-3 axis), me	Prognosis, TT
34	R, iv	miR-195-5p, miR-211-5p	88/88	TS	Higher (p<0.001)	iv (p=0.016)	N (p<0.01), Stage (p<0.05)	Progression (axis not studied)	Diagno-prognostic biomarker
35	R, iv	miR-130b-3p, miR-15b-3p, miR-151a-3p, miR-1246	7/3	O	Higher (p<0.05)	Urine (miR-1246 higher: p<0.05)	miR15b-3p: prognosis (p<0.05) miR-151a-3p: bad OS (p<0.05)	c,p,a (miR-15b-3p: DYNLT1/ Caspase-3/-9 axis)	Diagno-prognostic biomarker, TT
36	R, iv	miR-10b-5p	169/52	O	Higher (p<0.05)	iv, GC tissue (higher: p=0.016)	N (p=0.002), Stage (p=0.02)	Proliferation (*via* PTEN), promotion (TGFβ1)	Diagnosis
37	P, iv	miR-122-5p	Not provided	TS	Lower (p<0.05)	iv (lower: p<0.05)	Not studied	Proliferation, me (*via* GIT1 expression)	Marker of c and progression
38	R, iv	miR-590-5p	168/50	TS	Lower (p<0.05)	Not studied	Lower in Stage 3/4 *vs.* Stage 1/2 (p<0.05); T, bad OS (p<0.001)	Invasion (axis not studied)	Diagnosis
39	R	miR-92a-3p	131/122	TS	Lower (p<0.0001)	Not available	N and Stage (p<0.05)	Proliferation, me	Diagnosis
40	P, iv	miR-374a-5p	59/34	O	Higher (p<0.001)	iv (higher: p<0.05)	Size (p=0.01); higher in oxaliplatin-resistance (p<0.05)	Chemoresistance (*via* Neurod1 expression)	Drug resistance appraisal, TT
41	P	miR-181b-5p	92/73	TS	Not studied	PLG (lower: p<0.001)	PM (p<0.001)	me (axis not studied)	MA diagnosis
42	P, iv	miR-1246	85/80	O	Higher (p<0.001)	Not studied	Stage (p<0.033); M (p<0.035)	Not studied	Early diagnosis
43	P, iv	miR-1290	20/10	O	Higher (p<0.05)	iv (higher: p<0.05)	Not studied	P (*via* NKD1 expression inhibition)	TT
44	P, iv	miR-135b	non-explicit	O	Higher (p<0.05)	iv, GC tissue (higher: p<0.05)	Not studied	Angiogenesis (*via* IL-8/FOXO1 axis)	TT (anti-VEGF drug)
45	P, iv	miR-107	non-explicit	O	Higher (p<0.01)	iv, GC tissue (higher: p<0.01)	Not studied	P (*via* DICER1/ PTEN/ARG1 axis)	TT
46	P	miR-23b	232/20	TS	Lower (p<0.05)	Not studied	T (p=0.03), Stage (p<0.03); Size (p<0.02);	Not studied	Prognosis and recurrence prediction
47	P, iv	miR-423-5p	80/80	O	Higher (p<0.01)	iv, GC tissue (higher: p<0.01)	N (p=0.014), poor OS (p=0.039)	p and mi *via* SUFU (TS) inhibition	Diagno-prognostic biomarker
48	P, iv	miR-221	40/20	O	Higher (p<0.05)	iv (higher: p<0.001)	and DFS (p=0.046) Stage (p=0.02)	p, mi *via* PTEN/p27	TT

*Compared with control group (adjacent normal tissues/benign tissues/non-GC patients). R: Retrospective; GC: gastric cancer; iv: *in vitro*/*in vivo*; EMT: epithelial-mesenchymal transition); P: prospective; O: oncogene; MA: malignant ascites; PLF: peritoneal lavage fluid; p: progression; PM: peritoneal metastasis; TS: tumor suppressor; OS: overall survival; RFS: recurrence-free survival; c: carcinogenesis; AT: adipose tissue; mi: migration; me: metastasis; EMT: epithelial-mesenchymal transition; TT: therapeutic target; a: angiogenesis.

Table II. *Literature on exosomal microRNAs in liquid biopsy (serum or peritoneal lavage fluid), stomach tissue and cell lines from gastric cancer patients.*

Ref	Study type	Biomarker name	Number of GC/Controls	Role	Serum expression*	Other tissue/fluid expression*	Pathologic associations	Mechanisms	Potential utility for GC
49	P, iv	ZFAS1	94/94	O	Higher (p<0.001)	GC tissue (higher: p<0.001)	N (p=0.008), Stage (p=0.034)	Cell cycle progression, EMT progress, mig	Diagnostic biomarker, novel TT
50	R, iv	NR038975	86/47	O	Higher (p<0.001)	GC tissue (higher: p<0.001)	T (p=0.002), N (p=0.006), Stage (p=0.003)	Proliferation, mig (*via* NF45/NF90 complex)	Diagnostic biomarker, novel TT (NF90)
51	R, iv	ENDOG-1:1 (lncFERO)	112/104	O	Higher (p<0.01)	Not declared	Not studied	Tumor ferroptosis inhibition (TS) (*via* SCD1/hnRNPA1)	Chemoresistance and recurrence
52	P, iv	CRNDE	35/not explicit	O	Higher (p<0.01)	GC tissue (higher: p<0.01)	Not studied	p, invasion, drug resistance (*via* PTEN axis inactivation)	Cisplatin resistance reversion
53	R, iv	FRLnc1	Serum: 60/60, tissue: 68/30	O	Higher (p<0.01)	GC tissue (higher: p<0.01)	N (p=0.004), Stage (p=0.009)	proliferation, mig, invasion (*via* cyclin D1 mRNA)	Diagnosis, treatment
54	P, iv	X26nt	16/16	O	Higher (p<0.01)	iv, GC tissue (higher: p<0.01)	Not studied	angiogenesis (VE-cadherin expression)	Not declared
55	P, iv	H19	81/78	O	Higher (p<0.01)	Not studied	Stage (p=0.007)	Not studied	Diagno-prognostic marker
56	P	MIAT	109/98	O	Higher (p<0.001)	Not studied	N (p=0.0006), Stage (p<0.0001)	Not studied	Prognostic marker
57	P	PCSK2-2:1	63/29	TS	Lower (p=0.006)	Not studied	Size (p=0.044), Stage (p=0.006), LVI (p=0.036)	p	Diagnosis
58	P	lnc-GNAQ-6:1	43/27	TS	Lower (p=0.001)	Not studied	all clinical features: p>0.05	Not studied	Diagnosis
59	P, iv	lncUEGC1	51/60	O	Higher (p<0.0001)	iv (higher: p<0.01)	Stages I-II (p<0.0001)	Not studied	EGC diagnosis
60	P, iv	HOTTIP	126/120	O	Higher (p<0.001)	iv (higher (p<0.001)	T(p=0.029), Stage (p<0.001), bad OS (p<0.001)	Not studied	Diagno-prognostic marker
61	P, iv	lncRNA1 (lncRNA-GC1)	522/304	O	Higher (p<0.001)	iv (higher (p=0.002)	G (p<0.001), Stage (p<0.001), Lauren (p<0.001)	p (axis not studied)	EGC diagnosis; follow-up

*Compared with control group (adjacent normal tissues/benign tissues/non-GC patients). GC: Gastric cancer; O: oncogene; R: retrospective; iv: *in vivo*/*in vitro*; EMT: epithelial-mesenchymal transition); mig: migration; p: progression; TS: tumor suppressor; OS: overall survival.; c: carcinogenesis; EMT: epithelial-mesenchymal transition; TT: therapeutic target; LVI: lymphovascular invasion.

III, Table IV and Table V) (29-78). Tumor progression and metastasis are also facilitated by TEX with two other main mechanisms: on one hand this type of EVs can make tumor microenvironment (and its extracellular matrix) more favorable for secondary deposits with the release of specific integrins; on the other hand, they can suppress host innate and adaptive immune responses with the regulation of transforming growth factor-β, interleukin-6, prostaglandin E2 and other mediators (19, 79-81). With a total number of 50 studies and 3,552 patients, the important dimension reached by our review corroborates the pivotal role of soluble exosomes for GC (Table I, Table II, Table III, Table IV and Table V). With the help of modern analytical techniques such as exosome precipitation kits, *in vitro* cell culture, quantitative reverse transcription-polymerase chain reaction, flow cytometry and many others, in fact, currently GC-derived exosomes can be easily isolated not only from tissues but also in several liquid compartments of affected patients such as blood, peritoneal lavage fluid/ascitis and gastric juice/gastric lavage (30-78). As already proven for other cancers, GC also uses exosomes as intercellular heralds to promote cell proliferation, progression, migration,

Table III. *Literature on exosomal microRNAs in liquid biopsy (serum or peritoneal lavage fluid), stomach tissue and cell lines from gastric cancer patients.*

Ref	Study type	Biomarker name	Number of GC/Controls	Role	Serum expression*	Other tissue/fluid expression*	Pathologic associations	Mechanisms	Potential utility for GC
62	P	circ_0001190	40/40	TS	Lower (p<0.05)	GC tissue (lower: p<0.05)	Shorter OS (p<0.05)	*via* miR-586 (sponge)/ SOSTDC1 (O) axis, angiogenesis	Prognostic biomarker
63	R, iv	circ_0001400 (circRELL1)	64/64	TS	Lower (p=0.0025)	iv, GC tissue (lower p<0.001)	G (p=0.044), T (p=0.015), N (p=0.039), Stage (p=0.002), bad OS (p=0.009), DFS (p=0.004)	*via* miR-637 (O) (sponge)/EPHB3 axis	Diagno-prognostic biomarker; TT
64	R, iv	circ_0005151 (circUBE2Q2)	60/60	O	Not studied	iv, GC tissue (higher: p<0.01)	N (p=0.037), Size (p=0.018)	c, mig, prog *via* miR-370-3p (sponge)/STAT3 axis	Prognostic factor; TT
65	R, iv	circ_0088300	60/60	O	Higher (p<0.01)	iv, GC tissue (higher: p<0.01)	shorter OS (p<0.01)	c, prog *via* miR 1305 (sponge)/ JAK/STAT axis	Diagno-prognostic biomarker
66	R, iv	circ_0044366 (circ29)	10/0	O	Higher (p<0.01)	iv	Not studied	c, prog, a (sponging miR-29a (TS)/VEGF)	TT
67	P, iv	circ-ITCH	61/33	TS	Lower (p<0.05)	iv, GC tissue (lower: p<0.001)	T (p=0.021)	me (*via* miR-199a-5p sponge/Khloto axis)	Diagnosis, therapy
68	P, iv	circ_0000260	27/27	O	Higher (p<0.01)	GC tissue (higher: p<0.001)	Higher in cisplatin resistant group (p<0.01)	Cisplatin resistance (*via* miR-129-5p sponge/MMP11 axis)	Appraisal of CT resistance /TT
69	P, iv	circNHSL1	20/20	O	Higher (p<0.05)	iv, GC tissue (higher: p<0.05)	N (p=0.04), Stage (p=0.02), M (p=0.02), Size (p=0.006)	Progression (*via* miR-149-5p sponge/ YWHAZ axis)	TT
70	P, iv	circ-PVT1	not available	O	Higher (p<0.05)	iv, GC tissue (higher: p<0.05)	Not studied	Progression (*via* miR-30a-5p/ YAP1 axis)	Appraisal of CT resistance /TT
71	P, iv	circ_0000936 (circSHKBP1)	224 (serum: 20)	O	Higher (p<0.01)	iv, GC tissue (higher: p=0.0008)	G (p=0.001), Stage (p=0.027), LVI (p=0.036), Size (p=0.033)	c,mig,prog,a (*via* miR-582-3p sponge/ HUR/VEGF)	Diagno-prognostic marker, TT
72	P, iv	circ_0063526 (RanGAP1)	97 (serum: 30)	O	Higher (p<0.05)	Higher (p<0.05)	N (p=0.001), Stage (p=0.001), Size (p=0.016), OS (p=0.023)	Invasion, me *via* miR-877-3p (sponge)/VEGFA	Diagno-prognostic marker
73	P, iv	circ_0032683 (circNEK9)	30/30	O	Higher (p<0.0076)	iv, GC tissue (higher: p=0.0018)	Stage (p=0.0001), Size (p=0.0002)	prog, invasion *via* miR-409-3p/ MAP7 axis	Follow-up

*Compared with control group (adjacent normal tissues/benign tissues/non-GC patients). R: Retrospective; GC: gastric cancer; iv: *in vitro*; P: prospective; O: oncogene; prog: progression; TS: tumor suppressor; OS: overall survival; DFS: disease-free survival; c: carcinogenesis; EMT: epithelial-mesenchymal transition; mig: migration; a: angiogenesis; TT: therapeutic target; CT: chemotherapy. me: metastasis.

metastasis, neoangiogenesis and a favorable microenvironment for tumor growth and drug resistance (30-78). The leading and most commonly studied functional molecules encapsulated in GC-related exosomes are non-coding RNAs and DNAs. The former include EmiRs (or EmiRNAs), lncRNAs and circularRNAs. As elucidated by our review, the knowledge on the profile of exosomal non-coding RNAs is still limited since it has been only a few years since the literature began dealing with these types of encapsulated biomarkers. EmiRs regulate tumor process with oncogenic or antioncogenic activity interacting with target messenger RNAs (mRNAs) and causing their degradation and translational repression (19, 30-48). Through the body fluids, as reported in our review, GC promotes an EV-mediated cell-to-cell pro-tumoral

Table IV. *Literature on exosomal microRNAs in liquid biopsy (serum or peritoneal lavage fluid), stomach tissue and cell lines from gastric cancer patients.*

Ref	Study type	Biomarker name	Number of GC/Controls	Role	Intragastric expression*	Other tissue/fluid expression*	Pathologic associations	Mechanisms	Potential utility for GC
74	P	circ_000780	78/60	TS	Lower (p<0.001)	GC tissue (lower: p<0.001)	T (p=0.029), LVI (p=0.039), Stage (p=0.001), Size (p=0.02)	Not studied (hypothesis of several miRNAs sponge)	EGC screening, prognosis
75	P	circ_0014717	96*	TS	Lower (p<0.05)	GC tissue (lower p<0.001)	M (p=0.048), Stage (p=0.037), CEA (p=0.001), Ca 19.9 (p=0.021)	Not studied	GC screening
19	P, iv	miR16-5p, 191-5p	18/0	?	Present (no p provided)	iv, GC tissue (higher: p<0.01)	Advanced stage (no p provided)	Microenvironment (fibroblasts recruitment)	diagnosis

*Compared with control group (adjacent normal tissues/benign tissues or fluids/non-GC patients). GC: Gastric cancer; P: prospective; EGC: early gastric cancer; iv: *in vitro*; TS: tumor suppressor; LVI: lymphovascular invasion; ?: role not specified.

Table V. *Literature on exosomal DNAs in the gastric juice samples from gastric cancer patients.*

Ref	Study type	Biomarker name	Number of GC/Controls	Role	Gastric juice expression*	Other tissue/fluid expression*	Pathologic associations	Mechanisms	Potential utility for GC
76	P, iv	LINE1 gene, SOX17 gene	20/0	O, TS	Low methylation (p=0.014)	iv (low methylation: p=0.013)	Concordance of nuclear with exosomal methylations	DNA methylation	Non-invasive diagnosis
77	P, iv	BARHL2 gene	70/32	TS	Higher methylation (p=0.0025)	iv: high methylation (p=0.002)	BARHL2 protein silencing in EGC (p=0.03)	DNA methylation takes to loss of protein	EGC detection
78	P	miR-34b/c gene	10/0	TS	Higher methylation (p=0.01)	not studied	Lower miR-34 levels (p=0.001)	miR-34 modulation	GC diagnosis

*Compared with control group (adjacent normal tissues/benign tissues/non-GC patients). GC: Gastric cancer; P: prospective; iv: *in vitro*; EGC: early gastric cancer.

communication enhancing the exosomal production of the oncogenic EmiRs (up-regulation of miR-19b-3p, miR-106a-5p, miR-552-5p, miR-195-5p, miR-211-5p, miR-130b-3p, miR-15b-3p, miR-151a-3p, miR-1246, miR-10b-5p, miR-374a-5p, miR-1246, miR-1290, miR-135b, miR-107, miR-423-5p and miR-221) or down-regulating the expression of those EmiRs functioning as tumor suppressors (miR-122-5p, miR-590-5p, miR-92a-3p and miR-23b) (Table I and Table IV). To potentiate its pro-tumoral efficacy, GC can also synergistically take advantage of ElncRNAs and EcircRNAs. Previously classified as competing endogenous RNAs (ceRNAs), such molecules can regulate gene expression through several interesting mechanisms including the sponging of miRNAs (49-75). Similarly to what was observed with EmiRs, in fact, according to their oncogenic or antioncogenic activity, EceRNAs can show hyper- or hypo-expression in the liquid biopsies of GC patients (Table II, Table III and Table IV) (49-75). Our review also highlighted that the measurements of most reported exosomal non-coding RNAs (EmiRs, ElncRNAs and circRNAs) taken from serum, peritoneal lavage fluid/ascitis and GJ/GL of GC patients significantly correlated with the clinicopathological characteristics of an advanced disease such as tumor invasion depth (T3-T4), lymph node metastasis, late stage and larger size (Table I, Table II, Table III and Table IV). Furthermore, the dysregulated level of some exosomal nucleic acids was also identified as significant or independent factor of poor prognosis (32, 35, 38, 46, 47, 60, 62, 63, 65, 72). At last, we underscore the utility of investigating other non-blood liquid sources of

exosomal cargoes such as PLF/ascitis (31, 32, 41) and GJ/GL (19, 74, 75). In these samples, in fact, altered levels of EmiR-21, EmiR-1225-5p, EmiR-29b-3p, EmiR-181b-5p, EmiR-16-5p, EmiR-191-5p, Ecirc_000780 and Ecirc_0014717 correlated with peritoneal metastases, stage IV and shorter overall survival for GC patients (Table I and Table IV). All the clinical analyses herein displayed confirm soluble exosomes as bioclinical factors potentially useful to diagnosis, screening, prognosis, and target therapy of GC (30-78). Differently from non-coding ERNAs, EDNAs have been rarely addressed in the literature: in fact, only three studies have been published and only 4 exosomal genes (LINE1, SOX17, BARHL2 and miR-34b/c gene) have been examined so far (Table V) (76-78). Nevertheless, the study of these EDNAs appears extremely important and useful because it demonstrated that GC could modulate post-transcriptional expression accomplishing epigenetic gene silencing (*via* reversible methylation of DNA) not only in the primary cancer and metastatic foci but also in soluble exosomes and use such carriers with pro-tumoral and pro-metastatic intent (76-78).

Conclusion

Our review of the world literature on exosomal biomarkers isolated from liquid biopsy of GC patients demonstrates that future genetic and clinical investigations on this type of microbodies can revolutionize the strategies of diagnosis, screening, prognostic stratification, recurrence/metastasis prevention and treatment currently adopted against GC.

Conflicts of Interest

The Authors declare no conflicts of interest.

Authors' Contributions

All the Auhors agreed with the content of the article. Dr. Virgilio conceived the research and wrote the manuscript. Dr. Virgilio, Dr. Montali, Dr. Annicchiarico and Dr. Salvemini reviewed the literature. Dr Giarnieri, Dr. Montagnini and Dr. Villani verified the appropriateness of the articles to include in this review. Dr. Proietti and Dr. D'Urso reviewed the molecular pathways associated with the biomarkers included. Dr. Virgilio, Dr. Baldinu, Dr. Montali, and Dr. Annicchiarico reviewed the statistical analyses. Dr. Costi and Dr. Virgilio supervised the project.

References

1 Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA and Jemal A: Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin *68(6)*: 394-424, 2018. PMID: 30207593. DOI: 10.3322/caac.21492

2 Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A and Bray F: Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin *71(3)*: 209-249, 2021. PMID: 33538338. DOI: 10.3322/caac.21660

3 In H, Solsky I, Palis B, Langdon-Embry M, Ajani J and Sano T: Validation of the 8th edition of the AJCC TNM staging system for gastric cancer using the National Cancer Database. Ann Surg Oncol *24(12)*: 3683-3691, 2017. PMID: 28895113. DOI: 10.1245/s10434-017-6078-x

4 Japanese Gastric Cancer Association: Japanese classification of gastric carcinoma: 3rd English edition. Gastric Cancer *14(2)*: 101-112, 2011. PMID: 21573743. DOI: 10.1007/s10120-011-0041-5

5 Virgilio E, D'Antonio C and Balducci G: Mesogastrium recurrence as expression of the fifth metastatic route of gastric cancer. Med Hypotheses *82(3)*: 403-404, 2014. PMID: 24472868. DOI: 10.1016/j.mehy.2014.01.005

6 Virgilio E, Giarnieri E, Montagnini M, Villani S, Giovagnoli MR, Mercantini P, Balducci G and Cavallini M: Advances in intraluminal exfoliative cytology of gastric cancer: oncologic implication of the sixth metastatic route (Metastasis VI). Anticancer Res *39(8)*: 4019-4022, 2019. PMID: 31366483. DOI: 10.21873/anticanres.13557

7 Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, Scarffe JH, Lofts FJ, Falk SJ, Iveson TJ, Smith DB, Langley RE, Verma M, Weeden S, Chua YJ and MAGIC Trial Participants: Perioperative chemotherapy *versus* surgery alone for resectable gastroesophageal cancer. N Engl J Med *355(1)*: 11-20, 2006. PMID: 16822992. DOI: 10.1056/NEJMoa055531

8 Ychou M, Boige V, Pignon JP, Conroy T, Bouché O, Lebreton G, Ducourtieux M, Bedenne L, Fabre JM, Saint-Aubert B, Genève J, Lasser P and Rougier P: Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J Clin Oncol *29(13)*: 1715-1721, 2011. PMID: 21444866. DOI: 10.1200/JCO.2010.33.0597

9 Virgilio E, Balducci G, Mercantini P, Ferri M, Bocchetti T, Caterino S, Salvi PF, Ziparo V and Cavallini M: Reconstruction after distal gastrectomy for gastric cancer: Billroth 2 or Roux-En-Y procedure? Anticancer Res *37(10)*: 5595-5602, 2017. PMID: 28982875. DOI: 10.21873/anticanres.11993

10 Virgilio E, Balducci G, Mercantini P, Giarnieri E, Giovagnoli MR, Montagnini M, Proietti A, D'Urso R and Cavallini M: Laparoscopic intragastric surgery for treating early gastric cancer. Anticancer Res *38(4)*: 1911-1916, 2018. PMID: 29599306. DOI: 10.21873/anticanres.12428

11 Virgilio E, Ceci D and Cavallini M: Surgical endoscopic vacuum-assisted closure therapy (EVAC) in treating anastomotic leakages after major resective surgery of esophageal and gastric cancer. Anticancer Res *38(10)*: 5581-5587, 2018. PMID: 30275175. DOI: 10.21873/anticanres.12892

12 Necula L, Matei L, Dragu D, Neagu AI, Mambet C, Nedeianu S, Bleotu C, Diaconu CC and Chivu-Economescu M: Recent advances in gastric cancer early diagnosis. World J Gastroenterol *25(17)*: 2029-2044, 2019. PMID: 31114131. DOI: 10.3748/wjg.v25.i17.2029

13 Uda H, Kanda M, Tanaka C, Kobayashi D, Inaoka K, Tanaka Y, Hayashi M, Iwata N, Yamada S, Fujii T, Sugimoto H, Murotani K, Fujiwara M and Kodera Y: Perioperative serum carcinoembryonic antigen levels predict recurrence and survival

of patients with pathological T2-4 gastric cancer treated with curative gastrectomy. Dig Surg *35(1)*: 55-63, 2018. PMID: 28441659. DOI: 10.1159/000471931

14 Lin JX, Wang W, Lin JP, Xie JW, Wang JB, Lu J, Chen QY, Cao LL, Lin M, Tu R, Zheng CH, Huang CM, Zhou ZW and Li P: Preoperative tumor markers independently predict survival in stage III gastric cancer patients: should we include tumor markers in AJCC staging? Ann Surg Oncol *25(9)*: 2703-2712, 2018. PMID: 29971670. DOI: 10.1245/s10434-018-6634-z

15 Kim JH, Jun KH, Jung H, Park IS and Chin HM: Prognostic value of preoperative serum levels of five tumor markers (Carcinoembryonic antigen, CA19-9, Alpha-fetoprotein, CA72-4, and CA125) in gastric cancer. Hepatogastroenterology *61(131)*: 863-869, 2014. PMID: 26176088.

16 Sun Z and Zhang N: Clinical evaluation of CEA, CA19-9, CA72-4 and CA125 in gastric cancer patients with neoadjuvant chemotherapy. World J Surg Oncol *12*: 397, 2014. PMID: 25543664. DOI: 10.1186/1477-7819-12-397

17 Stánitz E, Juhász K, Tóth C, Gombos K, Natali PG and Ember I: Evaluation of MicroRNA expression pattern of gastric adenocarcinoma associated with socioeconomic, environmental and lifestyle factors in northwestern Hungary. Anticancer Res *33(8)*: 3195-3200, 2013. PMID: 23898078.

18 Arita T, Ichikawa D, Konishi H, Komatsu S, Shiozaki A, Shoda K, Kawaguchi T, Hirajima S, Nagata H, Kubota T, Fujiwara H, Okamoto K and Otsuji E: Circulating long non-coding RNAs in plasma of patients with gastric cancer. Anticancer Res *33(8)*: 3185-3193, 2013. PMID: 23898077.

19 Rajgopal S, Fredrick SJ and Parvathi VD: CircRNAs: insights into gastric cancer. Gastrointest Tumors *8(4)*: 159-168, 2021. PMID: 34722469. DOI: 10.1159/000517303

20 Virgilio E, Giarnieri E, Giovagnoli MR, Montagnini M, Proietti A, D'Urso R, Mercantini P, Valabrega S, Balducci G and Cavallini M: Gastric cancer cells in peritoneal lavage fluid: a systematic review comparing cytological with molecular detection for diagnosis of peritoneal metastases and prediction of peritoneal recurrences. Anticancer Res *38(3)*: 1255-1262, 2018. PMID: 29491048. DOI: 10.21873/anticanres.12347

21 Virgilio E, Giarnieri E, Giovagnoli MR, Montagnini M, Proietti A, D'Urso R, Mercantini P, Balducci G and Cavallini M: Gastric juice MicroRNAs as potential biomarkers for screening gastric cancer: a systematic review. Anticancer Res *38(2)*: 613-616, 2018. PMID: 29374683. DOI: 10.21873/anticanres.12265

22 Virgilio E, Giarnieri E, Giovagnoli MR, Montagnini M, Proietti A, D'Urso R, Mercantini P, Balducci G and Cavallini M: Long non-coding RNAs in the gastric juice of gastric cancer patients. Pathol Res Pract *214(9)*: 1239-1246, 2018. PMID: 30078471. DOI: 10.1016/j.prp.2018.07.023

23 Virgilio E, Proietti A, D'Urso R, Cardelli P, Giarnieri E, Giovagnoli MR, Montagnini M, Villani S, Balducci G and Cavallini M: Elevated gastric juice carbohydrate antigen 72.4 (Ca 72.4) is an independent prognostic factor of poor survival for gastric cancer patients. Anticancer Res *40(3)*: 1691-1695, 2020. PMID: 32132076. DOI: 10.21873/anticanres.14121

24 Virgilio E, Giarnieri E, Giovagnoli MR, Montagnini M, Proietti A, D'Urso R, Nigri G, Mercantini P, Ramacciato G, Cavallini M and Balducci G: Presence of cancer cells in gastric lavage of gastric cancer patients as an indicator of advanced disease, predictor of tumour aggressive phenotype and independent prognostic factor for poor survival: The endoluminal metastatic pathway of gastric cancer and GL0/GL1 classification. Cytopathology *29(1)*: 41-48, 2018. PMID: 29063636. DOI: 10.1111/cyt.12484

25 Virgilio E, Balducci G, Mercantini P, Giarnieri E, Giovagnoli MR, Montagnini M, Proietti A, D'Urso R and Cavallini M: Utility of nasogastric tube for medical and surgical oncology of gastric cancer: a prospective institutional study on a new and precious application of an old and economic device. Anticancer Res *38(1)*: 433-439, 2018. PMID: 29277806. DOI: 10.21873/anticanres.12241

26 Yu D, Li Y, Wang M, Gu J, Xu W, Cai H, Fang X and Zhang X: Exosomes as a new frontier of cancer liquid biopsy. Mol Cancer *21(1)*: 56, 2022. PMID: 35180868. DOI: 10.1186/s12943-022-01509-9

27 Grabuschnig S, Bronkhorst AJ, Holdenrieder S, Rosales Rodriguez I, Schliep KP, Schwendenwein D, Ungerer V and Sensen CW: Putative origins of cell-free DNA in humans: a review of active and passive nucleic acid release mechanisms. Int J Mol Sci *21(21)*: 8062, 2020. PMID: 33137955. DOI: 10.3390/ijms21218062

28 Page MJ, Moher D, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P and McKenzie JE: PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. BMJ *372*: n160, 2021. PMID: 33781993. DOI: 10.1136/bmj.n160

29 Kagota S, Taniguchi K, Lee SW, Ito Y, Kuranaga Y, Hashiguchi Y, Inomata Y, Imai Y, Tanaka R, Tashiro K, Kawai M, Akao Y and Uchiyama K: Analysis of extracellular vesicles in gastric juice from gastric cancer patients. Int J Mol Sci *20(4)*: 953, 2019. PMID: 30813244. DOI: 10.3390/ijms20040953

30 Wang N, Wang L, Yang Y, Gong L, Xiao B and Liu X: A serum exosomal microRNA panel as a potential biomarker test for gastric cancer. Biochem Biophys Res Commun *493(3)*: 1322-1328, 2017. PMID: 28986250. DOI: 10.1016/j.bbrc.2017.10.003

31 Tokuhisa M, Ichikawa Y, Kosaka N, Ochiya T, Yashiro M, Hirakawa K, Kosaka T, Makino H, Akiyama H, Kunisaki C and Endo I: Exosomal miRNAs from peritoneum lavage fluid as potential prognostic biomarkers of peritoneal metastasis in gastric cancer. PLoS One *10(7)*: e0130472, 2015. PMID: 26208314. DOI: 10.1371/journal.pone.0130472

32 Ohzawa H, Saito A, Kumagai Y, Kimura Y, Yamaguchi H, Hosoya Y, Lefor AK, Sata N and Kitayama J: Reduced expression of exosomal miR 29s in peritoneal fluid is a useful predictor of peritoneal recurrence after curative resection of gastric cancer with serosal involvement. Oncol Rep *43(4)*: 1081-1088, 2020. PMID: 32323853. DOI: 10.3892/or.2020.7505

33 Zhu L, Zhang S, Chen S, Wu H, Jiang M and Liu A: Exosomal miR-552-5p promotes tumorigenesis and disease progression *via* the PTEN/TOB1 axis in gastric cancer. J Cancer *13(3)*: 890-905, 2022. PMID: 35154457. DOI: 10.7150/jca.66903

34 Yang J, Li X, Wei S, Peng L, Sang H, Jin D, Chen M, Dang Y and Zhang G: Evaluation of the diagnostic potential of a plasma exosomal miRNAs panel for gastric cancer. Front Oncol *11*: 683465, 2021. PMID: 34422636. DOI: 10.3389/fonc.2021.683465

35 Qian X, Xie F, Wei H and Cui D: Identification of key circulating exosomal microRNAs in gastric cancer. Front Oncol *11*: 693360, 2021. PMID: 34336682. DOI: 10.3389/fonc.2021.693360

36 Yan T, Wang X, Wei G, Li H, Hao L, Liu Y, Yu X, Zhu W, Liu P, Zhu Y and Zhou X: Exosomal miR-10b-5p mediates cell communication of gastric cancer cells and fibroblasts and facilitates cell proliferation. J Cancer *12(7)*: 2140-2150, 2021. PMID: 33754012. DOI: 10.7150/jca.47817

37 Jiao Y, Zhang L, Li J, He Y, Zhang X and Li J: Exosomal miR-122-5p inhibits tumorigenicity of gastric cancer by downregulating *GIT1*. Int J Biol Markers *36(1)*: 36-46, 2021. PMID: 33752480. DOI: 10.1177/1724600821990677

38 Zheng GD, Xu ZY, Hu C, Lv H, Xie HX, Huang T, Zhang YQ, Chen GP, Fu YF and Cheng XD: Exosomal miR-590-5p in serum as a biomarker for the diagnosis and prognosis of gastric cancer. Front Mol Biosci *8*: 636566, 2021. PMID: 33681295. DOI: 10.3389/fmolb.2021.636566

39 Lu X, Lu J, Wang S, Zhang Y, Ding Y, Shen X, Jing R, Ju S, Chen H and Cong H: Circulating serum exosomal *miR-92a-3p* as a novel biomarker for early diagnosis of gastric cancer. Future Oncol *17(8)*: 907-919, 2021. PMID: 33533649. DOI: 10.2217/fon-2020-0792

40 Ji R, Zhang X, Gu H, Ma J, Wen X, Zhou J, Qian H, Xu W, Qian J and Lin J: miR-374a-5p: a new target for diagnosis and drug resistance therapy in gastric cancer. Mol Ther Nucleic Acids *18*: 320-331, 2019. PMID: 31614322. DOI: 10.1016/j.omtn.2019.07.025

41 Yun J, Han SB, Kim HJ, Go SI, Lee WS, Bae WK, Cho SH, Song EK, Lee OJ, Kim HK, Yang Y, Kwon J, Chae HB, Lee KH and Han HS: Exosomal miR-181b-5p downregulation in ascites serves as a potential diagnostic biomarker for gastric cancer-associated malignant ascites. J Gastric Cancer *19(3)*: 301-314, 2019. PMID: 31598373. DOI: 10.5230/jgc.2019.19.e27

42 Shi Y, Wang Z, Zhu X, Chen L, Ma Y, Wang J, Yang X and Liu Z: Exosomal miR-1246 in serum as a potential biomarker for early diagnosis of gastric cancer. Int J Clin Oncol *25(1)*: 89-99, 2020. PMID: 31506750. DOI: 10.1007/s10147-019-01532-9

43 Huang J, Shen M, Yan M, Cui Y, Gao Z and Meng X: Exosome-mediated transfer of miR-1290 promotes cell proliferation and invasion in gastric cancer *via* NKD1. Acta Biochim Biophys Sin (Shanghai) *51(9)*: 900-907, 2019. PMID: 31435644. DOI: 10.1093/abbs/gmz077

44 Bai M, Li J, Yang H, Zhang H, Zhou Z, Deng T, Zhu K, Ning T, Fan Q, Ying G and Ba Y: miR-135b delivered by gastric tumor exosomes inhibits FOXO1 expression in endothelial cells and promotes angiogenesis. Mol Ther *27(10)*: 1772-1783, 2019. PMID: 31416776. DOI: 10.1016/j.ymthe.2019.06.018

45 Ren W, Zhang X, Li W, Feng Q, Feng H, Tong Y, Rong H, Wang W, Zhang D, Zhang Z, Tu S, Zhu X and Zhang Q: Exosomal miRNA-107 induces myeloid-derived suppressor cell expansion in gastric cancer. Cancer Manag Res *11*: 4023-4040, 2019. PMID: 31190980. DOI: 10.2147/CMAR.S198886

46 Kumata Y, Iinuma H, Suzuki Y, Tsukahara D, Midorikawa H, Igarashi Y, Soeda N, Kiyokawa T, Horikawa M and Fukushima R: Exosome encapsulated microRNA 23b as a minimally invasive liquid biomarker for the prediction of recurrence and prognosis of gastric cancer patients in each tumor stage. Oncol Rep *40(1)*: 319-330, 2018. PMID: 29749537. DOI: 10.3892/or.2018.6418

47 Yang H, Fu H, Wang B, Zhang X, Mao J, Li X, Wang M, Sun Z, Qian H and Xu W: Exosomal miR-423-5p targets SUFU to promote cancer growth and metastasis and serves as a novel marker for gastric cancer. Mol Carcinog *57(9)*: 1223-1236, 2018. PMID: 29749061. DOI: 10.1002/mc.22838

48 Ma M, Chen S, Liu Z, Xie H, Deng H, Shang S, Wang X, Xia M and Zuo C: miRNA-221 of exosomes originating from bone marrow mesenchymal stem cells promotes oncogenic activity in gastric cancer. Onco Targets Ther *10*: 4161-4171, 2017. PMID: 28860826. DOI: 10.2147/OTT.S143315

49 Pan L, Liang W, Fu M, Huang ZH, Li X, Zhang W, Zhang P, Qian H, Jiang PC, Xu WR and Zhang X: Exosomes-mediated transfer of long noncoding RNA ZFAS1 promotes gastric cancer progression. J Cancer Res Clin Oncol *143(6)*: 991-1004, 2017. PMID: 28285404. DOI: 10.1007/s00432-017-2361-2

50 Wei S, Dai S, Zhang C, Zhao R, Zhao Z, Song Y, Shan B and Zhao L: LncRNA NR038975, a serum-based biomarker, promotes gastric tumorigenesis by interacting with NF90/NF45 complex. Front Oncol *11*: 721604, 2021. PMID: 34900675. DOI: 10.3389/fonc.2021.721604

51 Zhang H, Wang M, He Y, Deng T, Liu R, Wang W, Zhu K, Bai M, Ning T, Yang H, Liu Y, Wang J and Ba Y: Chemotoxicity-induced exosomal lncFERO regulates ferroptosis and stemness in gastric cancer stem cells. Cell Death Dis *12(12)*: 1116, 2021. PMID: 34845198. DOI: 10.1038/s41419-021-04406-z

52 Xin L, Zhou LQ, Liu C, Zeng F, Yuan YW, Zhou Q, Li SH, Wu Y, Wang JL, Wu DZ and Lu H: Transfer of LncRNA CRNDE in TAM-derived exosomes is linked with cisplatin resistance in gastric cancer. EMBO Rep *22(12)*: e52124, 2021. PMID: 34647680. DOI: 10.15252/embr.202052124

53 Zhang Y, Chen L, Ye X, Wu Z, Zhang Z, Sun B, Fu H, Fu C, Liang X and Jiang H: Expression and mechanism of exosome-mediated A FOXM1 related long noncoding RNA in gastric cancer. J Nanobiotechnology *19(1)*: 133, 2021. PMID: 33971889. DOI: 10.1186/s12951-021-00873-w

54 Chen X, Zhang S, Du K, Zheng N, Liu Y, Chen H, Xie G, Ma Y, Zhou Y, Zheng Y, Zeng L, Yang J and Shen L: Gastric cancer-secreted exosomal X26nt increases angiogenesis and vascular permeability by targeting VE-cadherin. Cancer Sci *112(5)*: 1839-1852, 2021. PMID: 33205567. DOI: 10.1111/cas.14740

55 Zhou H, Shen W, Zou H, Lv Q and Shao P: Circulating exosomal long non-coding RNA H19 as a potential novel diagnostic and prognostic biomarker for gastric cancer. J Int Med Res *48(7)*: 300060520934297, 2020. PMID: 32660285. DOI: 10.1177/0300060520934297

56 Xu H, Zhou J, Tang J, Min X, Yi T, Zhao J and Ren Y: Identification of serum exosomal lncRNA MIAT as a novel diagnostic and prognostic biomarker for gastric cancer. J Clin Lab Anal *34(8)*: e23323, 2020. PMID: 32274858. DOI: 10.1002/jcla.23323

57 Cai C, Zhang H, Zhu Y, Zheng P, Xu Y, Sun J, Zhang M, Lan T, Gu B, Li S and Ma P: Serum exosomal long noncoding RNA pcsk2-2:1 as a potential novel diagnostic biomarker for gastric cancer. Onco Targets Ther *12*: 10035-10041, 2019. PMID: 31819499. DOI: 10.2147/OTT.S229033

58 Li S, Zhang M, Zhang H, Hu K, Cai C, Wang J, Shi L, Ma P, Xu Y and Zheng P: Exosomal long noncoding RNA lnc-GNAQ-6:1 may serve as a diagnostic marker for gastric cancer. Clin Chim Acta *501*: 252-257, 2020. PMID: 31730812. DOI: 10.1016/j.cca.2019.10.047

59 Lin LY, Yang L, Zeng Q, Wang L, Chen ML, Zhao ZH, Ye GD, Luo QC, Lv PY, Guo QW, Li BA, Cai JC and Cai WY: Tumor-originated exosomal lncUEGC1 as a circulating biomarker for early-stage gastric cancer. Mol Cancer *17(1)*: 84, 2018. PMID: 29690888. DOI: 10.1186/s12943-018-0834-9

60 Zhao R, Zhang Y, Zhang X, Yang Y, Zheng X, Li X, Liu Y and Zhang Y: Exosomal long noncoding RNA HOTTIP as potential novel diagnostic and prognostic biomarker test for gastric cancer. Mol Cancer *17(1)*: 68, 2018. PMID: 29486794. DOI: 10.1186/s12943-018-0817-x

61 Guo X, Lv X, Ru Y, Zhou F, Wang N, Xi H, Zhang K, Li J, Chang R, Xie T, Wang X, Li B, Chen Y, Yang Y, Chen L and Chen L: Circulating exosomal gastric cancer-associated long noncoding RNA1 as a biomarker for early detection and monitoring progression of gastric cancer: a multiphase study. JAMA Surg *155(7)*: 572-579, 2020. PMID: 32520332. DOI: 10.1001/jamasurg.2020.1133

62 Liu C, Yang J, Zhu F, Zhao Z and Gao L: Exosomal circ_0001190 regulates the progression of gastric cancer *via* miR-586/SOSTDC1 axis. Biochem Genet, 2022. PMID: 35138469. DOI: 10.1007/s10528-021-10180-6

63 Sang H, Zhang W, Peng L, Wei S, Zhu X, Huang K, Yang J, Chen M, Dang Y and Zhang G: Exosomal circRELL1 serves as a miR-637 sponge to modulate gastric cancer progression *via* regulating autophagy activation. Cell Death Dis *13(1)*: 56, 2022. PMID: 35027539. DOI: 10.1038/s41419-021-04364-6

64 Yang J, Zhang X, Cao J, Xu P, Chen Z, Wang S, Li B, Zhang L, Xie L, Fang L and Xu Z: Circular RNA UBE2Q2 promotes malignant progression of gastric cancer by regulating signal transducer and activator of transcription 3-mediated autophagy and glycolysis. Cell Death Dis *12(10)*: 910, 2021. PMID: 34611143. DOI: 10.1038/s41419-021-04216-3

65 Shi H, Huang S, Qin M, Xue X, Guo X, Jiang L, Hong H, Fang J and Gao L: Exosomal circ_0088300 derived from cancer-associated fibroblasts acts as a miR-1305 sponge and promotes gastric carcinoma cell tumorigenesis. Front Cell Dev Biol *9*: 676319, 2021. PMID: 34124064. DOI: 10.3389/fcell.2021.676319

66 Li S, Li J, Zhang H, Zhang Y, Wang X, Yang H, Zhou Z, Hao X, Ying G and Ba Y: Gastric cancer derived exosomes mediate the delivery of circRNA to promote angiogenesis by targeting miR-29a/VEGF axis in endothelial cells. Biochem Biophys Res Commun *560*: 37-44, 2021. PMID: 33965787. DOI: 10.1016/j.bbrc.2021.04.099

67 Wang Y, Wang H, Zheng R, Wu P, Sun Z, Chen J, Zhang L, Zhang C, Qian H, Jiang J and Xu W: Circular RNA ITCH suppresses metastasis of gastric cancer *via* regulating miR-199a-5p/Klotho axis. Cell Cycle *20(5-6)*: 522-536, 2021. PMID: 33499704. DOI: 10.1080/15384101.2021.1878327

68 Liu S, Wu M and Peng M: Circ_0000260 regulates the development and deterioration of gastric adenocarcinoma with cisplatin resistance by upregulating MMP11 *via* targeting MiR-129-5p. Cancer Manag Res *12*: 10505-10519, 2020. PMID: 33122949. DOI: 10.2147/CMAR.S272324

69 Hui C, Tian L and He X: Circular RNA circNHSL1 contributes to gastric cancer progression through the miR-149-5p/YWHAZ axis. Cancer Manag Res *12*: 7117-7130, 2020. PMID: 32848466. DOI: 10.2147/CMAR.S253152

70 Yao W, Guo P, Mu Q and Wang Y: Exosome-derived circ-PVT1 contributes to cisplatin resistance by regulating autophagy, invasion, and apoptosis *via* miR-30a-5p/YAP1 axis in gastric cancer cells. Cancer Biother Radiopharm *36(4)*: 347-359, 2021. PMID: 32799541. DOI: 10.1089/cbr.2020.3578

71 Xie M, Yu T, Jing X, Ma L, Fan Y, Yang F, Ma P, Jiang H, Wu X, Shu Y and Xu T: Exosomal circSHKBP1 promotes gastric cancer progression *via* regulating the miR-582-3p/HUR/VEGF axis and suppressing HSP90 degradation. Mol Cancer *19(1)*: 112, 2020. PMID: 32600329. DOI: 10.1186/s12943-020-01208-3

72 Lu J, Wang YH, Yoon C, Huang XY, Xu Y, Xie JW, Wang JB, Lin JX, Chen QY, Cao LL, Zheng CH, Li P and Huang CM: Circular RNA circ-RanGAP1 regulates VEGFA expression by targeting miR-877-3p to facilitate gastric cancer invasion and metastasis. Cancer Lett *471*: 38-48, 2020. PMID: 31811909. DOI: 10.1016/j.canlet.2019.11.038

73 Yu L, Xie J, Liu X, Yu Y and Wang S: Plasma exosomal CircNEK9 accelerates the progression of gastric cancer *via* miR-409-3p/MAP7 axis. Dig Dis Sci *66(12)*: 4274-4289, 2021. PMID: 33449227. DOI: 10.1007/s10620-020-06816-z

74 Song J, Yu S, Zhong D, Yang W, Jia Z, Yuan G, Li P, Zhang R, Li Y, Zhong G and Chen Z: The circular RNA hsa_circ_000780 as a potential molecular diagnostic target for gastric cancer. BMC Med Genomics *14(1)*: 282, 2021. PMID: 34838011. DOI: 10.1186/s12920-021-01096-6

75 Shao Y, Li J, Lu R, Li T, Yang Y, Xiao B and Guo J: Global circular RNA expression profile of human gastric cancer and its clinical significance. Cancer Med *6(6)*: 1173-1180, 2017. PMID: 28544609. DOI: 10.1002/cam4.1055

76 Yoshida Y, Yamamoto H, Morita R, Oikawa R, Matsuo Y, Maehata T, Nosho K, Watanabe Y, Yasuda H and Itoh F: Detection of DNA methylation of gastric juice-derived exosomes in gastric cancer. Integr Mol Med *1*: 17-21, 2014. DOI: 10.15761/IMM.1000105

77 Yamamoto H, Watanabe Y, Oikawa R, Morita R, Yoshida Y, Maehata T, Yasuda H and Itoh F: BARHL2 methylation using gastric wash DNA or gastric juice exosomal DNA is a useful marker for early detection of gastric cancer in an H. pylori-independent manner. Clin Transl Gastroenterol *7(7)*: e184, 2016. PMID: 27441821. DOI: 10.1038/ctg.2016.40

78 Tsuji K, Yamamoto H, Suenaga D, Morita R, Yoshida Y, Yasuda H, Otsubo T and Itoh F: Molecular analysis of gastric juice-derived exosomes in patients with gastric cancer. St. Marianna Med J *46*: 111-118, 2018. DOI: 10.14963/stmari.46.111

79 Wang J, Sun X, Zhao J, Yang Y, Cai X, Xu J and Cao P: Exosomes: a novel strategy for treatment and prevention of diseases. Front Pharmacol *8*: 300, 2017. PMID: 28659795. DOI: 10.3389/fphar.2017.00300

80 Chen KB, Chen J, Jin XL, Huang Y, Su QM and Chen L: Exosome-mediated peritoneal dissemination in gastric cancer and its clinical applications. Biomed Rep *8(6)*: 503-509, 2018. PMID: 29774141. DOI: 10.3892/br.2018.1088

81 Zhu M, Zhang N, Ma J and He S: Integration of exosomal miR-106a and mesothelial cells facilitates gastric cancer peritoneal dissemination. Cell Signal *91*: 110230, 2022. PMID: 34958869. DOI: 10.1016/j.cellsig.2021.110230

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