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Original Article

Expression of plasma exosomal circLPAR1 in patients with gastric cancer and its clinical application value

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Abstract: Objective: To determine plasma exosomal circular RNA LPAR1 (circLPAR1) expression in gastric cancer (GC) and analyze its clinical value in GC diagnosis and prognosis evaluation. Methods: The research subjects were 64 GC patients, 30 chronic gastritis (CG) patients (disease control group) and 30 healthy controls (HCs; healthy control group). RT-PCR quantified circLPAR1 expression in GC tissues and adjacent counterparts of GC patients as well as plasma exosomal circLPAR1 in each group. The correlation of differentially expressed circLPAR1 with clinicopathological indexes was analyzed, and receiver operating characteristics (ROC) and Kaplan-Meier curves were drawn to evaluate the value of plasma exosomal circLPAR1 in GC diagnosis and prognosis assessment. Results: GC patients exhibited lower plasma exosomal circLPAR1 levels than CG patients and HCs (P<0.05). Lower circLPAR1 expression was determined in GC tissues than in adjacent counterparts (P<0.05), and a positive connection between GC tissue circLPAR1 and plasma exosomal circLPAR1 was identified in GC patients (P<0.05). Evidently elevated plasma exosomal circLPAR1 was observed in post-surgical GC patients (P<0.05). ROC curves showed that the areas under the curve (AUCs) of plasma exosomal circLPAR1, serum carcinoembryonic antigen (CEA), and serum carbohydrate antigen 19-9 (CA19-9) for the diagnosis of GC were 0.836, 0.767 and 0.746, respectively, and the AUC of their combined diagnosis was 0.914. Low plasma exosomal circLPAR1 was strongly linked to tumor size, differentiation degree, tumor-node-metastasis (TNM) staging, vascular invasion, lymphatic metastasis, and HER2 expression of GC patients (P<0.05). GC patients with high plasma exosomal circLPAR1 expression had significantly longer prognostic survival time than those with low expression (P<0.05). According to univariate and multivariate Cox regression analyses, tissue differentiation degree (HR=1.415), TNM stage (HR=1.637), HER2 expression (HR=1.831), and low plasma exosomal circLPAR1 expression (HR=2.042) were risk factors for adverse prognosis in GC patients. Conclusions: circLPAR1 expression is related to GC progression, and the detection of plasma exosomal circLPAR1 has promising clinical application value in assisting the diagnosis and prognosis evaluation of GC.

Keywords: Gastric cancer, exosome, circular RNA, diagnosis, prognosis

Introduction

Gastric cancer (GC), one of the commonest malignancies across the globe with a high risk of metastasis and recurrence, has a global incidence and a mortality ranking 5th and 3rd, respectively [1]. Despite the great progress made in GC treatment by traditional radical surgery combined with chemoradiotherapy and immunotargeted therapy, the diagnosis of GC is always delayed and the best treatment opportunity is missed due to the lack of early diagnostic indicators, resulting in diagnosis at an advanced stage that is accompanied by adverse prognoses [2]. Therefore, there is an urgent need to find new highly sensitive and specific non-invasive biomarkers to improve the early diagnosis and prognosis of GC. In recent years, circular RNAs (circRNAs) have been found to be present widely in human tissues and body fluids (e.g., blood and urine), with species conservation as well as tissue and disease specificity, which can be used as potential new molecular markers for a wide spectrum of diseases [3]. circRNAs are a kind of natural endogenous non-coding RNAs that act as epigenetic regulators and play a regulating role in multiple diseases, including tumors [4]. They have been reported to be aberrantly expressed in multiple tumors including breast, lung, colorectal, and

stomach cancers, and to modulate some certain oncogenes through sponge adsorption of miRNAs [5]. According to the latest research findings [6, 7], circRNAs are enriched and stably expressed in exosomes-extracellular vesicles (50-100 nm in diameter) released by various cells. Cancer cell-derived exosomes are rich in a large number of proteins, lipids, miRNAs, lncRNAs, circRNAs and other small molecular nucleic acids that are significantly different from those of normal cells. Thus, they can be used for tumor diagnosis and treatment monitoring, playing a vital role in the field of liquid biopsy. In the current research, we investigated the expression level of plasma exosomal circular lysophosphatidic acid receptor 1 (circLPAR1) in GC and analyzed its clinical application value in assisting GC diagnosis and prognosis evaluation.

Materials and methods

Source of data

Sixty-four patients with primary GC, including 35 male and 29 female patients aged (59.6±7.8) years on average, who were first diagnosed in the Department of General Surgery of The Sixth Medical Center of PLA General Hospital from July 2015 to 2016 were included. All patients included were diagnosed as primary GC by gastroscopy and histopathology for the first time without receiving chemoradiotherapy and had complete case data. The excluded patients were those with other malignancies or obvious heart, liver, kidney and immune dysfunction. Additionally, 30 concurrent sex- and age-matched patients with chronic gastritis (CG) and 30 healthy physical examinees were recruited as the disease control group and the healthy control (HC) group, respectively. This study has obtained informed consent from patients and their families, and was approved by the Ethics Review Committee of our hospital.

Detection methods

(1) Source of plasma and tissue specimens: Fresh GC tissues and adjacent paracancerous tissues >5 cm away from the tumor margin were obtained from GC patients undergoing radical surgery and stored at -80°C for later use. Venous blood (5 mL) samples were collected into anticoagulant tubes the next morning after admission and on the 10th day after radical operation. A two-step method was adopted for plasma separation, specifically as follows: Plasma samples were first collected using a 5702R low-temperature and low-speed centrifuge (Eppendorf Company, Germany, 4°C 3,000×g) for 10 min into 1.5 ml RNase-free tubes, and then re-centrifuged (4°C 12,000×g) for 10 min. The resulting supernatant was stored at -80°C or directly used for exosome extraction.

(2) Isolation and identification of plasma exosomes: Following the ExoQuick solution Kit (System Biosciences Company, USA) operating instructions, a plasma sample of 250 μl was thoroughly mixed with 63 μl of EXO Quick reagent and allowed to stand at 4°C for 30 min, followed by 30 min of centrifugation (1,500×g) with a low-speed centrifuge that was performed twice. Exosomes were harvested through abandoning the supernatant to obtain the precipitates. After the precipitates were resuspended by PBS, the morphology and size were identified by transmission electron microscopy (TEM) technology (Zeiss, Germany) with reference to previous literature methods [8].

(3) RT-PCR detection: After adding liquid nitrogen into the GC tissues and adjacent counterparts of surgically resected GC patients, as well as grinding and homogenizing, the total RNA was isolated following the Trizol kit (Thermo Scientific Company, USA) instructions. Plasma exosomal RNA samples were then extracted using a miRNeasy Micro Kit (Qiagen, USA). cDNA was obtained by reverse transcription with a Prime Script TM RT Master Mix kit (Takara, Japan). With cDNA as the target template and following SYBR qRT-PCR Kit (Takara, Japan) instructions, RT-PCR amplification reaction was performed using 7500 ABI real-time fluorescence quantitative PCR instrument with GAPDH as the internal reference. circLPAR1 primer sequence: forward (F): 5'-GGAA TCGGGATACCATGATGAGTCT-3'; reverse (R): 5'-CAGGTACTCAG ATAGGTGGATGGGG-3'. GAPDH primersequence: F: 5'-CTCTGCTCCTCCTGTTCGAC-3'; R: 5'-CTCTGCTCCTCCTGTTCGAC-3'. All primers were synthesized by Shanghai Sangon Biotech. The expression differences of target genes among groups were calculated and compared by using the formula $2^{-\Delta\Delta Ct}$.

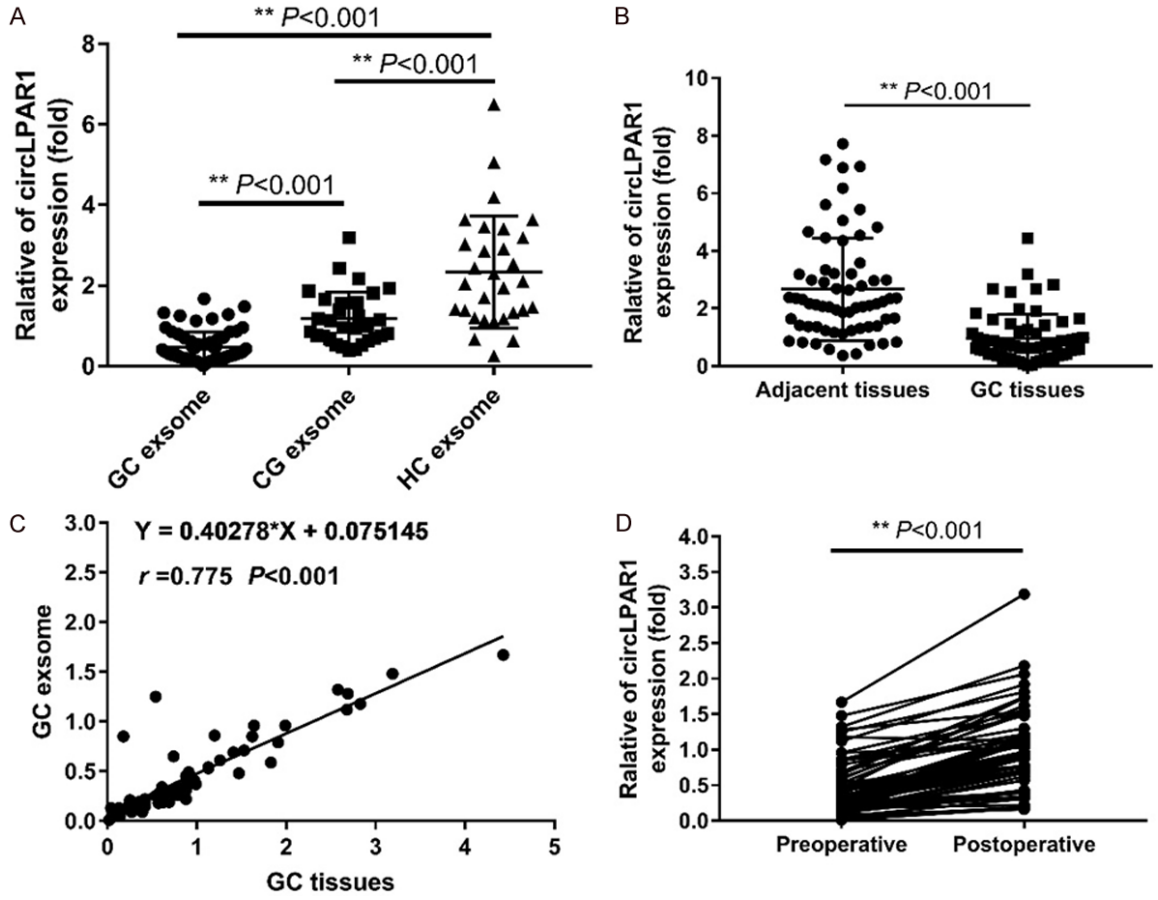

Figure 1. circLPAR1 expression in plasma exosomes and tissues of gastric cancer (GC). A. qRT-PCR detection of plasma exosomal circLPAR1 levels in GC group, chronic gastritis (CG) group, and healthy control group. B. qRT-PCR quantification of circLPAR1 expression in GC and adjacent tissues. C. Correlation of circLPAR1 expression levels between plasma exosomes and GC tissues in GC patients. D. Comparison of plasma exosomal circLPAR1 expression in GC patients before and after surgery. *P<0.05; **P<0.001.

(4) Serum carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) measurements: Serum samples from patients or healthy subjects were collected to quantify CEA and CA19-9 levels using COBAS E602 immunoassay instrument and matching reagents (Roche Company, USA) according to the chemical immunoluminescence method. The reference ranges were 0-5 ng/ml and 0-35 U/ml for serum CEA and CA19-9, respectively.

Data collection

Clinical data such as sex, age, tumor location, histological type, tumor-node-metastasis (TNM) stage, tissue differentiation degree, vascular invasion and lymph node metastasis (LNM) were collected. Follow-up data were also queried. The 5-year overall survival (OS) rate and survival time of the patients were recorded starting from patient discharge.

Statistical methods

SPSS 20.0 software was employed for statistical analysis after database establishment using EpiData. Continuous variables that accorded with a normal distribution were represented by $\bar{x}\pm s$ and analyzed by the independent samples t test. Age, histological type, TNM stage and other count data were denoted by the number of cases (n) and percentage (%) and tested by the χ^2 test. Receiver operating characteristic (ROC) curves were drawn to evaluate the diagnostic value of plasma exosomal circLPAR1, serum CEA, and serum CA19-9 in GC. The Kaplan-Meier method was used to draw the survival curve, and the Log-rank test was used to test the survival difference. Independent prognostic indicators were identified using the Cox regression model. The difference represented by P<0.05 was statistically significant.

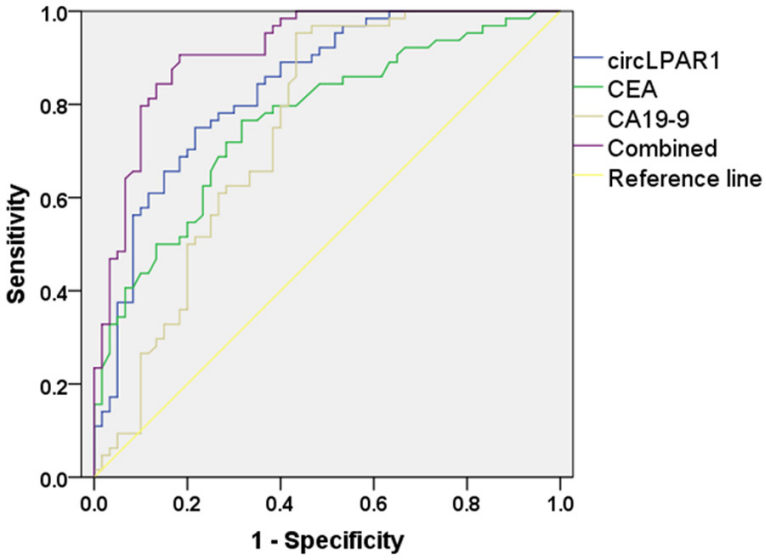

Figure 2. ROC curves of plasma exosomal circLPAR1, serum CEA and serum CA19-9 in patients with gastric cancer. Notes: ROC: Receiver operating characteristic; CEA: carcinoembryonic antigen; CA19-9: carbohydrate antigen 19-9.

Table 1. ROC curve parameters of plasma exosomal circLPAR1, serum CEA and serum CA19-9 in patients with gastric cancer

	Area under the curve	Standard error	Asymptotic significance	95% CI	
				Lower bound	Upper bound
circLPAR1	0.836	0.036	0.000	0.765	0.906
CEA (ng/ml)	0.767	0.042	0.000	0.684	0.849
CA19-9 (U/ml)	0.746	0.046	0.000	0.656	0.836
Combined	0.914	0.025	0.000	0.865	0.964

Notes: circLPAR1: plasma exosomal circLPAR1; ROC: Receiver operating characteristic; CEA: carcinoembryonic antigen; CA19-9: carbohydrate antigen 19-9.

Results

Differences in plasma exosomal circLPAR1 levels in different groups

First, RT-PCR quantified plasma exosomal circLPAR1 expression in each group (**Figure 1A**). The 64 GC patients were found to have evidently lower plasma exosomal circLPAR1 expression (relative expression: 0.46±0.12) than CG patients (relative expression: 0.98±0.23) (t=6.584, *P*<0.001) and HCs (relative expression: 2.18±0.53) (t=9.972, *P*<0.001); while notably lower expression was determined in CG group when compared to HC group (t=4.077, *P*<0.001). It is suggested that exosomal circLPAR1 is closely related to GC and may play an important role in GC progression.

circLPAR1 expression in GC and its adjacent tissues

Then, circLPAR1 expression in surgical specimens of GC patients was detected, which was found to be (0.96±0.12) in GC tissues and (2.67±0.34) in adjacent counterparts, demonstrating markedly lower circLPAR1 expression in GC tissues than in adjacent tissues (t=6.928, *P*<001). See **Figure 1B** for details.

Correlation of plasma exosomal circLPAR1 with GC tissue circLPAR1 expression in GC patients

Subsequently, a linear correlation analysis was conducted between plasma exosomal circLPAR1 of GC patients and circLPAR1 expression in GC tissues, and the results showed a significant positive correlation between them (r=0.775, *P*<0.01), as shown in **Figure 1C**.

Changes in plasma exosomal circLPAR1 levels in GC patients before and after surgery

Furthermore, we observed changes in plasma exosomal circLPAR1 expression in GC patients before and after gastrectomy (R0 resection), and found its sharp increase after tumor resection (t=6.282, *P*<0.05), suggesting that GC tissue is the source of influence on plasma exosomal circLPAR1 production (**Figure 1D**).

Diagnostic value of plasma exosomal circLPAR1 in GC

ROC curves were drawn to evaluate the diagnostic efficacy of plasma exosomal circLPAR1, serum CEA, and serum CA19-9 in GC. The AUC of plasma exosomal circLPAR1 was found to be 0.836 (95% CI=0.765-0.906, *P*<0.001), significantly higher than that of CEA (AUC: 0.767, 95% CI=0.684-0.849, *P*<0.001) and CA19-9 (AUC: 0.746, 95% CI=0.656-0.836, *P*<0.001);

Table 2. Correlation of plasma exosomal circLPAR1 expression with clinicopathological indexes in gastric cancer patients

Pathological factors	Number of cases (n=64)	Low circLPAR1 group [n (%)]	High circLPAR1 group [n (%)]	χ^2 value	*P* value
Gender				0.567	0.451
Male	35	19 (54.29)	16 (45.71)		
Female	29	13 (44.83)	16 (55.17)		
Age				0.254	0.614
<60	28	13 (46.43)	15 (53.57)		
≥60	36	19 (52.78)	17 (47.22)		
Tumor site				2.073	0.355
Gastric antrum	43	22 (51.16)	21 (48.84)		
Proximal (cardia)	16	9 (56.25)	7 (43.75)		
Distal pylorus	5	1 (20.00)	4 (80.00)		
Histological type				0.850	0.654
Squamous cell carcinoma	49	26 (53.06)	23 (46.94)		
Adenocarcinoma	12	5 (41.67)	7 (58.33)		
Adenosquamous carcinoma	3	1 (33.33)	2 (66.67)		
TNM stage				9.328	0.002
I+IIa	38	13 (34.21)	25 (65.79)		
IIb+III	26	19 (73.08)	7 (26.92)		
Tumor size				5.067	0.024
<5 cm	31	11 (35.48)	20 (64.52)		
≥5 cm	33	21 (63.64)	12 (36.36)		
Tissue differentiation degree				8.212	0.004
Low differentiation	23	17 (73.91)	6 (26.09)		
Moderate-high differentiation	41	15 (36.59)	26 (63.41)		
Vascular infiltration				4.655	0.031
Yes	20	14 (70.00)	6 (30.00)		
No	44	18 (40.91)	26 (59.09)		
Lymph node metastasis				9.057	0.003
Yes	19	15 (78.95)	4 (21.05)		
No	45	17 (37.78)	28 (62.22)		
Chemotherapy				3.473	0.062
With	21	25 (58.14)	18 (41.86)		
Without	21	7 (33.33)	14 (66.67)		
HER2 expression				5.189	0.023
Positive	37	23 (62.16)	14 (37.84)		

while the AUC of their combined diagnosis for GC was 0.914 (95% CI=0.865-0.964, *P*< 0.001), with significantly improved diagnostic efficiency. It is suggested that plasma exosomal circLPAR1 is a potential marker for GC diagnosis. See **Figure 2** and **Table 1** for details.

Correlation of plasma exosomal circLPAR1 with clinicopathological indexes in GC patients

The clinical features of GC patients were collected. Further, they were grouped as low (n=32) and high (n=32) circLPAR1 groups according to the median plasma exosomal circLPAR1 expression (Relative expression level is 0.310). The inter-group comparison of clinical characteristics revealed that plasma exosomal circLPAR1 was closely correlated with tumor size, differentiation degree, TNM stage, vascular infiltration, LNM, and HER2 positivity in GC patients (*P*<0.05), but it was independent of age, sex and tumor location (*P*>0.05; **Table 2**). It is suggested that the advance the stage, the higher the malignant degree of GC patients,

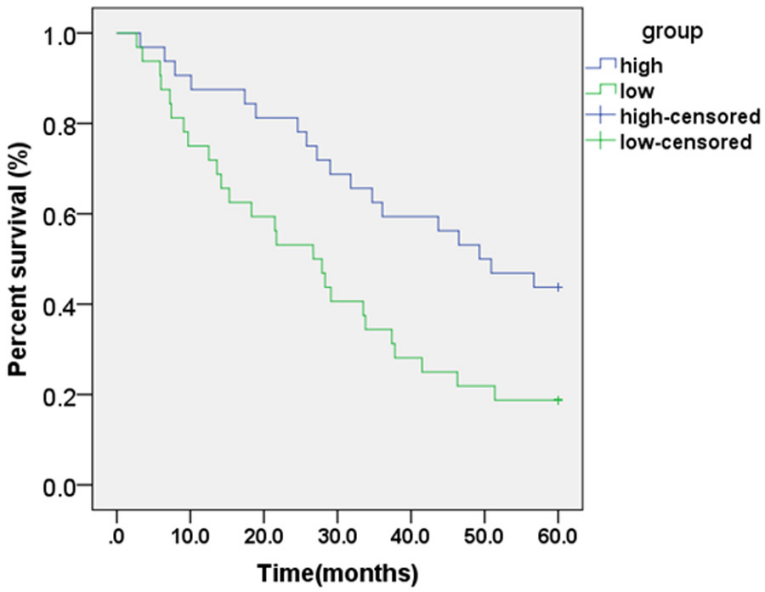

Figure 3. Comparison of the survival rate of gastric cancer patients with low and high expression of plasma exosomal circLPAR1 by Kaplan-Meier survival curve analysis.

and the lower the relative plasma exosomal circLPAR1 expression.

Relationship between plasma exosomal circLPAR1 and prognosis in GC patients

According to the follow-up results, the 5-year OS rate and median survival of high circLPAR1 group were 43.8% and 49.3 months, respectively, while those of low circLPAR1 group were 18.8% and 26.7 months, respectively. Kaplan-Meier curve analysis showed that GC patients with high plasma exosomal circLPAR1 expression had significantly better prognostic survival than those with low expression (**Figure 3**). The factors influencing prognosis were further analyzed by Cox model regression, and the results showed that tissue differentiation degree (HR=1.415, 95% CI=1.036-1.932, *P*=0.029), TNM stage (HR=1.637, 95% CI=1.142-1.932, *P*=0.007), HER2 expression (HR=1.831, 95% CI=1.124-2.983, *P*=0.015), and low plasma exosomal circLPAR1 expression (HR=2.042, 95% CI=1.337-3.119, *P*=0.001) were related to the poor prognosis of GC patients (**Table 3**).

Discussion

circRNAs are essential in the onset and progression of human tumors [9]. In the comparative analysis of circRNA expression profiles in GC and adjacent tissues using the microarray technique, Shao et al. [10, 11] found the presence of statistical differences in the expression of various circRNAs in GC compared with adjacent counterparts and identified the application value of circRNA molecules as biomarkers for the clinical diagnosis of GC. circLPAR1 (hsa_circ_0087960) is a 226 bp circRNA derived from the exon sequence of the LPAR1 gene. Reduced circLPAR1 levels in bladder tumors are shown to be associated with the prognosis of muscle-invasive bladder cancer, and circLPAR1, which is resistant to actinomycin D and RNase R, is a promising biomarker [12]. Similarly, according to the analysis of circLPAR1 levels in this study, circLPAR1 was markedly lower in GC than in adjacent counterparts, suggesting favorable tissue specificity of circLPAR1 and a correlation of its expression with the onset and progression of GC.

Exosomes, as one of the three targets for liquid biopsy at present, are widely distributed in body fluids and have a membrane lipid bilayer structure that can protect the carried contents from being easily degraded, allowing them to be absorbed by neighboring and distal cells to realize intercellular communication [13]. In recent years, a number of reports [14-16] have shown that using exosomes as transport carriers, circRNAs can be released into the peripheral circulation along with cancer cell-derived exosomes to realize extensive distribution in blood exosomes. Moreover, circRNAs with a covalent closed-loop structure are more stable and less degradable than linear RNAs with a longer half-life, making them more suitable as circulating biomarkers for liquid biopsy. In addition, there is growing evidence that plasma exosomal circRNAs are abnormally expressed in a variety of tumors, and that differences in plasma exosomal circRNA expression can be used to distinguish cancer patients from healthy individuals [6, 17, 18]. As reported by Zheng et al. [19], circLPAR1 was obviously down-regulated

Table 3. Cox univariate and multivariate regression analyses for 5-year postoperative overall survival rate in patients with gastric cancer

Factors	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P*	HR	95% CI	*P*
Age (≥60 vs. <60)	1.317	0.958-1.809	0.090	-	-	-
Tumor size (≥5 cm vs. <5 cm)	1.278	0.975-1.674	0.076	-	-	-
Tissue differentiation degree (low differentiation *vs.* medium and high differentiation)	1.409	1.032-1.924	0.031	1.415	1.036-1.932	0.029
TNM stage (III+IV *vs.* I+II)	1.802	1.157-2.807	0.009	1.637	1.142-1.932	0.007
Vascular infiltration (yes *vs.* no)	2.079	0.783-5.518	0.142	-	-	-
Chemotherapy (with vs. without)	1.680	0.937-3.013	0.082	-	-	-
HER2 expression	1.726	1.106-2.694	0.016	1.831	1.124-2.983	0.015
Plasma exosomal circLPAR1 (low expression *vs.* high expression)	2.540	1.211-5.327	0.014	2.042	1.337-3.119	0.001

Notes: Univariate and multivariate survival analyses, Cox Proportional Hazards Regression Model. HR: hazard ratio; 95% CI: 95% confidence interval.

in cancer tissues and plasma exosomes of colorectal cancer patients, and the specific underexpression of plasma exosomal circLPAR1 was strongly linked to the prognosis and survival rate of colorectal cancer patients. This study compared plasma exosomal circLPAR1 levels among GC patients, CG patients, and HCs. The results showed markedly lower plasma exosomal circLPAR1 in GC patients than in non-cancer individuals, and consistent circLPAR1 expression in GC patients with that in circulating blood exosomes. It indicates that changes in circLPAR1 expression in GC patients can be observed by liquid biopsy of plasma exosomes instead of invasive examinations such as histopathological test. Furthermore, ROC curve analysis identified notably higher efficacy of plasma exosomal circLPAR1 versus serum tumor markers CEA and CA19-9 in diagnosing GC, as well as significantly improved diagnostic value of the combined detection of the three indicators, suggesting that plasma exosomal circLPAR1 can be used as a potential marker for GC diagnosis. Moreover, by analyzing GC patients' clinicpathological data, it was found that the low plasma exosomal circLPAR1 expression was significantly related to tumor size, TNM stage, differentiation degree, HER2 expression and LNM of GC patients, suggesting the potential involvement of plasma exosomal circLPAR1 in the malignant progression and metastasis of GC. But the specific mechanism needs further basic research.

Further, we analyzed plasma exosomal circLPAR1 levels in pre- and post-operative GC patients to more comprehensively analyze its effect on postoperative curative effects and prognosis of GC patients. Plasma exosomal circLPAR1 was found to be elevated significantly in GC patients after surgery, suggesting that plasma exosomal circLPAR1 can reflect the tumor changes in vivo in real time. Subsequently, the Kaplan-Meier curve analysis revealed significantly longer average survival time of GC patients with high plasma exosomal circLPAR1 expression compared to those with low expression. And according to Cox regression analysis, low plasma exosomal circLPAR1 expression, tissue differentiation degree, TNM stage and HER2 expression were all risk factors for adverse prognosis in GC patients. Therefore, plasma exosomal circLPAR1 can be used to evaluate the adverse outcomes of GC patients.

In summary, the significant reduction of circLPAR1 in GC tissue and plasma exosomes in GC patients is closely related to GC progression, and plasma exosomal circLPAR1 is expected to be an effective molecular marker for the auxiliary diagnosis and prognosis evaluation of GC. Later, we will further explore the molecular mechanism of circLPAR1 in GC progression, and expand the sample size to verify its clinical application value in GC diagnosis and prognosis evaluation.

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Disclosure of conflict of interest

None.

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