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Original Article

Downregulation of serum miR-205 as a potential biomarker for gastric cancer diagnosis, prognosis, and chemosensitivity prediction

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Abstract: Purpose: Accumulating evidence has demonstrated the great potential of circulating microRNAs (miRs) as noninvasive tumor biomarkers. Our study aimed to measure the expression level of serum miR-205 in patients with gastric cancer (GC) and investigate its clinical significance. Methods: Serum miR-205 levels in 145 GC patients and 145 healthy controls were detected by RT-PCR. Then, the association of serum miR-205 expression with clinicopathologic factors was evaluated by the Chi-square test. Kaplan-Meier survival curves and cox regression analysis were performed to test the prognostic value of serum miR-205 in GC. Results: Serum miR-205 was significantly downregulated in GC patients, and its downregulation was closely related to deep local invasion ($P < 0.001$), positive lymphatic metastasis ($P = 0.009$), advanced TNM stage ($P = 0.001$), and poor tumor response to neoadjuvant chemotherapy ($P < 0.001$). Low levels of serum miR-205 correlated with poor overall survival independently ($P = 0.005$, HR = 4.16). In addition, receiver-operating characteristic (ROC) curve analyses showed that serum miR-205 could discriminate GC patients from healthy controls with the area under the curve (AUC) of 0.909 (95% CI, 0.870-0.949), and distinguish pathologic responders from nonresponders with the AUC of 0.893 (95% CI: 0.812-0.973). Conclusions: These findings revealed decreased serum miR-205 expression in patients with GC and indicated its potential value as a noninvasive biomarker for the diagnosis, prognosis, and chemosensitivity prediction of GC.

Keywords: miR-205, gastric cancer, biomarkers, diagnosis, prognosis

Introduction

Gastric cancer (GC) is one of the most prominent global health threats, with approximately 1 million new cases and 0.7 million deaths per year [1]. Despite the development of diagnostic technologies and treatment modalities, the detection of early GC is < 15%, and the overall 5-year survival rate of GC patients is less than 30% at present [2]. The traditional tumor markers, such as carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9), have limited utility in early diagnosis of GC due to the lack of sufficient sensitivity and specificity [3]. Therefore, identification of novel biomarkers for GC early detection and prognosis prediction is a major focus of current investigation.

MicroRNAs (miRs) comprise a family of small, non-coding RNA molecules that post-transcriptionally modulate gene expression through binding to 3'-untranslated regions of target mRNAs [4]. Accumulating evidence suggests that some miRs can function as oncogenes or tumor suppressor genes, and deregulation of miR expression is involved in the development of numerous types of cancer, including GC [5, 6]. More importantly, miRs can circulate in the bloodstream in a cell-free form [7]. Circulating miRs in the plasma/serum are extremely stable and protected from endogenous ribonuclease activity, indicating the great potentiality of circulating miRs as candidate biomarkers for multiple diseases including cancer [8, 9]. For example, serum miR-22 level was upregulated in patients with non-small cell lung cancer, and its upregulation was closely related to cancer metastasis and advanced TNM stage [10]. High expression of serum miR-224 could discriminate early-stage hepatocellular carcinoma from

Table 1. Association of serum miR-205 expression with clinicopathologic features of gastric cancer

	Low serum miR-205 (< 0.36)	High serum miR-205 (≥ 0.36)	*P*-value
Age			
> 60	40 (56.3%)	31 (43.7%)	
≤ 60	33 (44.6%)	41 (55.4%)	0.185
Gender			
Male	48 (51.1%)	46 (48.9%)	
Female	25 (49.0%)	26 (51.0%)	0.863
Differentiation			
Well-moderate	39 (48.1%)	42 (51.9%)	
Poor	34 (52.1%)	30 (47.9%)	0.530
Tumor size			
≥ 5 cm	44 (56.4%)	34 (43.6%)	
< 5 cm	29 (43.3%)	38 (56.7%)	0.135
Invasion depth			
T1, T2	20 (33.3%)	40 (66.7%)	
T3, T4	53 (62.4%)	32 (37.6%)	< 0.001
TNM stage			
I/II	17 (31.5%)	37 (68.5%)	
III	56 (61.5%)	35 (38.5%)	0.001
Lymphatic metastasis			
Negative	13 (32.5%)	27 (67.5%)	
Positive	60 (57.1%)	45 (42.9%)	0.009
Chemosensitivity			
Responders (n = 43)	16 (37.2%)	27 (62.8%)	
Nonresponders (n = 25)	18 (72.0%)	7 (28.0%)	< 0.001

liver cirrhosis, chronic hepatitis B, and healthy controls [11]. Serum miR-335 level in hepatocellular carcinoma patients was associated with tumor response to trans-arterial chemoembolization and overall survival [12]. Serum miR-372 was a potential diagnostic and prognostic biomarker for early colorectal cancer [13]. However, the clinical value of circulating miRs as blood-based, noninvasive biomarkers for GC remains largely unknown.

miR-205, located in human chromosome 1q32.2, is a well-acknowledged cancer-related miR. Recent studies have revealed aberrant miR-205 expression and its oncogenic or tumor suppressive function in various malignancies, including glioma [14], osteosarcoma [15], breast cancer [16], esophageal squamous cell carcinoma (ESCC) [17], colorectal cancer [18], bladder cancer [19], prostate cancer [20], ovarian cancer [21], and GC [22, 23]. Circulating miR-205 could serve as a diagnostic and/or prognostic biomarker for human glioma [14], lung cancer [24], breast cancer [25], ESCC [26], cervical cancer [27], and bladder cancer [19]. Yin et al. confirmed decreased miR-205 expression in GC tissues and its correlation with deep local invasion [23]. In vitro functional experiments showed that inhibition of miR-205 significantly promoted GC cell proliferation [23], while miR-205 overexpression suppressed GC cell migration and invasion [22]. However, circulating miR-205 expression and its clinical significance in GC has not been reported. This prompted us to detect serum miR-205 levels in GC patients and investigate its relation to clinicopathological parameters and patient outcome. We also explored whether serum miR-205 could act as a useful biomarker for GC diagnosis and chemosensitivity prediction.

Materials and methods

Study population

The study protocol was approved by the Research Ethics Committee of The First Hospital of Shijiazhuang (Shijiazhuang 050011, Hebei Province, China) and all participants provided signed informed consent paper.

A total of 145 newly diagnosed and histologically confirmed GC patients (clinical tumor stage $T_{1-4}N_{0-2}M_0$), treated in The First Hospital of Shijiazhuang between September 2007 and January 2012, were enrolled in this study. All patients underwent radical resection, and 68 cases received three cycles of neoadjuvant chemotherapy (FOLFOX 4 regime) before operation. For each patient, 5 ml of whole blood was collected at the time of primary diagnosis and prior to any treatment. Serum separation was accomplished by centrifugation at 3,000 g for 15 min at 4°C. The supernatant serum was stored at -80°C until further analysis. Control samples were obtained from 145 age- and sex-matched healthy volunteers. The detailed information of GC patients is summarized in **Table 1**. Clinical follow-up data were available for all patients, and overall survival was defined as the time from the date of diagnosis to the date of death or last follow-up. For patients received preoperative chemotherapy, pathologic tumor

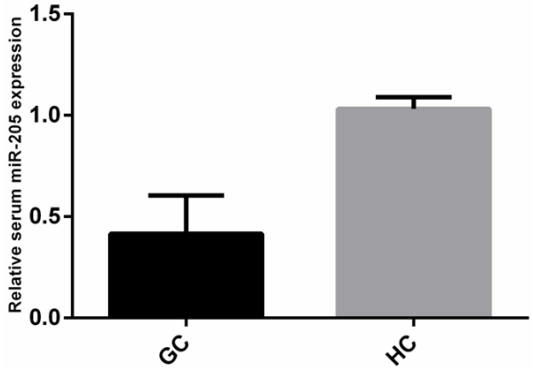

Figure 1. miR-205 levels in serum from gastric cancer patients were significantly lower than those in healthy controls (P < 0.01).

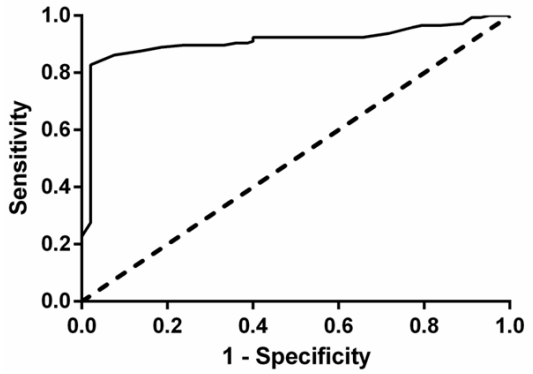

Figure 2. ROC curve analysis illustrated that serum miR-205 was a potential biomarker for discriminating gastric cancer patients from healthy controls (AUC = 0.909, 95% CI; 0.870-0.949; Cutoff value: 0.495; sensitivity: 97.9%; specificity: 82.8%).

response was assessed by using a three-point pathologic regression grade system, Becker score, as previously described [28]. Patients with grade 1 (< 10% residual tumor) or 2 (10% to 50% residual tumor) regression were classified as responders, while grade 3 (> 50% residual tumor) was defined as a pathologic nonresponse.

RNA extraction and real-time quantitative RT-PCR

Total RNA was extracted from 300 μL of serum using a MiRcute miRNA Isolation Kit (TianGene, Beijing, China). cDNA was synthesized with 2 μL of extracted RNA using a RevertAid Fist Strand cDNA Synthesis Kit (Thermo Fisher Scientific, Waltham, MA, USA) in a 10 μL reaction system. Quantitative PCR was run on a CFX96 real-time

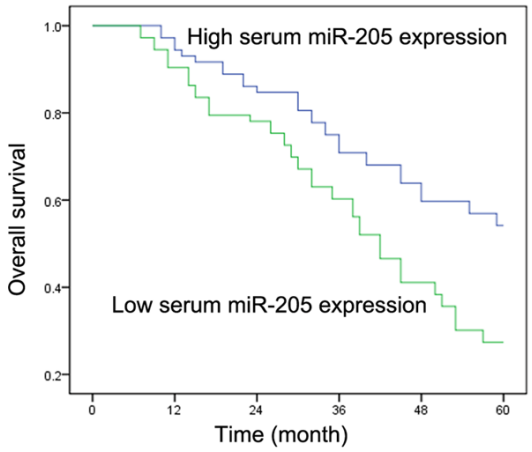

Figure 3. Kaplan-Meier overall survival curves for gastric cancer patients with high versus low serum miR-205 expression (Cutoff value: 0.36; P < 0.001, log rank test).

PCR system (Bio-Rad, Hercules, CA, USA) with iTaq Universal SYBR Green Supermix. The cycling conditions were 95°C for 30 s (predenaturation), followed by 40 cycles of 95°C for 5 s (denaturation), 57°C for 30 s (annealing), and 72°C for 30 s (extension). The PCR primers used in this study were as follows: miR-205 forward, 5'-TCC TTC ATT CCA CCG GAG TCT G-3' and reverse 5'-GCG AGC ACA GAA TTA ATA CGA C-3'. Synthetic cel-miR-39 was used for normalization according to previous reports [29, 30], and the relative level of miR-205 was calculated by using the $2^{-\Delta\Delta Ct}$ method [31].

Statistics

Statistical analyses were carried out using SPSS 17.0 software (SPSS, Chicago, IL, USA) and P < 0.05 was considered to be statistically significant. MiR-205 levels between GC patients and healthy controls were compared by Mann-Whitney U-test. The Chi-square test was used to evaluate correlations between serum miR-205 levels and clinicopathological factors. The potential of serum miR-205 as a biomarker for GC diagnosis and chemosensitivity prediction was evaluated by the receiver-operating characteristic (ROC) curve analysis. Survival curves were traced by the Kaplan-Meier method, and survival differences between groups were assessed using the log-rank test. Cox regression analysis was performed to test the independence of each variable.

Table 2. Cox regression analysis of factors associated with overall survival in gastric cancer patients

Variables	Univariate analysis		Multivariate analysis	
	HR	*P*-value	HR	*P*-value
Age	0.83	0.387	--	--
Gender	1.05	0.492	--	--
Differentiation	1.21	0.089	--	--
Tumor size	2.06	0.035	1.19	0.092
Invasion depth	3.98	0.007	4.64	0.001
Lymphatic metastasis	2.85	0.016	2.65	0.018
TNM stage	4.91	< 0.001	2.93	0.015
Chemosensitivity	4.47	0.003	2.38	0.024
Serum miR-205 expression	4.78	< 0.001	4.16	0.005

Variables	Univariate analysis			Multivariate analysis			
	Beta	HR	*P*-value	Beta	HR	Reference	*P*-value
Age (years) (> 60/≤ 60)	-0.186	0.83	0.387		--	--	--
Gender (Male/Female)	0.049	1.05	0.492		--	--	--
Differentiation(Well-moderate/Poor)	0.191	1.21	0.089		--	--	--
Tumor size (cm) (≥ 5/< 5)	0.723	2.06	0.035	0.174	1.19	< 5	0.092
Invasion depth (T_{1-2}/T_{3-4})	1.381	3.98	0.007	1.535	4.64	T_{1-2}	0.001
Lymphatic metastasis (Positive/Negative)	1.047	2.85	0.016	0.975	2.65	Negative	0.018
TNM stage (I-II/III)	1.591	4.91	< 0.001	1.075	2.93	I-II	0.015
Chemosensitivity (Responder/Nonresponder)	1.487	4.47	0.003	0.867	2.38	Responder	0.024
Serum miR-205 expression (Low/high, cutoff value: 0.36)	1.564	4.78	< 0.001	1.426	4.16	High	0.005

Results

Decreased serum miR-205 expression in GC patients and its diagnostic value

The expression levels of serum miR-205 in 145 GC patients and 145 healthy controls were examined using qRT-PCR. The results indicated that serum miR-205 expression was significantly downregulated in GC patients compared to healthy controls (P < 0.01; **Figure 1**). ROC curve analysis was carried out to evaluate whether serum miR-205 could be used as potential diagnostic marker for GC. The area under the curve (AUC) was 0.909 (95% CI, 0.870-0.949, **Figure 2**). The optimal cutoff value was indicated at 0.495, with a sensitivity of 97.9% and a specificity of 82.8%.

Correlation between serum miR-205 levels and the clinicopathological factors in GC patients

To further analyze the potential association of serum miR-205 levels with various clinicopathological features of GC, the levels of serum miR-205 were classified as low or high on the basis of the median value. The statistical analysis revealed that low expression of serum miR-205 significantly correlated with deep local invasion (P < 0.001), positive lymphatic metastasis (P = 0.009), and advanced TNM stage (P = 0.001) (**Table 1**). No significant associations were found between serum miR-205 levels and other clinical features.

Prognostic value of serum miR-205 in GC

Then, we investigated the prognostic value of serum miR-205 in GC. The Kaplan-Meier curves showed that high level of serum miR-205 was associated with prolonged postoperative survival (log-rank test, P < 0.001, **Figure 3**). Univariate survival analyses indicated that GC patients with large tumor size, deep local infiltration, positive lymphatic metastasis, late clinical stage, poor tumor response to chemotherapy, and low serum miR-205 levels had worse overall survival. Moreover, the multivariate analysis identified serum miR-205 level (P = 0.005), tumor invasion (P = 0.001), lymph node metastasis (P = 0.018), TNM stage (P = 0.015), and chemosensitivity (P = 0.024) as independent prognostic factors for GC (**Table 2**).

Low level of serum miR-205 correlates with chemoresistance

In the present study, a total of 68 patients received neoadjuvant chemotherapy and the

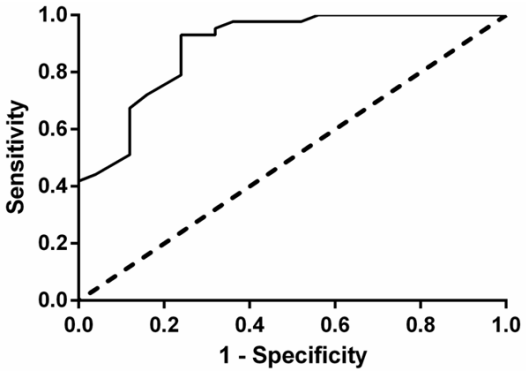

Figure 4. ROC curve analysis showed that serum miR-205 in gastric cancer patients treated with preoperative chemotherapy could differentiate pathologic responders from nonresponders (AUC = 0.893, 95% CI: 0.812-0.973; Cutoff value: 0.415; sensitivity: 93.0%; specificity: 76.0%).

resected specimens were analyzed to determine the chemotherapeutic effects. According to the Becker score, 13 of the 68 specimens were classified as grade 1, 30 as grade 2, and 25 as grade 3. In total, 43 patients were categorized as pathologic responders and 25 as non-responders. Low serum miR-205 expression was closely related to poor chemosensitivity ($P < 0.001$, **Table 1**). ROC curve analysis revealed that serum miR-205 was a valuable biomarker to distinguish pathologic responders from nonresponders with an AUC of 0.893 (95% CI: 0.812-0.973; sensitivity: 93.0%, specificity: 76.0%; **Figure 4**).

Discussion

Although the incidence of GC has declined in recent decades, GC is still the fourth most common cancer and one of the leading causes of cancer-related death worldwide [2]. miRs have been proven to play important roles in GC carcinogenesis and progression. For example, upregulation of miR-647 inhibited GC cell proliferation, promoted cell cycle arrest at the G0/G1 phase and induced cell apoptosis [32]. Ectopic expression of miR-181a-5p promoted GC cell invasion and migration [33]. Decreased miR-126 expression in GC tissues was associated with malignant clinical factors and poor overall survival [6]. Overexpression of miR-939 and miR-129 enhanced GC cell chemosensitivity to 5-fluorouracil and cisplatin respectively [5, 34].

For many decades, cell-free nucleic acids have been known to be present in peripheral blood. Extensive research has demonstrated the potential value of circulating miRs as novel biomarkers for various cancers [7]. In this study, we showed decreased serum miR-205 levels in GC patients and its correlation with aggressive clinicopathological features. Low level of serum miR-205 was identified as an independent unfavorable prognostic factor. Furthermore, serum miR-205 could discriminate GC patients from healthy controls and predict tumor response to neoadjuvant chemotherapy. To our knowledge, this study investigated circulating miR-205 levels and its clinical significance in GC patients for the first time.

Previous studies have demonstrated the oncogenic or tumor suppressive function of miR-205 in different types of human malignancies. Accordingly, upregulation or downregulation of circulating miR-205 expression has been reported in patients with these malignancies. Yue et al. confirmed decreased serum miR-205 expression in human glioma and its association with high pathological grades, low Karnofsky Performance Scale score, and poor prognosis [14]. Serum miR-205 levels were significantly increased in postoperative samples and were reduced again during glioblastoma recurrences. Ma et al. reported that serum miR-205 was significantly upregulated in cervical cancer patients, and its up-regulation was correlated with positive lymph node metastasis and advanced tumor stage [27]. They also identified serum miR-205 as an independent prognostic marker for cervical cancer patients. Fang et al. indicated increased plasma miR-205 in patients with bladder cancer compared to healthy controls [19]. High level of plasma miR-205 was associated with poor tumor differentiation, muscle invasion, and late clinical stage. Moreover, serum miR-205 has been confirmed as a novel biomarker for the detection of ESCC and breast cancer [25, 26]. The potential diagnostic and prognostic values of circulating miR-205 in other human cancers are worthy of future investigation.

At present, the majority of GC patients are diagnosed at an advanced stage, and neoadjuvant chemotherapy has been increasingly used to improve long-term survival of these patients [35]. However, the chemotherapeutic effects are often limited by the occurrence of intrinsic or acquired chemoresistance, and the selection of appropriate patients who will benefit

from chemotherapy is still a major challenge in oncology. Several research has confirmed the crucial role for miR-205 in cancer chemoresistance. miR-205 could impair the autophagic flux and increase chemosensitivity of prostate cancer cells to cisplatin [36]. miR-205 also enhanced chemosensitivity of breast cancer cells to TAC regime (docetaxol, doxorubicin plus cyclophosphamide) by suppressing both VEGFA and FGF2 [37]. Moreover, Li et al. revealed the association between serum miR-205 expression and the sensitivity of breast cancer patients to neoadjuvant chemotherapy with Epirubicin plus Paclitaxel [38]. Our study also showed a close relationship between low level of serum miR-205 and poor tumor response to preoperative chemotherapy. ROC curve analysis identified serum miR-205 as a valuable biomarker for differentiating pathologic responders from nonresponders. The use of circulating miR-205 as a blood-based biomarker for chemotherapeutic efficacy prediction in other human malignancies needs to be further clarified.

In summary, our study showed that serum miR-205 was significantly down-regulated in patients with GC and might serve as a noninvasive biomarker for its diagnosis, prognosis, and chemosensitivity prediction. However, this is a retrospective study, and the sample size was relatively small. Prospective studies with larger sample size should be carried out to confirm these conclusions in future.

Disclosure of conflict of interest

None.

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