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Low expression of lncRNA MGC27345 is associated with poor prognosis in gastric cancer patients

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Abstract. – OBJECTIVE: A series of evidence showed that long non-coding RNAs (lncRNAs) play an essential regulatory role in the occurrence and development of human cancer, and is a potential biological target in the fight against cancer.

PATIENTS AND METHODS: In this research, we investigated the role of lncRNA MGC27345 in gastric cancer (GC), the expression of MGC27345 in GC was detected by quantitative Real-Time PCR in GC tissue from 235 patients. The correlations between MGC27345 expression and clinicopathological variables and survival were evaluated by the Chi-square test. Kaplan-Meier method (log-rank test), univariate and multivariate Cox regression assays were carried out for the identification of the survival and independent risk factors for GC.

RESULTS: MGC27345 expression levels were significantly decreased in GC tissues than in adjacent normal specimens. Lower expression of MGC27345 was found in advanced tumor stages. GC patients with low-expression of MGC27345 had a poorer overall survival compare to those with high-expression of MGC27345. Furthermore, MGC27345 was an independent protective prognosis factor in GC development.

CONCLUSIONS: Our data indicated that MGC27345 may have a diagnostic and prognostic value for patients with advanced gastric cancer and assist to improve clinical outcomes for GC patients.

Key Words:
Gastric Cancer (GC), MGC27345, LncRNA expression, Prognosis.

Introduction

Gastric cancer (GC) in one of the most prevalent malignant tumors of the digestive system and third leading cause of cause-related deaths worldwide[1]. According to the latest global cancer statistics, almost over 780,000 death case of GC occurred in the United States in 2018, followed by 1,000,000 patients dying of the disease over the world[1]. Approximately more than 40% of newly diagnosed cases with GC in China[2]. In clinical practice, although the mortality of GC has an evident decrease with the recent improvement of therapeutic and diagnostic techniques in the past few years[3], the prognosis of advanced GC remains poor due to the absences of evident symptoms at early[4]. The long-term overall survival (OS) for patients is less than 30%[5,6]. Therefore, it is necessary to explore the molecular mechanisms of GC, and identify novel prognostic biomarkers to help early diagnosis and prognosis of patients with GC to achieve precise and personalized treatment in GC.

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Long non-coding RNAs (lncRNAs) have been considered in the tumorigenesis and development of tumor[7-9]; they are a group of longer than 200 nucleotides (nt) in length with limited or no protein-coding capacity[10], but lncRNAs are involved in regulating various biological processes including tumor growth, invasion and metastasis[11]. Of note, high expression of lncRNA PVT1 confers an aggressive phenotype to esophageal adenocarcinoma and associated with poor differentiation, lymph node metastases, shorter survival[12], meanwhile, lncRNA PVT1 regulates cell proliferation, migration, and invasion and related with malignancies and worse overall survival in gallbladder cancer[13]. Moreover, lncARSR correlated with clinically poor sunitinib response and unsatisfied prognosis by acting as a miR-34/miR-449 competing endogenous RNA (ceRNA) in renal cancer[14]. Due to lncRNAs diverse biological functions in tumor progression, they have the potential to be diagnostic and prognosis predicted biomarkers for cancer[15].

In our previously study, we analyzed the lncRNAs array of 5 gastric cancer patients after undergoing radical surgery combined with hyperthermic intraperitoneal chemotherapy (HIPEC), and identified a novel lncRNA named MGC27345, which is abnormally expressed after treatment. Notably, no research concerned with MGC27345 has been reported yet. To determine the role of MGC27345 in GC, we investigated the relationship between its expression level, prognostic significance and clinical characteristics of GC patients.

Patients and Methods

GC Tissue Specimens

GC tissues and paired adjacent normal gastric mucosa epithelial tissues in this research from 235 patients were surgically collected at Sun Yat-sen University Cancer Center (Guangzhou, China) from 2007 to 2011. None of the patients accepted systemic treatment before the clinical operation. The diagnosis of all GC patients was checked using clinical investigation and histopathological assays of the tissues. The clinical stage was determined based on the TNM classification. Overall survival (OS) was the time from the date of radical surgery to the date of death or last follow-up. This research was approved by the Committee for Ethical Review of Research involving Human Subjects of Sun Yat-sen University and all samples were used after obtaining informed consent from each patient.

Quantitative Real Time-PCR (qRT-PCR)

Total RNA from GC tissues was extracted using TRIzol reagent (Invitrogen, Carlsbad, CA, USA) according to the manufacturer's protocol. Then, a NanoDrop 2000 spectrophotometer (Thermo Fisher Scientific, Waltham, MA, USA) was used for the examination of the RNA concentration and integrity. cDNA was obtained by using GoScript Reverse Transcription (RT) system (Promega, Madison, WI, USA). The quantitative Real-Time Polymerase Chain Reaction (qRT-PCR) for the detection of the expression of lncRNA was performed on the GoTaq qPCR Master Mix system (Promega, Madison, WI, USA) and Roche LightCycler480 (Roche Diagnostics, Mannheim, Germany). The housekeeping gene glyceraldehyde 3-phosphatedehydrogenase (GAPDH) was used as an internal control. The relative expression of MGC27345 was calculated using the $2^{-\Delta\Delta Ct}$ method. All experiments were performed in triplicate. The primer sequences respectively were: glyceraldehyde 3-phosphatedehydrogenase (GAPDH): 5'-CTCCTCCTGTTCGACAGTCAG-3'(forward), 5'-CCCAATACGACCAAATCCGTT-3' (reverse); MGC27345: 5'-TCCCAGAGAGCCAGTTGTTA-3'(forward), 5'-GGAAGGATAAGAAAGAGAGTCGG-3' (reverse).

Statistical Analysis

The original data were analyzed using Statistical Product and Service Solution 25.0 (IBM Corp., Armonk, NY, USA) or GraphPad Prism V8 (GraphPad Prism, Inc., La Jolla, CA, USA). The differences between two groups were evaluated using the Student's *t*-test or the paired-sample *t*-test. The chi-squared test or Fisher's exact test was used to examine the correlation between MGC27345 expression and various clinicopathological variables. Kaplan-Meier method and the log-rank test were performed for the survival analysis between different patient groups. The associations between the expression of MGC27345 and OS were examined by univariate and multivariate Cox proportional hazards regression model. The statistical significance between data sets was expressed as *p*-values, and *p* less than 0.05 was considered statistically significant.

Results

MGC27345 Was Downregulated in GC Tissues

To explore the expression level of MGC27345 in GC tissues and the certain role of MGC27345

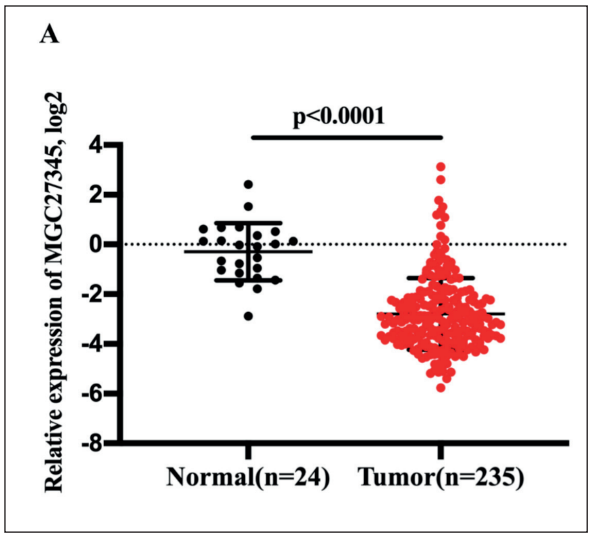

Figure 1. MGC27345 expression is significantly downregulated in GC tissues. **A**, The expression of MGC27345 in 235 GC tissues (T) and 24 adjacent normal tissues (N) determined by qRT-PCR. Results are presented as the logarithmic relative expression in tumor tissues compared with normal tissues.

in GC, we examined its expression level in 24 adjacent normal tissues (N) and 235 gastric cancer tissues (T) by qRT-PCR. Compared with adjacent noncancerous tissues, the expression of MGC27345 was significantly downregulated in GC tissues and imply that it functions as a tumor suppressor in GC (Figure 1A).

Downregulated Expression of MGC27345 is Positively Associated With Cancer Progression in GC Patients

Next, we evaluated the relationship between MGC27345 and clinicopathological of GC patients, the 235 GC patients were divided into high ($\geq 75^{th}$ percentile of expression level of MGC27345, n=118) and low ($<75^{th}$ percentile of expression level of MGC27345, n=117). Chi-squared analysis indicated that low MGC27345 expression in GC was significantly associated with tumor well differentiation (p=0.006), T4 stage (p=0.013), N3 stage (p<0.001), distant metastasis (p<0.001), and advanced TNM stage IV (p<0.001). No significant difference was found between the relative expression level of MGC27345 and other clinicopathological variables, including gender, age, tumor size, tumor location and drinking or smoking states (Table I).

We further investigated the relative expression of MGC27345 in different subgroups. The expression of MGC27345 decreased with increases in advanced T stage, N stage, M stage, and TNM stage. Significant difference was found between stage T3 and T4 (p=0.0025), stage N2 and N3 (p<0.0001), M0 and M1 (p=0.0024), TNM stage I and II (p=0.0462), TNM stage III and IV (p=0.0016) However, no statistical association was observed among stages T1, T2 and T3, among stages N0, N1 and N2, and between TNM stage II and stage III (Figure 2A-2D). In addition, there was also no significant difference between tumors of differentiation or location (Figure 2E-2F). Taken together, these results suggest that MGC27345 is intimately involved in GC progression.

MGC27345 Downregulation is Correlated With Poor Prognosis in GC

For investigating the prognostic value of MGC27345 in GC patients, the Cox regression model was performed to analyzed between clinicopathological features and clinical outcomes. In univariate analysis, T stage, N stage, M stage, TNM stage and MGC27345 expression were significant prognostic factors for OS in GC patients (all p<0.05). In multivariate analysis, MGC27345 expression was an independent favorable predictor of OS (hazard ratio [HR]=0.571; 95% confidence interval [CI]= 0.373-0.874; p=0.01). N stage (HR=1.319; 95% CI=1.039-1.674, p=0.023) and advanced TNM stage (HR=1.372; 95% CI=1.004-1.875; p=0.047) also were independent predictor of poorer OS in GC patients (Table II).

To further explore the impact of MGC27345 expression on survival, the log-rank test and Kaplan-Meier curves was used in our GC cohort. GC patients with low MGC27345 expression had a shorter 5-year OS rate (39.4% *vs.* 63.7%) compared with those in high MGC27345 expression group (p<0.0001) (Figure 3A). Next, we divided 235 GC patients into subgroups to analyze the effects of different expression levels of MGC27345 on the survival time of GC patients. In early stage T1-T2, MGC27345 expression showed no statistical significance on OS, but in advanced stage T3-T4, the survival benefits of GC patients were found in those with high MGC27345 level on OS rate (Figure 3B); Moreover, regardless of the presence of lymph node metastasis in GC patients, high MGC27345 expression group had predictive value for longer OS rate (Figure 3C). Additionally, in advanced TNM III and IV stage group, patients with lower MGC27345 expression had a shorter OS than those with higher MGC27345 expression (Figure 3D).

Table I. Correlation between MGC27345 expression levels and clinicopathological parameters in patients with GC. NOTE: GC, gastric cancer, TNM, tumor node metastasis. Bold type indicates $p<0.05$.

Variables	No. (%)	MGC27345 expression (%)		*p*-value
		Low (N, %)	High (N, %)	
Gender				
Male	166 (70.6%)	82 (49.4%)	84 (50.6%)	0.887
Female	69 (29.4%)	35 (57.1%)	34 (42.9%)	
Age(years)				
<60	131 (55.7%)	69 (52.7%)	62 (47.3%)	0.359
≥ 60	104 (44.3%)	48 (46.2%)	56 (53.8%)	
Location				
Upper and Middle	114 (48.5%)	53 (46.5%)	61 (53.5%)	0.362
Lower	121 (51.5%)	64 (52.9%)	57 (47.1%)	
Tumor Size (cm)				
≤5	99 (42.1%)	50 (50.5%)	49 (49.5%)	0.895
>5	136 (57.9%)	67 (49.3%)	69 (50.7%)	
Differentiation				
Moderate and Poor	210 (89.4%)	111 (52.9%)	99 (47.1%)	0.006
Well	25 (10.6%)	6 (24%)	19 (76.0%)	
Drinking				
Ever	189 (80.4%)	96 (50.8%)	93 (49.2%)	0.532
Never	46 (19.6%)	21 (45.7%)	25 (54.3%)	
Smoking				
Ever	151 (64.3%)	72 (47.7%)	79 (52.3%)	0.387
Never	84 (35.7%)	45 (53.6%)	39 (46.6%)	
T stage				
T1	14 (6.0%)	4 (28.6%)	10 (71.4%)	0.013
T2	21 (9.0%)	10 (47.6%)	11 (52.4%)	
T3	52 (22.1%)	18 (34.6%)	34 (65.4%)	
T4	148 (62.9%)	85 (57.4%)	63 (42.6%)	
N stage				
N0	51 (21.8%)	24 (47.1%)	27 (52.9%)	<0.001
N1	65 (27.8%)	21 (32.3%)	44 (67.7%)	
N2	73 (31.2%)	43 (95.6%)	2 (4.4%)	
N3	45 (19.2%)	1 (100%)	0 (0.0%)	
M stage				
M0	197 (83.8%)	85 (43.1%)	112 (56.9%)	<0.001
M1	38 (16.2%)	32 (84.2%)	6 (15.8%)	
TNM stage				
I	15	4 (26.7%)	11(73.3%)	<0.001
II	54	28 (51.9%)	26 (48.1%)	
III	126	52 (41.3%)	74 (58.7%)	
IV	40	33 (82.5%)	7 (17.5%)	

MGC27345 Combined with TNM Stage Better Predicts Patient Overall Survival in GC

The recent TNM staging system has a well-defined and effective role in the management for human cancers. However, the TNM staging system in our cohort is insufficient to distinguish the survival outcomes of GC patients with stage I and II. (OS, $p=0.2055$) (Figure 4A). Thus, a sensitive biomarker is needed to improve the distinguishing power of the TNM stage system.

Next, we performed a receiver operating characteristic (ROC) curve analysis to compare the discriminative power of MGC27345 expression, TNM stage, and MGC27345 combined with TNM stage (MGC27345+TNM stage) for predicting patient survival. Compared with MGC27345 and TNM stage, the ROC curve for MGC27345+TNM stage illustrated best among the three predictors and significantly improved the predictive accuracy for OS (area under the ROC curves [AUC]: 0.678 *vs*. 0.634 *vs*.0.614) (Figure 4B). These observations suggest that MGC27345 could be a novel

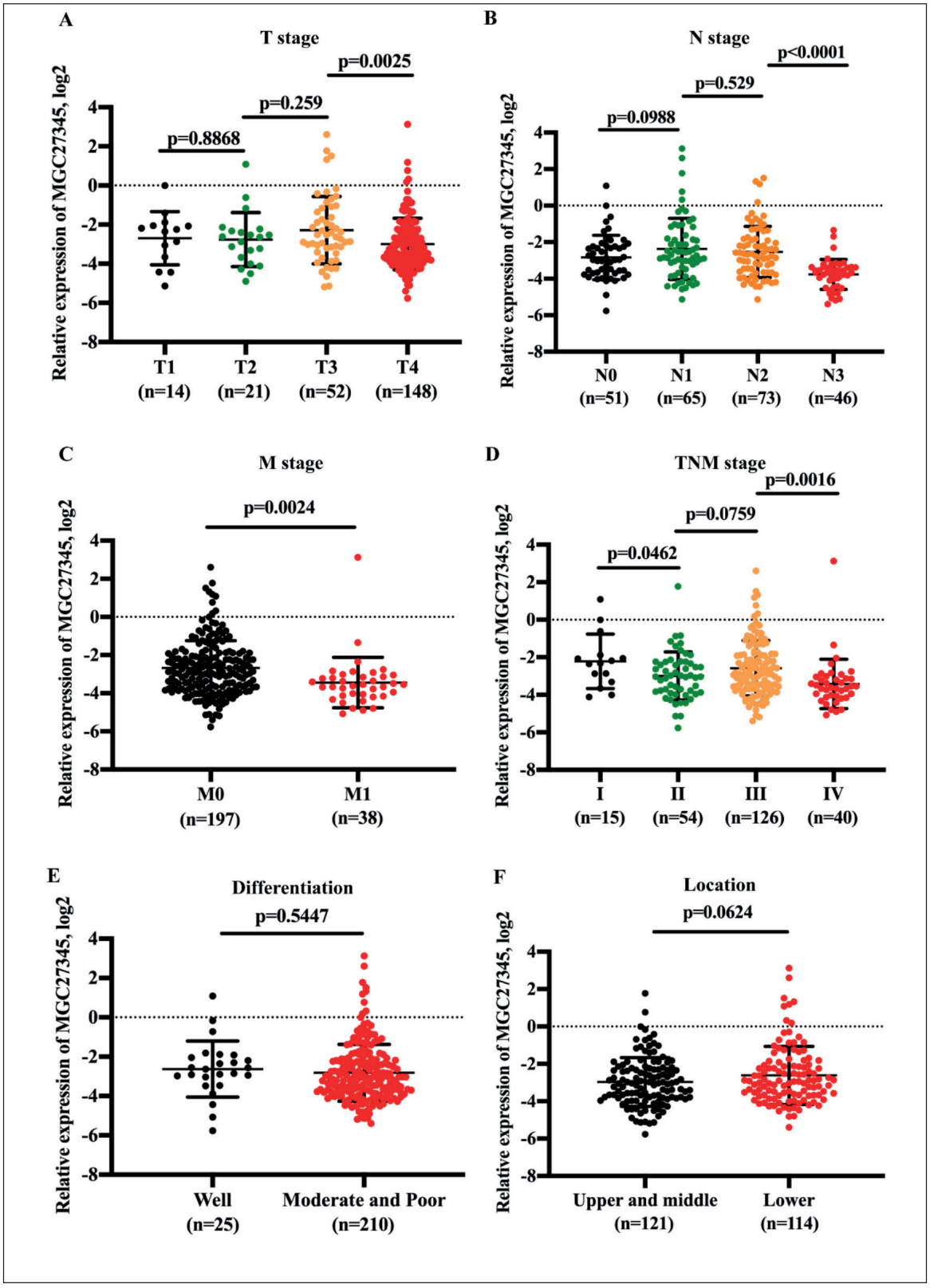

Figure 2. MGC273453 expression was markedly decreased in patients with advanced GC. qRT-PCR was performed to assess the relative expression of MGC27345 in GC tissues with different (**A**) T stages, (**B**) N stages, (**C**) M stages and (**D**) TNM stages. **E**, Relative expression of MGC27345 in GC tissues with well or moderate and poor differentiation of GC, and (F) GC tissues with different location. Results are presented as the logarithmic relative expression in tumor tissues.

Table II. Univariate and multivariate Cox regression analysis of MGC27345 and survival in patients with GC. NOTE: TNM, tumor node metastasis. GC, gastric cancer. HR, hazard ratio. CI, confidence interval. Bold type indicates $p<0.05$.

Clinical variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Overall Survival						
Gender (male vs. female)	1.399	0.938-2.086	0.100			
Age (≥60 vs. <60)	1.045	0.711-1.534	0.823			
Tumor location (lower vs. upper/middle)	0.952	0.651-1.394	0.802			
Tumor size (≥5 cm *vs.* <5 cm)	1.169	0.790-1.728	0.435			
Differentiation (well vs. moderate/poor)	0.742	0.387-1.424	0.370			
Drinking (never *vs.* ever)	0.954	0.586-1.551	0.848			
Smoking (never *vs.* ever)	1.022	0.687-1.521	0.913			
T stage (T4 *vs.* T3 *vs.* T2 *vs.* T1)	1.492	1.143-1.948	**0.003**			
N stage (N3 *vs.* N2 *vs.* N1 *vs.* N0)	1.669	1.363-2.044	**<0.001**	1.319	1.039-1.674	**0.023**
M stage (M1 *vs.* M0)	2.227	1.410-3.518	**0.001**			
TNM stage (IV *vs.* III *vs.* II *vs.* I)	1.799	1.371-2.361	**<0.001**	1.372	1.004-1.875	**0.047**
MGC27345 expression (high vs. low)	0.441	0.298-0.654	**<0.001**	0.571	0.373-0.874	**0.010**

prognostic marker for GC patients, and could supply more prognostic information to help developing effective treatment strategies.

Discussion

At present, there are no accurate biomarkers for gastric cancer in the early diagnosis and prognosis[16]. Most patients are diagnosed at advanced stage[4]. Owing to the unsatisfactory prognosis for GC patients, it is essential to find the key molecular mechanism of gastric cancer development in order to improve early diagnosis and personally treatment strategies for this disease[17].

In recent years, previous studies focused on lncRNAs have greatly improved our understanding of the intrinsic molecular mechanisms of tumor development, lncRNAs are involved in various biological functions including tum-

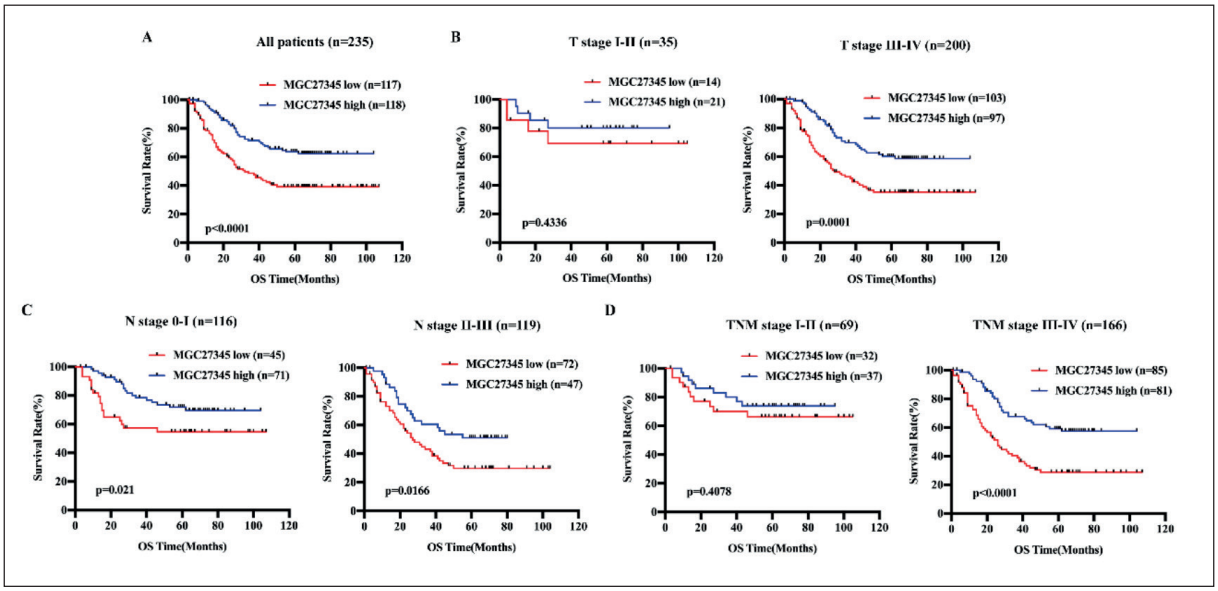

Figure 3. Low expression of MGC27345 was positively correlated with a poor overall survival (OS). Kaplan-Meier curves of OS based on MGC27345 expression in (**A**) all 235 patients with GC, (**B**) patients with T stage I-II and III-IV, (**C**) patients with N stage 0-I and II-III, and (**D**) patients with TNM stage I–II and III-IV. P-values were obtained by log-rank tests.

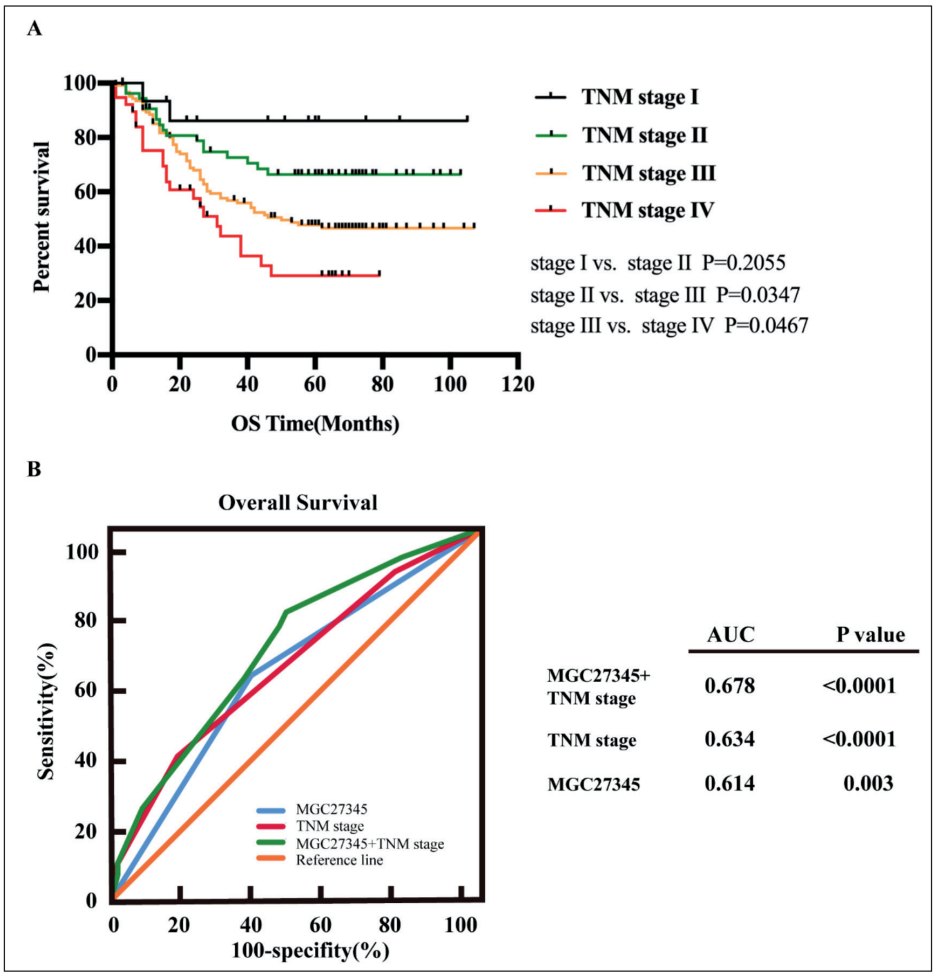

Figure 4. Combination of MGC27345 expression and TNM stage has the best predictive value in GC patients. **A**, OS of 235 GC patients were predicted by the TNM staging system. **B**, Receiver operating characteristic (ROC) analysis compares OS of GC patients by TNM stage, MGC27345 expression, MGC27345 combined with TNM stage (MGC27345+TNM stage). The result shows that the area under the curve (AUC) of MGC27345+TNM stage is largest among the three predictors for OS.

origenesis and metastasis in human cancers[18,19]. In GC, the dysregulation of multiple lncRNAs have been reported, such as HOXC-AS3[20], HOTTIP[21], GATA6-AS1[22], UCA1[23,24], SNHG3[25], and MALAT1[26,27], they inhibit or promote procession, metastasis and drug resistance of tumors and is closely related with prognosis of tumors. Meanwhile, because of high specificity and easy detection in the tissues, serum, plasma, urine and saliva, lncRNAs also acting as valuable biomarkers for diagnosis and prognosis of human cancers[28,29]. Some lncRNAs, such as PCA3, is now routinely used in the clinic for the diagnosis of prostate cancer[30]. But the relationship between MGC27345 and GC has not yet been explored.

In this study, we investigated the role of MGC27345 in GC due to it has not been reported yet. Our results showed that the expression of MGC27345 was downregulated in GC tissue, and associated with advanced T stage, N stage, M stage, TNM stage and poor differentiation. Moreover, GC patients with advanced cancer stage or distant metastasis resulted in a poor prognosis after systemic treatment. Therefore, an effective and sensitive biomarker was needed to personally apply treatment strategies for patients with different situations. Our survival analysis in distinct subgroups revealed that GC patients with lower expression of MGC27345 had a poorer overall prognosis. In summary, the relationship between MGC27345 and overall survival of advanced GC patients cannot be ignored, these results suggested that MGC27345 may serve as a tumor suppressor, and it may have potential to have a diagnostic and prognostic value in GC.

In clinical practice, most of oncologists have recognized that the TNM staging system alone cannot have a better predictive value in series of human cancers. Hence, we assessed the effects of MGC27345 combined with TNM stage on GC patient prognosis. Fortunately, a new prediction model based on a combination of MGC27345 and TNM stage had a better sensitivity and specificity

for the overall survival of GC patients than TNM staging system alone. These findings implied that this method could offer more power for predicting the prognosis of GC patients and fighting against gastric cancer.

However, the precise molecular mechanism of MGC27345 exerting its biological function in GC remains unclear. Further studies *in vitro* or *in vivo* are needed to demonstrate the underlying molecular mechanism.

Conclusions

Our findings firstly provide evidence that MGC27345 is downregulated and may serve as a tumor suppressor to participate in GC progression. MGC27345 shows a significantly association with overall survival and clinical outcomes for GC patients, patients with low expression of MGC27345 have a shorter overall survival than that with higher expression of MGC27345, and lower expression of MGC27345 could be implicated in advanced stage of GC development. These results suggesting MGC27345 may have potential value in GC prognosis.

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Conflict of Interests

There are no conflicts of interest to disclosure for any author.

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