# High ADAMTS18 expression is associated with poor prognosis in stomach adenocarcinoma

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**Abstract.** Stomach adenocarcinoma (STAD) is the most pathological type of gastric cancer. ADAM metallopeptidase with thrombospondin type 1 motif 18 (ADAMTS18) plays an essential role in organ development and tumorigenesis; however, its function in STAD, and its impact on clinical outcome remain unclear. Thus, the present study aimed to investigate the association between ADAMTS18 expression and the prognosis of patients with STAD. Data from 300 patients with STAD in The Cancer Genome Atlas (TCGA) database were analyzed, and the median survival time and overall survival (OS) rate of these patients were assessed. Subsequently, 40 paired tumor and non-tumor tissue samples from patients with STAD were collected, and the relative ADAMTS18 mRNA expression levels were determined. Results from TCGA database demonstrated that high tumor ADAMTS18 expression was associated with a poorer prognosis in patients with STAD. Similarly, results from the assessed patient cohort indicated that ADAMTS18 expression was significantly higher in STAD tissues compared with non-tumor tissues. Furthermore, ADAMTS18 expression was significantly associated with tumor differentiation, lymph node metastasis and tumor node metastasis stage. Taken together, these results suggest that ADAMTS18 is highly expressed in STAD tissues, and thus may act as a potential indicator of poor prognosis in patients with STAD.

## Introduction

Gastric cancer has some of the highest morbidity and mortality rates among cancers of the digestive system (1). In China in 2015, the incidence and mortality rates of gastric cancer ranked second for all types of cancer, with an estimated 679,100 new cases and 498,000 cancer-associated mortalities (2). Stomach adenocarcinoma (STAD) accounts for 80-90% of all gastric cancer cases and surgery is considered a plausible curative treatment, particularly in the early stages of disease (3). However, effective biomarkers for prognosis following surgery are still lacking for patients with gastric cancer. Thus, the discovery and application of novel predictive biomarkers are critical to improve therapeutic efficacy and prediction of clinical response.

ADAM metallopeptidase with thrombospondin type 1 motif 18 (ADAMTS18) is a novel member of the metalloproteinase family, which plays an essential role in the physiological growth and development of several organisms (4,5). Loss of expression, genetic mutation and gene methylation of ADAMTS18 can lead to abnormal development and disease, such as arthritis, cancer and cardiovascular disease (6). Aberrant ADAMTS18 expression has been reported to be closely associated with the development of the bone, eye and central nervous system, as well as thrombosis and tumorigenesis (4). Furthermore, a previous study has demonstrated that abnormal ADAMTS18 expression is associated with tumor occurrence and development (7). Evidence suggests that ADAMTS18 may be a tumor suppressor (8); however, overexpression of ADAMTS18 has been reported to promote the proliferation and migration of HCC cells (9). These findings suggest that the biological function of ADAMTS18 varies between different types of tumor.

To the best of our knowledge, few studies have focused on the role of ADAMTS18 in STAD, whereby the results are contradictory. Therefore, the present study aimed to investigate the prognostic value of ADAMTS18 expression in patients with STAD, and to determine its association with STAD occurrence and development.

## Materials and methods

*Study population and data collection from the cancer genome atlas (TCGA) database.* Data on the survival time,

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clinicopathological characteristics and gene expression profiles of patients with STAD were downloaded from TCGA database (tcga-data.nci.nih.gov/tcga/) (10,11). The cohort included 191 men and 109 women with an age range of 30 to 90 years old and median age of 67 years. The clinical data included: Ethnicity, sex, age, tumor stage, lymph node metastasis, Tumor-Node-Metastasis (TNM) stage (12), survival time and status.

*Association between ADAMTS18 expression and survival in TCGA database*. Tumor ADAMTS18 expression levels from TCGA were divided into two groups based on the 50% cut-off values. The Kaplan-Meier method and log-rank tests were used to assess the median survival time and OS rate, with adjustment for sex, age, tumor grade, tumor stage, lymph node metastasis and TNM stage.

*Patient information and data collection*. The present study was approved by the Ethics Committee of the First Affiliated Hospital of Guangxi Medical University (Nanning, China), and written informed consent was obtained from all patients prior to study commencement. A total of 40 paired tumor and non-tumor tissue samples were collected from 30 male and 10 female subjects at the First Affiliated Hospital of Guangxi Medical University between October 2016 and February 2017. The age range of these patients was 34 to 87 and the median age was 63 years. STAD diagnoses were pathologically confirmed by the Department of Pathology of the First Affiliated Hospital of Guangxi Medical University following gastrointestinal surgery. The following patient data were acquired: Name, sex, age, degree of tumor differentiation, infiltration depth, lymph node metastasis and clinical stage. Patients were divided into high and low expression level groups based on their 50% cut-off values of relative ADAMTS18 expression levels in tumor tissues. The association between ADAMTS18 mRNA expression and the clinicopathological characteristics was then assessed.

*Reverse transcription-quantitative (RT-q)PCR*. Total RNA was extracted from tissue samples using TRIzol® reagent (Aidlab; aidlab.cn). The RNA was then reverse transcribed into cDNA using the PrimeScript™ RT reagent kit, with gDNA Eraser (Takara Bio, Inc). qPCR was subsequently performed using FastStart Universal SYBR Green Master (Rox) (Roche Life Science) on the ABI PRISM 7500 Sequence Detection System (Applied Biosystems; Thermo Fisher Scientific, Inc.) (13). All methodologies were performed according to the manufacturer's protocols. The following primer sequences (Sangon Biotech Co., Ltd.) were used for qPCR: ADAMTS18 forward, 5'-ACC TTGACCAGAACACCATCGAG-3' and reverse, 5'-CAGGGT CCAGGTCAGGTGTGTA-3'; and GAPDH forward, 5'-GGA GATTACTGCCCTGGCTCCTA-3' and reverse, 5'-GACTCA TCGTACTCCTGCTTGCTG-3'. The reaction system had a total volume of 20 $\mu$l, and the following thermocycling conditions were used for qPCR: Initial denaturation at 95˚C for 30 sec, followed by 50 cycles of 95˚C for 5 sec and 60˚C for 30 sec. Relative mRNA expression levels were measured using the $2^{-\Delta\Delta Cq}$ method (14) and normalized to the internal reference gene GAPDH. All experiments were performed in triplicate.

*Prediction analysis of ADAMTS18 gene and protein interactions*. The GeneMANIA database (genemania.org) was used to identify genes potentially associated with ADAMTS18, in order to predict ADAMTS18 gene function and determine its role in cancer development. A gene interaction network was constructed using Cytoscape software (version 3.6.1) (15). Similarly, The Search Tool for the Retrieval of Interacting Genes/Proteins (STRING) database was used to construct a protein interaction network (16), depicting proteins associated with ADAMTS18. Gene Ontology (GO) functional enrichment analysis of the associated genes and proteins was performed using the Database for Annotation, Visualization and Integrated Discovery (DAVID) (david.ncifcrf.gov/).

*Statistical analysis*. Statistical analysis was performed using SPSS software (version 22.0; IBM Corp.). The Kaplan-Meier method with log-rank test was used for median survival time and OS analysis. A paired Student's t-test was used to evaluate the differences in relative ADAMTS18 mRNA expression levels between STAD and normal adjacent tissues. The association between ADAMTS18 expression and clinicopathological characteristics was assessed using the $\chi^2$ and Fisher's exact probability tests. $P<0.05$ was considered to indicate a statistically significant difference.

## Results

*TCGA patient characteristics*. The clinical characteristics of 300 patients from TCGA database with survival times >2 months are presented in Table I. The results demonstrated that lymph node metastasis (P=0.003; HR, 2.02; 95% CI, 1.28-3.19) and TNM stage (P=0.002; HR, 1.84; 95% CI, 1.25-2.72) were significantly associated with OS rate.

*Association between ADAMTS18 mRNA expression level and survival*. Data from TCGA database was used to divide the patients into two groups based on the 50% cut-off values of ADAMTS18 mRNA expression. The results indicated that ADAMTS18 expression was significantly associated with OS rate (Fig. 1) (P=0.001; HR, 1.87; 95% CI, 1.27-2.73; Table II), even after adjusting for age, sex, ethnicity, tumor differentiation degree, tumor stage, lymph-node metastasis and TNM stage (adjusted P=0.002; adjusted HR, 1.81; adjusted 95% CI, 1.24-2.65; Table II).

*Analysis of ADAMTS18 expression in STAD and non-tumor tissues*. In order to determine whether ADAMTS18 was differentially expressed in tumor and non-tumor tissues, relative ADAMTS18 gene expression was analyzed between 40 paired independent samples. The results demonstrated that ADAMTS18 expression was significantly higher in STAD tissues than in normal adjacent tissues (P=0.001; Fig. 2).

*Association between ADAMTS18 expression and clinicopathological characteristics in patients with STAD*. ADAMTS18 expression was significantly associated with tumor differentiation degree (P=0.013; $\chi^2$=7.795), lymph node metastasis (P=0.001; $\chi^2$=12.379) and TNM stage (P=0.001; $\chi^2$=12.379). However, ADAMTS18 expression was not associated with sex, age, ethnicity, tumor size or tumor stage (Table III).

*Prediction analysis of the biological function of ADAMTS18 and associated signaling pathways*. Prediction analysis using

Table I. Clinical characteristics of 300 patients with stomach adenocarcinoma in The Cancer Genome Atlas database.

| Characteristic | Patient, n | MST, (days) | Overall survival rate | |
|---|---|---|---|---|
| | | | HR (95% CI) | P-value |
| Sex | | | 0.83 (0.56-1.22) | 0.342 |
| Male | 191 | 1,153 | | |
| Female | 109 | NA | | |
| Age, years | | | 1.22 (0.84-1.76) | 0.301 |
| <67 | 148 | 1,407 | | |
| ≥67 | 152 | 805 | | |
| Ethnicity | | | 0.79 (0.49-1.28) | 0.343 |
| White and black | 223 | 1,043 | | |
| Asian | 77 | NA | | |
| Tumor-grade | | | 1.45 (0.97-2.16) | 0.069 |
| G1+G2 | 111 | 1,747 | | |
| G3 | 189 | 832 | | |
| Tumor stage | | | 1.57 (0.96-2.58) | 0.073 |
| T1+T2 | 72 | 1,811 | | |
| T3+T4 | 228 | 874 | | |
| LN metastasis | | | 2.02 (1.28-3.19) | 0.003[a] |
| N0+ NX | 100 | 1,811 | | |
| N1+N2+N3 | 200 | 782 | | |
| Metastasis | | | 1.26 (0.55-2.89) | 0.579 |
| M0+MX | 287 | 1,153 | | |
| M1 | 13 | 476 | | |
| TNM stage | | | 1.84 (1.25-2.72) | 0.002[a] |
| I+II | 144 | 1,811 | | |
| III+IV | 156 | 766 | | |

[a]P<0.05. MST, median survival time; HR, hazard ratio; CI, confidence interval; NA, not available; LN, lymph node; TNM, tumor node metastasis.

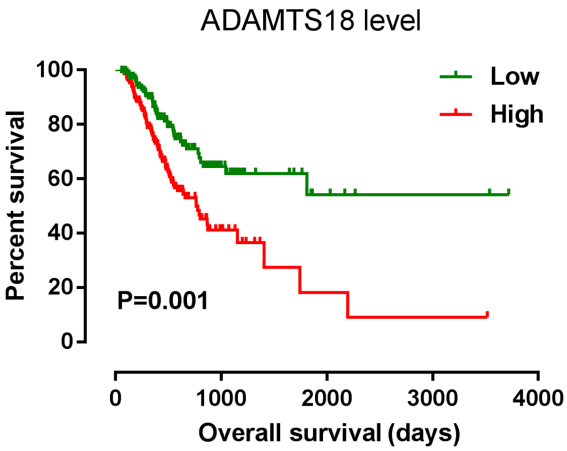


Figure 1. Kaplan-Meier overall survival analysis of patients with stomach adenocarcinoma from The Cancer Genome Atlas database.

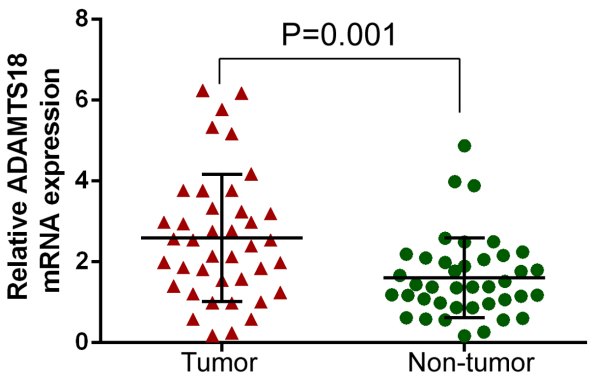


Figure 2. ADAMTS18 mRNA expression in stomach adenocarcinoma tissues compared with normal adjacent tissues in the assessed patient cohort. ADAMTS18, ADAM Metallopeptidase with Thrombospondin Type 1 Motif 18.

GeneMANIA demonstrated that ADAMTS18 interacts with FAM218A, ATP8A2, ANKRD45, SRPK2, CHD7, RAB9B and other member of the ADAMTS and ADAM family (Fig. 3A). Protein interaction network analysis using the STRING database demonstrated that the ADAMTS18 gene primarily interacts with THBS1, ACAN, B3GALTL, POFUT2

Table II. Prognostic survival analysis of ADAMTS18 gene expression in 300 patients with stomach adenocarcinoma from The Cancer Genome Atlas database.

| Gene | Patient, n | MST, day | Crude HR (95% CI) | Crude P-value | Adjusted HR (95% CI) | Adjusted P-value[b] |
|---|---|---|---|---|---|---|
| ADAMTS18 | | | | | | |
| Low | 150 | 2,281 | | 0.001[a] | | 0.002[a] |
| High | 150 | 1,148 | 1.87 (1.27-2.73) | | 1.81 (1.24-2.65) | |

[a]P<0.05; [b]Adjusted for sex, age, ethnicity, tumor grade and tumor stage. ADAMTS18, ADAM metallopeptidase with thrombospondin type 1 motif 18; MST, median survival time; HR, hazard ratio; CI, confidence interval.

Table III. Association between ADAMTS18 expression and clinicopathological characteristics in patients with stomach adenocarcinoma (n=40).

| | | ADAMTS18 expression | | | |
|---|---|---|---|---|---|
| Characteristic | Patient, n | Low, n=20 | High, n=20 | $\chi^2$-value | P-value |
| Sex | | | | 0.520 | 0.716 |
| Male | 30 | 16 | 14 | | |
| Female | 10 | 4 | 6 | | |
| Age, years | | | | 0.902 | 0.527 |
| <63 | 19 | 8 | 11 | | |
| ≥63 | 21 | 12 | 9 | | |
| Tumor size, cm | | | | 0.921 | 0.337 |
| <5 | 23 | 13 | 10 | | |
| ≥5 | 17 | 7 | 10 | | |
| Differentiation | | | | 7.795 | 0.013[a] |
| Poor | 26 | 9 | 17 | | |
| Well + medium | 12 | 10 | 2 | | |
| Missing | 2 | 1 | 1 | | |
| Tumor stage | | | | 1.758 | 0.185 |
| T1+T2 | 14 | 9 | 5 | | |
| T3+T4 | 26 | 11 | 15 | | |
| LN metastasis | | | | 12.379 | 0.001[a] |
| Yes | 23 | 6 | 17 | | |
| No | 17 | 14 | 3 | | |
| TNM stage | | | | 12.379 | 0.001[a] |
| I+II | 17 | 14 | 3 | | |
| III+IV | 23 | 6 | 17 | | |

[a]P<0.05. ADAMTS18, ADAM metallopeptidase with thrombospondin type 1 motif 18; LN, lymph node; TNM, Tumor-Node-Metastasis.

and other ADAMTS family members (Fig. 3B). GO functional enrichment analysis suggested that ADAMTS18 is likely to be involved in 'protein O-linked fucosylation', 'proteolysis', 'glycoprotein metabolic process', 'carbohydrate derivative metabolic process', 'carbohydrate derivative biosynthetic process', 'carbohydrate metabolic process', 'glycoprotein biosynthetic process', 'extracellular matrix organization', 'post-translational protein modification', 'response to tumor necrosis factor', 'negative regulation of chondrocyte differentiation', 'extracellular matrix', 'proteinaceous extracellular matrix', 'endoplasmic reticulum lumen', 'extracellular region part', 'extracellular region', 'metalloendopeptidase activity', 'metallopeptidase activity', 'zinc ion binding', 'metal ion binding' and 'glycosaminoglycan binding' (Fig. 4).

## Discussion

ADAMTS18 is a member of the newly discovered ADAMTS metalloproteinase family (17-19) and has been associated with tumor occurrence and development in nasopharyngeal

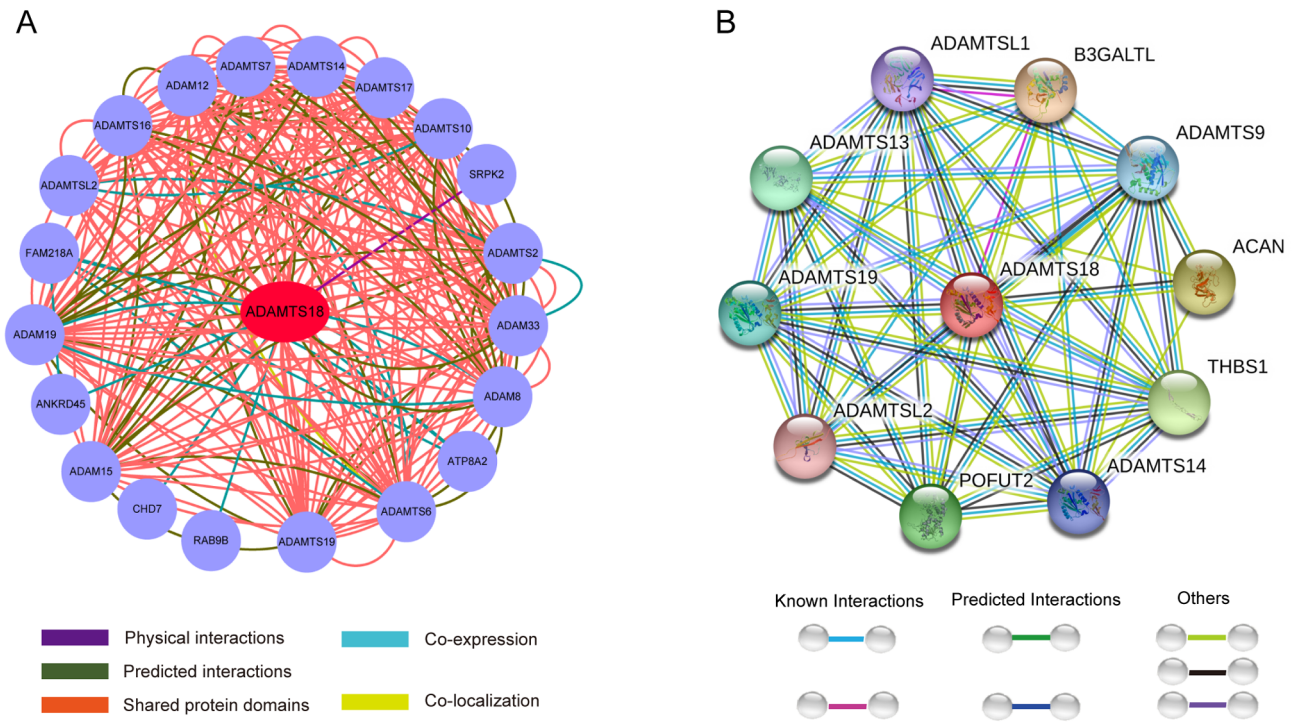


Figure 3. (A) GeneMANIA database was used to construct a gene interaction network between ADAMTS18 and other genes. (B) Search Tool for the Retrieval of Interacting Genes/Proteins database was used to construct a protein interaction network between ADAMTS18 and other proteins. ADAMTS18, ADAM metallopeptidase with thrombospondin type 1 motif 18.

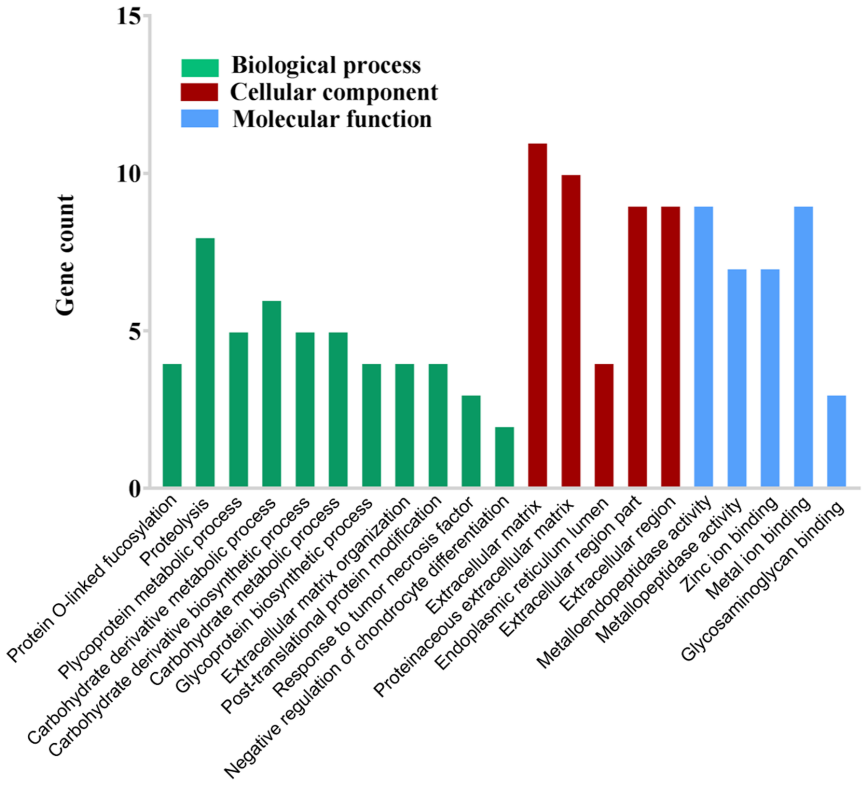


Figure 4. Gene Ontology functional enrichment analysis of the interaction networks for ADAM metallopeptidase with thrombospondin type 1 motif 18.

carcinoma, cervical cancer, colorectal cancer, breast cancer, renal clear cell carcinoma and esophageal adenocarcinoma (20-23). However, to the best of our knowledge, few studies have focused on the role of ADAMTS18 in STAD. Thus, the present study aimed to investigate the association between ADAMTS18 expression and the clinicopathological characteristics and prognosis of patients with STAD. The results of the present study demonstrated that ADAMTS18

was upregulated in gastric tumor tissues and positively associated with tumor differentiation, lymph node metastasis and TNM stage, compared with normal adjacent tissues. ADAMTS18 expression was demonstrated to be an adverse prognostic factor for STAD, which may potentially be used as a prognostic marker.

ADAMTS18 has been associated with both tumor suppression and induction, which suggests that the biological function of ADAMTS18 varies between different types of tumor. Previous study reported that ADAMTS18 expression levels are decreased in cervical cancer tissues compared with normal adjacent tissues, furthermore, low expression levels of ADAMTS18 were positively associated with high tumor stage, positive lymph node metastasis and distant metastasis (8). Xu *et al* (7) reported that ADAMTS18 expression is lower in breast cancer cell lines and *in situ* breast cancer tissue compared with normal breast cells and tissues, and that the ADAMTS18 promoter is up to 70.8% methylated in breast cancer tissue. ADAMTS18 can inhibit metastasis and the invasion of breast cancer both *in vivo* and *in vitro*, which was demonstrated using overexpression and subcutaneous transplantation experiments in nude mice. However, the results of the present study suggest that ADAMTS18 is likely to be cancer promoting and a marker of poor prognosis in patients with STAD. Consistent with previous findings, this suggests that ADAMTS18 may possess diverse biological functions during STAD development. In a melanoma study, genome sequencing led to the discovery of a mutation in the ADAMTS18 gene, and subsequent *in vitro* analysis demonstrated that the mutant promoted the proliferation, migration and metastasis of melanoma cells (24). Notably, it has also been reported that ADAMTS18 expression is associated with tumor stage in STAD (25). The results of the present study demonstrated that ADAMTS18 expression was closely associated with tumor grade, lymph node metastasis and TNM stage, and significantly affected the postoperative survival time of patients with STAD.

The ADAMTS family includes 19 members that are involved in several pathological and physiological processes, including tumor formation, thrombosis, angiogenesis and cellular migration (6,26). Different ADAMTS members play varying roles in different tissue types (4). For example, ADAMTS1 and ADAMTS8 are expressed at low levels in breast cancer and can exhibit an antitumor effect through their platelet reactive protein-1 domain (27,28). Furthermore, ADAMTS12 can regulate extracellular signals to modulate kinase signaling pathways and inhibit tumor formation (29). However, high ADAMTS8 and ADAMTS18 expression levels have been reported in breast cancer, suggesting a tumor-inducing role (30). These observations highlight a complex role of the ADAMTS family members in tumor development. Other members of the ADAMTS family, such as ADAMTS4, 5, 8, 10 and 17, are highly expressed in several cancers and cell lines (31-34), and silencing or overexpressing these genes can inhibit or promote the proliferation, migration and invasiveness of cancer cells, indicating that the ADAMTS family serves a role in tumor biology and progression. Li *et al* (22) reported that the frequency of ADAMTS18 gene methylation in STAD, colorectal cancer and pancreatic cancer tissues is significantly higher compared with that in the respective normal adjacent tissues, suggesting that gene hypermethylation may cause decreased ADAMTS18 expression in cancer tissues. A recent report demonstrated that upregulated ADAMTS18 expression is associated with a significantly higher immune response score in lymph nodes with metastasis, and in gastric adenocarcinoma tissues compared with normal gastric tissues; ADAMTS18 expression in STAD tissues was also positively associated with tumor TNM staging (35). Consistent with these findings, the results of the present study demonstrated that ADAMTS18 expression increased in cancer tissues at both the mRNA and protein levels, indicating that this gene may promote STAD occurrence and development.

In conclusion, the present study demonstrated that ADAMTS18 was highly expressed in STAD tissues compared with normal gastric tissues. Furthermore, ADAMTS18 expression was significantly associated with STAD prognosis, and thus may potentially be used as a prognostic biomarker for patients with STAD. However, a validation study implementing larger sample sizes and a long-term follow-up period in multiple centers is required to confirm the findings of the present study and the potential biological function of the ADAMTS18 gene needs further experimental exploration.

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**Availability of data and materials**

The datasets used and/or analyzed during the present study are available from the corresponding author upon reasonable request.

**Authors' contributions**

QX and YX designed and supervised the present study. KJ and LL performed the literature review, analyzed the data and drafted the initial manuscript. DX performed RT-qPCR and helped analyze the data. All authors read and approved the final manuscript.

**Ethics approval and consent to participate**

The present study was approved by The Ethics Committee of The First Affiliated Hospital of Guangxi Medical University (Nanning, China), and written informed consent was obtained from all patients prior to study commencement.

**Patient consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

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