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Original Article

High expression of KMT2D is a promising biomarker for poor gastric cancer prognosis

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Abstract: Objective: To investigate the expression of histone lysine N-methyltransferase 2D (KMT2D) in gastric cancer patients and its relationship with the prognosis. Methods: A total of 126 gastric cancer patients admitted to Hubei Provincial Hospital of TCM from January 2014 to June 2017 were selected as the research subjects, and patients' clinical data were analyzed retrospectively. First, the KMT2D mRNA or protein expression in the patient's tissue was detected using quantitative real-time PCR or immunohistochemistry. Afterwards, the relationship between the KMT2D protein expression and the prognosis of patients was analyzed using a Kaplan-Meier curve. Also, the predictive value of the KMT2D mRNA and protein expression for the prognosis and death rate of gastric cancer patients was evaluated using a receiver operating characteristic curve. Finally, the risk factors for poor prognosis and death of the gastric cancer patients were analyzed using a Cox regression analysis. Results: Overall, the KMT2D mRNA expression level and positive rate of protein expression in the gastric cancer tissues were significantly higher than that in paracancerous tissues (P<0.05). A positive expression of the KMT2D protein in gastric cancer tissues was correlated with the following factors in patients: age ≥60 years, tumor differentiation degree, TNM stage III-IV, lymph node metastasis, depth of invasion T3-T4, distant metastasis and high serum carbohydrate antigen 19-9 (CA19-9) levels (P<0.05). Also, the 5-year overall survival and progression-free survival of gastric cancer patients with a positive KMT2D expression were lower than those with negative KMT2D expressions (P<0.05). The resulting areas under the curve for predicting the prognosis and death of gastric cancer patients with the KMT2D mRNA and protein expression were 0.823 and 0.645, respectively. In addition, tumor maximum diameter >5 cm, poor differentiation, TNM stage III-IV, lymph node metastasis, high serum CA19-9 level, KMT2D mRNA expression ≥1.48 and KMT2D protein positive expression were risk factors affecting the prognosis and death of gastric cancer patients (P<0.05). Conclusion: KMT2D is highly expressed in gastric cancer tissue and it is expected to be a potential biomarker for predicting the poor prognosis of gastric cancer patients.

Keywords: Histone lysine N-methyltransferase 2D, gastric cancer, prognosis

Introduction

As the third leading cause of cancer-related death, gastric cancer is a global health problem, and its incidence is increasing with age. Although the 5-year survival rate of early gastric cancer is up to 90%, the early diagnosis rate is low due to the lack of typical symptoms in the early stage and efficient diagnostic and prognostic indicators [1, 2]. Gastric cancer is a highly heterogeneous disease regarding genotype and phenotype, and despite advances in comprehensive treatment strategies, its mortality remains high due to the large number of patients in advanced disease stages [3]. Therefore, the development of new biomarkers and therapeutic targets for early detection and treatment is essential to improve the prognosis of gastric cancer patients.

Previous studies have shown that the occurrence and development of gastric cancer are affected by various factors such as environment and genetics, and are closely related to gene expression mutations and epigenetic changes related to the carcinogenesis process [4]. Histone lysine N-methyltransferase 2D (KMT2D/MLL2/MLL4), as one of the most common mutation driver genes in cancer, is responsible for catalyzing the aminomethylation of

histone 3 lysine 4 and shows a high mutation frequency in some cancers [5, 6]. It has been reported that KMT2D mutation is associated with poor overall survival (OS) or progression-free survival (PFS) in patients with non-small cell lung cancer, nasal T/NK cell lymphoma and other tumors [7, 8]. Furthermore, KMT2D deficiency enhances the anticancer activity of L48H37 in pancreatic ductal adenocarcinoma [9]. Recent studies have shown that KMT2D is a frequently mutated gene in gastric cancer tissue and closely correlated with the clinical characteristics of patients, suggesting that KMT2D may be an oncogene that can promote the proliferation of gastric cancer cells [10]. Although there have been many reports on the role of KMT2D in cancer, the clinical value of KMT2D in gastric cancer is still largely unknown and needs to be verified by more studies.

Therefore, in order to further clarify the value of KMT2D in gastric cancer and find a potential prognostic biomarker for gastric cancer patients, in this study, the expression of KMT2D in gastric cancer tissues was detected, and its relationship with the clinicopathological characteristics and the prognosis of patients were analyzed.

Materials and methods

Case selection

A total of 126 patients with gastric cancer who were pathologically diagnosed in Hubei Provincial Hospital of TCM from January 2014 to June 2017 and received surgical treatment were selected as the research subjects, and patients' clinical data were analyzed retrospectively. This study was approved by Ethics Committee of Hubei Provincial Hospital of TCM (approval number: 201301235).

Inclusion criteria: (1) patients who were diagnosed with gastric cancer by pathological examination of the postoperative tissue samples according to World Health Organization standards; (2) patients who received no anti-tumor treatments such as radiotherapy and chemotherapy before surgery; (3) patients with age of 38 to 85 years; patients with complete clinical data. Exclusion criteria: (1) patients with malignant tumors of other organs; (2) patients with severe heart, liver, kidney or other organ insufficiency; (3) patients with blood system diseases or immune system diseases; (4) patients with mental or intellectual disability and cannot cooperate with the treatment.

Collection and preservation of tissue samples

Gastric cancer tissue and corresponding paracancerous tissue (no cancer cells confirmed by histopathological examination) were collected during the surgery. Some of the samples were washed with normal saline, and then stored in a refrigerator at -80°C. The remaining samples were placed in 10% formalin fixative solution to prepare conventional paraffin tissue sections (4 μm in thickness) for later use.

Detection of KMT2D mRNA expression in tissues by quantitative real-time PCR (qRT-PCR)

Using the tissue stored at -80°C, total RNA was extracted with the use of TRIzol™ reagent (Invitrogen, USA), and the RNA was reverse transcribed to cDNA with a reverse transcription kit (Invitrogen, USA) after detecting the purity of the RNA and quantifying its concentration. The reaction system was prepared using SYBR Green qPCR Master Mix (Universal) (MedChemExpress, USA). The specific primers for KMT2D and its internal reference gene (GenePharma Co., Ltd., Shanghai, China) were amplified on a qRT-PCR instrument (Bio-Rad, USA) to obtaine the cycle threshold (Ct value). Relative quantitative analysis of KMT2D mRNA expression was performed by $2^{-\Delta\Delta Ct}$ method. KMT2D F: 5'-TGACAAGTGTGAATCCCGTGAAG-3', R: 5'-AACCATTTCATCCGTTGTTACGAAG-3'; glyceraldehyde-3-phosphate dehydrogenase (GAPDH) F: 5'-CCTGCCGTCTAGAAAAACCTG-3', R: 5'-AGTGGGTGTCGCTGTTGAAGT-3'.

Immunohistochemical detection of KMT2D protein expression in tissues

Paraffin tissue sections were subjected to dewaxing, hydration, antigen thermal repair, and endogenous peroxidase activity blocking, and then blocked with 10% goat serum according to the instructions of immunohistochemical kit (Zhong Shan-Golden Bridge Co., Ltd., Beijing, China). Thereafter, they were incubated overnight with rabbit anti-human KMT2D antibody (Abcam, UK; 1:200) at 4°C and washed with PBS. Then, the sections were incubated with

Table 1. Comparison of KMT2D mRNA expression level and positive rate of protein expression between gastric cancer tissue and paracancerous tissue [($\bar{x}$ ± sd)/*n* (%)]

Group	*n*	KMT2D mRNA	KMT2D protein	
			Negative	Positive
Paracancerous tissue	126	1.02±0.13	93 (73.81)	33 (26.19)
Gastric cancer tissue	126	1.51±0.16	41 (32.54)	85 (67.46)
t/χ^2	-	26.680	43.094	
P	-	<0.001	<0.001	

KMT2D: Histone Lysine N-Methyltransferase 2D.

biotin-labeled secondary antibody at room temperature for 1 h and washed with PBS. DAB kit (Zhong Shan-Golden Bridge Co., Ltd., Beijing, China) was used for color rendering. After washing with distilled water, the nuclei were stained with hematoxylin (Solarbio Co., Ltd., Beijing, China), then dehydrated, cleared and sealed, and the staining results were observed and photographed under an optical microscope (Olympus, Japan).

The staining results were double-blindly read by two or more professionals from the pathology department. The positive cell rate 0-5%, 6-25%, 26-50%, 51-75% and 7%-100% were recorded as 0, 1, 2, 3 and 4 points, respectively. For cell staining intensity, no staining or unclear staining, pale yellow, brownish yellow and tan were recorded as 0, 1, 2 and 3 points, respectively. The product of the positive cell rate and the cell staining intensity scores were used as the final criterion: a score of 0 to 2 was defined as negative expression of KMT2D protein, and a score of 3 and above as positive expression of KMT2D protein.

Follow-up

The 126 patients were followed up after surgery for 5 years (60 months) by outpatient visit or telephone call, and the OS and PFS of the patients were recorded. OS refers to the time from surgery to death or the end of follow-up. PFS refers to the time from surgery to the first tumor progression or death or the end of follow-up.

Statistical analysis

Data were analyzed by SPSS 25.0 software. The KMT2D mRNA expression level was measurement data meeting normal distribution, which were expressed as mean ± standard deviation ($\bar{x}$ ± sd), and processed by paired *t* test. The count data such as age and sex were represented by *n* (%), and processed by χ^2 test. Kaplan-Meier curve was used to analyze the relationship between KMT2D protein expression in gastric cancer tissue and the prognosis of patients. Receiver operating characteristic (ROC) curve was used to analyze the predictive value of KMT2D mRNA and protein expressions on the prognosis and death of gastric cancer patients. Cox regression analysis was used to analyze the risk factors of death in gastric cancer patients. $P<0.05$ was considered statistically significant.

Results

General data of gastric cancer patients

General data of the patients were collected and analyzed. There were 86 cases with age ≥60 years and 40 cases with age <60 years, 71 males and 55 females, 47 cases with tumor maximum diameter ≥5 cm and 79 cases with tumor <5 cm, 70 cases with midgut type and 56 cases with diffuse type by Lauren classification, 75 cases with high-moderate differentiation and 51 cases with poor differentiation, 45 cases in TNM stage III-IV and 81 cases in stage I-II, 33 cases with depth of invasion T3-T4 and 93 cases with T1-T2, 54 cases with lymph node metastasis and 39 cases with distant metastasis, 72 cases with high serum carbohydrate antigen 19-9 (CA19-9) level (preoperative, >37 U/mL), and 85 cases with serum high carcinoembryonic antigen (CEA) level (preoperative, >5.0 ng/mL).

KMT2D mRNA and protein expression in gastric cancer tissue

The results of qRT-PCR showed that the expression level of KMT2D mRNA in gastric cancer tissue was significantly higher than that in paracancerous tissue ($P<0.05$) (**Table 1**). Immunohistochemical results showed that KMT2D was expressed in both cytoplasm and nucleus, but was mainly in the nucleus (**Figure 1**). Statistical analysis showed that the positive rate of

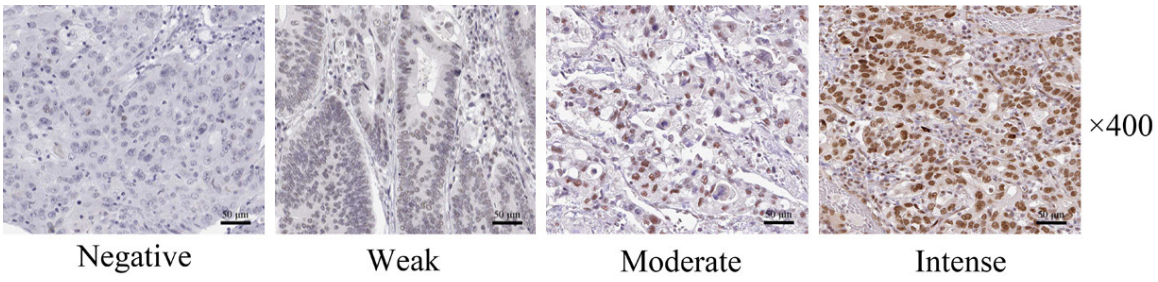

Figure 1. KMT2D protein expression in gastric cancer tissues (immunohistochemistry, scale bar =50 μm, × 400).

KMT2D protein expression in gastric cancer tissue was higher than that in paracancerous tissue (P<0.05) (**Table 1**).

The relationship between KMT2D protein expression in gastric cancer tissue and clinicopathological characteristics of patients

According to the expression of KMT2D protein, 126 gastric cancer patients were divided into 85 cases with KMT2D positive expression and 41 cases with KMT2D negative expression. The results of χ^2 test analysis showed that the positive expression of KMT2D protein in gastric cancer tissue was significantly correlated with age ≥60 years, tumor poor differentiation, TNM stage III-IV, depth of invasion T3-T4, lymph node metastasis, distant metastasis and high serum CA19-9 level (P<0.05), but it was not related to sex, tumor maximum diameter, Lauren type and serum CEA (P>0.05) (**Table 2**).

The relationship between expression of KMT2D protein in gastric cancer and prognosis and survival

The 126 gastric cancer patients were followed up for 4-60 months without loss to follow-up. The 5-year OS was 48.41% (61/126), and the 5-year PFS was 37.30% (47/126). Kaplan-Meier curve analysis showed that the 5-year OS of the patients with positive KMT2D expression (37.65%, 32/85) was significantly lower than that in those with negative KMT2D expression (70.73%, 29/41) (χ^2=10.515, P=0.001), and the 5-year PFS of the patients with positive KMT2D expression (29.41%, 25/85) was also significantly lower than that in those with negative KMT2D expression (53.66%, 22/41) (χ^2=6.527, P=0.011) (**Figure 2**).

Predictive value of KMT2D mRNA and protein expressions for prognosis and death in gastric cancer patients

The ROC curve was drawn with KMT2D mRNA expression level and KMT2D protein positive/negative expression in gastric cancer tissues as test variables, and whether gastric cancer patients died within 5 years as state variable. The results showed that the areas under curve (AUCs) of KMT2D mRNA and protein expressions for predicting the prognosis and death of gastric cancer patients were 0.823 (0.745-0.885) and 0.645 (0.555-0.729), with Youden index of 0.583 and 0.291, sensitivity of 86.15% and 81.54%, and specificity of 72.13% and 47.54%, respectively, and the corresponding critical value of KMT2D mRNA expression was 1.48, indicating that KMT2D mRNA and protein expressions had certain predictive value for the prognosis of gastric cancer patients (**Figure 3**).

Analysis of risk factors affecting the prognosis and death of gastric cancer patients

Univariate and multivariate Cox regression analyses were performed with the clinicopathological characteristics and KMT2D mRNA and protein expressions as independent variables, and whether the gastric cancer patients died within 5 years as the dependent variable. It was found that TNM stage III-IV, lymph node metastasis, high serum CA19-9 level, KMT2D mRNA expression ≥1.48 and KMT2D protein positive expression were risk factors affecting the prognosis and death of gastric cancer patients (P<0.05) (**Table 3**).

Discussion

Gastric cancer, mainly caused by Helicobacter pylori infection, is one of the most common

Table 2. The relationship between KMT2D protein expression in gastric cancer tissue and clinicopathological characteristics of patients [n (%)]

Clinicopathological characteristics	*n*	KMT2D		χ^2	P
		Positive expression (*n*=85)	Negative expression (*n*=41)		
Age (years)				5.975	0.015
≥60	86	64 (75.29)	22 (53.66)		
<60	40	21 (24.71)	19 (46.34)		
Sex				0.118	0.731
Male	71	47 (55.29)	24 (58.54)		
Female	55	38 (44.71)	17 (41.46)		
Tumor maximum diameter (cm)				2.850	0.091
≥5	47	36 (42.35)	11 (26.83)		
<5	79	49 (57.65)	30 (73.17)		
Lauren type				2.610	0.106
Diffuse type	56	42 (49.41)	14 (34.15)		
Intestinal type	70	43 (50.59)	27 (65.85)		
Differentiation				16.846	<0.001
High-moderate differentiation	75	40 (47.06)	35 (85.37)		
Poor differentiation	51	45 (52.94)	6 (14.63)		
TNM stage				6.949	0.008
Stage I-II	81	48 (56.47)	33 (80.49)		
Stage III-IV	45	37 (43.53)	8 (19.51)		
Infiltration depth				8.492	0.004
T1-T2	93	56 (65.88)	37 (90.24)		
T3-T4	33	29 (34.12)	4 (9.76)		
Lymph node metastasis				10.846	0.001
No	72	40 (47.06)	32 (78.05)		
Yes	54	45 (52.94)	9 (21.95)		
Distant metastasis				10.005	0.002
No	87	51 (60.00)	36 (87.80)		
Yes	39	34 (40.00)	5 (12.20)		
Serum CA19-9				13.124	<0.001
Low level	54	27 (31.76)	27 (65.85)		
High level	72	58 (68.24)	14 (34.15)		
Serum CEA				1.839	0.175
Low level	41	31 (36.47)	10 (24.39)		
High level	85	54 (63.53)	31 (75.61)		

CA19-9: Carbohydrate Antigen 19-9; KMT2D: Histone Lysine N-Methyltransferase 2D; CEA: Carcinoembryonic Antigen.

malignant tumors in the digestive system and a major contributor to global cancer morbidity and mortality, usually with a poor prognosis [11]. Reducing the mortality and improving the life quality of gastric cancer patients have been the direction of clinicians and researchers. Most gastric cancer patients benefit from surgery and chemoradiotherapy. In recent years, targeted therapy has also achieved remarkable results in clinical trials on patients with locally advanced or metastatic disease [12]. With the rise of molecular biotechnology, some gastric cancer biomarkers that can be used to diagnose, predict treatment sensitivity and prognosis have been reported and used as therapeutic targets for antitumor drugs [13]. Therefore, it is of great significance to understand the molecular mechanism of gastric cancer occur-

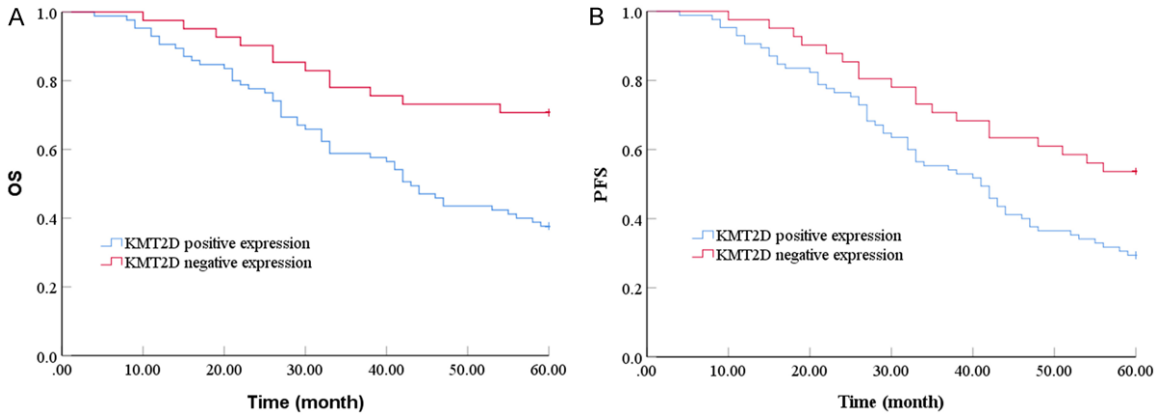

Figure 2. Relationship between expression of KMT2D protein in gastric cancer tissue and 5-year OS and PFS of patients. A. Relationship between expression of KMT2D protein and 5-year OS of patients; B. Relationship between expression of KMT2D protein and 5-year PFS of patients. OS: Overall Survival; KMT2D: Histone Lysine N-Methyltransferase 2D; PFS: Progression-Free Survival.

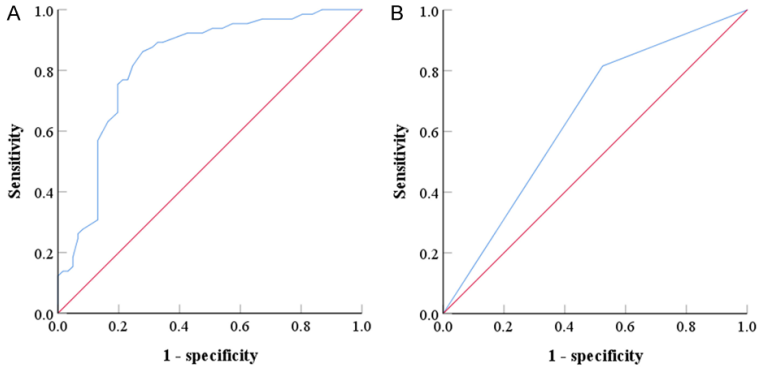

Figure 3. ROC curve of KMT2D mRNA and protein expressions predicting the prognosis and death of gastric cancer patients. A. ROC curve of KMT2D mRNA expression predicting the prognosis and death; B. ROC curve of KMT2D protein expression predicting the prognosis and death. KMT2D: Histone Lysine N-Methyltransferase 2D; ROC: Receiver Operating Characteristic.

rence and development and find reliable molecular targets for the diagnosis and prognosis evaluation of gastric cancer.

It is known that the occurrence of gastric cancer, colorectal cancer and other cancers is related to somatic cell mutations [14, 15]. Studies have shown that about 47.1% of Chinese gastric cancer patients carry at least one operable mutation, among which TP53, ERBB2, CDH1 and KMT2D genes are the most common somatic mutations [16], and KMT2D is the most common mutant gene in histone modification genes [17]. In this study, it was found by qRT-PCR and immunohistochemical detection that the mRNA expression level and positive rate of KMT2D protein expression were higher in gastric cancer tissue than those in paracancerous tissue, suggesting that the high expression of KMT2D may play a role in promoting gastric cancer, which is consistent with the results of Li et al. [10]. In addition, it has been confirmed that KMT2D expression increased in patients with a history of bladder cancer, and pathogenicity KMT2D variants are mainly seen in patients with non-pelvic or multifocal tumors [18]. Targeted inhibition of KMT2D significantly inhibited the migration of prostate cancer cells [19]. Other studies have shown that KMT2D, as an epigenetic regulator, has a low expression in bladder cancer tissue and cells, is related to tumor stage and lymph node metastasis, and has an anti-tumor effect [20]. The specific deletion of KMT2D in the lung promotes lung tumorigenesis in mice and upregulates tumorigenic pathways, including glycolysis [21]. These results suggest that KMT2D may have different functions and biological effects in different cancers. In this study, we further analyzed the relationship between the expression of KMT2D protein and the clinicopathological characteristics of gastric cancer patients, and the results showed that positive expression of KMT2D protein in gastric cancer

Table 3. Cox regression analysis of risk factors for prognosis and death in gastric cancer patients

Independent variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P*	HR	95% CI	P
Age (≥60 years *vs.* <60 years)	3.215	0.841-12.286	0.088	-	-	-
Sex (Male *vs.* Female)	2.046	0.744-5.625	0.165	-	-	-
Tumor maximum diameter (≥5 cm *vs.* <5 cm)	5.184	1.523-17.647	0.008	6.578	2.928-14.779	<0.001
Lauren type (Intestinal type *vs.* Diffuse type)	2.163	0.768-6.088	0.144	-	-	-
Differentiation (High-moderate differentiation *vs.* Poor differentiation)	0.421	0.211-0.839	0.014	0.376	0.222-0.636	<0.001
TNM stage (Stage III-IV *vs.* Stage I-II)	6.137	3.220-11.695	<0.001	6.864	3.031-15.543	<0.001
Infiltration depth (T3-T4 *vs.* T1-T2)	3.472	0.817-14.750	0.092	-	-	-
Lymph node metastasis (Yes *vs.* No)	5.238	2.551-10.754	<0.001	4.569	2.034-10.265	<0.001
Distant metastasis (Yes *vs.* No)	2.564	0.983-6.686	0.054	-	-	-
Serum CA19-9 (High level *vs.* Low level)	5.139	1.556-18.178	0.008	4.985	1.743-14.253	0.003
Serum CEA (High level *vs.* Low level)	3.012	0.987-9.188	0.053	-	-	-
KMT2D mRNA (≥1.48 *vs.* <1.48)	3.538	2.197-5.696	0.001	4.123	2.072-8.203	<0.001
KMT2D protein (positive *vs.* negative)	6.348	2.089-19.288	0.001	6.956	2.084-23.220	0.002

HR: Hazard Ratio; CEA: Carcinoembryonic Antigen; KMT2D: Histone Lysine N-Methyltransferase 2D; CA19-9: Carbohydrate Antigen 19-9.

tissue was related to patients' age ≥60 years, poor differentiation, TNM stage III-IV, lymph node metastasis, depth of invasion T3-T4, distant metastasis and high serum CA19-9 level, suggesting that KMT2D may play an important regulatory role in the occurrence and malignant progression of gastric cancer. The expression of KMT2D was also related to the age of patients, which may be due to the low immunity and anti-tumor ability of elder patients.

It has been reported that the expression of KMT2D is heterogeneous in different cancers. Patients with high expression of KMT2D in adrenocortical carcinoma, brain low-grade glioma and mesothelioma have a poor prognosis, while patients with high expression of KMT2D in renal clear cell carcinoma have a good prognosis [22]. In this study, the 5-year OS and PFS of gastric cancer patients with KMT2D positive expression were lower than those with KMT2D negative expression, indicating that high expression of KMT2D in gastric cancer tissue can indicate a higher probability of disease progression or death, which is consistent with the study of Xiong et al. [23], who found that the overexpression of KMT2D in gastric cancer tissue was closely related to poor survival rate. In addition, the AUCs of KMT2D mRNA and protein expressions for predicting the prognosis of gastric cancer patients were 0.823 and 0.645, respectively, indicating that KMT2D detection at a gene or protein level has a certain predictive value for the prognosis and death of gastric cancer patients. In addition, qRT-PCR may be more sensitive for detecting gene expression, so the predictive value of KMT2D mRNA expression level was higher. These results indicate that KMT2D is expected to be used as a potential predictor for the prognosis of gastric cancer.

Cox regression analysis showed that the tumor maximum diameter >5 cm, poor differentiation, TNM stage III-IV, lymph node metastasis, high serum CA19-9 level, expression of KMT2D mRNA ≥1.48 and positive expression of KMT2D protein were the risk factors for poor prognosis and death of gastric cancer patients, which further confirmed the role of KMT2D in the prognosis of gastric cancer patients. A few studies [4, 24-26] have pointed out that the elevated levels of serum tumor markers such as CEA and CA19-9 are helpful for determining the prognosis of patients with gastric cancer, especially CA19-9, which can be used as an important prognostic marker for patients with stomach cancer.

Based on the above results, the possible mechanism of KMT2D in gastric cancer is speculated as follows. Under the action of unfavorable external environmental conditions or internal biological factors, somatic mutations in gastric tissues lead to the increase of KMT2D expression level, and the high expression of KMT2D regulates relevant signal transduction or affects tumor immune surveillance, and then promotes the proliferation, invasion and tumorigenesis of gastric cancer cells and inhibits

apoptosis and other biological processes, resulting in malignant progression of tumors, poor prognosis and death [10, 23, 27].

However, the clinical sample number included in this study was small and only from one hospital, which may lead to biased research results. So, the findings need to be further verified by large sample size and multi center research. In addition, the specific mechanism of KMT2D in gastric cancer needs to be verified by basic experimental research (in vitro cell experiment, in vivo animal experiment), so as to provide more evidence supporting KMT2D as a prognostic biomarker for gastric cancer. Although this study has some limitations, it provides novel ideas and insights for the prognosis evaluation of gastric cancer.

In conclusion, KMT2D is highly expressed in gastric cancer patients, and closely related to the clinicopathological characteristics and poor prognosis of patients. KMT2D is expected to become a potential biomarker to predict the prognosis of gastric cancer.

Disclosure of conflict of interest

None.

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