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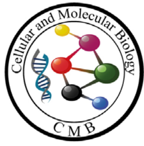

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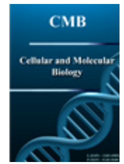

Original Article

Diagnostic efficacy of SEPT9 and PAX5 gene methylation in gastrointestinal cancer and precancerous lesions

Zhong Yan, Hongdao Liu*, Kun Wang

Department of Gastroenterology, Huai'an Huai'an Hospital, Huai'an, Jiangsu 223200, China

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Abstract

To assess the diagnostic efficacy of SEPT9 along with PAX5 gene methylation detection in gastrointestinal cancer and precancerous lesions, the peripheral blood of 62 patients with gastric cancer (GC) and 60 patients with no evidence of disease (as the control group) were retrospectively collected. The methylation rates of PAX5 and SEPT9 gene promoters in blood samples of GC group were detected by PCR. At the same time, the differences in methylation rates of genes in the two groups were compared, and the predictive value of plasma methylation PAX5 and SEPT9 in GC was evaluated by receiver operating characteristic (ROC) curve. We found that there were 41 cases of methylated PAX5 gene promoter region and 39 cases of methylated SEPT9 gene promoter region in GC group. The control group contained 14 cases of PAX5 gene promoter methylation and 12 cases of RNF[1]80 gene promoter methylation. The occurrence of PAX5 promoter methylation was correlated with age of GC patients. There were statistically significant differences in mSEPT9 gene in patients with different TNM stages. Kaplan-Meier survival curve analysis revealed that the three-year overall survival rate of GC patients with PAX5 methylation was lower than that of GC patients without PAX5 methylation. No significant difference was discovered in 3-year overall survival rate between GC patients with SEPT9 methylation and those without SEPT9 methylation. Combined detection could not improve the diagnostic value of GC, but could promote diagnosis sensitivity. In summary, the risk of PAX5 and SEPT9 gene methylation in GC patients presents higher when compared with healthy people. PAX5 gene methylation is closely related to age, while SEPT9 is closely related to tumor TNM stage, and PAX5 gene methylation can decrease the survival rate of GC patients. Detection of PAX5 gene methylation level can assist in evaluating the prognosis of GC patients.

Keywords: Diagnostic efficiency, Gastric cancer, Gene methylation, PAX5, SEPT9.

1. Introduction

Gastric cancer (GC) is one of the most common malignant tumors. Epidemiological research data show that the incidence of GC ranks fifth among all malignant tumors, but its mortality rate is relatively higher, ranking third [1]. At present, the gold standard for the diagnosis of GC is the pathological results of endoscopic biopsy, but this method is technically complex and has poor compliance, especially for asymptomatic individuals. Clinically, tumor markers used for prognostic indicators of GC mainly include carcinoembryonic antigen (CEA), CA19-9 and CA72-4. The sensitivity of single diagnosis of GC is 20.1%-27.6%, and the sensitivity of combined detection is 48.2% [2]. These detection methods are either technically complex, or have low sensitivity and specificity, so it is urgent to find simple, sensitive and efficient detection methods. Relevant studies have shown that the major risk factors for GC contain long-term consumption of pickled products and H. pylori infection [3, 4]. Paired box protein 5 (PAX5) is widely found in embryo and adult tissues, and is down-regulated in esophageal and breast cancer tissues, showing diverse biological functions [5, 6]. SEPTIN9 (SEPT9) gene is a tumor suppressor gene. When it is methylated, its gene expression is inhibited, which can cause abnormal cell division and even cancer. Studies have confirmed that [7, 8] mSEPT9 is closely linked to the development of human colorectal cancer, liver cancer, stomach cancer, breast cancer and other malignant tumors. Studies have found that SEPT9 and PAX5 genes are abnormally expressed in GC tissues, but the situation of mSEPT9 and mPAX5 in peripheral blood of GC patients is not clear. This study further analyzed the clinicopathological parameters of mSEPT9 and mPAX5 and patients with gastric cancer by comparing the methylation of mSEPT9 and mPAX5 in GC patients and healthy people in our hospital, in order to provide a basis for the potential pathogenic mechanism and further clinical application of mSEPT9 and mPAX5.

2. Materials and methods

2.1. Research object

All cases of detection of mSEPT9 and mPAX5 in peripheral blood of our hospital from January 2021 to September 2023 were retrospectively gathered. 62 GC patients were screened, including 48 males and 14 females. GC

* Corresponding author.
E-mail address: liuhongdao1973@163.com (H. Liu).
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group: 1) GC was confirmed by histopathology and met the diagnostic criteria of Chinese Clinical Oncology Society (CSCO) Primary Gastric Cancer Diagnosis and Treatment Guidelines; 2) None of the patients received radiotherapy or chemotherapy before enrollment; 3) Patients with other tumors, gastrointestinal diseases, pregnancy and immune deficiency were excluded. Another 60 patients with no evidence of disease were used as controls, including 24 males and 36 females. Meanwhile, relevant clinical data of all included cases were collected. Telephone clinical follow-up was implemented for all GC patients, and the survival time, survival state, cause of death and other information of the patients were recorded. The total survival was defined as the date of diagnosis to the date of death or the date of last follow-up. The primary endpoint of the study was tumor-related survival, and follow-up ended November 30, 2023.

2.2. Instruments and reagents

mSEPT9 and mPAX5 detection kit (PCR fluorescence quantification, Beijing Bocheng Technology Company), ultraviolet spectrophotometer (Thermo Fisher NanoDrop One, USA), real-time fluorescence quantitative PCR instrument (ABI7500, FAST USA).

2.3. Specimen collection

The samples of patients without evidence of disease were collected during physical examination, and the samples of the GC group were gathered on the first day of hospitalization. 10 mL of fasting (fasting for 8-12 h) venous blood was collected from the subjects in the morning, EDTA-K2 anticoagulant was centrifuged (1350±150) × g for 12 min, repeated once, and 3.5 mL of plasma was obtained and placed at 20°C for use and unified detection.

2.4. Detection of mSEPT9 in peripheral blood

All tests were performed in the hospital's molecular pathology laboratory. Refer to the kit instructions. Cracking, magnetic bead enrichment of DNA, washing, elution, and sulfite transformation were implemented successively. The sequence of methylated SEPT9 gene primers has been shown in Table 1. The transformed DNA was added to the PCR pre-reaction solution and activated at 94°C for 20 min. 45 cycles were performed at 62°C for 5s, 55.5°C for 35 s, 93°C for 30 s. Results judgement: Under the premise of ensuring the validity of the control sample, the CT value of the internal reference gene (β-actin) was less than 32, and the CT value of the sample to be tested was less than 41.0, which was considered positive. CT value >41.0 or no time results were negative. Positive and negative controls were set up in each experiment, and the treatment methods and procedures of positive/negative controls were the same as those of the samples to be tested.

2.5. Detection of mPAX5 in peripheral blood

2 μL was selected to be modified with bisulfite, followed the instructions strictly, and 30 μL EB was used to redissolve the modified DNA for methylation-specific PCR detection. The primer sequence of methylated PAX5 gene was shown in Table 1. Reaction system: DNA 1 μL, Taq enzyme 12.5 μL, MSP upstream primer 0.5 μL, MSP downstream primer 0.5 μL, ultra-pure water 10.5 μL, a total of 25 μL. Reaction conditions: 95°C for 10 min, 95°C for 1 min, 55°C for 30 s, 72°C for 30 s, 40 cycles. After PCR amplification, the amplified products were subjected to 2.5% agarose gel electrophoresis, monitored by UV detector and photographed.

2.6. Detection of digestive tract tumor markers

Serologic tumor markers CEA, CA199 and AFP were all detected by electroluminescence (electrochemical luminescence apparatus) in the hospital laboratory. Interpretation criteria: CEA reference range was 0 ~ 6.5 ng/mL, AFP reference range was 0 ~ 9 ng/mL, and CA199 reference range was 0 ~ 34 U/mL.

2.7. Statistical method

SPSS 24.0 and GraphPad Prism 8.0 were used for statistical analysis. The counting data were expressed as cases (n) and percentage (%), and the χ^2 test or Fisher exact probability method was used for comparison between groups. The diagnostic value of mSEPT9 in peripheral blood was predicted by calculating the area under curve (AUC) of ROC. Kappa test (Kappa ≥0.75) was used to test the consistency of matched data, indicating that the two methods had good consistency in diagnosis, while Kappa<0.4 had poor consistency. Survival analysis was performed by Kaplan-Meier method, and risk ratio was performed by Cox regression model (log-rank test). P<0.05 was considered statistically significant.

3. Results

3.1. Methylation rates of plasma PAX5 and SEPTI9 genes in 2 groups

In GC group, there were 41 cases of methylated PAX5 gene promoter region and 39 cases of methylated SEPT9

Table 1. Gene primer sequences.

Gene	Primer sequence (5'→3')	Product size (bp)
PAX5 (F)	Upstream TATCATAATAAATTATTTACGAATA	333
	Downstream TGGTTGCCGACCACATCCCAGAACC	
PAX5 (M)	Upstream AAATAAAAATTCGGTTTGCGTTC	220
	Downstream AAACATACGCTTAAAAATCGCG	
PAX5 (U)	Upstream TAAAAATAAAAATTTGGTTTGTGTTT	230
	Downstream TTAAAACATACACTTAAAAATCACA	
SEPT9 (F)	Upstream GGTTAGTTTTGTATTGTAGGAG	384
	Downstream AATACCCCTAACAAAATCCCC	
SEPT9 (M)	Upstream TATTAGTTATTATGTCGGATTTCGC	198
	Downstream GCCTAAATTAAAAATCCCGTC	
SEPT9 (U)	Upstream ATTAGTTATTATGTTGGATTTTGTGG	202

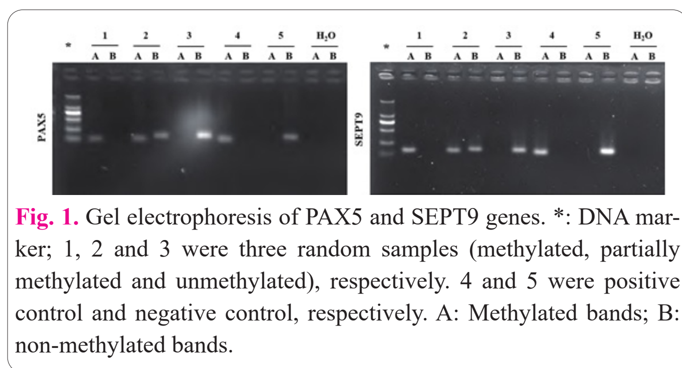

Fig. 1. Gel electrophoresis of PAX5 and SEPT9 genes. *: DNA marker; 1, 2 and 3 were three random samples (methylated, partially methylated and unmethylated), respectively. 4 and 5 were positive control and negative control, respectively. A: Methylated bands; B: non-methylated bands.

gene promoter region. The control group contained 14 cases of PAX5 gene promoter methylation and 12 cases of RNF[1]80 gene promoter methylation. The methylation rate of PAX5 and SEPT9 gene promoter region in GC group was higher when compared with control group (χ^2=20.394, P<0.001; χ^2=14.764, P<0.001). The electrophoretic methylation of PAX5 and SEPT9 genes in plasma of GC patients is shown in Fig. 1.

3.2. Relationship between promoter methylation of two genes and clinicopathological parameters of GC

The occurrence of PAX5 promoter methylation was correlated with age of GC patients (P<0.05), but not with gender, tumor size, TNM stage along lymph node metastasis. There were significant differences in mSEPT9 gene in patients with different TNM stages (P<0.05), but there were no differences in age, sex, lymph node metastasis, pathological classification, differentiation degree, depth of invasion, etc. (P>0.05), as displayed in Table 2.

3.3. Relationship between plasma methylation of PAX5 and SEPT9 genes and prognosis in GC patients

All 62 GC patients were followed up successfully, and no cases were lost to follow-up. After 32 months of follow-up, 14 cases died. Kaplan-Meier survival curve analysis displayed that the 3-year overall survival rate of GC patients with PAX5 methylation (75.61%, 31/41) was lower than that of GC patients without PAX5 methylation (90.48%, 19/21) (χ2=3.626, P=0.028). No significant difference was discovered in 3-year overall survival rate between GC patients with SEPT9 methylation (64.10%, 25/39) and those without SEPT9 methylation (65.22%, 15/23) (χ2=2.824, P=0.718), as revealed in Figures 2 and 3.

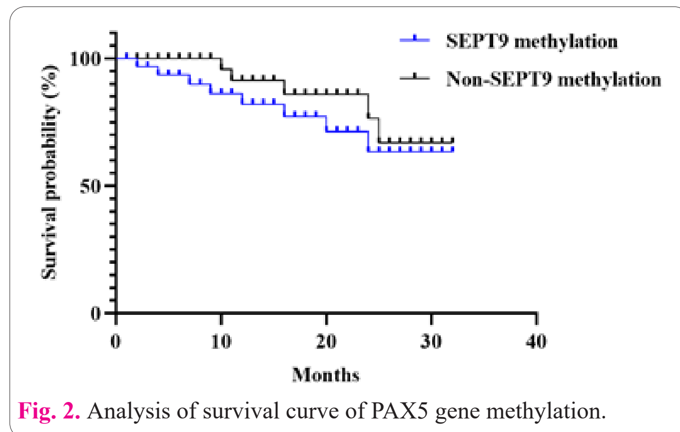

Fig. 2. Analysis of survival curve of PAX5 gene methylation.

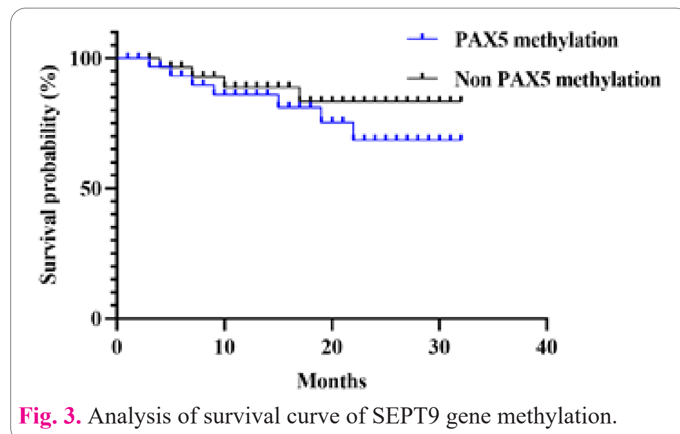

Fig. 3. Analysis of survival curve of SEPT9 gene methylation.

Table 2. Relationship between promoter methylation of two genes and clinicopathological parameters of GC.

		PAX5 gene methylation (n=41)			SEPT9 gene methylation (n=39)		
Items	N		χ^2	P		χ^2	P
Age			6.732	0.001		1.931	0.126
<55 years	29	14 (48.28)			17 (58.62)		
≥55 years	33	27 (81.82)			21 (63.64)		
Gender			1.239	0.737		1.132	0.268
Male	39	25 (64.10)			24 (61.54)		
Female	23	16 (69.56)			15 (65.22)		
Diameter of tumor			2.120	0.145		2.986	0.084
<2.5 cm	32	22 (68.75)			21 (65.63)		
≥2.5 cm	30	19 (63.33)			18 (60.00)		
Differentiation degree			1.651	0.187		0.298	0.585
Low-medium differentiation	38	23 (60.52)			21 (55.26)		
High differentiation	33	19 (57.58)			18 (54.55)		
TNM stage			1.072	0.839		4.866	0.015
Stage I-II	46	30 (65.22)			27 (58.69)		
Stage -N	16	11 (68.75)			12 (75.00)		
Lymph node metastasis			3.152	0.078		0.941	0.901
Yes	25	18 (72.00)			16 (64.00)		
No	37	24 (64.86)			23 (62.16)		

3.4. Comparison of the positive rates of PAX5 and SEPT9 in peripheral blood and serum tumor markers CEA, CA199 and AFP in GC

In the GC group, the positive rates of mSEPT9 and mPAX5 in peripheral blood were higher than those of CEA, CA199 and AFP (Kappa value <0.4), as shown in Table 3 and Fig. 4. Combined with peripheral blood PAX5, SEPT9, CEA, CA199 and AFP, ROC curve analysis showed that combined indexes could not improve the diagnostic value of GC (P>0.05). However, combined detection could promote the sensitivity of GC diagnosis.

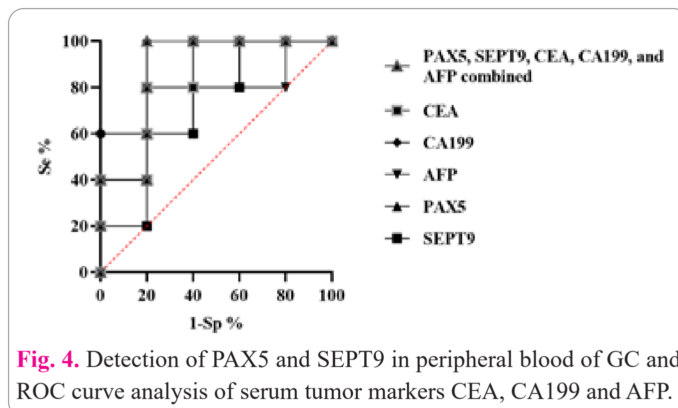

Fig. 4. Detection of PAX5 and SEPT9 in peripheral blood of GC and ROC curve analysis of serum tumor markers CEA, CA199 and AFP.

4. Discussion

GC, as a digestive system tumor, mostly originates from gastric mucosal epithelium. Since symptoms are not obvious in the early stage, most patients have progressed to the middle and advanced stages when diagnosed, and surgical resection is often used in clinical treatment. However, patients in the advanced stage are affected by various factors such as blood and lymph node metastasis, and the prognosis is relatively poor. Therefore, accurate diagnosis and reasonable treatment at an early stage are very important, and exploring the molecular mechanism of the development of GC is beneficial to improving the quality of its prognosis [9].

PAX5 is located in chromosome 9p13, has a biological role in the metabolic process of the body, such as regulating the differentiation and proliferation of tissue cells and participating in organ development, and is widely expressed in normal epithelial tissues and tumor tissues [10, 11]. Relevant studies have unveiled that hypermethylation of PAX5 promoter in patients with liver cancer can cause gene silencing [5]. Other studies have displayed that PAX5 exerts a tumor repressor role in the progression of GC, and its promoter methylation directly affects the survival of GC patients [12]. In this study, the methylation rate of PAX5 gene promoter region in the GC group presented higher when compared with the control group, implying that the risk of plasma PAX5 gene methylation in GC patients presented higher than that in healthy people, and the methylation of the PAX5 gene promoter region was implicated in the development of GC. PAX5 can effectively inhibit the transmission of β-Canal-Nin signal in the Wnt signaling pathway, and can also effectively downregulate the expression levels of human myeloid proliferative oncogene and cyclin D1, delaying the progression of tumor cells to the S phase and inhibiting proliferation. Methylation of PAX5 gene promoter region can restrict its biological function, accelerate the growth of tumor cells and inhibit apoptosis, further promote cell proliferation and differentiation, and accelerate the progression of GC. Meanwhile, it can also weaken the anti-tumor efficacy of PAX5, resulting in the downregulation of tumor suppressor genes P21 and P53, and promote the proliferation of tumor cells. Moreover, the expression of matrix metalloproteinase and B-cell lymphoma/leukemia-2 gene is upregulated, which increases the malignant degree [11].

The SEPT9 gene is presented on human chromosome 17q25.3 and contains 17 exons with a length of about 24×103 bp. SEPT9 takes part in many biological processes, including cytoplasmic division, polarization, vesicle transport, membrane reconstitution, DNA repair, cell migration and apoptosis, and exerts a crucial function in the development of malignant tumors. The alteration of SEPT9 expression can lead to cancer, including colorectal cancer, breast cancer, ovarian cancer, hematological system tumors, head and neck squamous cell carcinoma, stomach cancer, lung cancer, prostate cancer, etc. SEPT9 gene is tissue-specific and its transcriptional products can be spliced, and the transcriptional expression pattern is different in different tumors, which can be reduced expression, overexpression, or fusion gene generation, and finally lead to the expression imbalance of SEPT9 subtypes. For example, in colon cancer, SEPT9v2 is mainly highly methylated [13]. SEPT9v1 and v4* are highly expressed in ovarian cancer epithelium [14] and SEPT9v1 is highly expressed and v2 is low in breast cancer [15]. In this study, the incidence of methylation in the promoter region of SEPT9 gene in the GC group presented higher than that in the control group, and the incidence of methylation in patients with stage I to II in the GC group presented lower than that in patients with stage III to IV. These findings suggested that the risk of plasma SEPT9 gene methylation in GC patients presented higher than that in healthy people, which was closely related to TNM stage, and the methylation of SEPT9 gene promoter region was involved in the development of GC. SEPT9 can up-regulate the expression of CDKN2A and tissue inhibitor of matrix metalloproteinase 3, which can accelerate the apoptosis of tumor cells and repress the growth of tumors. Methylation

Table 3. Diagnostic efficacy of PAX5 and SEPT9 in peripheral blood and serum tumor markers CEA, CA199 and AFP in the diagnosis of primary GC.

Gene	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	Youden index	AUC (95% CI)
AFP	46.91 (35.7~58.3	94.87 (82.7~99.4	0.418	0.709 (0.644~0.774)
PAX5	38.27 (27.7~49.7)	92.31 (79.1~98.4)	0.306	0.653 (0.585~0.721)
SEPT9	34.57 (24.3~46.0)	89.74 (75.8~97.1)	0.243	0.622 (0.551~0.693)
CEA	55.56 (44.1~66.6)	89.74 (75.8~97.1	0.453	0.726 (0.638~0.804)
CA199	56.79 (45.3~67.8)	87.18 (72.6~95.7)	0.440	0.720 (0.631~0.798)
Combined	61.73 (50.3~72.3)	84.62 (69.5~94.1)	0.463	0.732 (0.653~0.810)

of SEPT9 promoter region can lead to changes in SEPT9 gene structure and functional abnormalities, resulting in the decline or even complete loss of SEPT9's pro-apoptotic function, which cannot inhibit tumor proliferation, differentiation and metastasis [16]. In addition, in this study, the 3-year survival rate of GC patients without PAX5 gene methylation was significantly higher than that of patients with methylation, and no significant difference was discovered in 3-year survival rate between GC patients without SEPT9 methylation and those with methylation, implying that the poor prognosis of GC after operation was closely related to PAX5 gene methylation, which could be used to predict the prognosis of GC.

At present, the main diagnostic methods for GC are gastroscopy and serological indicators (common tumor markers, etc.). Gastroscopy is an invasive test, and patient compliance is poor, in addition, the accessibility of gastroscopy at the grass-roots level still cannot meet the needs. Commonly used tumor markers in digestive tract, such as CEA, CA199 and AFP, are also commonly used for clinically assisted diagnosis of GC, but their specificity and sensitivity are poor, making it difficult to achieve early and accurate diagnosis of GC [17]. Liquid biopsy is a rapidly developing means of detection in recent years. Its biggest advantage is that it is micro-invasive, and the detection purpose is achieved by collecting peripheral blood and separating free nucleic acids in plasma. The results of this study displayed that the diagnostic efficacy of mSEPT9 and mPAX5 presented higher than that of serological markers CEA, CA199 and AFP, but mSEPT9 and mPAX5 combined with CEA, CA199 and AFP or with any of them could not effectively improve the diagnostic efficacy, which was consistent with literature reports [18]. However, combined detection was beneficial to promote the sensitivity of GC diagnosis, suggesting that it may better meet the needs of clinical screening for GC, and it also suggested that the clinical could adopt appropriate combined detection items according to the patient's situation to improve the detection rate.

5. Conclusion

In summary, the risk of plasma PAX5 and SEPT9 gene methylation in GC patients was higher than that in healthy people. PAX5 is closely related to age, while SEPT9 is closely related to tumor TNM stage, and PAX5 gene methylation can decrease the survival rate of GC patients. Detecting the methylation level of PAX5 gene can assist in evaluating the prognosis of GC patients. However, due to the retrospective analysis method in this study, case selection is highly subjective, which may lead to information bias. Moreover, due to the small number of cases along with short observation time, the results need to be verified.

Conflict of Interests

The authors declare no competing interests.

Consent for publications

The author read and approved the final manuscript for publication.

Ethics approval and consent to participate

We have received approval from the Ethics Committee of Huai'an Huai'an Hospital.

Informed Consent

We have received informed consent from the Ethics Committee of Huai'an Huai'an Hospital.

Availability of data and material

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authors' contributions

LH contributed to the study conception and design. Data collection and analysis were performed by YZ. Experimental operation was performed by WK. The first draft of the manuscript was written by YZ and all authors commented on previous versions of the manuscript.

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