

Downregulation of long non-coding RNA LINC-PINT serves as a diagnostic and prognostic biomarker in patients with non-small cell lung cancer

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Abstract. Long non-coding RNAs (lncRNAs) play an important role in gene regulation. Several lncRNAs have been demonstrated to be associated with the diagnosis and prognosis of non-small cell lung cancer (NSCLC). The present study aimed to investigate the role of lncRNA long intragenic non-protein-coding RNA p53-induced transcript (LINC-PINT) in NSCLC to identify a novel non-invasive biomarker for the diagnosis and prognosis of patients with NSCLC. Reverse transcription-quantitative PCR analysis was performed to detect LINC-PINT expression in the tissue and serum samples of patients with NSCLC. The diagnostic and prognostic values of LINC-PINT were assessed via the receiver operating characteristic curve, and Kaplan-Meier and Cox regression analyses, respectively. The results demonstrated that LINC-PINT expression was significantly downregulated in NSCLC serum samples and tissues. In addition, serum LINC-PINT exhibited diagnostic value in patients with NSCLC, and may be used to predict prognosis. Furthermore, aberrant LINC-PINT expression in tumor tissues was significantly associated with lymph node metastasis, tumor size, differentiation and TNM stage. Taken together, the results of the present study suggest that lncRNA LINC-PINT may be an independent diagnostic and prognostic biomarker in NSCLC.

Introduction

Lung cancer is the most common cause of cancer-associated mortality worldwide (1,2). The 10-year survival rate of patients following diagnosis across all stages of lung cancer is <7% (3).

Despite advancements in diagnosis, classification and therapy, the overall survival rate of patients with lung cancer remains poor (4). Non-small cell lung cancer (NSCLC) accounts for 85% of all lung cancers (5). Patients with advanced or metastatic NSCLC have poor survival outcomes, thus highlighting the need for more effective therapies (6). Although the diagnosis and treatment of NSCLC are continuously being improved, patient prognosis remains unfavorable (7). Currently, the 5-year overall survival rate is only 15% (8). Thus, it remains critical to identify novel effective biomarkers for accurate early diagnosis and improved prognosis of patients with NSCLC.

Long non-coding RNAs (lncRNAs) are a novel class of non-coding RNAs, usually defined as RNA molecules >200 nucleotides in length (9). lncRNAs function as major regulators for gene expression, and thus play key roles in several biological functions and disease processes, including cancer (10,11). The lncRNA, long intragenic non-protein-coding RNA p53-induced transcript (LINC-PINT), is abnormally expressed in several tumors, including gastric cancer, renal cell carcinoma and glioblastoma, and exhibits certain diagnostic and prognostic values (12-15). In NSCLC, LINC-PINT has been demonstrated to act as a tumor suppressor by sponging microRNA (miRNA/miR)-208a-3p and regulating programmed cell death 4 (PDCD4) (16). Wang *et al* (17) reported that LINC-PINT plays an important role in NSCLC by sponging miR-543 and inducing PTEN. However, the clinical value of LINC-PINT in the diagnosis and prognosis of NSCLC remains unclear.

Thus, the present study aimed to investigate the clinical significance of LINC-PINT in patients with NSCLC. The diagnostic and prognostic values of LINC-PINT were also assessed via the receiver operating characteristic (ROC) curve, and Kaplan-Meier and Cox regression analyses.

Materials and methods

Patients and tissue collection. A total of 122 patients who were pathologically diagnosed with NSCLC and received resection surgery between March 2011 and June 2014 in Zibo Central Hospital were enrolled in the present study. The patients included 53 women and 69 men with a mean age of 61.7±13.2 years (age range, 38-84 years old). All patients were included following the inclusion criteria: i) Tumor tissues

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were histopathologically diagnosed with NSCLC; ii) Cases had complete demographic and clinical data; iii) Cases signed informed consent for the use of clinical samples and data. In addition, the exclusion criteria for patient recruitment were as follows: i) Patients with a history of other types of cancer; ii) Cases aged <18 years; iii) Pregnant or lactating women; iv) Cases received preoperative antitumor therapy. In addition, 62 age (mean age, 60.8±13.8 years; age range, 37-82 years) and sex (25 women and 37 men) matched healthy individuals willing to participate in the present study during this period were enrolled to serve as controls. Blood samples were collected from all participants and immediately centrifuged at 1,500 x g for 10 min at 4°C for serum extraction.

NSCLC tissues and adjacent normal tissues (at least 3 cm from the edge of tumor) were extracted from the patients during resection surgery and frozen in liquid nitrogen at -80°C. Demographic and clinicopathological characteristics, and the 5-year follow-up survey (range, 0-60 months), monthly phone calls were made for each patient and collected survival information of the patients for subsequent analyses. Cases that died from external events were excluded. The present study was approved the Ethics Committee of Zibo Central Hospital (Zibo, China; approval no. ZCHh-110824), and written informed consent was provided by all participants prior to the study start.

Bioinformatics analysis based on The Cancer Genome Atlas (TCGA) database. LINC-PINT expression in NSCLC and its association with survival prognosis was assessed using the Gene Expression Profiling Interactive Analysis (GEPIA) database (<http://gepia.cancer-pku.cn/index.html>) (18), based on TCGA database (<https://cancergenome.nih.gov>).

Reverse transcription-quantitative (RT-q)PCR. Total RNA was extracted from fresh tissue and serum samples using the GenElute Total RNA Purification kit (Sigma-Aldrich; Merck KGaA; cat. no. RNB100). The concentration and quality were assessed using the NanoDrop 2000 (Thermo Fisher Scientific, Inc.), in which RNA with an absorbance ratio of optical density (OD) 260/OD 280 results close to 2.0 were used for subsequent RT. RT was performed using the Applied Biosystems High-Capacity cDNA Reverse Transcription kit (Thermo Fisher Scientific, Inc.; cat. no. 43-688-13), and the resulting cDNA was stored at -20°C. cDNA was subsequently used as the template for qPCR, which was performed using the SYBR-Green I Master Mix kit (Invitrogen; Thermo Fisher Scientific, Inc.; cat. no. 4334973) and the 7500 Real-Time PCR System (Applied Biosystems; Thermo Fisher Scientific, Inc.). The following thermocycling conditions were used: 95°C for 10 min, followed by 40 cycles of 95°C for 30 sec, 58°C for 20 sec and 72°C for 30 sec. The primer sequences were as follows: LINC-PINT forward, 5'-CGTGGGAGCCCCTTT AAGTT-3' and reverse, 5'-GGGAGGTGGCGTAGTTTC TC-3'; GAPDH forward 5'-CCTCTGACTTCAACAGCG ACAC-3' and reverse, 5'-TGGTCCAGGGGTCTTACTCC-3'. Relative expression levels were calculated using the 2^{-ΔΔCq} method (19) and normalized to the internal reference gene GAPDH. Each analysis was repeated at least three times.

Statistical analysis. Statistical analysis was performed using SPSS 21.0 software (IBM Corp.) and GraphPad 7.0 software

(GraphPad Software, Inc.). Data are presented as the mean ± standard deviation. Paired Student's t-test was used to compare the difference in LINC-PINT expression between NSCLC tissues and adjacent normal tissues, while unpaired Student's t-test was used to compare serum LINC-PINT expression between patients with NSCLC and healthy individuals, and perform expression analysis of LINC-PINT using the GEPIA database. The χ^2 test was used to assess the association between LINC-PINT expression and the clinicopathological characteristics of patients with NSCLC. ROC curves were used to determine the diagnostic value of LINC-PINT, while Kaplan-Meier and Cox regression analyses were performed to determine the prognostic value of LINC-PINT in NSCLC. P<0.05 was considered to indicate a statistically significant difference.

Results

LINC-PINT expression in NSCLC based on TCGA database. Data mining TCGA database using the GEPIA database demonstrated that LINC-PINT expression is significantly downregulated in NSCLC tissues compared with normal tissue (P<0.05; Fig. 1A). Kaplan-Meier survival analysis demonstrated that patients with low LINC-PINT expression had a shorter overall survival time than those with high LINC-PINT expression (Fig. 1B). In addition, the survival curve plotted by GEPIA demonstrated that low LINC-PINT expression was significantly associated with poor prognosis of patients with NSCLC (P=0.00084).

LINC-PINT expression in NSCLC. To further determine the role of LINC-PINT in NSCLC, RT-qPCR analysis was performed to detect LINC-PINT expression in NSCLC tissue and serum samples. The results demonstrated that serum LINC-PINT expression was significantly downregulated in patients with NSCLC compared with the healthy individuals (P<0.001; Fig. 2A). Similarly, LINC-PINT expression was significantly downregulated in NSCLC tissues compared with adjacent normal tissues (P<0.001; Fig. 2B). These experimental results are consistent with the analysis results from TCGA database.

Diagnostic value of serum LINC-PINT in patients with NSCLC. The diagnostic value of LINC-PINT in patients with NSCLC was assessed. A ROC curve was established (Fig. 3), which demonstrated that LINC-PINT had high diagnostic value, with an area under the curve (AUC) value of 0.873, sensitivity of 90.9% and specificity of 75.8%. The ideal cut-off value was 1.236.

Association between LINC-PINT expression and the clinicopathological characteristics of patients with NSCLC. As presented in Table I, LINC-PINT expression was significantly associated with lymph node metastasis (P=0.019), differentiation (P=0.028), tumor-node-metastasis (TNM) stage (20) (P=0.020) and tumor size (P=0.027). Conversely, no significant associations were observed between LINC-PINT expression and age, sex and smoking history (all P>0.05).

Prognostic value of LINC-PINT in patients with NSCLC. Due to the ectopic expression of LINC-PINT in NSCLC (16), its prognostic value in patients with NSCLC was assessed.

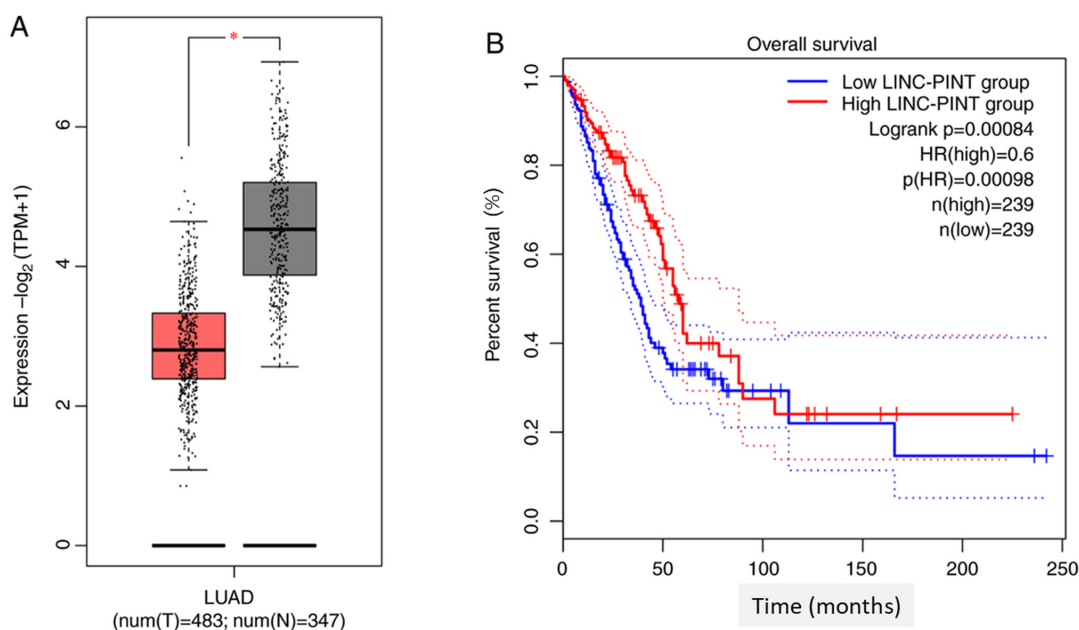


Figure 1. LINC-PINT expression in NSCLC based on The Cancer Genome Atlas database. (A) LINC-PINT expression in NSCLC tissues and normal tissues. (B) Survival analysis of patients with NSCLC, with different expression levels of LINC-PINT. * $P < 0.05$. LINC-PINT, long intragenic non-protein-coding RNA p53-induced transcript; NSCLC, non-small cell lung cancer; T, tumor; N, normal.

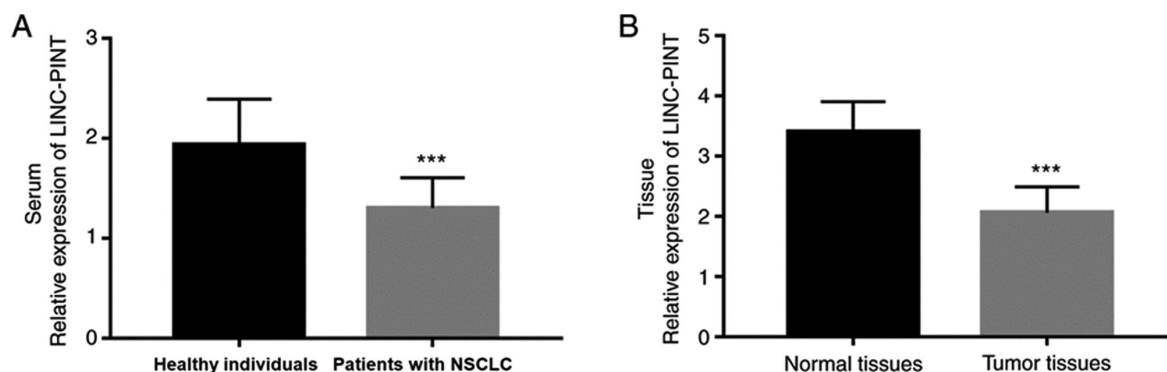


Figure 2. LINC-PINT expression in NSCLC. (A) Serum LINC-PINT expression was significantly downregulated in patients with NSCLC compared with the healthy individuals. (B) LINC-PINT expression was significantly downregulated in NSCLC tissues compared with adjacent normal tissues. *** $P < 0.001$. LINC-PINT, long intragenic non-protein-coding RNA p53-induced transcript; NSCLC, non-small cell lung cancer.

Kaplan-Meier survival analysis was performed to assess the association between LINC-PINT expression and overall survival of patients with NSCLC (Fig. 4). The results demonstrated that patients with high LINC-PINT expression had a significantly longer overall survival time than those with low LINC-PINT expression ($P = 0.002$). Furthermore, the univariate and multivariate Cox regression analysis demonstrated that LINC-PINT [hazard ratio (HR), 2.628; 95% confidence interval (CI), 1.589-4.348; $P < 0.001$] and TNM stage (HR, 1.810; 95% CI, 1.091-3.004; $P = 0.022$) were two independent prognostic factors for the survival of patients with NSCLC (Table II).

Discussion

Lung cancer is the most common malignant tumor worldwide, with the highest mortality rate (17,21). NSCLC is the main type of lung cancer, which accounts for ~85% of all

lung cancer cases (22), and ~30% of patients have metastatic disease at diagnosis (23). NSCLC has slower proliferation and division of cancer cells, and relatively late spread and metastasis compared with small cell carcinoma (24). Thus, despite advancements in treatment, the prognosis of patients with NSCLC remains poor, and the 5-year overall survival rate does not exceed 16% (25). Accurate biomarkers are useful in predicting the diagnosis and prognosis of different diseases, including NSCLC. Previous studies have proposed several biomarkers for NSCLC (26-28). Among these, lncRNAs offer a new direction and have attracted notable attention.

Several types of lncRNAs have been studied in NSCLC. For example, Zhang *et al* (29) demonstrated that lncRNA FENDRR inhibits the progression of NSCLC by binding to miR-761 and regulating TIMP2 expression. In addition, lncRNA FEZF1-AS1 can act as a tumor promoting regulator in NSCLC and may provide a target for the treatment of NSCLC (30). It has been demonstrated that MALAT1

Table I. Association between LINC-PINT expression and the clinicopathological characteristics of patients with non-small cell lung cancer (n=122).

Characteristic	Number of patients, n	LINC-PINT expression		P-value
		Low (n=64)	High (n=58)	
Age, years				0.961
≤60	46	24	22	
>60	76	40	36	
Sex				0.943
Female	53	28	25	
Male	69	36	33	
Smoking history				0.639
Never	52	26	26	
Ever	70	38	32	
Tumor size, cm				0.027
≤3	65	28	37	
>3	57	36	21	
Differentiation				0.028
Well/moderate	63	27	36	
Poor	59	37	22	
Lymph node metastasis				0.019
Negative	60	25	35	
Positive	62	39	23	
TNM stage				0.020
I-II	56	23	33	
III-IV	66	41	25	

TNM, tumor-node-metastasis.

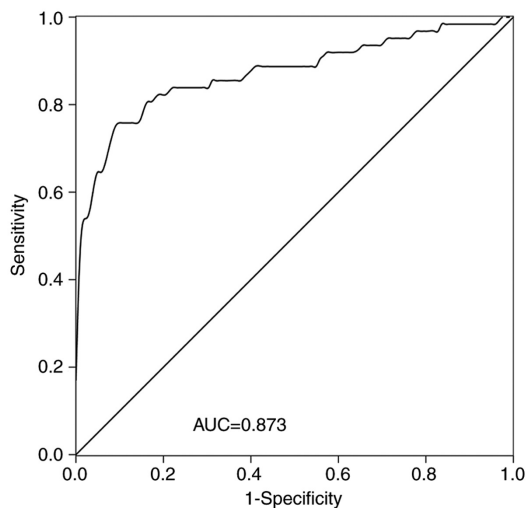


Figure 3. Diagnostic value of LINC-PINT in NSCLC. Receiver operating characteristic curve for patients with NSCLC, based on LINC-PINT expression. LINC-PINT, long intragenic non-protein-coding RNA p53-induced transcript; NSCLC, non-small cell lung cancer; AUC, area under the curve.

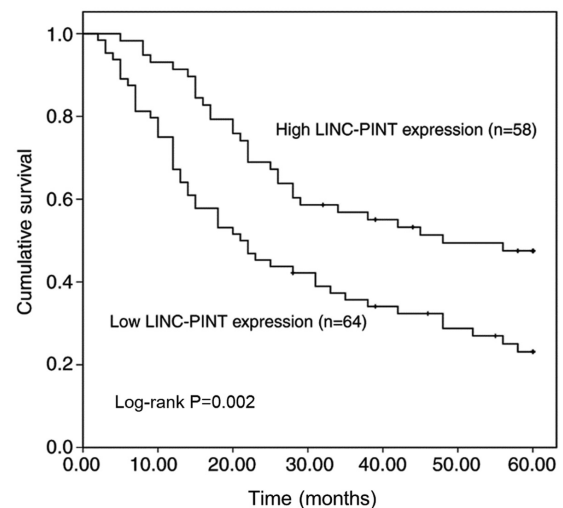


Figure 4. Prognostic value of LINC-PINT in NSCLC. Kaplan-Meier survival analysis for patients with NSCLC, based on LINC-PINT expression. LINC-PINT, long intragenic non-protein-coding RNA p53-induced transcript; NSCLC, non-small cell lung cancer.

can alter chemoresistance of NSCLC cells by targeting miR-197-3p and regulating p120-ctn expression, which may assist in improving chemotherapies for NSCLC (31).

Collectively, these results suggest that lncRNAs play important roles in the development and progression of NSCLC. Recently, lncRNA LINC-PINT has been extensively studied.

Table II. Cox regression analysis of patients with non-small cell lung cancer.

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	P-value	HR	95% CI	P-value
LINC-PINT	2.845	1.629-4.555	<0.001	2.628	1.589-4.348	<0.001
Age, years	1.141	0.761-1.674	0.499	1.167	0.721-1.888	0.529
Sex	1.411	0.857-2.166	0.285	1.479	0.915-2.390	0.110
Smoking	1.418	0.869-2.087	0.221	1.323	0.833-2.102	0.236
Tumor size	1.396	0.925-1.968	0.104	1.146	0.714-1.838	0.573
Differentiation	1.401	0.991-2.120	0.059	1.358	0.832-2.218	0.221
Lymph node metastasis	1.446	1.089-2.047	0.037	1.316	0.819-2.115	0.257
TNM stage	2.041	1.351-3.184	0.010	1.810	1.091-3.004	0.022

TNM, tumor-node-metastasis; HR, hazard ratio; CI, confidence interval.

It has been suggested that LINC-PINT may mediate cancer cell proliferation, invasion and migration in osteosarcoma by binding to miRNA-21 (32). Furthermore, Zhang *et al* (16) demonstrated that LINC-PINT mediates inhibition of cell proliferation, cell cycle, and cell migration and invasion in NSCLC via the miR-208a-3p/PDCD4 axis. However, the clinicopathological characteristics of LINC-PINT in NSCLC remain unclear.

In the present study, TCGA data mining and RT-qPCR analyses demonstrated that LINC-PINT expression was significantly downregulated in NSCLC tissues compared with normal tissues, which was consistent with the findings by Wang *et al* (17). Thus, it was predicted that LINC-PINT may be involved in the progression of NSCLC. To further investigate its role in the development of NSCLC, the association between LINC-PINT expression and the clinicopathological characteristics of patients with NSCLC was assessed. The results demonstrated that LINC-PINT expression in NSCLC was significantly associated with lymph node metastasis, differentiation, TNM stage and tumor size.

The clinical significance of LINC-PINT in NSCLC was further investigated. The results demonstrated that abnormal LINC-PINT expression was associated with the diagnosis or prognosis of patients with NSCLC. lncRNAs are considered ideal diagnostic tools for different human diseases due to their specific expression and stability in blood samples (11). For example, decreased serum lncRNA-DI6366 levels serve as a non-invasive diagnostic biomarker in patients with hepatocellular carcinoma (33), and enhanced serum lncRNA-XLOC_009167 levels may serve as a biomarker for the diagnosis of patients with lung cancer (34). The results of the present study demonstrated that downregulated LINC-PINT expression increased diagnostic accuracy in patients with NSCLC. Previous studies have investigated the diagnostic value of some lncRNAs and a study by Xie *et al* (35), which investigated circulating lncRNAs for NSCLC diagnosis, reported that SOX2OT, ANRIL, CEA, CYFRA211 and SCCA may serve as candidate diagnostic biomarkers. In addition, the combined diagnostic accuracy of the lncRNAs exhibited an AUC value of 0.853. The results of the present study demonstrated that

the AUC value of LINC-PINT was 0.873, suggesting that LINC-PINT may be a potential diagnostic biomarker for patients with NSCLC. The prognostic value of LINC-PINT in NSCLC was also assessed in the present study. Cancer prognosis relies on the TNM system, which requires medical imaging support such as CT, magnetic resonance and bone scan (36). The TNM method not only consumes manpower and material resources, but also has a long-time cycle (37), thus, there is an urgent requirement to identify and develop novel prognostic biomarkers. lncRNAs have been used as biomarkers in different types of cancer (38). In the present study, the prognostic value of LINC-PINT was assessed based on the 5-year follow-up survival information of patients with NSCLC. Kaplan-Meier survival analysis demonstrated that patients with low LINC-PINT expression had a shorter overall survival time than those with high LINC-PINT expression. In addition, multivariate Cox regression analysis confirmed that LINC-PINT expression can effectively be used to predict the prognosis of patients with NSCLC.

The biological function of LINC-PINT has been investigated in NSCLC progression. For example, Wang *et al* (17) demonstrated that LINC-PINT can inhibit the cell proliferation and cell colony formation of NSCLC cells, and it was concluded that LINC-PINT plays an important biological role in NSCLC by sponging miR-543 and inducing PTEN expression. Although this study provides evidence for the clinical value of LINC-PINT in the diagnosis and prognosis of patients with NSCLC, the miRNA that may be regulated by LINC-PINT in NSCLC was not investigated in the present study. Considering the regulatory association between LINC-PINT and miRNA in NSCLC, the clinical significance of LINC-PINT may be improved by co-analyzing the expression changes in the miRNAs. Thus, further studies are required to confirm and develop the clinical application potential of LINC-PINT, with a larger study population and analyses of related miRNAs.

In conclusion, the results of the present study demonstrated that lncRNA LINC-PINT expression is downregulated in NSCLC tissue and serum samples. Furthermore, serum LINC-PINT may serve as a candidate diagnostic biomarker

to distinguish patients with NSCLC from healthy individuals, and low LINC-PINT expression in tumor tissues may predict poor prognosis of patients with NSCLC.

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Availability of data and materials

All data generated or analyzed during the present study are included in this published article.

Authors' contributions

CZ and JT contributed to the conception of the work, bioinformatics analysis, data analysis and interpretation, manuscript writing and revision, and confirmed the authenticity of all the raw data. CG and JL collected the clinical samples and data and performed the experiments. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved the Ethics Committee of Zibo Central Hospital (Zibo, China; approval no. ZCHh-110824), and written informed consent was provided by all participants prior to the study start.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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