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*Review Article*

# Relationship between clinicopathological effects and prognosis of triple negative breast cancer and LncRNA00310

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**Abstract:** Objective: This study set out to explore the relationship between LncRNA00310 and clinicopathological effects of triple-negative breast cancer (BC) and its prognosis. Methods: Eighty-seven patients with triple-negative BC from February 2012 to April 2014 were investigated. The LncRNA00310 expression was detected by qRT-PCR. The relationship between LncRNA00310 and clinical data of patients was observed. Their 5-year overall survival rate and progression-free survival rate were counted. They were divided into high and low expression groups by LncRNA00310's median value. The Kaplan-Meier (K-M) curve was used to compare the differences of the two rates between high and low expression groups. Receiver operating characteristic curve (ROC) was employed to analyze the diagnostic value and death prediction value of LncRNA00310 in TNM staging and lymph node metastasis of patients. Multivariate Cox regression was employed to analyze the independent prognostic factors of patients according to their 5-year overall survival rate. Results: LncRNA00310 expression was dramatically correlated with TNM staging, lymph node metastasis and Ki67 ($P<0.05$). The K-M curve revealed that the overall survival rate and progression-free survival rate in the high expression group were dramatically lower than those in the low expression group ($P<0.05$). The area under ROC curve of TNM staging in diagnosing patients was 0.722, and the specificity and sensitivity were 86.54% and 51.43%; the area under ROC curve for diagnosing lymph node metastasis was 0.779, and the specificity and sensitivity were 77.78% and 69.05%; the area under ROC curve for predicting patient death was 0.799, and the specificity and sensitivity were 82.61% and 75.61%. Cox multivariate analysis revealed that lymph node metastasis (OR: 2.078, 95% CI: 1.067-4.050), lung metastasis (OR: 2.176, 95% CI: 1.013-4.673), Ki67 (OR: 2.739, 95% CI: 1.241-6.044), and LncRNA00310 (OR: 6.851, 95% CI: 2.761-17.002) were independent prognostic factors for survival of triple-negative BC patients. Conclusion: LncRNA00310 was dramatically correlated with TNM staging, lymph node metastasis and Ki67. LncRNA00310 has good diagnostic and predictive value for patients' TNM staging, lymph node metastasis and 5-year survival.

**Keywords:** LncRNA00310, triple-negative breast cancer, pathological effects, prognosis

## Introduction

Breast cancer (BC) is the most frequent type of cancer among women in the world, and is also the main cause of cancer death among them. There are many clinical subtypes with high recurrence rates [1, 2]. It was estimated that the United States had an increase of 250,000 cases of invasive BC and 60,000 cases of non-invasive BC in 2017, and 40,000 women died of BC [3]. Patients with BC are tested for estrogen (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER-2) upon admission. BC with negative detection of all three is classified as triple-negative BC, accounting for 15%-20% of all breast cancers [4]. Compared with other breast cancers, triple-negative BC is more prone to metastasis and recurrence. Compared with many specific therapies of other BC subtypes, triple-negative BC has fewer applicable therapies and poor efficacy and prognosis [5, 6]. At present, there is still a lack of clinical indicators and treatments that have good effect on the prognosis of patients with triple-negative BC.

Long non-coding RNA (LncRNA) is a class of non-coding single-stranded RNA with a length

**Table 1.** Primer sequence

| Geng | Upstream primer | Downstream primer |
|---|---|---|
| LncRNA00310 | 5'-TCTCTTGGGTCTTGCTTGCT-3' | 5'-ACATGGGGATTATGGGGATT-3' |
| GAPDH | 5'-ATGGTGAAGGTCGGT-GTGA-3' | 5'-CCATGTAGTTGAG-GTCAATGAG-3' |

greater than 200 nucleotides [7]. It has been found that it can bind mRNA by acting as competitive endogenous RNA, thus targeting microRNA and target proteins to participate in development and progression of some diseases, as well as having the possibility of becoming new diagnostic prognosis markers and therapeutic targets [8, 9]. Many cancers have some LncRNAs that can affect and regulate the disease state. For example, lncRNA LL22-NC03-N64E9.1 is expressed in lung cancer (LC) and promotes proliferation of LC cells. LncRNA AF147447 can inhibit proliferation and invasion of gastric cancer cells [10-12]. LncRNA00310 is a kind of LncRNA [13, 14], and Li et al [15] discovered it was related to BC development and papillary thyroid cancer. In their research, LncRNA00310 was found to be highly expressed in BC patients and could promote the proliferation of cancer cells. However, it is not clear whether LncRNA00310 has some relationship with some pathological features in triple-negative BC, and whether it has prognostic abilities in a patients' prognosis.

Therefore, this study hopes to provide the basis and direction for clinical research by observing the relationship between the LncRNA00310 expression and the clinicopathological characteristics and prognosis of triple-negative BC.

## Methods

### *Patient data*

From February 2012 to April 2014, 87 patients with triple-negative BC were collected, all of whom were women. The study was approved by the Medical Ethics Committee of Affiliated Hospital of Hebei Engineering University, and all patients were informed and they signed an informed consent form.

### *Inclusion and exclusion criteria*

Inclusion criteria: All patients were diagnosed with BC by pathology. The diagnostic criteria were based on the diagnostic guidelines for BC issued by the European Society of Oncology in 2012 [16]. ER, PR and HER-2 tests were negative. No anti-cancer treatment had been carried out. The patients had complete clinical data and cooperated with treatment and follow-up.

Exclusion criteria were as follows: Those suffering from congenital immune deficiency; those with severe infectious and inflammatory diseases; those complicated with other serious cardiovascular and cerebrovascular diseases; those suffering from other malignant tumors, liver and renal insufficiency; those with expected survival time <2 months; pregnant or lactating women.

### *Follow-up of patients*

Patients were followed up for 5 years, and the follow-up methods were conducted by telephone and outpatient follow-up. In the first year of follow-up, it was performed in the 3rd, 6th, 9th and 12th month respectively; in the following 4 years, it was conducted every 4 months.

### *Main kits and instruments*

Main kits and instruments are as follows: PCR instrument (ABI, 7500, USA), TRIzol (Invitrogen, 15596018, USA), TransScript II Green Two-Step qRT-PCR SuperMix (TransGen Biotech, Beijing, China, AQ202-01, AQ301-01), primers designed and synthesized by Shanghai Sangon Biological Engineering Technological Co., Ltd. (China) (**Table 1**).

### *qRT-PCR detection*

Altogether, 5 ml venous blood of all patients was collected. After coagulation, a centrifuge was used to collect serum (3000 × g at 4°C for 10 min). Serum was used to extract RNA with TRIzol kit. The purity, concentration and integrity of total RNA were detected with ultraviolet spectrophotometer and agarose gel electrophoresis. We used 5X TransScript® II All-in-One SuperMix for qPCR and gDNA Remover kits to carry out reverse transcription operation procedures in strict conformity with the manufac-

turer's insturctions. Then we carried out PCR amplification experiments. The PCR reaction system was as follows: cDNA 1 μL, upstream and downstream primers 0.4 μL each, 2X TransScript® Tip Green qPCR SuperMix 10 μL, Passive Reference Dye (50X), Nuclease-free Water made up to 20 μL. PCR reaction conditions were as follows: pre-denaturation 30 s at 94°C, denaturation 5 s at 94°C, annealing extension 30 s at 60°C, a total of 40 cycles. Each sample was supplied with 3 repeated wells, and the test was performed 3 times. GAPDH was used as the internal reference and the data were analyzed by $2^{-\Delta ct}$.

*Outcome measures*

Main outcome measures: We observed the relationship between LncRNA00310 expression and pathological characteristics of patients, and counted the 5-year overall survival rate and progression-free survival rate. The patients were divided into high and low expression groups according to the median LncRNA00310. The difference of the two rates between high and low expression groups were compared by Kaplan-Meier (K-M) curve.

Secondary outcome measures: Receiver operating characteristic curve (ROC) was employed to analyze the diagnostic value and death prediction value of LncRNA00310 in TNM staging and lymph node metastasis of patients, and multivariate Cox regression was employed to analyze independent prognostic factors of patients according to their total survival for 5 years.

*Statistical analysis*

In our research, the collected data were statistically analyzed by SPSS 20.0 (Shanghai Cabit Information Technology Co., Ltd., China). The illustrations were drawn by GraphPad Prism 7 (Shenzhen Qiruitian Software Technology Co., Ltd., China). The usage (%) of the counting data was performed under chi-square test and expressed by $x^2$. The measurement data were expressed by mean ± standard deviation (Meas ± SD), and all those were in accordance with normal distribution. Comparison between the two groups was under independent-samples t test, and expressed by *t*. ROC evaluated the diagnostic value and death prediction value of LncRNA00310 in TNM staging and lymph node metastasis of patients. Their 5-year overall survival rate and progression-free survival rate were under K-M survival analysis. It was checked through Log rank test, and A *p* value lower than 0.05 was considered statistically different between the two groups.

## Results

*Relationship between clinical and pathological characteristics of LncRNA00310*

By observing the relationship between Lnc RNA00310 expression and clinicopathological characteristics, we found that LncRNA00310 expression was significantly correlated with TNM staging, lymph node metastasis and Ki67 ($P<0.05$), but not with age, menopause, tumor size, differentiation degree, pathological type, lung metastasis and liver metastasis ($P>0.05$) (**Table 2**).

*Survival of high and low expression of LncRNA00310*

Based on the 5-year survival data, 46 patients were still alive, with a total survival rate of 52.87%; and 41 patients with progression-free survival, with a rate of 47.13% progression-free survival. According to their median value of LncRNA00310 expression, we divided them into high and low expression groups, with a total survival rate of 37.21% for high expression, 30.23% for progression-free survival; and 68.18% for low expression and 63.64% for progression-free survival. The K-M curve revealed that the total survival rate and progression-free survival rate of the high expression group were obviously lower than those of the low expression group ($P<0.05$) (**Figure 1**).

*Predictive value of LncRNA00310 in TNM staging, lymph node metastasis and death diagnosis*

The ROC curve was employed to evaluate the predictive value of LncRNA00310 in TNM staging, lymph node metastasis and death diagnosis. It was found that the area under ROC curve was 0.722, 95% CI was 0.611-0.834 in diagnosing TNM staging; when the cut-off point was 1.972, the best specificity and sensitivity were 86.54% and 51.43%, and the Youden index was 37.97%. The area under ROC curve for diagnosing TNM staging was 0.779, and

**Table 2.** LncRNA00310 clinicopathological characteristics

| | n=87 | LncRNA00310 | t | P |
|---|---|---|---|---|
| Age (years) | | | 0.369 | 0.713 |
| <50 | 27 (31.03) | 1.80±0.33 | | |
| ≥50 | 60 (68.97) | 1.83±0.36 | | |
| Menopause | | | 0.531 | 0.597 |
| Yes | 51 (58.62) | 1.80±0.35 | | |
| No | 36 (41.38) | 1.84±0.34 | | |
| Tumor size (cm) | | | 0.766 | 0.446 |
| ≤2 | 31 (35.63) | 1.78±0.35 | | |
| >2 | 56 (64.37) | 1.84±0.35 | | |
| TNM staging | | | 4.115 | <0.001 |
| I+II | 52 (59.77) | 1.70±0.31 | | |
| III+IV | 35 (40.23) | 1.99±0.34 | | |
| Degree of differentiation | | | 0.655 | 0.514 |
| Poorly differentiated | 33 (37.93) | 1.85±0.37 | | |
| Moderately and highly differentiated | 54 (62.07) | 1.80±0.33 | | |
| Lymph node metastasis | | | 4.429 | <0.001 |
| Yes | 45 (51.72) | 1.96±0.36 | | |
| No | 42 (48.28) | 1.66±0.26 | | |
| Pathological type | | | 0.103 | 0.918 |
| Infiltrative type | 68 (78.16) | 1.82±0.34 | | |
| Non-infiltrative type | 19 (21.84) | 1.83±0.39 | | |
| Pulmonary metastasis | | | 0.416 | 0.678 |
| Yes | 16 (18.39) | 1.85±0.38 | | |
| No | 71 (81.61) | 1.81±0.34 | | |
| Liver metastasis | | | 0.530 | 0.598 |
| Yes | 11 (12.64) | 1.87±0.36 | | |
| No | 76 (87.36) | 1.81±0.35 | | |
| Ki67 (%) | | | 3.933 | <0.001 |
| ≥50 | 41 (47.13) | 1.96±0.35 | | |
| <50 | 46 (52.87) | 1.69±0.29 | | |

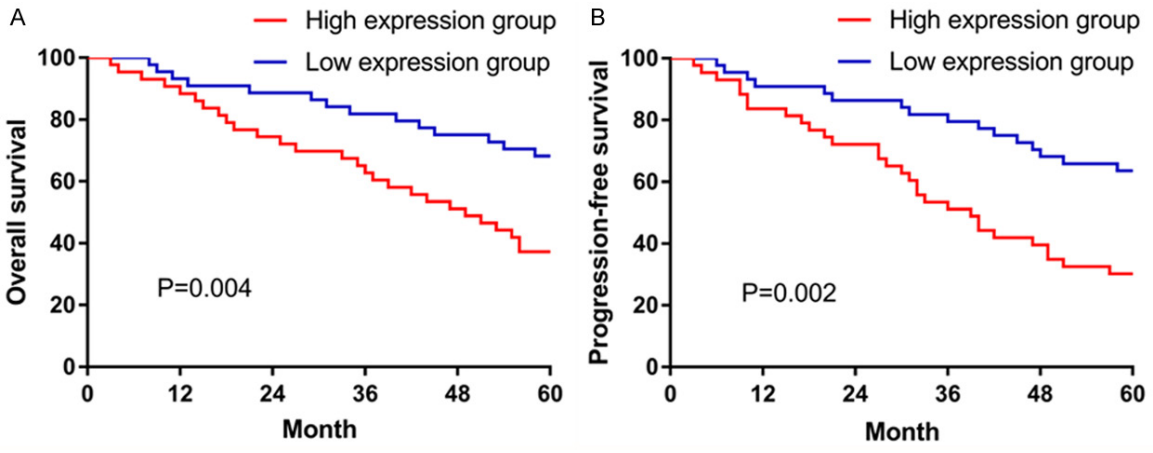


**Figure 1.** K-M curve of LncRNA00310 high and low expression groups. A. Total survival rate of high expression group was obviously lower than that of low expression group (P=0.004). B. Progression-free survival rate in high expression group was obviously lower than that in low expression group (P=0.002).

**Table 3.** ROC curve

| | AUC (area under the curve) | 95% CI | Specificity | Sensitivity | Youden index | Cut-off |
|---|---|---|---|---|---|---|
| TNM staging | 0.722 | 0.611-0.834 | 86.54% | 51.43% | 37.97% | >1.972 |
| Lymph node metastasis | 0.779 | 0.678-0.879 | 77.78% | 69.05% | 46.83% | <1.792 |
| Prediction of death | 0.799 | 0.698-0.900 | 82.61% | 75.61% | 58.22% | >1.885 |

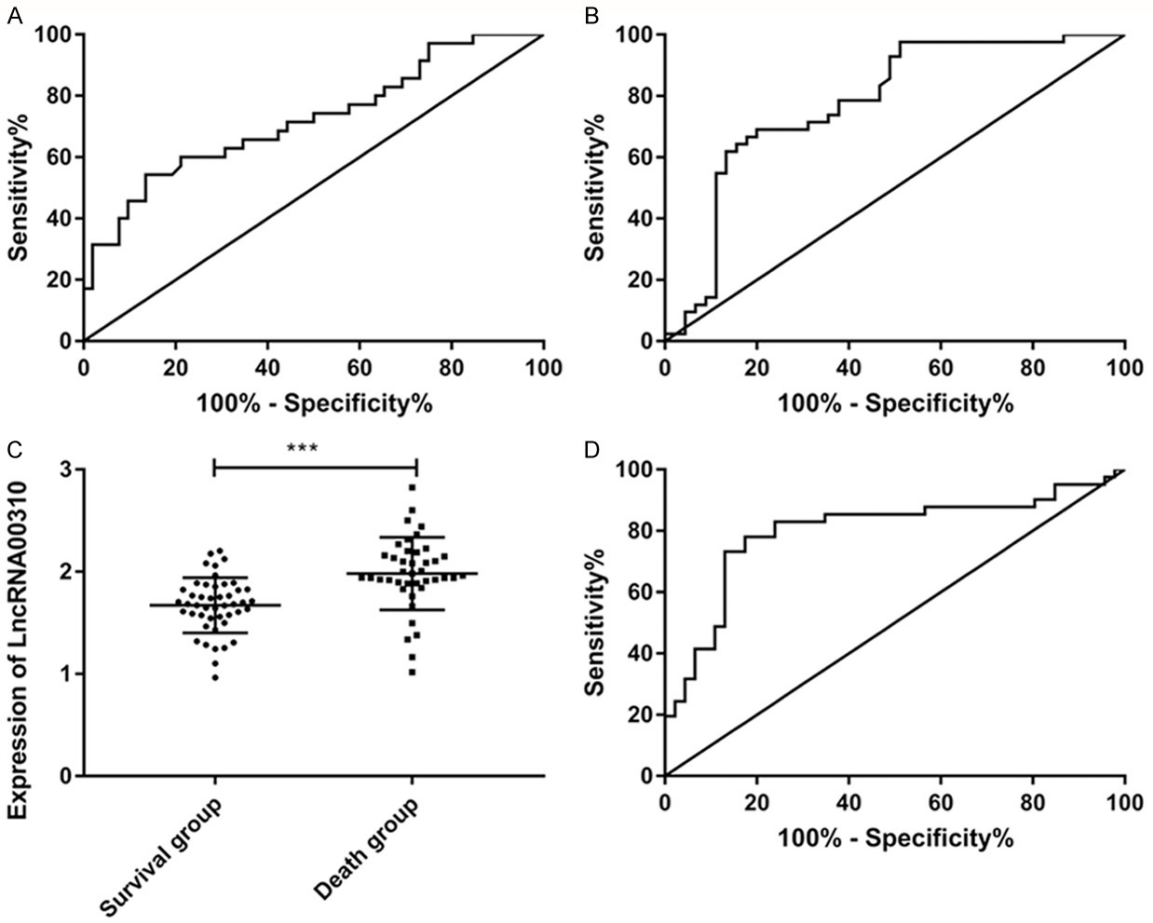


**Figure 2.** Predictive value of LncRNA00310 in TNM staging, lymph node metastasis and death diagnosis. A. Through diagnosing ROC curve of TNM staging of patients, AUC was 0.722, and the specificity and sensitivity were 86.54% and 51.43%. B. Through diagnosing ROC curve for diagnosis of lymph node metastasis, AUC was 0.779, and specificity and sensitivity were 77.78% and 69.05%. C. LncRNA00310 level in living patients was dramatically lower than that in dead patients (t=4.574, P<0.001). D. Through diagnosing ROC curve for predicting patient death, AUC was 0.799, and specificity and sensitivity were 82.61% and 75.61%. *** indicates P<0.001.

95% CI was 0.678-0.879; when the cut-off point was 1.792, the best specificity and sensitivity were 77.78% and 69.05%, and the Youden index was 46.83%. The area under ROC curve for prediction of death was 0.799, and 95% CI was 0.698-0.900; when the cut-off point was 1.885, the best specificity and sensitivity were 82.61% and 75.61%, and the Youden index was 58.22%. Comparing the LncRNA00310 expression of the dead patients and the living patients, we found that the expression of the former was obviously higher than that of the latter (**Table 3**; **Figure 2**).

*Univariate analysis of patient survival*

Univariate analysis of clinical data collected from patients in the survival group and death group revealed that there was no difference in age, menopause, differentiation degree, pathological type, and liver metastasis between both groups (P>0.05). There was however, a statistical difference in tumor size, TNM staging, lymph

**Table 4.** Single factors

| | Survival group (n=46) | Death group (n=41) | $X^2$/t | P |
|---|---|---|---|---|
| Age (years) | | | 0.641 | 0.424 |
| <50 | 16 (34.78) | 11 (26.83) | | |
| ≥50 | 30 (65.22) | 30 (73.17) | | |
| Menopause | | | 2.990 | 0.084 |
| Yes | 23 (50.00) | 28 (68.29) | | |
| No | 23 (50.00) | 13 (31.71) | | |
| Tumor size (cm) | | | 6.328 | 0.012 |
| ≤2 | 22 (47.83) | 9 (21.95) | | |
| >2 | 24 (52.17) | 32 (78.05) | | |
| TNM staging | | | 8.120 | 0.004 |
| I+II | 34 (73.91) | 18 (43.90) | | |
| III+IV | 12 (26.09) | 23 (56.10) | | |
| Degree of differentiation | | | 2.330 | 0.127 |
| Poorly differentiated | 14 (30.43) | 19 (46.34) | | |
| Moderately and highly differentiated | 32 (69.57) | 22 (53.66) | | |
| Lymph node metastasis | | | 4.244 | 0.039 |
| Yes | 19 (41.30) | 26 (63.41) | | |
| No | 27 (58.70) | 15 (36.59) | | |
| Pathological type | | | 2.358 | 0.127 |
| Infiltrative type | 33 (71.74) | 35 (85.37) | | |
| Non-infiltrative type | 13 (28.26) | 6 (14.63) | | |
| Pulmonary metastasis | | | 6.113 | 0.013 |
| Yes | 4 (8.70) | 12 (29.27) | | |
| No | 42 (91.30) | 29 (70.73) | | |
| Liver metastasis | | | 1.377 | 0.241 |
| Yes | 4 (8.70) | 7 (17.07) | | |
| No | 42 (91.30) | 34 (82.93) | | |
| Ki67 (%) | | | 10.914 | <0.001 |
| ≥50 | 14 (30.43) | 27 (65.85) | | |
| <50 | 32 (69.57) | 14 (34.15) | | |
| LncRNA00310 | 1.67±0.27 | 1.98±0.36 | 4.574 | <0.001 |

node metastasis, lung metastasis, Ki67, and LncRNA00310 (P<0.05) (**Table 4**).

*Cox multivariate analysis on survival of patients*

We included the indicators with differences in univariate analysis into assignments (**Table 5**). Then we selected Forward: LR to perform multivariate logistic regression analysis. The results signified that tumor size and TNM staging were not independent prognostic factors for patient survival, while lymph node metastasis (OR: 2.078, 95% CI: 1.067-4.050), lung metastasis (OR: 2.176, 95% CI: 1.013-4.673), Ki67 (OR: 2.739, 95% CI: 1.241-6.044), and LncRNA00310 (OR: 6.851, 95% CI: 2.761-17.002) were independent prognostic factors for survival of triple-negative BC patients (**Table 6**).

## Discussion

Triple-negative BC is characterized by high metastasis and poor clinical results. Rahimian and others [17] discovered that histone deacetylase (HDAC) was associated with epithelial-mesenchymal transition (EMT) of triple-negative BC. When HDAC was inhibited, its EMT would also be inhibited to reduce the metastasis of cancer cells. However, the previous diagnosis of the condition of patients often requires biopsy or imaging [18], so trauma can be reduced if their condition can be direct-

**Table 5.** Assignment table

| Factor | Assignment |
|---|---|
| Tumor size | >2 cm=1, ≤2 cm=0 |
| TNM staging | III+IV=1, I+II=0 |
| Lymph node metastasis | Yes =1, no =0 |
| Pulmonary metastasis | Yes =1, no =0 |
| Ki67 | ≥50%=1, <50%=0 |
| LncRNA00310 | Data are continuous variables and are analyzed using original data |
| Survival | Death =1, survival =0 |

**Table 6.** Multiple factors

| Factor | B | S.E. | Wals | Sig. | Exp (B) | 95% CI of EXP (B) | |
|---|---|---|---|---|---|---|---|
| | | | | | | Lower limit | Upper limit |
| Lymph node metastasis | 0.732 | 0.340 | 4.620 | 0.032 | 2.078 | 1.067 | 4.050 |
| Pulmonary metastasis | 0.777 | 0.390 | 3.976 | 0.046 | 2.176 | 1.013 | 4.673 |
| Ki67 | 1.008 | 0.404 | 6.225 | 0.013 | 2.739 | 1.241 | 6.044 |
| LncRNA00310 | 1.924 | 0.464 | 17.220 | 0.001 | 6.851 | 2.761 | 17.002 |

ly understood through good serum detection [19]. Some LncRNAs are robust in the development of triple-negative BC. LncRNA AWPPH can promote the proliferation of triple-negative BC cells by up-regulating FZD7 [20], LncRNA SNHG12 can promote their migration by regulating MMP13 expression [21], and these LncRNA may become therapeutic targets after diagnostic indicators. It is not clear whether LncRNA00310 also has some applicable clinical significance in triple-negative BC.

In this research, the relationship between LncRNA00310 levels and clinicopathological characteristics of triple-negative BC was first explored. It was found that LncRNA00310 expression was markedly correlated with TNM staging, lymph node metastasis and Ki67. Among them, the expression in patients with stages III and IV was dramatically higher than that in those with stages I and II, the expression in patients with lymph node metastasis was dramatically higher than that in those without lymph node metastasis, and the expression in patients with Ki67≥50% was higher than that in those with Ki67<50%. Then we collected the 5-year overall survival rates (52.87%) and relapse-free survival rates (47.11%) of patients in the observation group. According to the median of LncRNA00310 expression in patients, they were divided into high and low expression groups; through K-M curve analysis, we verified that the 5-year overall survival rate and progression-free survival rate in the high expression group were obviously lower than those in the low expression group. At the same time, we also found that the expression of living patients was obviously lower than that of patients who died. Accurate understanding of TNM staging can reveal the severity and prognosis of the patients and therefore help carry out corresponding treatment methods [22]. Lymph node metastasis is a good predictor of BC recurrence and also affects the prognosis of patients [23]. However, LncRNA00310 level is tied to these characteristics and survival, so can it also be used as a diagnostic or predictive marker for these characteristics? Therefore, we used ROC curves to detect the value of LncRNA00310 in diagnosis and prediction of TNM staging, lymph node metastasis and death. It was found that the AUC for diagnosing TNM staging was 0.722, and the specificity and sensitivity were 86.54% and 51.43%; the AUC for diagnosing lymph node metastasis was 0.779, and the specificity and sensitivity were 77.78% and 69.05%; the AUC for predicting death was 0.799, and the specificity and sensitivity were 82.61% and 75.61%. This also suggested that LncRNA00310 might be a potential biomarker for diagnosing TNM staging, lymph node metastasis and predicting death in patients with triplenegative BC.

In the end, we collected clinical data of patients and carried out logistics multivariate analysis. It was found that lymph node metastasis, lung metastasis, high Ki67 and LncRNA00310 were

independent death factors of triple-negative BC patients. In previous studies, Cox regression analysis has found that Ki67, lymph node metastasis and lung metastasis are the death factors of those patients [24-26]; while in our study, we have noticed that LncRNA00310 is also an independent mortality factor. Therefore, the death situation can be predicted by observing these characteristics of patients.

There are also some limitations in this study. First of all, the samples we included are all triple-negative BC patients, but healthy people and other BC subtypes are not included. We have not studied their varability of LncRNA00310. Secondly, our investigation does not discuss the treatment methods of patients. It is not clear whether their prognosis and the expression of LncRNA00310 are affected by different treatment methods. We hope to further explore this corresponding research in the future. Finally, this study did not study the specific mechanism of influence between LncRNA00310 and triple-negative BC. Whether LncRNA00310 may become a therapeutic target for triple-negative BC patients still needs to be discussed through related basic experiments in the future.

To sum up, LncRNA00310 is significantly correlated with TNM staging, lymph node metastasis and Ki67, and has excellent diagnostic and predictive value for patients' TNM staging, lymph node metastasis and 5-year survival.

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## Disclosure of conflict of interest

None.

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