# Upregulated expression of AT-rich interactive domain-containing protein 1B predicts poor prognosis in patients with triple-negative breast cancer

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**Abstract.** The expression of AT-rich interactive domain-containing protein 1B (ARID1B) was investigated in triple-negative breast cancer (TNBC). The association between ARID1B protein expression and the prognosis of patients with TNBC was investigated. The expression of ARID1B was examined in TNBC (n=142) and adjacent normal breast tissues (n=64) using immunohistochemical staining prior to the patients receiving any treatment. Furthermore, the association between ARID1B protein expression and various clinicopathological features was analyzed, including the survival status of patients with TNBC. Of the 142 TNBC tissues, ARID1B was highly expressed in 89 (62.7%) and poorly expressed in 53 (37.3%). ARID1B expression was associated with lymph node metastasis status, histological grade and p53 expression. ARID1B expression was upregulated significantly in the nuclei of TNBC cells compared with those of normal mammary epithelial cells. This upregulation was associated with a decreased progression-free survival rate (P=0.002) and overall survival rate (P=0.003). The results of the present study indicate that significant association exists between the nuclear expression of ARID1B and adverse prognosis in TNBC. Therefore, ARID1B may be a useful prognostic biomarker in TNBC.

## Introduction

Breast cancer is the most frequently diagnosed type of cancer and the second leading cause of cancer-associated mortality among females. This malignancy accounted for 29% (232,670) of total novel cancer cases and 15% (40,000) of total cancer-associated mortalities in 2014 (1). Although estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor-2 (HER-2) have been used as theranostic references in clinical practice, triple-negative breast cancers (TNBCs) account for between 15 and 20% of all breast cancers, which are defined by the lack of expression of ER, PR and HER-2 (2). No targeted agent is currently available for TNBC. Cytotoxic chemotherapy is the only option for postoperative therapy owing to the shortage of specific therapeutic targets (2). In addition, TNBC is associated with more aggressive histological characteristics, poor therapeutic outcome and decreased survival rate compared with other breast cancer subtypes (3). No standard therapeutic regimens for TNBC have been established, and information on TNBC is insufficient. Therefore, identifying novel prognostic and predictive biomarkers is highly important, and the development of novel therapeutic options for patients with TNBC is required.

SWItch/sucrose non-fermentable (SWI/SNF) complex acts as a conserved chromatin remodeling complex, which performs key roles in cellular differentiation, proliferation and DNA repair, in an ATP-dependent manner (4). SWI/SNF includes two major subclasses, namely BRG1/BRM-associated factor (BAF) and polybromo-associated BAF (PBAF) complexes (5). AT-rich interactive domain-containing protein 1B (ARID1B) is a component of the human SWI/SNF chromatin remodeling complex that is involved in transcriptional activation and inhibition of selected genes by chromatin remodeling (6). ARID1B is important in mammalian development, since it regulates the cell cycle during differentiation (7). Previous studies (7,8) have demonstrated that ARID1B performs key roles in neurodevelopment, and haploinsufficiency of ARID1B is a frequent cause of intellectual disability. Mutations identified in ARID1B indicated that this molecule acts as a potential tumorigenic driver in certain tumors (9). In breast cancer, ARID1B has been implicated in the development of breast cancer through the identification of driver mutations, which confer clonal selective advantage on cancer cells (10). An *in vitro* study revealed that ARID1B is a specific determinant of SWI/SNF complexes with an extensive role in promoting proliferation and an evidently non-essential role in repressing cell cycle activity, making

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ARID1B an attractive target for anticancer therapy (7). Although previous studies have demonstrated that ARID1B performs an important role in several types of human malignancy (9,11,12), ARID1B in patients with TNBC has not been reported.

In the present study, immunohistochemical staining was performed to analyze ARID1B expression in 142 TNBC tissues from the Harbin Medical University Cancer Hospital (Harbin, China), and the data were compared with the clinicopathological features of patients. To the best of our knowledge, the present study is the first to associate ARID1B expression with clinicopathological features and survival rate of patients with TNBC.

## Patients and methods

*Patients and samples*. A total of 142 patients with TNBC were evaluated, and a complete set of follow-up data was reviewed and analyzed. All patients were female with a mean age of 48.6 years (range, 32-69 years). Patients with recurrent tumors, distant metastasis sites, other tumors and bilateral tumors, as well as patients who received neoadjuvant therapy, were excluded from the present study. A total of 64 adjacent normal breast tissues were used as controls. All formalin-fixed paraffin-embedded specimens used in immunohistochemistry were collected from patients who underwent surgery in the Harbin Medical University Cancer Hospital. Each sample was independently examined and analyzed by two pathologists. All patients were treated postoperatively with adjuvant systemic therapy according to the National Comprehensive Cancer Network guidelines (13). Tumors were confirmed histopathologically and were staged according to tumor-node-metastasis (TNM) classification. Tumor size was measured by the pathologists, and normal breast tissues were isolated from >5 cm outside of the tumor. All patients were routinely tested for proliferation marker protein Ki67 (Ki67) and p53 using corresponding antibodies (cat. no. TA500265; dilution, 1:50; cat. no. TA502780; dilution, 1:100; Origene Technologies Inc., Rockville, MD, USA). Samples with at least 14% $Ki67^+$ tumor cells were considered Ki67-positive (14). p53 was considered positive if positive nuclear staining was ≥10%, regardless of the intensity (15). The present study was approved by the Ethical Committee of Harbin Medical University (Harbin, China). Written informed consent was obtained from all study participants.

*Immunohistochemistry*. Immunohistochemical staining for ARID1B was performed on 4-$\mu$m thick formalin-fixed and paraffin-embedded sections. The tissue sections were dried for between 12 and 24 h at 37˚C. Subsequently, sections were deparaffinized in xylene and rehydrated by passing through a graded series of ethanol to distilled water. The tissue sections were treated with sodium citrate buffer with a pH of 6.0 at 98˚C for 20 min and incubated with a mouse anti-ARID1B polyclonal antibody (Abcam, Cambridge, UK; cat. no, ab57461; dilution of 1:300) for 60 min at room temperature. Subsequent to washing with PBS, sections were incubated with secondary biotinylated antibody (horseradish peroxidase-conjugated goat anti-mouse immunoglobulin G; cat. no. PV6002; Origene Technologies Inc.) for 30 min at 37˚C. Subsequent to washing with PBS, each section was then treated with an avidin-biotin complex (dilution, 1:1,000) at room temperature for between 30 and 60 min. The reaction products were visualized with diaminobenzidine. Finally, the sections were counterstained with hematoxylin, dehydrated and cleared with xylene, and the sections were sealed with coverslips. For negative control staining, sections were treated with 0.01 mol/l PBS in place of primary antibodies. Cells with distinct brown granules in the nuclei were considered positive for ARID1B expression. Sections were evaluated by two independent investigators who provided a consensus on the stain patterns using a light microscope at magnification, x400. Semi-quantitative expression levels were evaluated on staining intensity and distribution. Staining intensity was graded as follows: 0, no staining; 1, light brown; 2, brown; and 3, dark brown. The extent of reactivity was scored as follows: 0, <10%; 1, between 10 and 25%; 2, between 26 and 50%; 3, between 50 and 75%; and 4, ≥76%. The sum of the intensity and reactivity extension scores was used as the final staining score for ARID1B. For statistical analysis, final staining scores of >3 were classified as high expression, and scores of <3 indicated low expression.

*Statistical analysis*. Statistical analyses were performed using SPSS (version 13.0; SPSS, Inc., Chicago, IL, USA). Potential associations between ARID1B expression and age, menopausal status, lymph node metastasis (LNM), histological grade, TNM stage, tumor size, chemotherapy regimen and status of p53 and Ki67 were analyzed using a $\chi^2$-test. Progression-free survival (PFS) and overall survival (OS) rates were measured from the date when the primary surgery started. PFS was measured from the beginning of therapy until the time of disease progression or at the end of the observation period in patients without a progressive disease. OS was measured until mortality from any cause or the end of the observation period. The Kaplan-Meier estimator method was used to estimate PFS and OS, and survival differences according to ARID1B expression were analyzed using a log rank test. Clinicopathological features known to be associated with prognosis, including age (≥45 vs. <45 years), LNM (positive vs. negative), histological grade (3 vs. 1+2), TNM stage (III vs. II+I), tumor size (>2 vs. ≤2 cm), p53 (positive vs. negative), Ki67 (positive vs. negative), menopausal status (postmenopausal vs. premenopausal) and ARID1B expression (high vs. low) were evaluated by Cox's univariate analysis. Variables identified to be significant in univariate analysis were then entered in a multivariate analysis to identify these variables with independent prognostic value for PFS and OS. Risk ratios and 95% confidence intervals were recorded for each marker. $P<0.05$ was considered to indicate a statistically significant difference.

## Results

*Analysis of ARID1B expression in TNBC*. A total of 142 patients with TNBC were enrolled in the present study and analyzed for ARID1B expression. Expression scores >3 were classified as positive nuclear ARID1B staining, and the remainder were classified as negative. ARID1B was highly expressed in 62.3% (89/142) of the 142 TNBC specimens. ARID1B protein was significantly upregulated in the nuclei of cancer cells compared with that in normal tissues ($P<0.001$). In 64 normal controls, only 15 (23.4%) samples had

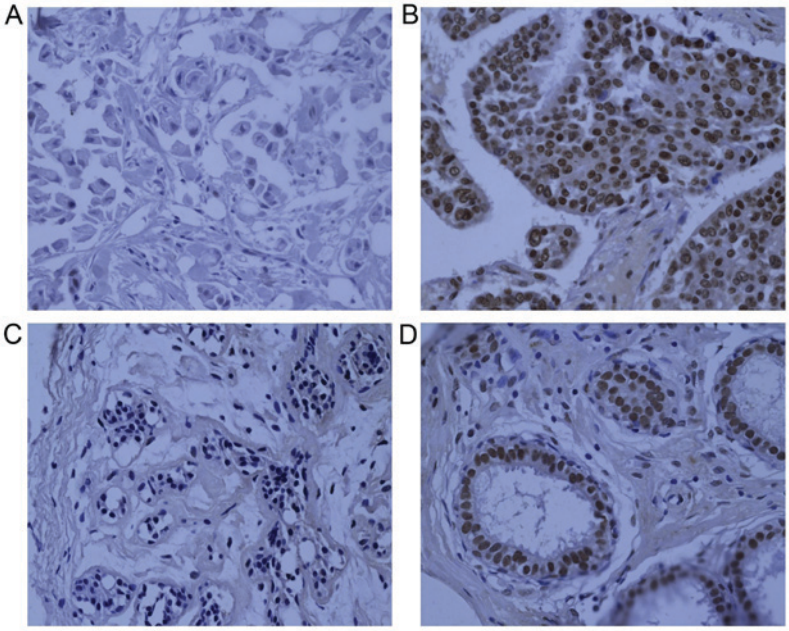


Figure 1. Immunohistochemical staining of ARID1B in breast tissues. (A) Nuclear ARID1B-negative specimen (tumor tissue). (B) Nuclear ARID1B-high expression specimen (tumor tissue). (C) Nuclear ARID1B-negative specimen (normal breast tissue). (D) Nuclear ARID1B-high expression specimen (normal breast tissue). Magnification, x400. ARID1B, AT-rich interactive domain-containing protein 1B.

positive nuclear ARID1B staining. The predominant location of ARID1B staining was the nuclei. ARID1B expression in TNBC and normal tissues is presented in Fig. 1.

*Analysis of association between ARID1B and clinicopathological characteristics*. Associations between ARID1B expression and a series of clinicopathological factors (age, menstrual status, histological grade, tumor size, LNM, TNM stage, the status of p53 and Ki67 and different chemotherapy strategies) are presented in Table I. ARID1B expression was associated with histological grade, p53 expression and LNM status. In total, 62/88 histological grade 3 patients (70.5%) exhibited significantly increased expression of ARID1B compared with grade 1 or 2 patients (50.0%; 27/54 patients; P=0.014). ARID1B overexpression was also observed in 73.6% of p53-positive patients (53/72) compared with 51.4% of p53-negative patients (36/70 patients; P=0.006). In addition, ARID1B expression was upregulated in LNM-positive breast cancer patients (P=0.033). ARID1B expression may be associated with invasion and metastasis in patients with TNBC.

*Univariate and multivariate survival analysis of prognosis*. Univariate and multivariate analyses were performed to evaluate the impact of ARID1B expression and clinicopathological features on the prognosis of patients with TNBC. Cox's regression analysis of univariate analysis demonstrated that OS was significantly associated with LNM (P=0.003), p53 (P=0.025), ARID1B (P=0.010) and TNM stage (P<0.001). PFS was also significantly associated with LNM (P=0.001), ARID1B (P=0.003) and TNM stage (P<0.001). Multivariate analysis was also conducted on the same set of patients using Cox's regression model. Results from the multivariate analysis confirmed that ARID1B expression was a significant independent prognostic factor for OS and PFS of patients with TNBC (P=0.006 and P=0.002, respectively). Additionally, TNM stage and p53 were independent prognostic factors for OS and PFS of patients with TNBC (Table II). These results indicated that upregulated expression of ARID1B was associated with poor prognosis in patients with TNBC.

*Kaplan-Meier survival analysis*. The Kaplan-Meier 5-year survival curves stratified for ARID1B expression are presented in Fig. 2. Among the 142 patients with TNBC, the status of nuclear ARID1B expression demonstrated significant effects on OS (P=0.003; Fig. 2A) and PFS (P=0.002; Fig. 2B) and. Patients with TNBC exhibiting high ARID1B expression had significantly poorer PFS (P=0.002) and OS compared with patients with low ARID1B expression (P=0.003).

## Discussion

TNBC has a poor overall prognosis, and available hormonal or targeted treatment options for this disease are insufficient (16,17). No targeted agent is currently available for TNBC despite the great advances in treating HER2-positive or ER-positive breast cancer (2). The TNBC phenotype is heterogeneous from a histopathological and molecular perspective, which indicates that molecular subsets exist (3). Therefore, identifying and evaluating predictive molecular signatures is important. These processes may be advantageous for the characterization of TNBC and the design of therapeutic modalities. In the present study, the expression and clinical significance of ARID1B was first evaluated in 142 cases of TNBC. Results identified that the status of ARID1B expression may be a prognostic factor of TNBC.

ARID1A and ARID1B belong to the SWI/SNF chromatin remodeling complex family, which may enhance or suppress gene transcription by mobilizing nucleosomes (18). ARID1A and ARID1B subunits are only present in BAF of SWI/SNF complexes (19). ARID1B is a mutually exclusive subunit

Table I. Association between AT-rich interactive domain-containing protein 1B and clinicopathological factors of patients with triple-negative breast cancer.

| Characteristic | Total, n | Negative, n | Positive, n | P-value |
|---|---|---|---|---|
| Patients | 142 | 53 (37.3) | 89 (62.7) | |
| Age, years | | | | 0.994 |
| ≤45 | 59 | 22 (37.3) | 37 (62.7) | |
| >45 | 83 | 31 (37.3) | 52 (62.7) | |
| Menopausal status | | | | 0.708 |
| Premenopausal | 91 | 35 (38.5) | 56 (61.5) | |
| Postmenopausal | 51 | 18 (35.3) | 33 (64.7) | |
| Lymph node | | | | 0.033 |
| Negative | 72 | 33 (45.8) | 39 (54.2) | |
| Positive | 70 | 20 (28.6) | 50 (71.4) | |
| Grade | | | | 0.014 |
| 1+2 | 54 | 27 (50.0) | 27 (50.0) | |
| 3 | 88 | 26 (29.5) | 62 (70.5) | |
| Tumor size, cm | | | | 0.916 |
| ≤2 | 49 | 18 (36.7) | 31 (63.3) | |
| >2 | 93 | 35 (37.6) | 58 (62.4) | |
| TNM stage | | | | 0.075 |
| I/II | 100 | 42 (42.0) | 58 (58.0) | |
| III | 42 | 11 (26.2) | 31 (73.8) | |
| p53 | | | | 0.006 |
| Negative | 70 | 34 (48.6) | 36 (51.4) | |
| Positive | 72 | 19 (26.4) | 53 (73.6) | |
| Ki67 | | | | 0.240 |
| Negative | 74 | 31 (41.9) | 43 (58.1) | |
| Positive | 68 | 22 (32.4) | 46 (67.6) | |
| Chemotherapy regimen | | | | 0.468 |
| Taxanes | 18 | 9 (50.0) | 9 (50.0) | |
| Anthracyclin | 84 | 29 (34.5) | 55 (65.5) | |
| Anthracycline + taxanes | 40 | 15 (37.5) | 25 (62.5) | |

TNM, tumor-node-metastasis; Ki67, proliferation marker protein Ki67.

and highly homologous with ARID1A (20). Multiple studies have revealed that ARID1A is an essential gene that serves a tumor suppressor role, which is primarily involved in negative regulation of cell cycle progression and has a tumor suppressor function (21-23). ARID1A and ARID1B subunits have distinct roles in cell proliferation; ARID1A exhibits an anti-proliferative function, in contrast with the pro-proliferative function of ARID1B (7). ARID1B and ARID1A, which reportedly have opposite functions in cell-cycle arrest, are 60% identical (24). For instance, mouse embryonic stem cells with biallelic inactivation of ARID1B revealed decreased proliferation rate and the abnormality of cell cycle dynamics (25). In addition, *Arid1b*-deficient human fibroblasts exhibited a delayed G1 to S phase cell cycle progression (26). ARID1B was demonstrated to be necessary in preosteoblast cell lines for increased c-Myc oncoprotein expression, which is frequently observed in various human malignancies and is known to be essential in preventing cell cycle arrest in response to growth inhibitory signals (27). In addition, a previous study demonstrated that ARID1B presents a specific vulnerability in human cancers with ARID1A mutant alleles, indicating that ARID1B is required for *Arid1a* mutations to promote tumorigenesis (28). Therefore, in view of its pro-proliferative function, ARID1B may have an opposing role in the tumorigenesis caused by ARID1A.

In the present study, it was established that ARID1B is a prognostic biomarker in patients with TNBC, considering that ARID1B-positive patients presented with a significantly decreased 5-year survival rate compared with ARID1B-negative patients. These results were consistent with a previous study on ARID1B expression in breast cancer; high expression of ARID1B was associated with a decreased 5-year disease-free survival rate (11). In the present study, patients with TNBC with high histological grade (G3) had increased ARID1B expression compared with those with low histological grade (G1/G2) (P=0.014; Table I). ARID1B

Table II. Univariate and multivariate Cox's regression analysis.

| | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| Variable | HR | 95% CI | P-value | HR | 95% CI | P-value |
| Overall survival | | | | | | |
| Age (≥45 vs. <45 years) | 1.274 | 0.534-3.037 | 0.585 | | | |
| Lymph node (positive vs. negative) | 5.225 | 1.768-15.445 | 0.003 | | | |
| Grade (3 vs. 1+2) | 2.272 | 0.838-6.160 | 0.107 | | | |
| Tumor size (>2 vs. ≤2 cm) | 2.503 | 0.847-7.398 | 0.097 | | | |
| TNM stage (III vs. II+I) | 4.892 | 2.05-11.669 | <0.001 | 4.543 | 1.893-10.902 | 0.001 |
| p53 (positive vs. negative) | 2.920 | 1.142-7.463 | 0.025 | 4.564 | 1.770-11.770 | 0.002 |
| Ki67 (positive vs. negative) | 1.383 | 0.597-3.200 | 0.449 | | | |
| Menopausal status (postmenopausal vs. premenopausal) | 1.559 | 0.673-3.609 | 0.300 | | | |
| ARID1B expression (high vs. low) | 6.742 | 1.575-28.855 | 0.010 | 7.868 | 1.812-34.157 | 0.006 |
| Progression-free survival | | | | | | |
| Age (≥45 vs. <45 years) | 0.716 | 0.382-1.343 | 0.298 | | | |
| Lymph node (positive vs. negative) | 3.155 | 1.570-6.343 | 0.001 | | | |
| Grade (3 vs. 1+2) | 1.785 | 0.888-3.585 | 0.104 | | | |
| Tumor size (>2 vs. ≤2 cm) | 1.191 | 0.603-2.351 | 0.615 | | | |
| TNM stage (III vs. II+I) | 3.133 | 1.670-5.879 | <0.001 | 2.994 | 1.584-5.659 | 0.001 |
| p53 (positive vs. negative) | 1.777 | 0.932-3.389 | 0.081 | 2.663 | 1.375-5.158 | 0.004 |
| Ki67 (positive vs. negative) | 1.230 | 0.656-2.305 | 0.518 | | | |
| Menopausal status (postmenopausal vs. pre-menopausal) | 1.005 | 0.522-1.933 | 0.988 | | | |
| ARID1B expression (high vs. low) | 3.420 | 1.508-7.757 | 0.003 | 3.885 | 1.679-8.988 | 0.002 |

HR, hazard ratio; CI, confidence interval; TNM, tumor-node-metastasis; Ki67, proliferation marker protein Ki67; ARID1B, AT-rich interactive domain-containing protein 1B.

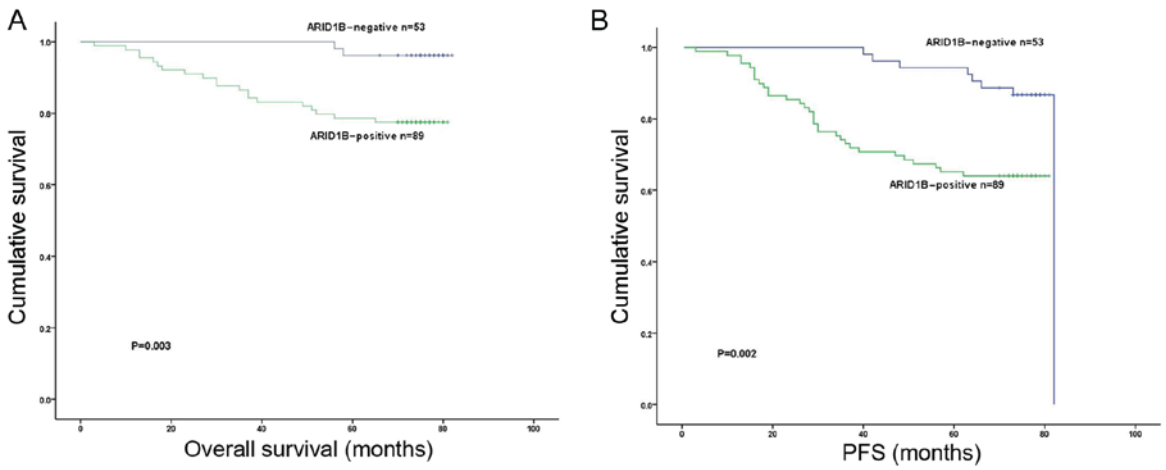


Figure 2. Kaplan-Meier analysis for (A) overall survival and (B) PFS based on the ARID1B expression status in patients with triple-negative breast cancer. PFS, progression-free survival; ARID1B, AT-rich interactive domain-containing protein 1B.

may serve a vital role in tumor progression and invasion. However, ARID1B has been demonstrated to serve as a tumor suppressor in pancreatic cancer cell lines (12). Therefore, the roles of ARID1B may differ depending on the cell type. Additionally, ARID1B expression was associated with LNM (P=0.033), indicating that ARID1B expression is a potential marker for predicting LNM in patients with TNBC. These results indicated that ARID1B serves an important role in the prognosis of TNBC and may be a novel prognostic factor for patients with TNBC.

To the best of our knowledge, the present study is the first to investigate the ARID1B expression and its association with prognosis in TNBC. However, the present study has several limitations. For instance, a relatively small number of Chinese patients were evaluated from a single center, and the present study is retrospective. In addition, the follow-up

period was not long, and the expression status of ARID1B was not analyzed in nodal or distant metastasis sites. However, the results of the present study identified that survival and prognosis of patients with TNBC may depend on ARID1B expression and clinicopathological factors, including TNM stage. Validation of these results using a larger sample size with multiple centers is required in future studies to explore the underlying molecular mechanisms and functional role of ARID1B.

In conclusion, TNBC may be classified into good and poor prognostic subtypes according to the ARID1B expression status. ARID1B may serve as a prognostic biomarker for TNBC. However, more robust studies are required to investigate the molecular mechanism underlying the upregulated ARID1B expression in TNBC and determine whether ARID1B is a potential therapeutic target.

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**Availability of data and materials**

The data used during the current study are available from the corresponding author on reasonable request.

**Authors' contributions**

YC contributed to the study design and the writing of the paper. XZ contributed to analysis and interpretation of data. XB performed the experiments. YQ contributed to the pathologic analysis. MN and DP contributed to the study design. All authors read and approved the manuscript.

**Ethics approval and consent to participate**

The present study was approved by the Ethical Committee of Harbin Medical University. Written consent was obtained from all study participants.

**Patient consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no completing interests.

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