Original Article

Construction of a predictive model for breast cancer metastasis based on lncRNAs

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Background: There is currently a lack of biological markers to determine the risk of lymph node metastasis in breast cancer. A single long non-coding RNA (lncRNA) cannot accurately describe the heterogeneity of tumors. Thus, more accurate algorithms are needed to screen key pathogenic lncRNAs, and quantitative models are needed to describe the heterogeneity of breast cancer.

Methods: A whole transcriptome sequencing data set of breast cancer tissue samples was downloaded from The Cancer Genome Atlas database (n=1,091). A weighted correlation network analysis was conducted to identify the hub lncRNAs associated with lymph node metastasis. A logistic regression analysis was conducted to construct the risk score model. The relationship between the risk scores and the key lncRNAs and the infiltration of the immune cell subtypes was also explored.

Results: A total of 3 common lncRNAs were identified between the differentially expressed lncRNA set and the hub lncRNA set; that is, zinc finger protein 582-antisense RNA 1 (ZNF582-AS1), metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), and actin filament associated protein 1-antisense RNA 1 (AFAP1-AS1). The following formula was used to calculate the risk score: risk score =1.31 + 0.51 * ZNF582-AS1 – 0.66 * MALAT1 – 0.50 * AFAP1-AS1. The receiver operating characteristic curve showed that the areas under the curve for the risk score, ZNF582-AS1, MALAT1, and AFAP1-AS1 were 0.975, 0.793, 0.685, and 0764, respectively (P<0.05). The risk score was positively correlated with immune cell subtype infiltration.

Conclusions: ZNF582-AS1, MALAT1, and AFAP1-AS1 are the key lncRNAs involved in the lymph node metastasis of breast cancer. Our risk score model, which was based on ZNF582-AS1, MALAT1 and AFAP1-AS1, can accurately predict the risk of breast cancer lymph node metastasis. ZNF582-AS1, MALAT1, and AFAP1-AS1 are potential biomarkers for the lymph node metastasis of breast cancer.

Keywords: Lymph node metastasis; breast cancer; biological markers

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Introduction

Breast cancer is a malignant tumor, is the most common cancer in women worldwide, and is known for its high mortality, recurrence, and metastasis rates (1). With the popularization of breast cancer screening, some types of breast cancer can be diagnosed and treated at an early stage. However, some breast cancer patients still have lymph node metastasis at the time of first diagnosis (2,3). In these patients, the cancer cells may have spread to other parts of the body and into the lymphatic system. In such patients, both the primary tumor and metastatic tumor require treatment (4). Thus, patients with lymph node

metastasis need complex treatment strategies and face a higher risk of recurrence and death. The cancer cells of breast cancer generally metastasize along lymphatic vessels. The first station of lymph node metastasis in breast cancer is supraclavicular lymph nodes. Breast cancer patients with lymph node metastasis are generally considered to be in the middle and late stages of the disease, indicating a poor prognosis. The mechanisms of lymph node metastasis of cancer cells are diverse. The infiltration of immune cells in most cases indicates a good prognosis, but a study has pointed out that macrophages and cancer cells form chimeras to assist cancer cells to achieve lymph node metastasis (5). In terms of treatment, patients with tumor metastasis are more likely to develop drug resistance. At present, there are no clinical biological markers for determining the risk of breast cancer lymph node metastasis.

Long non-coding RNA (lncRNA) refers to RNA molecules that encode proteins. The abnormal expression of lncRNA is involved in the occurrence and development of breast cancer, and is closely related to the subtype and prognosis of breast cancer patients. For example, the overexpression of lncRNA HOX transcript antisense RNA can activate the estrogen receptor signaling pathway and lead to tamoxifen drug resistance in patients (6). The high expression of lncRNA regulators of reprogramming (ROR) can promote the process of epithelial-mesenchymal transition and induce the invasion and metastasis of breast cancer cells (7). High expression of lncRNA MAPT-AS1 promotes the proliferation of breast cancer cells (8). The expression level of lncRNA is highly heterogeneous among breast cancer patients. At present, most studies have only examined the effect of a single lncRNA on the biological behavior of breast cancer. However, a single lncRNA cannot accurately describe the heterogeneity of tumors. Thus, more precise algorithms need to be developed to screen key pathogenic lncRNAs, and quantitative models need to be developed to describe the heterogeneity of breast cancer. One research has built models based on the expression of lncRNAs to predict the prognosis of breast cancer patients, but there are few models to predict the metastasis of breast cancer (9). In this study, a weighted correlation network analysis (WGCNA) was conducted to screen the hub lncRNAs related to the lymph node metastasis traits, and a logistic regression analysis was conducted to construct a risk score model to show the correlation between the risk score and immune cell subtype infiltration content. We present the following article in accordance with the TRIPOD reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-129/rc).

Highlight box

Key findings

- Zinc finger protein 582-antisense RNA 1 (ZNF582-AS1), metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), and actin filament associated protein 1-antisense RNA 1 (AFAP1-AS1) were the key lncRNA in lymph node metastasis of breast cancer. The risk score model based on ZNF582-AS1, MALAT1 and AFAP1-AS1 can accurately predict the risk of breast cancer lymph node metastasis.

What is known and what is new?

- At present, there is a lack of biological markers to determine the risk of lymph node metastasis in breast cancer. A single lncRNA cannot accurately explain the heterogeneity of tumors.
- A weighted correlation network analysis and logistic regression analysis were conducted to screen the hub lncRNAs associated with lymph node metastasis traits.

What is the implication, and what should change now?

- Our analysis suggests that ZNF582-AS1, MALAT1, and AFAP1-AS1 may be involved in the regulation of the breast cancer immune microenvironment.

Methods

Sample collection and download

The RNA-sequencing data and associated clinical information of patients with breast cancer (n=1,091) were downloaded from The Cancer Genome Atlas (TCGA) database (https://portal.gdc.cancer.gov/). There data set comprised 561 breast cancer tissue samples with lymph node metastasis, 516 breast cancer tissue samples with non-lymph node metastasis, and 14 samples with missing information. The data set was logarithmically transformed using the following transformation formula: relative gene expression=$\log_2$ [Fragments Per Kilobase of exon model per Million mapped fragments (FPKM)+1]. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Screening of key genes

The WGCNA was conducted using R software (Lucent Technologies, USA) and the WGCNA package. Based on this method, the co-expressed genes of metastatic breast cancer and non-metastatic breast cancer were screened. To obtain scale-free network, data are clustered to detect outliers

and appropriate soft thresholds are set. Gene modules were identified by hierarchical clustering tree and detected by hierarchical clustering based on topological overlap matrix. The correlation coefficient was calculated to determine the correlation between each module and clinical features. The shear height is set to 0.25 and the minimum number of module genes is set to 30. Gene modules with a |correlation| >0.5 and a P value <0.01 were retained. The module significance (MS) and the average gene significance (GS) within each module was calculated. The lncRNAs were considered key if they had a MS value >0.8 and a GS value >0.5.

Calculation of the infiltration content of the immune cell subtypes

The infiltration content of the immune cell subtypes in the breast cancer tissue samples was calculated using a single sample gene set enrichment analysis.

Evaluation of diagnostic efficacy

The diagnostic efficacy of the key lncRNAs for metastatic breast cancer was evaluated using receiver operating characteristic (ROC) curves. The larger the area under the curve (AUC), the better the performance of the risk model.

Statistical analysis

R software (V3.5.1, Lucent Technologies, USA) was used for the statistical analysis. Differences between groups were compared, and a correlation analysis was performed; a two-sided P value <0.05 indicated statistical significance.

Results

Acquisition of differentially expressed lncRNAs

The differentially expressed lncRNAs between the breast cancer samples with lymph node metastasis and breast cancer samples without lymph node metastasis were compared using the Wilcoxon test (|$\log_2$ fold change| >1, false discovery rate <0.05). In total, 36 lncRNAs were identified, of which 10 were downregulated and 26 were upregulated (*Figure 1*).

WGCNA

Each module contained at least 30 lncRNAs and the height was set at 0.25. We finally obtained 10 modules (*Figure 2*). The tan module (r=0.67, P=3e–23) and the magenta module (r=0.53, P=7e–14) were positively associated with non-metastatic breast cancer. The pink module was positively correlated with breast cancer lymph node metastasis traits (r=0.54, P=5e–14; *Figure 3*). The brown, magenta, and pink modules contained 9, 14, and 9 core lncRNAs (hub lncRNAs), respectively (*Figures 4-6*).

Building a predictive model

The differentially expressed lncRNA set and the hub lncRNA set had 3 common lncRNAs; that is, ZNF582-AS1, MALAT1, and AFAP1-AS1 (*Figure 7*). ZNF582-ASI was highly expressed in the non-metastatic samples, while MALAT1 and AFAP1-AS1 were lowly expressed in the metastatic breast cancer samples (*Figures 8-10*). A risk score formula was developed based on the logistic regression analysis. The following formula was used to calculate the risk score: risk score =1.31 + 0.51 * ZNF582-AS1 – 0.66 * MALAT1 – 0.50 * AFAP1-AS1.

Risk score and diagnostic efficacy evaluation of the key lncRNAs

The ROC curves (*Figures 11-14*) showed that the AUCs of the risk score, ZNF582-AS1, MALAT1, and AFAP1-AS1 were 0.975, 0.793, 0.685, and 0.764, respectively (P<0.05).

Correlation between the risk score and immune cell subtypes

In the breast cancer metastatic and non-metastatic tissue samples, there were statistical differences in the infiltration content of various immune cell subtypes (P<0.05; *Figure 15*). The risk score was positively correlated with the infiltration content of the immune cell subtypes (P<0.05; *Figure 16*).

Discussion

New molecular targets are of great significance in improving the clinical treatment strategies for and the outcomes of patients with tumors. There is emerging evidence that lncRNAs are involved in the biological regulation of tumors (10-12), and some lncRNAs have been reported to be extremely valuable tumor prognostic markers (13-15). Whole-genome sequencing has revealed that most of the human genome is transcribed; however, only <2% of the

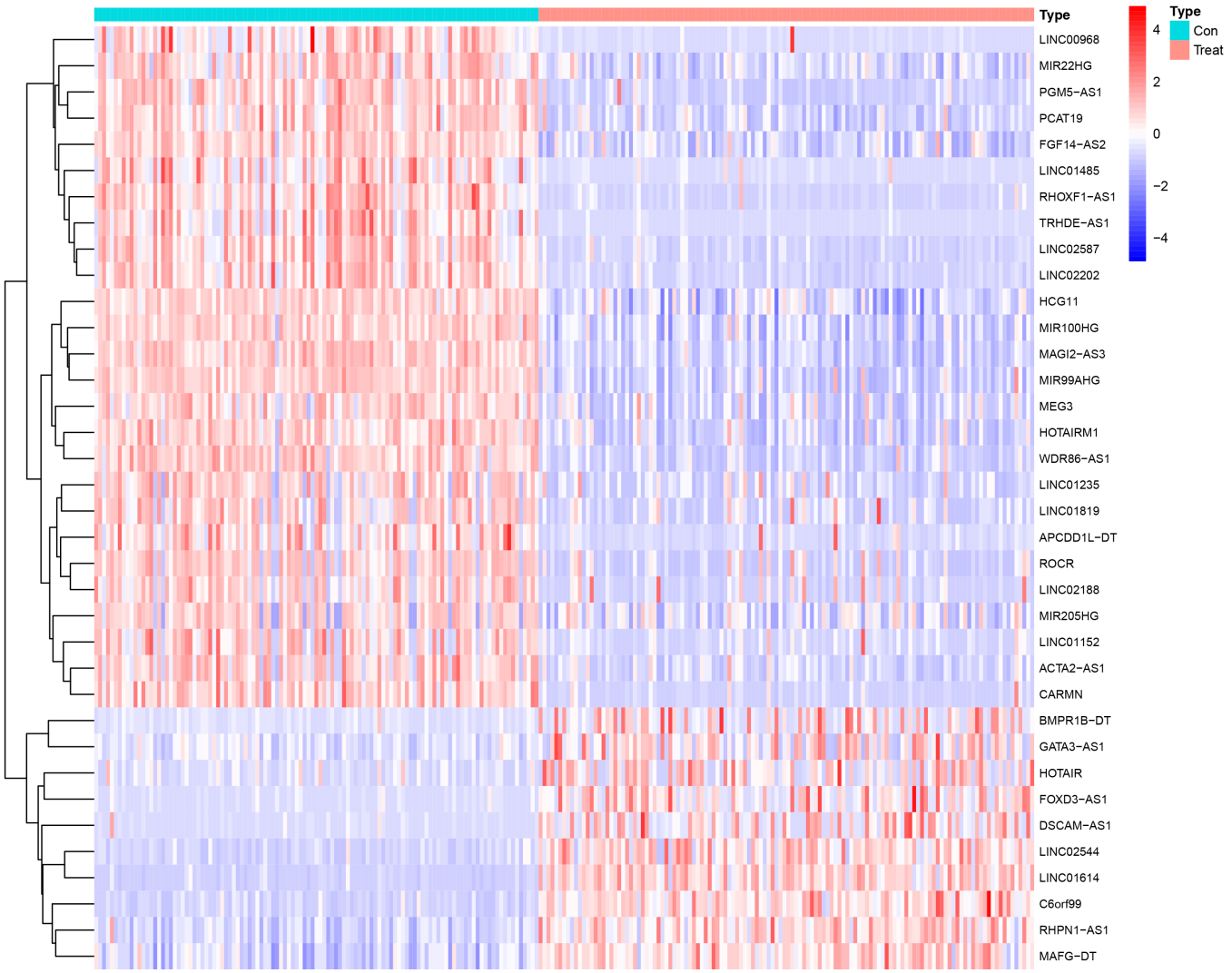

Figure 1 Heatmap of differentially expressed lncRNAs in the breast cancer lymph node metastasis tissue samples and non-lymph node metastasis tissue samples. Red indicates upregulation, and green indicates down-regulation. LncRNAs, long non-coding RNAs; Con, non-transferred samples; Treat, transferred samples.

genomes may encode proteins (16,17). Non-coding RNAs account for >90% of the entire human gene transcripts, participate in almost all epigenetic regulation, and play an important role in the complex life activities of advanced eukaryotes (16,17). Abnormal expressions of lncRNAs are involved in the process, metastasis, and prognosis of breast cancer (18-20). LncRNAs may play a role in promoting or inhibiting tumorigenesis and progression. This regulatory mechanism is relatively complex and diverse. The lncRNA Nkila can act on T cells, promoting immune escape (18). LncRNA DANCR promotes breast cancer cell proliferation and metastasis by upregulating VAPB (19). LncRNA152 acts as an angiogenesis inhibitor in triple-negative breast cancer that impedes cancer cell metastasis (20).

In the present study, we identified 3 key lncRNAs associated with breast cancer lymph node metastasis; that is, ZNF582-AS1, MALAT1, and AFAP1-AS1. MALAT1 is considered a potential oncogene. it's the transcription product of MALAT1 can regulate RNA alternative splicing by combining multiple splicing factors, can affect the localization of various proteins in the nucleus through scaffolding, and can also affect the signaling pathways, chromosomal rearrangement, histone modification, and small RNA construction, and other important physiological

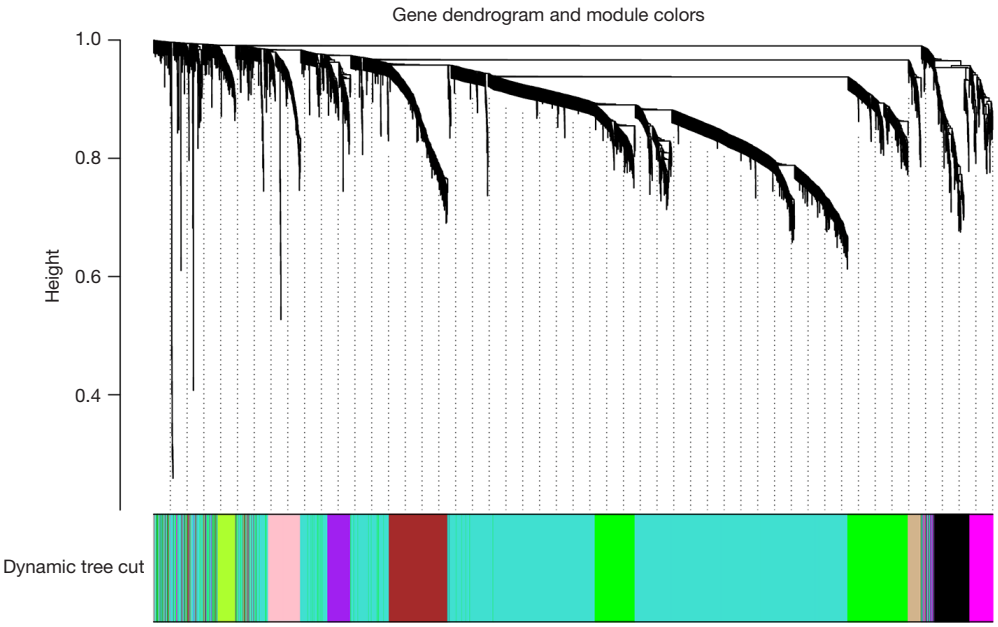

Figure 2 Screening of the breast cancer lymph node metastasis trait co-expressed lncRNA modules. LncRNAs, long non-coding RNAs.

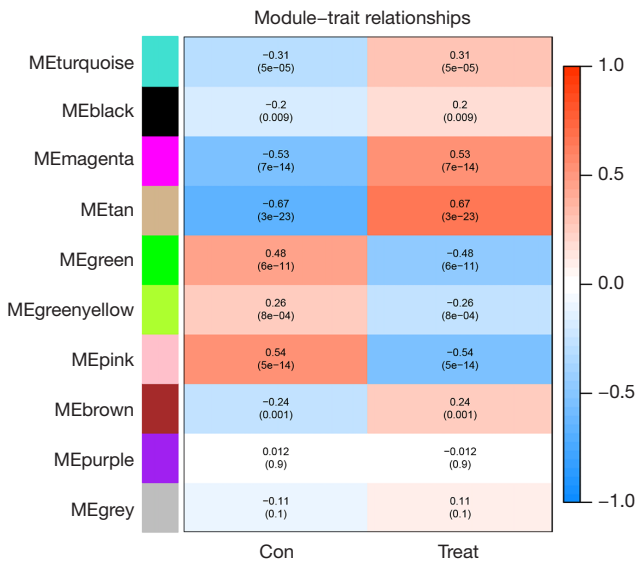

Figure 3 Correlations between the modules and the clinical traits of breast cancer [lymph node metastasis (Treat) and non-lymph node metastasis (Con)]. The colors indicate the correlation coefficients. The numbers in parentheses represent the P values, and the numbers outside the parentheses represent the correlation coefficients. Con, non-transferred samples; Treat, transferred samples.

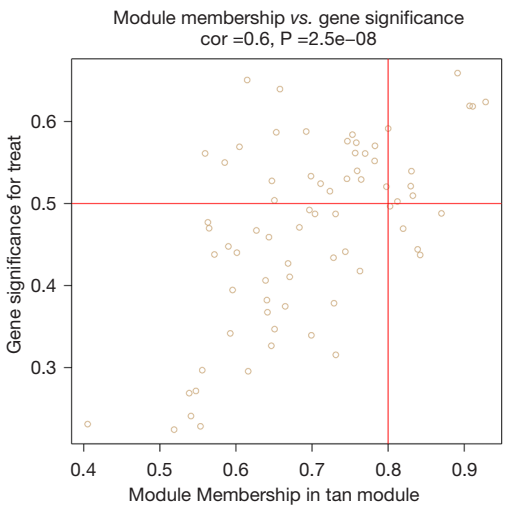

Figure 4 Core lncRNAs in the sepia-colored modules. LncRNAs, long non-coding RNAs.

processes (21). Additionally, MALAT1 can regulate biological behaviors, such as tumor cell proliferation, invasion and metastasis, and affect the occurrence and development of tumors (22). MALAT1 is closely related to the formation of breast cancer and various biological behaviors. MALAT1 is downregulated in breast cancer cells and tissues and promotes the epithelial-mesenchymal differentiation and metastasis of breast cancer cells (23-25).

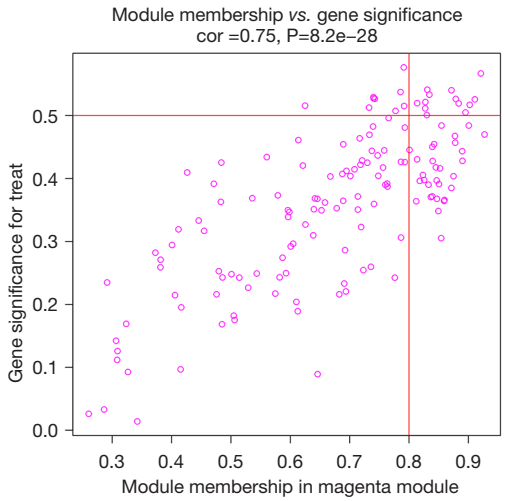

Figure 5 Core lncRNAs in the magenta module. LncRNAs, long non-coding RNAs.

Figure 6 Core lncRNAs in the pink module. LncRNAs, long non-coding RNAs.

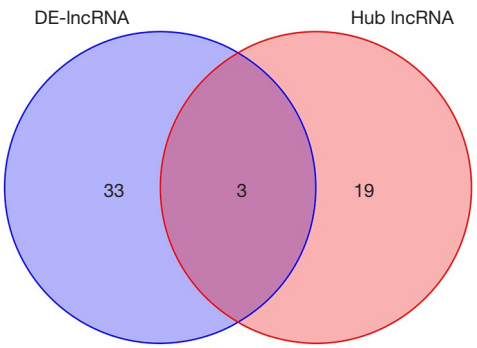

Figure 7 The intersection between the differentially expressed lncRNAs and hub lncRNAs. DE, differentially expressed; LncRNAs, long non-coding RNAs.

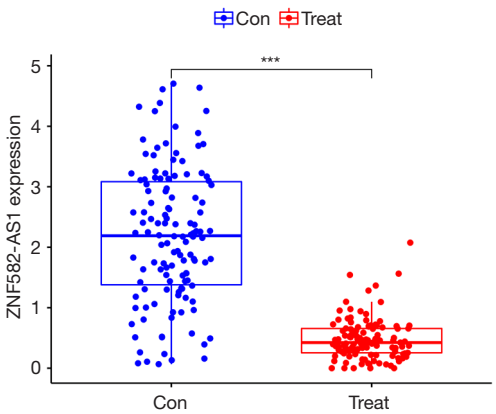

Figure 8 Comparison of the expression level of ZNF582-AS1 in lymph node metastatic breast cancer and non-lymph node metastatic breast cancer. ***, P<0.001. Con, non-transferred samples; Treat, transferred samples; ZNF582-AS1, zinc finger protein 582-antisense RNA 1.

Meseure *et al.* (26) showed that MALAT1 was upregulated in 14.13% of breast cancer patients. Jadaliha *et al.* (27) showed that MALAT1 was differentially upregulated in triple-negative breast cancer. Our research suggested that MALAT1 was related to the lymph node metastasis of breast cancer, but its mechanism still requires further exploration.

One study pointed out that the abnormal expression of AFAP1-AS1 is closely related to the clinical stage and lymph node metastasis of breast cancer (28). AFAP1-AS1 may be involved in the occurrence and development of breast cancer, and thus may have potential as a marker for the clinical diagnosis and prognosis of breast cancer (28). Dianatpour *et al.* (29) found that the expression of AFAP1-AS1 was upregulated in various cancers, including breast cancer. AFAP1-AS1 has also been reported to be more upregulated in breast cancer samples than adjacent tissues, and thus may be related to the onset and progression of breast cancer (29). AFAP1-AS1 has also been shown to be significantly downregulated in Ki-67-negative tumor samples (29). However, this study (29) did not observe any correlation between AFAP1-AS1 and clinical features. This differs to the results of the current study; however, this difference in results may be related to the small sample size

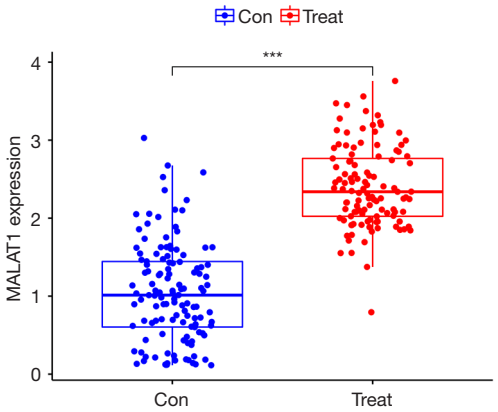

Figure 9 Comparison of the expression level of MALAT1 between lymph node metastatic breast cancer and non-lymph node metastatic breast cancer. ***, P<0.001. Con, non-transferred samples; Treat, transferred samples.

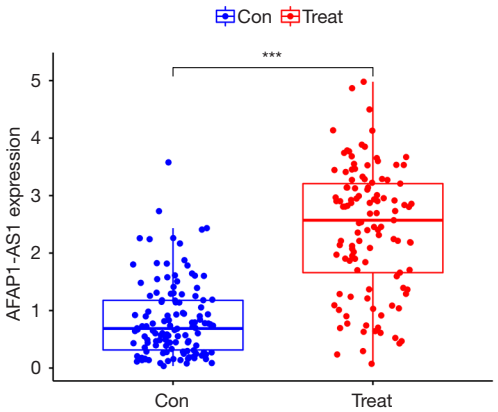

Figure 10 Comparison of the expression level of AFAP1-AS1 in metastatic breast cancer and non-metastatic breast cancer. ***, P<0.001. Con, non-transferred samples; Treat, transferred samples; AFAP1-AS1, actin filament associated protein 1-antisense RNA 1.

of the study (29). Zhang *et al.* (30) concluded that AFAP1-AS1 promotes the proliferation and metastasis of cancer cells through microRNA (miR)-145 in triple-negative breast cancer.

Our study found that ZNF582-AS1 was highly expressed in the non-lymph node metastatic samples and was positively correlated with the infiltration content of various immune cell subtypes. This is consistent with the findings of previous research. Notably, Wang *et al.* (31) showed that the expression of ZNF582-AS1 was downregulated in breast cancer tissues. Patients with high expressions of ZNF582-

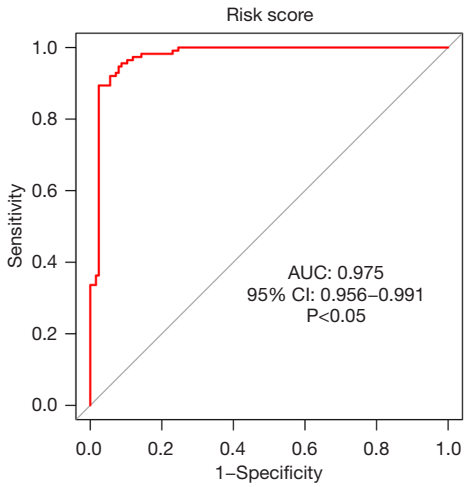

Figure 11 Evaluation of the risk score for the diagnostic performance of metastatic breast cancer. AUC, area under the curve; CI, confidence interval.

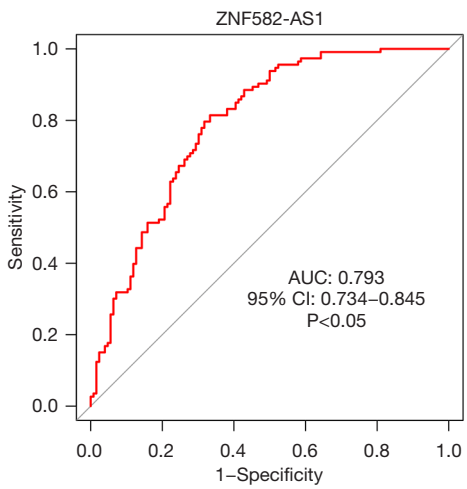

Figure 12 Evaluation of the diagnostic efficacy of ZNF582-AS1 for metastatic breast cancer. AUC, area under the curve; CI, confidence interval; ZNF582-AS1, zinc finger protein 582-antisense RNA 1.

AS1 have a good prognosis and a low recurrence rate. The study (31) also indicated ZNF582-AS1 is a protective factor and indicates a good prognosis in breast cancer patients.

We developed a risk score formula for breast cancer lymph node metastasis based on ZNF582-AS1, MALAT1, and AFAP1-AS1. The ROC curves showed that the model had good predictive performance. We also found that the risk score was positively correlated with the infiltration

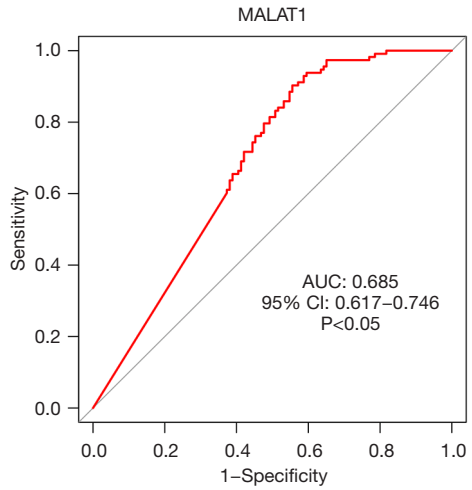

Figure 13 Evaluation of the diagnostic efficacy of MALAT1 for metastatic breast cancer. AUC, area under the curve; CI, confidence interval.

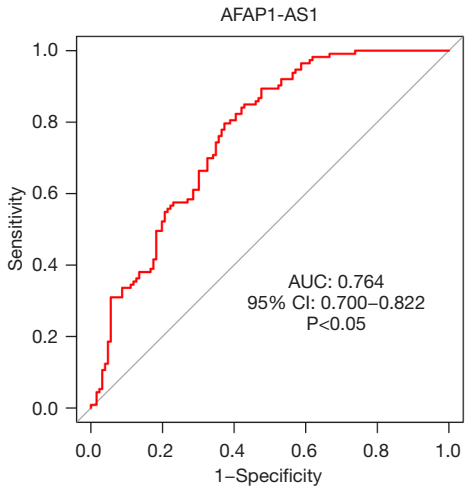

Figure 14 Evaluation of the diagnostic efficacy of AFAP1-AS1 for metastatic breast cancer. AUC, area under the curve; CI, confidence interval; AFAP1-AS1, actin filament associated protein 1-antisense RNA 1.

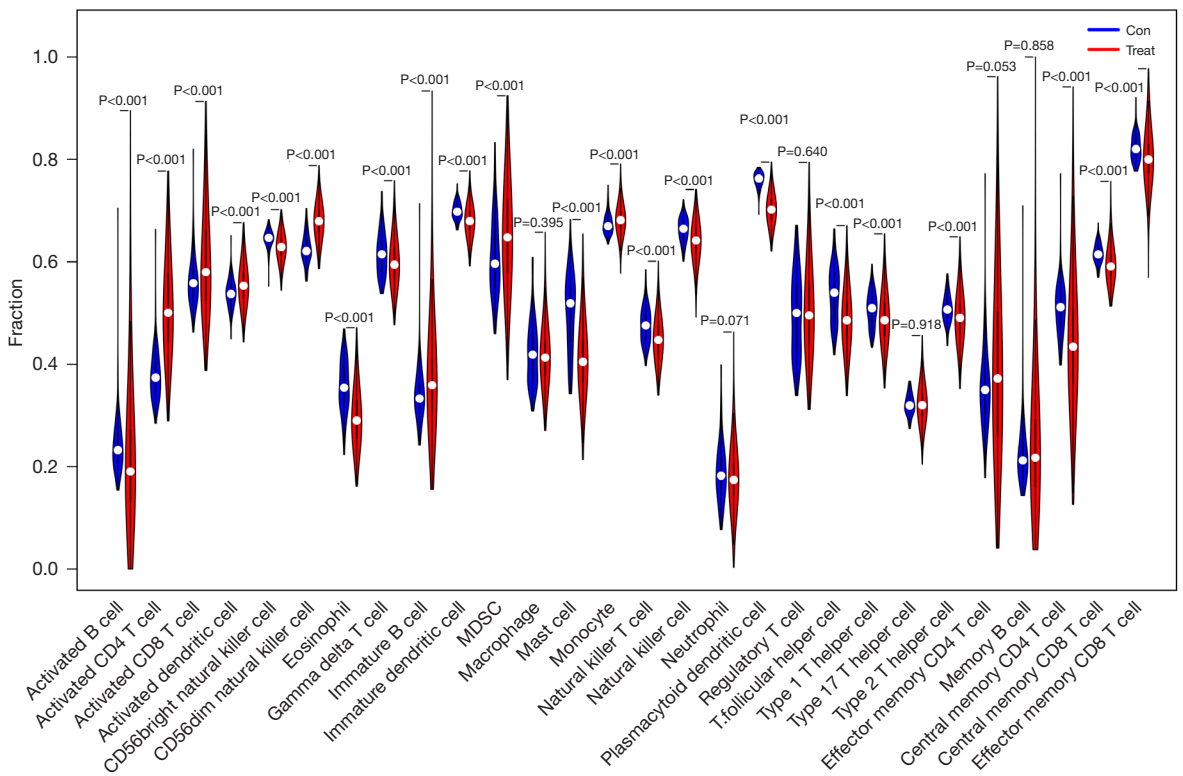

Figure 15 Comparison of the difference in the infiltration content of the immune cell subtypes in the breast cancer metastatic and non-metastatic tissue samples. Con, non-transferred samples; Treat, transferred samples; MDSC, myeloid-derived suppressor cells.

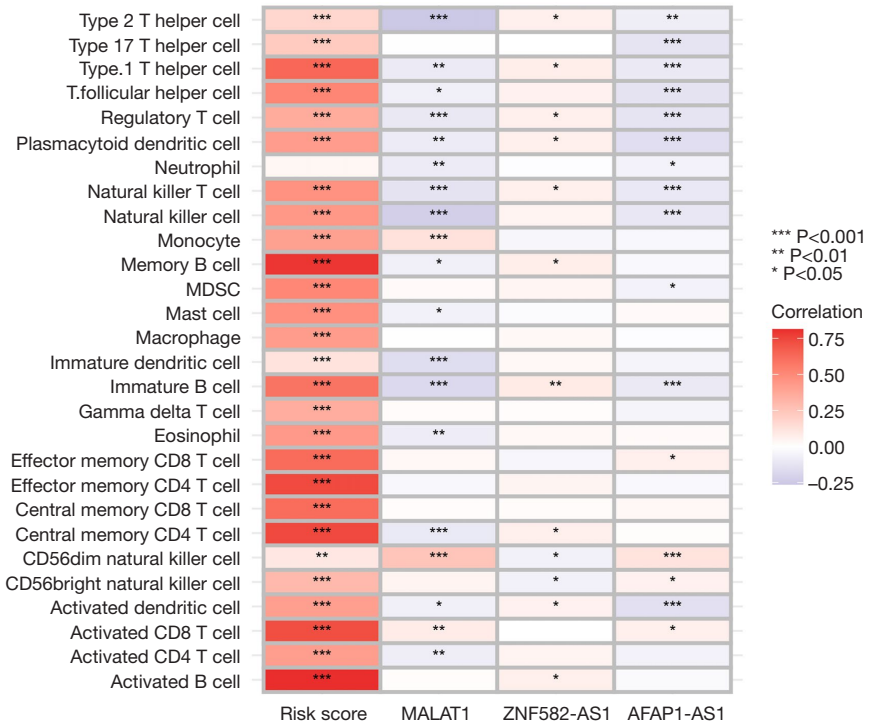

Figure 16 Correlation between the risk score, key lncRNAs, and infiltration content of immune cell subtypes. *, P<0.05; **, P<0.01; ***, P<0.001. LncRNAs, long non-coding RNAs; MDSC, myeloid-derived suppressor cells; ZNF582-AS1, zinc finger protein 582-antisense RNA 1; AFAP1-AS1, actin filament associated protein 1-antisense RNA 1.

content of multiple immune cell subtypes. According to our analysis, ZNF582-AS1, MALAT1, and AFAP1-AS1 may be involved in the regulation of the breast cancer immune microenvironment.

There are some limitations in this study. First, the accuracy of the model was not verified by external data. Second, there is a lack of *in vivo* and *in vitro* experiments to validate the results of our analysis without further insight into the specific roles and functions of key lncRNAs in breast cancer.

In summary, ZNF582-AS1, MALAT1, and AFAP1-AS1 are key lncRNAs for breast cancer lymph node metastasis and are potential biomarkers.

Conclusions

ZNF582-AS1, MALAT1 and AFAP1-AS1 are key lncRNAs for lymph node metastasis of breast cancer. The risk scoring model based on ZNF582-AS1, MALAT1 and AFAP1-AS1 can accurately predict the risk of lymph node metastasis of breast cancer. ZNF582-AS1, MALAT1 and AFAP1-AS1 are potential biomarkers of lymph node metastasis of breast cancer.

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Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-129/rc

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-129/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all

aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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