Correlation of sex-determining region Y-box 30 with tumor characteristics and its prognostic value in breast cancer

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Abstract

Objective: Sex-determining region Y-box 30 (SOX30) suppresses progression of several cancers, whereas its role in breast cancer is unclear. Therefore, we aimed to determine the correlation of SOX30 with tumor characteristics and prognosis in breast cancer patients.

Methods: The tumor samples of 510 breast cancer patients who underwent resection were obtained, and SOX30 expression was analyzed by immunohistochemistry. Clinical characteristics, disease-free survival (DFS), and overall survival (OS) of breast cancer patients were recorded.

Results: There were 368 breast cancer patients in SOX30 low-expression group and 142 in SOX30 high-expression group. SOX30 was negatively correlated with tumor size (P = .010), tumor (T) stage (P < .001), node (N) stage (P = .001), and tumor, node, metastasis (TNM) stage (P < .001) in breast cancer patients. For prognosis, patients in SOX30 high-expression group had prolonged DFS (P = .011) and OS (P = .002); moreover, increased SOX30 grade (assessed by semi-quantitative scoring method assessment) was correlated with better DFS (P = .015) and OS (P = .014). Univariate Cox’s regression analysis disclosed that SOX30 high expression was correlated with enhanced DFS (P = .012, hazard ratio (HR) = 0.582) and OS (P = .002, HR = 0.389); however, multivariate Cox’s regression analysis revealed that SOX30 could not independently predict DFS (P = .224, HR = 0.766) or OS (P = .087, HR = 0.582) in breast cancer patients, indicating it might interact with other independent predictive factors (such as pathological differentiation, T stage, and N stage) to influence DFS and OS in breast cancer patients.

Conclusion: Sex-determining region Y-box 30 is a potential prognostic biomarker in breast cancer, which might contribute to the better outcome of breast cancer patients.

Keywords
breast cancer, disease-free survival, overall survival, Sex-determining region Y-box 30, tumor characteristics
# INTRODUCTION

Breast cancer is the most frequent cancer that occurred in women worldwide, and there are about 1.7 million people diagnosed with breast cancer every year.\(^1\,^2\) Meanwhile, it ranks as the first in causing cancer death in women, leading to approximately 0.5 million deaths annually, which accounts for 15% of all cancer deaths.\(^3\,^4\) Although the diagnostic technology and management successfully lead to a decrease in the mortality of breast cancer, the prognosis of breast cancer patients is far from satisfactory.\(^5\,^6\) Therefore, it is vital to search for potential biomarkers to predict and thus improve the prognosis of breast cancer patients.

Sex-determining region Y-box 30 (SOX30), one of the members of the SOX protein family, is a transcription factor that suppresses tumors.\(^7\) It is reported that SOX30 induces apoptosis and inhibits proliferation, migration, and invasion in several cancer cells (such as lung adenocarcinoma cells and hepatocellular carcinoma cells) by regulating several pathways such as p53 and Wnt/β-catenin.\(^8\,^9\) Moreover, several clinical researches reveal that SOX30 is correlated with less advanced tumor characteristics in bladder cancer, lung adenocarcinoma, and ovarian cancer, for example.\(^10\,^12\) Meanwhile, previous studies disclose that SOX30 displays potential as a prognosis biomarker in lung cancer and bladder cancer;\(^10,\,13\); however, its significance in patients with breast cancer remains unclear. Based on the data mentioned above, we hypothesized that SOX30 might also predict the prognosis of breast cancer patients to some extent.

In this study, we determined SOX30 expression in tumor tissues from 510 breast cancer patients by immunohistochemistry (IHC), aiming to assess the correlation of SOX30 with tumor properties and prognosis in breast cancer patients.

## MATERIALS AND METHODS

### 2.1 Patients

A total of 510 breast cancer patients who underwent resection from January 2014 to December 2017 in our hospital were enrolled in this retrospective study. The patients were eligible if they met the following criteria: (a) newly diagnosed as primary breast cancer by pathology; (b) received resection; (c) 18 age<80 years old; (d) tumor tissues resected from surgery were well preserved and available for immunohistochemistry (IHC) assay; (e) tumor features before operation and follow-up data were complete; (f) without distant metastases; and (g) not complicated with other malignancies. In addition, pregnant or lactating women were excluded from this study. This study was approved by the Ethics Committee of our hospital, and all patients or their guardians provided the written informed consent.

### 2.2 Data and sample collection

Age and tumor features before operation (such as estrogen receptor (ER) status, progesterone receptor (PR) status, human epithelial growth factor receptor-2 (HER-2) status, pathological differentiation, tumor size, T stage, N stage, and TNM stage) were collected from medical records. Tumor tissue specimens were formalin-fixed and paraffin-embedded, which were obtained from the Pathology Department in our hospital. Meanwhile, the breast tissues of 40 patients who received detection for precancerous lesions were collected.

### 2.3 SOX30 measurement

The level of SOX30 in tumor tissue specimens was measured by IHC. In briefly, the tumor tissue specimens were cut into 4-μm sections, and then, the tissue sections were deparaffinized with xylene and rehydrated using graded ethanol. After antigen retrieval using microwave heating, the peroxidase activity of tissue sections was blocked by incubating with 0.3% H₂O₂ for 15 minutes. To prevent nonspecific binding, 10% normal goat serum (Sigma-Aldrich) was added to the tissue sections, and then, the tissue sections were incubated at room temperature for 2 hours. Subsequently, the tissue sections were incubated with the rabbit anti-SOX30 polyclonal antibody (1:50, Thermo, USA) overnight at 4°C. The next day, after three rinses in PBS, the tissue sections were incubated in a horseradish peroxidase-conjugated goat anti-rabbit IgG (H + L) secondary antibody for 1 hour at room temperature (1:2000, Thermo). Finally, the tissue sections were stained and counterstained using diaminobenzidine (DAB) (Dako) and hematoxylin (Sigma-Aldrich), respectively; then, the tissue sections were sealed by neutral resin (Sango Biotech). The staining results were observed on a Nikon ECLIPSE E200 microscope (Nikon Instruments).

### 2.4 Assessment of SOX30 expression

A semi-quantitative scoring method was used to assess the expression of SOX30 in tumor tissue specimens as previously described.\(^14\) The staining intensity was classified as follows: 0 (no staining); 1 (weak staining); 2 (moderate staining); and 3 (strong staining). And the proportion of positive tumor cells was scored as follows: 0 (no positive tumor cells); 1 (proportion of positive tumor cells <25%); 2 (proportion of positive tumor cells: 25%-50%); 3 (proportion of positive tumor cells: 51%-75%); and 4 (proportion of positive tumor cells >75%). The total score of IHC was calculated by multiplying the staining intensity score and the proportion of positive tumor cells score. All patients were divided into SOX30 low-expression group (total IHC score ≤3) and SOX30 high-expression group (total IHC score >3). The SOX30 high-expression group was further classified as SOX30 high+ (total IHC score 4–6), SOX30 high++ (total IHC score 7–9), and SOX30 high+++ (total IHC score 10–12).\(^14\)

### 2.5 Treatment and follow-up

Based on the clinical status, all patients received appropriated neo-adjuvant therapy or systemic adjuvant treatment according to the
guideline of breast cancer\textsuperscript{15} (for the patients received neoadjuvant therapy, their tumor features were recorded before operation after neoadjuvant therapy). Survival data were obtained from follow-up records, and the last follow-up date was June 30, 2019. The median follow-up duration was 38.0 months, and the minimum-to-maximum follow-up duration was ranging from 2.0 to 60.0 months. The disease-free survival (DFS) was calculated from the date of resection to the date of relapse or death, and overall survival (OS) was calculated from the date of resection to the date of death.

2.6 | Cell culture

Human breast cancer cell lines including T47D, MDAMB231, MCF7, MDAMB453, BT474, and MDAMB468 were purchased from American Type Culture Collection (ATCC), and human normal breast cell line MCF-10F was also purchased from ATCC. The T47D and BT474 cells were cultured in RPMI-1640 medium (Gibco), and MDAMB231, MCF7, MDAMB453, MDAMB468, and MCF-10F cells were cultured in DMEM medium (Gibco). All cells were maintained in the 95% air and 5% carbon dioxide (CO\textsubscript{2}). After culture, the relative expressions of SOX30 in these cells were determined by reverse transcription-quantitative polymerase chain reaction (RT-qPCR) with MCF-10F cells severed as control, which was performed according to a previous study.\textsuperscript{16}

2.7 | Statistical analysis

Statistical analysis was performed using SPSS 22.0 software (IBM), and figure was plotted with the use of GraphPad Prism 7.00 (GraphPad Software). Data were presented as mean ± standard deviation and count (percentage). Comparison of clinical characteristics between SOX30 high- and low-expression groups was determined by chi-square test or Wilcoxon rank-sum test. Multiple comparisons between cell lines were determined by Dunnett’s test. DFS and OS were described by Kaplan-Meier curves, and the differences of DFS or OS between SOX30 high- and low-expression groups or among SOX30 high/ SOX30 high+/SOX30 high++/SOX30 high+++/SOX30 low groups were determined by log-rank test. Factors predicting DFS or OS were analyzed by univariate and multivariate Cox’s proportional hazard regression models. \textit{P} value < .05 was considered significant.

3 | RESULTS

3.1 | Clinical characteristics

The mean age of breast cancer patients was 55.7 ± 12.9 years, and there were 184 (36.1%) patients under 50 years and 326 (63.9%) patients equal or above 50 years. The mean tumor size of breast cancer patients was 3.1 ± 1.9 cm, and there were 248 (48.6%) patients with tumor size smaller than 3 cm and 262 (51.4%) patients with tumor size larger than 3 cm. There were 116 (22.8%) patients with well pathological differentiation, 352 (69.0%) patients with moderate pathological differentiation, and 42 (8.2%) patients with poor pathological differentiation. For TNM stage, there were 93 (18.2%) patients with stage I, 294 (57.7%) patients with stage II, and 123 (24.1%) patients with stage III. Other detailed clinical characteristics were listed in Table 1.

3.2 | SOX30 expression

The IHC assay and the subsequent semi-quantitative scoring method assessment showed that there were 368 (72.2%) patients in SOX30 low-expression group and 142 (27.8%) patients in SOX30 high-expression group. Moreover, further classification displayed that there were 83 (16.3%) patients in SOX30 high + group, 35 (6.9%) patients in SOX30 high++ group and 24 (4.7%) patients in SOX30 high+++ group (Figure 1).

Additionally, SOX30 expression in non-cancerous tissues and breast cancer cell lines was investigated. For SOX30 expression in

| TABLE 1 | Clinical characteristics of breast cancer patients |
|-----------------|-------------------------------------------------|
| Items | Total patients (N = 510) |
| Age (y), mean ± SD | 55.7 ± 12.9 |
| <50 y, No. (%) | 184 (36.1) |
| ≥50 y, No. (%) | 326 (63.9) |
| ER positive, No. (%) | 300 (58.8) |
| PR positive, No. (%) | 263 (51.6) |
| HER-2 positive, No. (%) | 169 (33.1) |
| Pathological differentiation, No. (%) | |
| Well | 116 (22.8) |
| Moderate | 352 (69.0) |
| Poor | 42 (8.2) |
| Tumor size (cm), mean ± SD | 3.1 ± 1.9 |
| <3 cm, No. (%) | 248 (48.6) |
| ≥3 cm, No. (%) | 262 (51.4) |
| T stage, No. (%) | |
| T1 | 189 (37.1) |
| T2 | 267 (52.3) |
| T3 | 54 (10.6) |
| N stage, No. (%) | |
| N0 | 264 (51.8) |
| N1 | 144 (28.2) |
| N2 | 89 (17.5) |
| N3 | 13 (2.5) |
| TNM stage, No. (%) | |
| I | 93 (18.2) |
| II | 294 (57.7) |
| III | 123 (24.1) |

Abbreviations: ER, estrogen receptor; HER-2, human epithelial growth factor receptor-2; PR, progesterone receptor; SD, standard deviation.
non-cancerous tissues, data showed that there were 9 (22.5%) in the SOX30 low-expression group and 31 (77.5%) in the SOX30 high-expression group (including 10 (25.0%) in SOX30 high + group, 11 (27.5%) in SOX30 high++ group, and 10 (25.0%) in SOX30 high+++ group) (Figure S1). For SOX30 expression in breast cancer cell lines, SOX30 expression was decreased in breast cancer cell lines T47D, MDAMB231, MCF7, MDMAB453, TB474, and MDAMB468 compared to human normal breast cell line MCF-10F (all P < .001) (Figure S2). These data implied that SOX30 might be an anti-oncogene in breast cancer.

3.3 Correlation of SOX30 with clinical characteristics

SOX30 was negatively correlated with tumor size (P = .010), T stage (P < .001), N stage (P = .001), and TNM stage (P < .001), whereas no correlation was observed in SOX30 with age (P = .384), ER status (P = .759), PR status (P = .964), HER-2 status (P = .204), or pathological differentiation (P = .726) in breast cancer patients (Table 2).

3.4 Correlation of SOX30 with DFS and OS in breast cancer patients

For DFS, data illustrated that patients in SOX30 high-expression group had better DFS compared to patients in SOX30 low-expression group (P = .011) (Figure 2A), and increased SOX30 grade (assessed by semi-quantitative scoring method assessment) was correlated with superior DFS (P = .015) in breast cancer patients (Figure 2B). As to OS, patients in SOX30 high-expression group had enhanced OS compared to patients in SOX30 low-expression group (P = .002) (Figure 2C), and elevated SOX30 grade (assessed by semi-quantitative scoring method assessment) was also associated with better OS (P = .014) in breast cancer patients (Figure 2D). Furthermore, subgroup analysis was conducted; however, no correlation was observed between SOX30 and DFS in TNM stage I patients (P = .980) (Figure 3A), TNM stage II patients (P = .218) (Figure 3B), or TNM stage III patients (P = .338) (Figure 3C), as well as OS in TNM stage I patients (P = .169) (Figure 3D), TNM stage II patients (P = .315) (Figure 3E), or TNM stage III patients (P = .218) (Figure 3F). These might result from the prognostic value of SOX30 relied on its interaction with TNM stage, and the limited subgroup sample size decreased the statistical power.

3.5 Factors predicting DFS and OS in breast cancer patients

For DFS, univariate Cox’s regression showed that SOX30 high expression (P = .012, HR = 0.582) was correlated with better DFS, while poor pathological differentiation (P < .001, HR = 2.777), enhanced T stage (P < .001, HR = 2.423), and elevated N stage (P = .002, HR = 1.739) were associated with worse DFS in breast cancer patients. Multivariate Cox’s regression displayed that poor pathological differentiation (P < .001, HR = 3.073), enhanced T stage (P < .001, HR = 2.959), and elevated N stage (P = .004, HR = 1.789) were independent predictive factors for poor DFS. SOX30 could predict DFS independently in breast cancer patients to some tendency, while no statistical significance was observed (P = .224, HR = 0.766) (Table 3). Concerning OS, univariate Cox’s regression illustrated that SOX30 high expression (P = .002, HR = 0.389) and ER positive (P = .043, HR = 0.645) were correlated with better OS, while poor pathological differentiation (P < .001, HR = 3.799), enhanced T stage (P < .001, HR = 4.180), and elevated N stage (P < .001, HR = 2.431) were associated with worse OS in breast cancer patients. Multivariate Cox’s regression revealed that poor pathological differentiation (P < .001, HR = 4.638), enhanced T stage (P < .001, HR = 6.219), and elevated N stage (P = .002, HR = 2.296) were independent predictive factors for worse OS. SOX30 independently predict OS in breast cancer patients to some tendency, whereas no statistical significance was found (P = .087, HR = 0.582) (Table 4). These data revealed that SOX30 was not an independent factor predicting DFS and OS in breast cancer, indicating that it might interact with independent factors (pathological differentiation, T stage, and N stage), thereby influencing the prognosis of breast cancer patients.

4 DISCUSSION

The anti-tumor property of SOX30 has been revealed by various researches. For example, SOX30 directly attaches to the promoter

**FIGURE 1** Immunohistochemistry analysis of SOX30 expression in breast cancer patients. SOX30, Sex-determining region Y-box 30; IHC, immunohistochemistry.
part of p53 and thus activating the transcription of p53, thereby inducing apoptosis in lung cancer cells and inhibiting tumor progression in vivo.\textsuperscript{16} Meanwhile, it is reported that the knockout of SOX30 in mice promotes lung cancer metastasis, and further study discloses that SOX30 inhibits Wnt/\(\beta\)-catenin pathway by suppressing \(\beta\)-catenin transcription or by interacting with \(\beta\)-catenin.\textsuperscript{8} Moreover, it is revealed that both in colorectal cancer cells and hepatocellular carcinoma cells, the overexpression of SOX30 suppresses cell proliferation and induces apoptosis.\textsuperscript{9,17} Together, these researches clearly point out the anti-tumor property of SOX30.

The decreased expression of SOX30 is reported in several tumor tissues including bladder tumor tissues and lung adenocarcinoma tissues\textsuperscript{10,18}; however, the SOX30 expression in breast cancer patients remained to be explored. Therefore, 510 breast cancer patients were enrolled in this study and expression of SOX30 in them was analyzed by IHC. Data revealed that there were 368 (72.2\%) patients with SOX30 low expression, while 142 (27.8\%) patients with SOX30 high expression. Moreover, SOX30 was highly expressed in non-cancerous tissues and was decreased in breast cancer cell lines compared to human normal breast cell line, implying SOX30 might be an anti-oncogene in breast cancer.

As to the correlation of SOX30 with tumor burden, it is disclosed that SOX30 is negatively correlated with clinical stage and metastasis in ovarian cancer patients,\textsuperscript{12} with the stage and grade of malignancy in malignant lymphomas patients,\textsuperscript{19} with TNM stage in bladder cancer patients,\textsuperscript{10} and with tumor size in liver cancer patients,\textsuperscript{17} etc. In line with these researches, we discovered that SOX30 was correlated with reduced tumor size, ameliorated T stage, N stage, and TNM stage in breast cancer patients. These data could be explained by that: (1) In breast cancer, SOX30 might also exert similar anti-cancer properties as in lung adenocarcinoma, which inhibits the proliferation and induced apoptosis in breast cancer cells by activating p53 transcription, thus reducing tumor growth in breast cancer. Therefore, SOX30 was negatively associated with tumor size and T stage in breast cancer patients. (2) As described above, SOX30 suppresses metastasis in several kinds of tumor by inhibiting Wnt/\(\beta\)-catenin pathway, and in this study, SOX30 might also target Wnt/\(\beta\)-catenin pathway to prevent breast cancer cells from migrating and invading into nearby lymph nodes in patients. Therefore, SOX30 was negatively correlated with N stage in breast cancer patients.

Several previous researches disclose that SOX30 was correlated with better prognosis in cancer patients (including ovarian cancer patients and clear cell renal cell carcinoma patients).\textsuperscript{20-22} In the present study, prolonged DFS and OS were observed in SOX30 high-expression group, and increased SOX30 grade (assessed by semi-quantitative scoring method assessment) was correlated with enhanced DFS and OS in breast cancer patients. Moreover, patients with extreme SOX30 high expression had prolonged DFS and OS. Possible explanations might be that: (a) SOX30 is correlated with favorable tumor characteristics (tumor size, T stage, N stage, and TNM stage) in breast cancer; therefore, it might affect the prognosis of breast cancer patients by influencing these tumor characteristics. (b) SOX30 is known to promote p53 transcription, and the up-regulation of p53 is one of the solutions to chemoresistance in breast cancer, which is caused by the degradation of p53 by mouse double minute 2 homolog (MDM2).\textsuperscript{23} SOX30 might alleviate the inhibitory role of MDM2 toward p53, thereby increased the effect of neoadjuvant therapy or systematic adjuvant therapy in breast cancer patients; therefore, patients with increased SOX30 had improved prognosis. Notably, multivariant Cox’s regression analysis illustrated that SOX30 was not an

| TABLE 2 | Comparison of clinical characteristics between SOX30 high- and low-expression patients |
|-------------------|---------------------------------|-------------------|---|
| | Items | SOX30 | | P value |
| | | Low (n = 368) | High (n = 142) | |
| | Age, No. (%) | | | |
| | <50 y | 137 (37.2) | 47 (33.1) | .384 |
| | ≥50 y | 231 (62.8) | 95 (66.9) | |
| | ER status, No. (%) | | | |
| | Negative | 150 (40.8) | 60 (42.3) | .759 |
| | Positive | 218 (59.2) | 82 (57.7) | |
| | PR status, No. (%) | | | |
| | Negative | 178 (48.4) | 69 (48.6) | .964 |
| | Positive | 190 (51.6) | 73 (51.4) | |
| | HER-2 status, No. (%) | | | |
| | Negative | 240 (65.2) | 101 (71.1) | .204 |
| | Positive | 128 (34.8) | 41 (28.9) | |
| | Pathological differentiation, No. (%) | | | |
| | Well | 85 (23.1) | 31 (21.8) | .726 |
| | Moderate | 249 (67.7) | 103 (72.6) | |
| | Poor | 34 (9.2) | 8 (5.6) | |
| | Tumor size, No. (%) | | | |
| | <3 cm | 166 (45.1) | 82 (57.7) | .010 |
| | ≥3 cm | 202 (54.9) | 60 (42.3) | |
| | T stage, No. (%) | | | |
| | T1 | 119 (32.3) | 70 (49.3) | <.001 |
| | T2 | 201 (54.6) | 66 (46.5) | |
| | T3 | 48 (13.1) | 6 (4.2) | |
| | N stage, No. (%) | | | |
| | N0 | 175 (47.6) | 89 (62.7) | .001 |
| | N1 | 109 (29.6) | 35 (24.6) | |
| | N2 | 73 (19.8) | 16 (11.3) | |
| | N3 | 11 (3.0) | 2 (1.4) | |
| | TNM stage, No. (%) | | | |
| | I | 47 (12.8) | 46 (32.4) | <.001 |
| | II | 218 (59.2) | 76 (53.5) | |
| | III | 103 (28.0) | 20 (14.1) | |

Note: Comparison was determined by chi-square test or Wilcoxon rank-sum test.

Abbreviations: ER, estrogen receptor; HER-2, human epithelial growth factor receptor-2; PR, progesterone receptor; SD, standard deviation.
independent predictive factor for DFS and OS in breast cancer patients, implying that it might interact with other independent predictive factors (pathological differentiation, T stage, and N stage) to influence the prognosis in breast cancer patients, which needed further investigation. Interestingly, according to several previous studies, SOX30 lacks predictive value for prognosis in clear cell...
renal cell carcinoma and correlated with worse prognosis in hepatocellular carcinoma.\cite{9,22} The discrepancies in the results between these previous studies and our study might be caused by the difference in the types of cancer.

Several limitations, however, existed in the present study, and further investigations should be conducted. The first is that all of the 510 patients were newly diagnosed as breast cancer; therefore, the significance of SOX30 in recurrent breast cancer patients was not investigated. The second limitation lied to that breast cancer patients with distant metastasis were not enrolled, and the role of SOX30 in them, as well as the correlation of SOX30 with M stage and TNM stage IV, was unclear. Finally, fundamental biological assays could be conducted to explore the role of SOX30 in the proliferation, migration, and invasion of breast cancer cells and further evaluate SOX30 as a potential therapeutic option in breast cancer.

To be collective, SOX30 is negatively correlated with tumor size and stage, but positively correlated with DFS and OS in breast cancer patients. Therefore, SOX30 is a vital biomarker for breast cancer, which might contribute to the outcome of breast cancer patients.

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.

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