Original paper

FOXC1 expression profile in invasive breast carcinomas and its relationship with prognostic parameters

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This study aimed to investigate the expression profile of FOXC1 in molecular subtypes of invasive breast cancer. Additionally, it sought to explore the association between FOXC1 expression and clinicopathological prognostic parameters to evaluate its potential diagnostic and therapeutic implications.

A total of 122 invasive breast carcinoma cases from excision specimens were analysed. Immunohistochemical staining for FOXC1 was performed, with nuclear expression > 1% considered positive. The correlation between FOXC1 expression, molecular subtypes, and prognostic parameters was examined.

A significant negative correlation was found between FOXC1 expression and ER, PR, and HER2 in 122 cases, while FOXC1 expression was notably higher in the triple-negative breast cancer (TNBC) subtype. Additionally, FOXC1 expression showed a significant positive correlation with nuclear grade, histological grade, Ki67 index, and prognostic stage.

FOXC1 expression was found to be higher in TNBCs compared to other molecular subtypes, and FOXC1 expression was negatively correlated with hormone receptors and HER2. On the other hand, FOXC1 was significantly associated with high proliferation index, high-grade tumour, and prognostic stage. These findings suggest that high FOXC1 expression may indicate aggressive behaviour and may be a predictive marker for poor prognosis.

Key words: breast carcinoma, molecular subtype of breast cancer, FOXC1.

Introduction

Breast cancer is the most common malignancy among the female population worldwide and ranks fourth in terms of mortality [1]. The incidence of breast cancer continues to rise due to factors such as increasing obesity rates, delayed childbirth, decreasing birth rates and breastfeeding duration, longer life expectancy, and the use of exogenous hormones [2]. Five-year survival rates vary significantly depending on the disease stage, with a 91% survival rate in non-metastatic cases, decreasing to 86% in cases with regional lymph node involvement, and falling to as low as 30% in cases with distant metastases [3].

Historically, breast cancer has been classified based on histological type; however, the observation that patients with the same histological subtype can exhibit different clinical outcomes has highlighted the importance of molecular classification [4]. Based on gene expression profiles, breast cancer is now molecularly classified into three main subtypes: luminal (A and B), human epidermal growth factor recep-

tor 2 (HER2)-overexpressed, and triple-negative [4]. Triple-negative breast cancer (TNBC) is defined by the absence of oestrogen receptor (ER), progesterone receptor (PR), and HER2 expression [5]. Representing approximately 15–20% of all breast carcinomas, TNBC is known for its aggressive biological behaviour, high histological grade, and elevated mortality risk [4, 5]. Differentiation between these subtypes is crucial for determining treatment strategies. Therapeutic approaches vary widely, ranging from surgical interventions to chemotherapy, radiotherapy, and hormonal therapy, depending on the gene expression profile, disease stage, and hormonal status of the patient [6]. Although most patients respond well to treatment, research continues to identify new diagnostic biomarkers and therapeutic targets to further reduce morbidity and mortality.

Many genes and their products influence cell proliferation and tumour development. Among these, transcription factors play a key role by regulating the expression of specific genes, thus controlling protein production and other biological processes [7]. The forkhead box (FOX) gene family comprises several such transcription factors. FOXC1, a member of this family located on chromosome 6, is involved in the development of organs such as the eye, heart, bone, and brain during embryogenesis, as well as in maintaining tissue homeostasis and regulating cellular motility [8]. Increased FOXC1 activity has been shown to contribute to various biological processes in cancer cells, including proliferation, differentiation, survival, invasion, and metastasis, and is also associated with enhanced angiogenesis [7–9].

A study on invasive breast carcinoma found that FOXC1 expression, particularly in TNBC, was associated with higher histological grade, aggressive clinical features, and poor prognosis [10]. Other studies have also linked high FOXC1 expression with more aggressive phenotypes and poor outcomes in various cancers such as breast [11], liver [12], lung [13], and endometrial cancers [14].

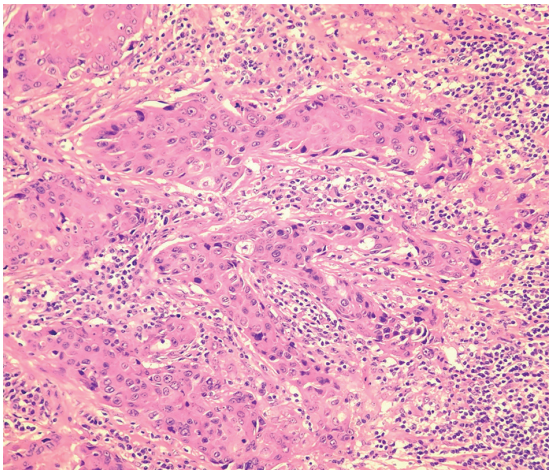

Fig. 1. Representative image of an invasive breast carcinoma with histological grade 3

The basal-like subtype of TNBC, which exhibits high histological grades and an aggressive clinical course, is frequently associated with elevated FOXC1 expression [7]. Although gene expression profiling remains the gold standard for diagnosing basal-like breast cancer, FOXC1 has been proposed as a sensitive biomarker not only for identifying TNBC but also for differentiating its basal-like subtype. As such, research on FOXC1 continues to be of interest.

The aim of our study is to determine the distribution of FOXC1 expression in invasive breast carcinomas, particularly across molecular subtypes, and to evaluate its correlation with clinicopathological prognostic parameters. The findings are then compared with data in the existing literature to assess the potential contribution of FOXC1 to diagnosis and treatment strategies.

Material and methods

The study was aprroved by Atatürk University Faculty of Medicine Clinical Research Ethics Committee (approval number: B.30.2.ATA.0.01.00/323).

A total of 122 lumpectomy and mastectomy specimens diagnosed with invasive breast carcinoma between 2018 and 2023 at Department of Pathology, Atatürk University Faculty of Medicine in Erzurum (Turkey) were included in this study. Cases with malignancy in another organ, unknown hormone receptor or HER2 status, issues in detection or follow-up, or unsuccessful immunohistochemical staining were excluded from the study. Formalin-fixed paraffin-embedded (FFPE) blocks and HE-stained slides of the eligible cases were retrieved from the pathology archive and re-evaluated to select the most representative block and slide for each tumour.

Data on patient age, histological tumour type, nuclear grade, histological grade, tumour size, presence of lymphovascular invasion (LVI), immunohistochemical markers (ER, PR, HER2, Ki67), molecular subtype, presence of accompanying *in situ* component, and lymph node metastasis status were obtained from the hospital's information management system and the national E-nabız system. Tumour grading was performed according to the Nottingham grading system, taking into account tubular formation, nuclear pleomorphism, and mitotic count (Fig. 1). Cases were staged using the 8th edition of the American Joint Committee on Cancer (AJCC) pathological prognostic staging system.

ER, PR, and HER2 status were re-evaluated based on the initial immunohistochemically stained diag-

nostic slides. Nuclear staining of more than 1% was considered positive for ER and PR. HER2 immunohistochemical scoring was based on the following: strong and complete membranous staining in more than 10% of tumour cells was scored as 3+; weak to moderate membranous staining as 2+; faint staining as 1+; and no staining or incomplete/faint staining in less than 10% of tumour cells as 0. Cases scoring 0 and 1+ were considered HER2-negative, while those scoring 3+ were considered HER2-positive. *In situ* hybridisation was used to confirm HER2 status in 2+ cases. Ki67 proliferation index was categorised into 2 groups based on a 14% cut-off value [15].

Sections with a thickness of 5 microns were taken from selected paraffin blocks using a Leica RM2145 microtome and placed on poly-L-lysine-coated charged slides. Following deparaffinisation, slides were stained with FOXC1 antibody (Rabbit Recombinant Monoclonal FOXC1 antibody, EPR20685, Abcam) at a dilution of 1 : 200 using the Ventana BenchMark ULTRA automated immunostainer. Internal mammary duct epithelium was used as a positive control for FOXC1. The immunohistochemical staining procedures were carried out in accordance with the instructions provided in the antibody data sheet. FOXC1 expression was considered positive when more than 1% of tumour cells showed nuclear staining, as previously described. Cytoplasmic staining was evaluated as negative. FOXC1 expression was classified based on the extent of nuclear staining in tumour cells as negative (no staining), low (1–10%), moderate (11–40%), and high (41–100%) [10], as illustrated in Figs. 2 and 3.

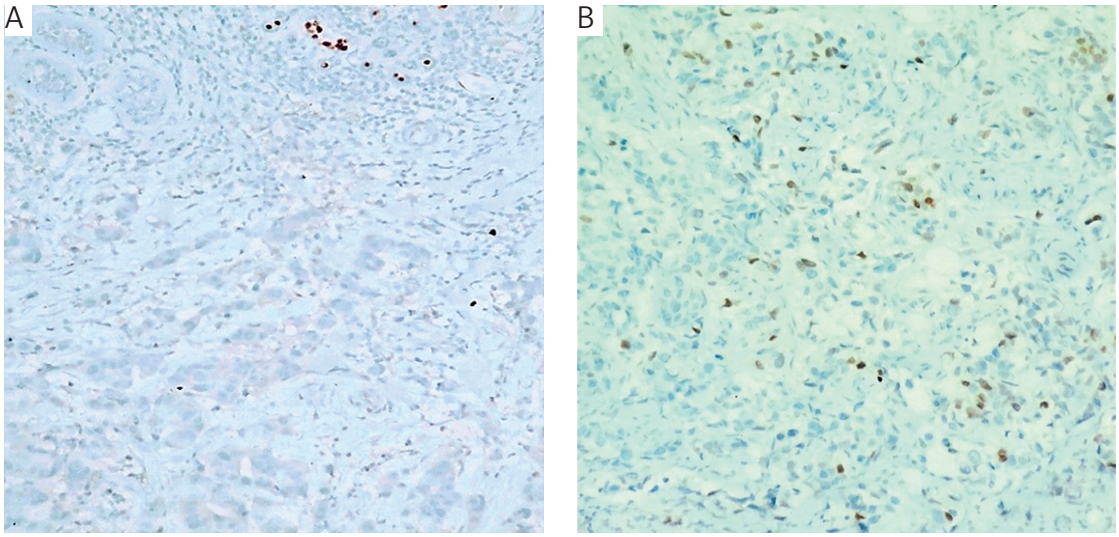

Fig. 2. FOXC1 immunohistochemistry: **A)** negative staining (with internal control); **B)** low expression (×200)

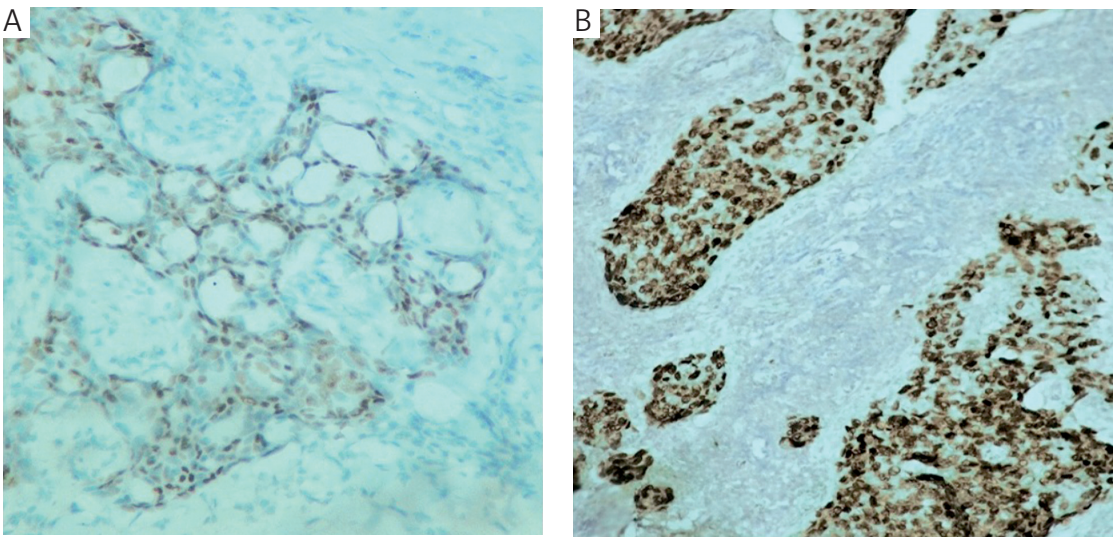

Fig. 3. FOXC1 immunohistochemistry: **A)** moderate expression; **B)** high expression (×200)

Statistical analysis

All data were analysed using IBM SPSS Statistics version 27.0.1 (IBM Corporation, Armonk, NY, USA). Clinicopathological parameters were compared between different groups using the chi-square test. A p-value of less than 0.05 was considered statistically significant.

Results

A total of 122 female patients diagnosed with invasive breast carcinoma were included in our study. The mean age at diagnosis was 52.08 years, ranging from 26 to 90 years. The average tumour size was calculated as 3.2 cm, with tumour diameters ranging from 0.3 cm to 15.9 cm.

Regarding histological type, the most common tumour subtype was invasive ductal carcinoma, observed in 96 cases (78.7%), followed by invasive lobular carcinoma in 10 cases (8.2%).

When nuclear grade was evaluated, half of the cases were grade 3, and 59 cases (48.4%) were grade 2. Based on the Nottingham histological grading system, 61 cases (50%) were grade 2, while 59 cases (48.4%) were grade 3.

Lymphovascular invasion was detected in 64 cases (52.5%). An accompanying *in situ* component was identified in 100 cases (82%), whereas 22 cases (18%) did not display an *in situ* component.

In terms of hormone receptor status, 64 cases (53.3%) were positive for both ER and PR. Only one case (0.81%) was ER-positive and PR-negative, while another case (0.81%) was PR-positive and ER-negative. Regarding HER2 status, 35 cases (28.7%) were HER2-positive, while 87 cases (71.3%) were HER2-negative. Based on the Ki-67 proliferation index, using a cutoff value of 14%, 34 cases (27.9%) were classified as low proliferation and 88 cases (72.1%) as high proliferation.

According to molecular subtyping based on ER, PR, and HER2 status, 66 cases (54.1%) were classified as luminal subtype, 22 cases (18%) as HER2-overexpressing subtype, and 34 cases (27.9%) as TNBC.

In terms of pathological T staging, 46 cases (37.7%) were classified as pT1, 51 cases (41.8%) as pT2, 18 cases (14.8%) as pT3, and 7 cases (5.7%) as pT4. Among the 122 cases, axillary lymph node dissection was not performed in 88 cases (72.13%) due to the absence of metastasis in sentinel lymph node biopsy. Considering all cases, lymph node (LN) metastasis was detected in 48 cases (39.3%), while 74 cases (60.7%) had no LN metastasis. Based on the pathological prognostic staging, 55 cases (45.1%) were classified as stage I, 42 cases (34.4%) as stage II, and 25 cases (20.5%) as stage III.

When evaluated for FOXC1 expression, 81 cases (66.4%) were negative. Among the 41 positive cases, 11 cases (9%) showed low-level expression, 6 cases (4.9%) moderate expression, and 24 cases (19.7%) high-level expression.

When the relationship between FOXC1 expression and hormone receptors was evaluated, none of the 65 ER-positive cases (53.27%) showed high FOXC1 positivity. In this group, 5 cases (4.09%) demonstrated low FOXC1 positivity, and 60 cases (49.18%) were FOXC1-negative. Among the 57 ER-negative cases (46.72%), 21 (17.21%) were FOXC1-negative, while 24 cases (19.67%) exhibited high FOXC1 expression.

Among the 65 PR-positive cases (53.27%), only one case (0.81%) showed high FOXC1 positivity, while 59 cases (48.36%) were FOXC1-negative. A statistically significant negative correlation was observed between FOXC1 expression and both ER and PR status ($p < 0.001$ for both).

Among the 35 HER2-positive cases (28.7%), only 6 (4.91%) were FOXC1-positive, whereas among the 87 HER2-negative cases (71.3%), 35 (28.7%) were FOXC1-positive. FOXC1 expression decreased as HER2 expression increased, indicating a significant inverse correlation between these two biomarkers ($p = 0.007$).

FOXC1 positivity was most commonly observed in TNBC. Among the 66 luminal subtype cases (54.09%), only one case (0.81%) showed high FOXC1 positivity, and 5 cases (4.09%) showed low expression, totalling 6 FOXC1-positive cases (4.91%). Among the 22 HER2-overexpressing subtype cases (18.03%), 6 cases (4.91%) were FOXC1-positive, with 4 showing low expression, one showing moderate expression, and none showing high expression; the remaining 16 cases (13.11%) were FOXC1-negative. Of the 34 TNBC cases (27.86%), 23 (18.85%) had high, 4 (3.27%) had moderate, and 2 (1.63%) had low FOXC1 expression, totalling 29 FOXC1-positive cases (23.77%) and only 5 (4.09%) FOXC1-negative. A statistically significant association was found between molecular subtypes and FOXC1 expression ($p < 0.001$). FOXC1 was strongly associated with the TNBC subtype, with its expression decreasing in luminal subtypes.

In the group of 61 low-grade cases (nuclear grade 1 and 2; 50%), FOXC1 expression was observed in 15 cases (12.29%). Among the other 61 cases with high nuclear grade (grade 3; 50%), 26 (21.31%) showed FOXC1 expression. Among the 63 cases with low histological grade (grade 1 and 2; 51.6%), 13 cases (10.65%) were FOXC1-positive. Of the 59 high-grade histological cases (grade 3; 48.4%), 28 (22.95%) were FOXC1-positive. A statistically significant and positive correlation was found between FOXC1 expression and both nuclear grade ($p = 0.035$) and histological grade ($p = 0.004$).

Table I. Demographic and prognostic data of the cases according to FOXC1 expression profile

Parameter	FOXC1				*p-value*
	Negative (%)	Low (%)	Moderate (%)	High (%)	
Age					
< 50	39 (31.9)	3 (2.45)	2 (1.63)	16 (13.11)	0.749
≥ 50	42 (34.2)	8 (6.55)	4 (3.27)	8 (6.55	
Tumour size					
≤ 2 cm	33 (27.04)	5 (4.09)	1 (0.81)	9 (7.37)	0.657
> 2 cm	48 (39.34)	6 (4.91)	5 (4.09)	15 (12.29)	
Histological type					
Invasive ductal carcinoma	61 (50)	10 (8.19)	5 (4.09)	20 (16.39)	0.760
Invasive lobular carcinoma	7 (5.73)	1 (0.81)	0 (0)	2 (1.63)	
Others	13 (10.65)	0 (0)	1 (0.81)	2 (1.63)	
Nuclear grade					
1 and 2	46 (37.70)	6 (4.91)	1 (0.81)	8 (6.55)	0.035*
3	35 (28.68)	5 (4.09)	5 (4.09)	16 (13.11)	
Histologic grade					
1 and 2	50 (40.98)	6 (4.91)	1 (0.81)	6 (4.91)	0.004
3	31 (25.40)	5 (4.09)	5 (4.09)	18 (14.75)	
Lymphovascular invasion					
Present	40 (32.78)	7 (5.73)	5 (4.09)	12 (9.83)	0.36
Absent	41 (33.6)	4 (3.27)	1 (0.81)	12 (9.83)	
Presence of *in situ* component					
Present	66 (54.09)	9 (7.37)	6 (4.91)	19 (15.57)	0.691
Absent	15 (12.29)	2 (1.63)	0 (0)	5 (4.09)	
ER Status					
Positive	60 (49.18)	5 (4.09)	0 (0)	0 (0)	< 0.001
Negative	21 (17.21)	6 (4.91)	6 (4.91)	24 (19.67)	
PR Status					
Positive	59 (48.36)	5 (4.09)	0 (0)	1 (0.81)	< 0.001
Negative	22 (17.21)	6 (4.91)	6 (4.91)	23 (18.85)	
HER2 status					
Positive	29 (23.77)	4 (3.27)	2 (1.63)	0 (0)	0.007
Negative	52 (42.62)	7 (5.73)	4 (3.27)	24 (19.67)	
Ki67					
Low (≤ 14%)	28 (22.95)	4 (3.27)	1 (0.81)	1 (0.81)	0.026
High (> 14%)	53 (43.44)	7 (5.73)	5 (4.09)	23 (18.85)	
Molecular subtype					
Luminal	60 (49.18)	5 (4.09)	0 (0)	1 (0.81)	< 0.001
HER2 overexpressed	16 (13.11)	4 (3.27)	2 (1.63)	0 (0)	
Triple negative	5 (4.09)	2 (1.63)	4 (3.27)	23 (18.85)	
Lymph node metastasis					
Present	30 (24.59)	6 (4.91)	1 (0.81)	11 (9.01)	0.397
Absent	51 (41.8)	5 (4.09)	5 (4.09)	13 (10.65)	

Table I. Cont.

Parameter	FOXC1				*p-value*
	Negative (%)	Low (%)	Moderate (%)	High (%)	
Pathologic T Stage					
pT1	33 (27.04)	5 (4.09)	1 (0.81)	7 (5.73)	0.841
pT2	32 (26.22)	4 (3.27)	3 (2.45)	12 (9.83)	
pT3 and pT4	16 (13.11)	2 (1.63)	2 (1.63)	5 (4.09)	
Pathologic N Stage					
pN0	51 (41.8)	5 (4.09)	5 (4.09)	13 (10.65)	0.392
pN1	23 (18.85)	4 (3.27)	0 (0)	10 (8.19)	
pN2 and pN3	7 (5.73)	2 (1.63)	1 (0.81)	1 (0.81)	
Prognostic Stage					
Stage I	46 (37.7)	4 (3.27)	1 (0.81)	4 (3.27)	0.002
Stage II	26 (21.31)	4 (3.27)	3 (2.45)	9 (7.37)	
Stage III	9 (7.37)	3 (2.45)	2 (1.63)	11 (9.01)	

**In the analysis of nuclear grade, the FOXC1 parameter was categorized into 2 groups (positive and negative) for statistical comparison*

Among the 88 cases (72.1%) with a high proliferation index based on Ki-67 immunohistochemistry, 35 cases (28.68%) were FOXC1-positive. Of the 34 cases (27.9%) with a low Ki-67 index, 28 (22.95%) were FOXC1-negative. A statistically significant positive correlation was observed between FOXC1 expression and the Ki-67 proliferation index ($p = 0.026$).

According to pathological prognostic staging, 9 of the 55 stage I cases (16.3%), 16 of the 42 stage II cases (38.1%), and 16 of the 25 stage III cases (64%) were FOXC1-positive. A significant association was found between FOXC1 expression and prognostic stage ($p = 0.002$).

In our study, no statistically significant relationship was found between FOXC1 expression and age ($p = 0.74$), tumour size ($p = 0.65$), histological type ($p = 0.76$), lymphovascular invasion ($p = 0.36$), presence of *in situ* component ($p = 0.69$), lymph node metastasis ($p = 0.39$), pathological T stage ($p = 0.84$), or pathological N stage ($p = 0.39$).

The FOXC1 expression profiles of the cases, along with their associations with demographic and prognostic data and the corresponding statistical values, are summarised in Table I.

Discussion Forkhead box (FOX) proteins, particularly members of the C subclass, have been found to directly influence cancer initiation, progression, maintenance, and drug resistance [7, 10]. Increased FOXC1 activity has been associated with malignancy [7]. Recently, FOXC1 has been investigated for its positive role in various cellular biological processes – such as cancer cell proliferation, differentiation, survival, and metastasis – across several cancers, including breast, liver, lung, endometrial, and nasopharyngeal carcinomas [11–14, 16].

Studies on breast cancer have reported that luminal and HER2-overexpressing tumours exhibit significantly lower FOXC1 expression compared to triple-negative tumours, emphasising the high levels of FOXC1 expression specifically in triple-negative breast cancer [8, 17–20]. In recent years, particularly in the basal-like subtype of TNBC – which is often characterised by high histological grade and aggressive clinical behaviour – elevated FOXC1 expression has been observed [7]. In a study conducted in 2025, Logan *et al.* demonstrated that FOXC1 expression increases in correlation with basal markers [21].

In a large cohort study conducted by Li *et al.*, approximately 80% of TNBC cases demonstrated FOXC1 expression, with 91.67% of these cases exhibiting moderate to high expression levels [10].

In line with previous findings, our study confirmed that FOXC1 is predominantly expressed in TNBC, while being rarely expressed in luminal-like and HER2-overexpressing subtypes. A statistically significant negative correlation was observed between FOXC1 and hormone receptors, as well as HER2 expression.

For instance, studies by Johnson *et al.* and Wang *et al.* emphasised the strong inverse correlation between FOXC1 and ER/PR negativity, a relationship also reported in separate studies by Li *et al.* in 2022 and 2024 [10, 17, 20, 22]. Additionally, even in luminal subtypes, FOXC1 expression has been associated with low ER expression or PR negativity [10]. In

a study by Hu *et al*. focusing on TNBC, HER2 negativity was grouped as scores 0 and 1, and FOXC1 expression was shown to be inversely correlated with HER2 [23].

Consistent with the literature, our study reinforces that high FOXC1 expression in hormone receptor-negative tumours may reflect FOXC1's significant role in the molecular pathogenesis of breast cancer. Understanding FOXC1's role in receptor-negative tumours could provide insight into potential targets for future therapeutic approaches.

A positive correlation between FOXC1 expression and both nuclear and histological grades was identified. FOXC1 expression increased in parallel with higher tumour grades. This finding is supported by several studies reporting that tumours with high FOXC1 expression tend to have higher nuclear and histological grades [10, 19–25].

FOXC1 also showed a statistically significant positive correlation with Ki67. Several studies – including those involving invasive breast carcinomas, particularly recent ones published in 2025 [21, 25], as well as earlier research [20, 22, 23] – have reported a similar association. Additionally, studies on gastric and pancreatic cancers have also demonstrated that FOXC1 expression is positively correlated with high Ki67 levels [26, 27]. Ki67 is a well-established marker of cellular proliferation and is typically associated with aggressive tumour phenotypes. Taken together with both the general and breast cancer-specific literature, the observed correlation in our study suggests that FOXC1 may be a key factor directly promoting tumour cell proliferation.

Our study also revealed a significant relationship between FOXC1 expression and prognostic stage. Supporting this, a meta-analysis by Kume *et al.* demonstrated that FOXC1 is more frequently expressed in advanced-stage cancers than in early-stage tumours [28]. Similarly, studies on pancreatic and colorectal cancers have also shown increased FOXC1 expression in more advanced disease stages [27, 29].

In the study conducted by Logan *et al*., it was concluded that patients with FOXC1-positive tumours tended to be younger [21]. However, in our study, no statistically significant association was found between FOXC1 expression and age ($p = 0.74$), tumour size ($p = 0.65$), histological type ($p = 0.76$), lymphovascular invasion (LVI) ($p = 0.36$), presence of an *in situ* component ($p = 0.69$), lymph node metastasis ($p = 0.39$), pathological T stage ($p = 0.84$), or pathological N stage ($p = 0.39$). These non-significant associations may be attributed to the sample size, distribution differences, or geographic and regional variations. Further studies with larger and more homogeneously distributed cohorts are needed to more clearly define the potential association between FOXC1 expression and age.

Overall, the positive correlation between FOXC1 expression and nuclear grade, histological grade, Ki67 proliferation index, and prognostic stage suggests an association with high-grade tumours. In this respect, our findings align with those in the literature. These results strengthen the potential role of FOXC1 as a biomarker in identifying aggressive tumours and guiding treatment decisions.

Conclusions

This study characterises FOXC1 expression across various invasive breast carcinoma subtypes. Notably, FOXC1 was found to be most highly expressed in TNBC, particularly in the basal-like subtype – a variant that tends to occur in younger patients and is associated with high histological grade, aggressive clinical behaviour, metastasis, and poor prognosis. While gene expression profiling remains the gold standard for identifying basal-like breast cancers, our findings suggest that FOXC1 may serve as a useful diagnostic biomarker for subclassifying TNBC and identifying the basal-like phenotype in the future.

Although our study found significant correlations between FOXC1 expression and various prognostic parameters, there are several limitations. These include a relatively small sample size and uneven distribution, with some subgroups underrepresented (e.g. only 2 cases with nuclear and histological grade 1, and a low number of cases in pT4 and pN3 stages). Additionally, patients' treatment histories were not considered, and the retrospective nature of the study based on archived material may introduce further limitations. It is also important to note that in heterogeneous cancers such as breast carcinoma, variations in protein expression may occur across different tumour regions.

Disclosures

1. Institutional review board statement: The study was aprroved by Atatürk University Faculty of Medicine Clinical Research Ethics Committee (approval number: B.30.2.ATA.0.01.00/323).
2. Assistance with the article: None.
3. Financial support and sponsorship: This study was financially supported by the Scientific Research Projects Coordination Unit (BAP) of Atatürk University [TTU-2023-12741].
4. Conflicts of interest: None.

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