Original Article

The prognostic significance of FMR1 autosomal homolog 1 (FXR1) in breast cancer

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Background: Breast cancer (BC) is a highly heterogeneous disease with variable histological appearance, biological features, clinical outcomes, and treatment responses. The number of BC cases in Saudi Arabia has more than tripled during the last 17 years to constitute 30% of all cancer cases in women. Therefore, greater efforts are needed to evaluate prognostic factors for BC in Saudi Arabia to improve prognostication and provide more personalized therapy. Recently, FMR1 autosomal homolog 1 (FXR1) was identified as a novel biomarker that contributes to oncogenesis; however, its role in BC has not been well studied. This study aims to evaluate the clinicopathological significance of FXR1 in women with primary BC.

Methods: The protein levels of FXR1 in BC tissue samples (n=100) were determined immunohistochemically. The associations between FXR1 levels and clinicopathological parameters and outcomes were evaluated, and significant associations were validated by assessing *FXR1* mRNA levels in publicly available cohorts in the BC Gene-Expression Miner database (version 5).

Results: High protein levels of *FXR1* were significantly associated with tumor aggressiveness, including stage IIB and IIIC and hormone receptor negativity, the triple-negative BC (TNBC) subtype, and poor outcomes. Consistent with the protein results, high mRNA levels of FXR1 were significantly associated with hormone receptor negativity and the TNBC subtype.

Conclusions: This study revealed that FXR1 is a prognostic factor for poor prognosis in women with BC. Further functional studies are needed to confirm its role in aggressive BC and its value as a therapeutic target.

Keywords: Breast cancer (BC); FMR1 autosomal homolog 1 (FXR1); prognosis; clinicopathological significance

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Introduction

Breast cancer (BC) accounts for 20% of all cancers in women and is the leading cause of cancer-related mortality worldwide. In Saudi Arabia, the number of BC cases has increased considerably from 545 to 2,463 (1). Therefore, BC is a substantial healthcare concern in Saudi Arabia that requires better monitoring. It is a highly heterogeneous disease with 28 distinct histological subtypes (2). The variation in BC development prompted studies to identify molecular subtypes of BC to improve BC taxonomy. While the molecular classification of BC has been shown to improve prognostic ability, it still has variable biological features, clinical outcomes, and treatment responses (2-4). Greater efforts are needed to identify better prognostic and diagnostic factors for BC in Saudi Arabia to improve prognostication and provide more personalized therapy.

The chromosomal region 3q26-29 has attracted considerable attention in cancer research due to its association with tumor growth and recurrence (5). Several gene amplification events in this region have been associated with negative medical outcomes, particularly survival rates, with various cancers (5). FMR1 autosomal homolog 1 (*FXR1*) is one of the genes in the 3q26-29 region. FXR1 has multiple functions in cells, such as promoting cell growth and regulating immune responses (5). FXR1 is a ribonucleic acid (RNA)-binding protein involved in regulating gene transcription and plays a vital role in the transport, translation, and degradation of messenger RNAs (mRNAs) (6,7). One study demonstrated that FXR1 contributes substantially to the progression of malignancies, and its overexpression is essential for the proliferation of non-small cell lung cancer cells (8).

In 2017, Qian *et al.* (9) determined the expression profiles of 4,801 BCs and reported that the 3q-19 gene expression signature was associated with poor outcomes in patients with triple-negative BC (TNBC). This 3q-19 gene signature is strongly associated with higher grade, larger tumor size, and negative estrogen receptor (ER) and progesterone receptor (PR) status. It also revealed that the 3q-19 gene signature was significantly associated with the basal-like, luminal B, and TNBC molecular BC subtypes and worse distant metastasis-free survival (9). Upregulation of *FXR1* in lung squamous cell carcinoma decreased apoptosis and enabled the evasion of cellular senescence (10). *FXR1* shows a propensity for co-expression with SRY-box transcription factor 2 (*SOX2*) in head and neck squamous cell carcinoma (11). *FXR1* was also found to interfere with the regulation of p21 and increase the stability of telomerase RNA component (TERC) activity (12).

All these data indicate that *FXR1* might act as a tumor promoter. However, the protein levels of FXR1 and its clinicopathological significance have not yet been studied in BC. Interrogating the protein levels of FXR1 in BC tissue and investigating their prognostic significance may improve the outcomes and treatments of patients with BC. Therefore, this study aimed to evaluate the clinicopathological and prognostic significance of FXR1 protein levels in women with primary BC. We present this article in accordance with the REMARK reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-1542/rc).

Highlight box

Key findings

- FMR1 autosomal homolog 1 (FXR1) is associated with aggressive features of tumor in breast cancer.
- FXR1 is a poor prognostic marker.

What is known and what is new?

- Breast cancer is a highly heterogeneous disease with variable clinical outcomes and is the most cause of cancer related death in women worldwide.
- FXR1 can be a prognosis predictor of invasive breast cancer.

What is the implication, and what should change now?

- Further investigation for the potential role of FXR1 in breast cancer progression and metastasis is needed.

Methods

Study cohort

Formalin-fixed paraffin-embedded (FFPE) blocks from 100 invasive BCs with sufficient tumor tissue were retrieved from the Histopathology Department at King Abdulaziz Specialist Hospital (KASH). This study was approved by the Institutional Review Board at King Abdulaziz Specialist Hospital (KASH; approval number: HAP-02-T-067) and was conducted according to the Declaration of Helsinki (as revised in 2013). All samples collected from King Abdulaziz Specialist Hospital used in this study were pseudonymized. Informed consent was obtained from all individuals prior to surgery to use their tissue materials in research. Patients clinicopathological characteristics were systematically recorded, including patient age, menopausal status, tumor

grade, tumor size, tumor-node-metastasis (TNM) stage, and lymph node status. Hormonal receptor status, including ER and PR, was available. Their human epidermal growth factor 2 (HER2) and marker of proliferation Ki-67 (MIK67) statuses were also available. They were considered HER2$^+$ if the immunohistochemistry (IHC) score was 3+ or if it was 2+ and fluorescence *in situ* hybridization confirmed the amplification of the *HER2* gene (13). They were considered Ki-67$^+$ if >20% of the tumor cells were positive for Ki-67. Their molecular subtype was determined based on their IHC profile and the St. Gallen surrogate classification for BC (13) as follows:

- Luminal A: ER$^+$ and/or PR$^+$, HER2$^-$, and low proliferation (Ki-67 <20%).
- Luminal B: ER$^+$ and/or PR$^+$, HER2$^{+/-}$, and high proliferation (Ki-67 ≥20%).
- HER2: ER$^-$ and/or PR$^-$, and HER2$^+$.
- TNBC: ER$^-$, PR$^-$, and HER2$^-$.

Outcome data, including overall survival (OS), were also available and recorded. The National Comprehensive Cancer Network guidelines were primarily used to guide patient treatment in this cohort (14).

FXR1 protein levels

The full-face section of FFPE samples was IHC stained for FXR1. Briefly, 4 µm tissue sections were cut using a rotary microtome (Minux® S700; Histo-Line Laboratories, Texas, USA) and adhered to positively charged microscope slides for IHC staining. Following dewaxing with xylene (X/2050; Fisher Scientific, Leicestershire, UK), sections were rehydrated with a decreasing ethanol gradient (E/0665DF, Fisher Scientific) to distilled water. Next, the sections were treated for 10 minutes with 100% methanol (M/4056, Fisher Scientific) and 0.9% hydrogen peroxide (H/1750, Fisher Scientific) to block endogenous peroxidases. Then, following the antibody manufacturer's recommendations, antigen retrieval was performed by heating a citrate buffer (pH 6) using a microwave (1,000 W for 10 minutes). Next, the sections were incubated with a blocking buffer consisting of 2% (w/v) bovine serum albumin (BSA; A8022; Sigma-Aldrich, Darmstadt, Germany) in phosphate-buffered saline (PBS) for 15 minutes.

For primary staining, the sections were incubated with the primary rabbit polyclonal antibody against FXR1 (NBP1-89546; Novus Biological Inc., Colorado, USA) diluted 1:50 in the blocking buffer at room temperature for one hour. Next, the sections were washed thrice with PBS for 5 minutes and then incubated with a biotinylated anti-rabbit secondary antibody diluted 1:200 in 2% BSA at room temperature for 40 minutes. Then, the sections were incubated with an anti-mouse secondary antibody (PK-6102; Vector Laboratories, California, USA) diluted 1:200. The excess antibody was removed by washing the sections thrice with PBS, and then the sections were incubated with avidin-biotin complexes (PK-6100, Vector Laboratories) at room temperature for 30 minutes. Next, the sections were incubated with diaminobenzidine (SK-4100, Vector Laboratories) and then washed thrice with PBS.

For counterstaining, the slides were washed in distilled water and then incubated with Mayers hematoxylin solution (MHS16, Sigma-Aldrich). After washing with distilled water, the sections were passed through an increasing ethanol gradient (2 minutes per step) and then xylene before being mounted in distyrene-tricresyl phosphate-xylene (06522, Sigma-Aldrich). Negative and positive controls were run with the samples. The negative control omitted the primary antibody. As recommended by the antibody manufacturer, colon cancer tissue was used as the positive control (*Figure 1A,1B*).

Scoring of FXR1 protein expression

The cytoplasmic expression of FXR1 was evaluated under 40× objective using a light microscope (Lecia DMI 3000B; Leica Microsystems, Wetzlar, Germany). FXR1 protein expression was scored semi-quantitatively using the modified histochemical score (H-score). A professional pathologist and the principal researcher anonymously and independently double-scored the sections. The final H-score for FXR1 was calculated by multiplying the staining intensity (0, no staining; 1+, weak staining; 2+, moderate staining; 3+, strong staining) by the percentage of stained tumor cells (0–100%) to produce values between 0 and 300 (15). There was a high concordance between the FXR1 scores of the two assessors [interclass correlation coefficient (ICC) =0.90, P<0.001]. Because the H-scores for FXR1 did not follow a normal distribution, the median was used as the cut-off for low and high FXR1 expression (H-score =140).

FXR1 transcriptomic analysis

In order to validate the correlations between FXR1 protein levels and multiple BC parameters, including patient

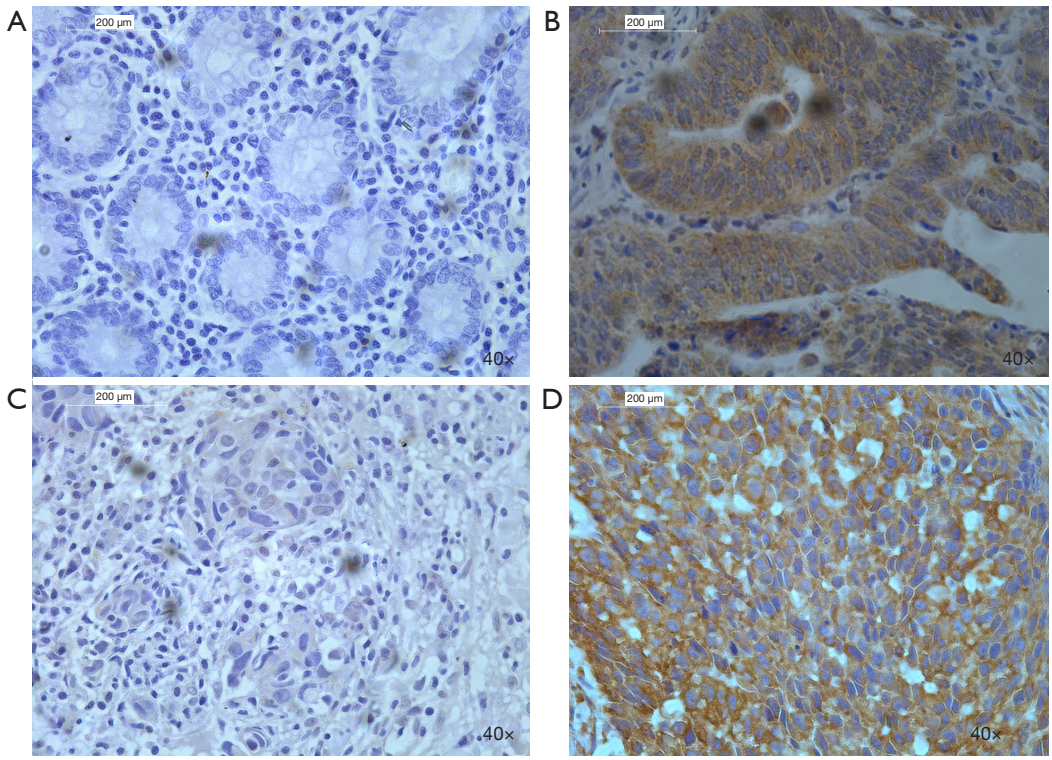

Figure 1 Light microscope images (×40 magnification, scale bars =200 µm) for immunohistochemical protein expression of FXR1 in breast tissue (A-D). (A) Negative control of colon tissue through the omission of FXR1 antibody in immunohistochemistry; (B) positive control of colon tissue exhibiting FXR1 staining in immunohistochemistry; (C) FXR1-negative immunohistochemistry expression; (D) FXR1-positive immunohistochemistry expression.

age, hormone receptors, and molecular subtypes, their correlations with *FXR1* mRNA levels were examined using all publicly available DNA microarray data (n=10,871) in the BC Gene Expression Miner database (version 5.0) (16).

Statistical analysis

The data were analyzed using the SPSS software (version 24.0; SPSS, Armonk, NY, USA). The ICC was calculated to determine the concordance of the FXR1 H-scores between the two assessors. The associations between low and high FXR1 protein levels and clinicopathological parameters were examined using the Chi-squared test. A univariate survival analysis (log-rank test and Kaplan-Meier curves) was conducted. Multivariate analysis was also conducted using the Cox regression model. A two-tailed P<0.05 was considered statistically significant for all tests.

Results

Association of FXR1 protein levels with clinicopathological parameters

FXR1 protein levels were determined in the cytoplasm of invasive BC cells, with levels ranging from nonexistent to high (*Figure 1C,1D*), more images were available in (Figures S1,S2). A high FXR1 protein level (H-score >140) was detected in 50/100 (50%) of patients with invasive BC. A high FXR1 protein level was significantly associated with stage IIB and IIIC (P=0.03); ER^-, PR^-, and $Ki\text{-}67^-$ (all P<0.001); and $HER2^-$ (P=0.03). No significant correlations were observed with the other clinicopathological parameters (*Table 1*).

Association of FXR1 protein levels with IHC subtypes:

Based on the St. Gallen guidelines for BC classification and

Table 1 Association of FXR1 protein expression level with clinicopathological parameters in KASH cohort (n=100)

Clinicopathological parameters	FXR1 expression, n [%]		P value
	Low (n=54)	High (n=46)	
Age (years)			
<50	25 [53]	22 [47]	>0.99
≥50	29 [55]	24 [45]	
Menopausal status			
Premenopausal	25 [53]	22 [47]	>0.99
Postmenopausal	29 [55]	24 [45]	
Tumor size			
<10 mm	17 [55]	14 [45]	0.60
≥10 mm	13 [46]	15 [54]	
Grade			
I	4 [50]	4 [50]	0.43
II	29 [52]	27 [48]	
III	19 [63]	11 [37]	
TNM stages			
Stage I	4 [44]	5 [56]	0.03
Stage IIA	11 [55]	9 [45]	
Stage IIB	2 [18]	9 [82]	
Stage IIIA	5 [100]	0 [0]	
Stage IIIB	2 [50]	2 [50]	
Stage IIIC	0 [0]	1 [100]	
Stage IV	6 [60]	4 [40]	
Lymph nodal status			
Negative	10 [40]	15 [60]	0.17
Positive	16 [62]	10 [38]	
ER (IHC)			
Negative	4 [18]	18 [82]	<0.001
Positive	49 [64]	28 [36]	
PR (IHC)			
Negative	6 [24]	19 [76]	<0.001
Positive	47 [64]	27 [36]	
HER2 (IHC)			
Negative	7 [28]	18 [72]	0.03
Positive	34 [47]	39 [53]	
Ki-67 (IHC)			
Negative (<20)	12 [32]	26 [68]	<0.001
Positive (>20)	39 [68]	18 [32]	

FXR1, FMR1 autosomal homolog 1; KASH, King Abdulaziz Specialist Hospital; TNM, tumor-node-metastasis; ER, estrogen receptor; IHC, immunohistochemistry; PR, progesterone receptor; HER2, human epidermal growth factor 2.

Table 2 Association of FXR1 protein expression level and IHC subtypes in KASH cohort (n=100)

IHC breast cancer subtypes	FXR1 expression, n [%]		P value
	Low (n=51)	High (n=46)	
Luminal A	12 [31]	27 [69]	<0.001
Luminal B	36 [100]	0 [0]	
HER2 positive	7 [88]	1 [12]	
Triple negative	2 [14]	12 [86]	

FXR1, FMR1 autosomal homolog 1; IHC, immunohistochemistry; KASH, King Abdulaziz Specialist Hospital; HER2, human epidermal growth factor 2.

Table 3 Multivariate Cox regression analysis for predictors of overall survival and FXR1 protein expression in KASH cohort (n=100)

Parameters	HR	95% CI		P value
		Lower	Upper	
FXR1 protein expression	3.079	1.055	8.986	0.04
Tumor size	0.491	0.179	1.346	0.17
Lymph node	1.900	0.768	4.702	0.17
Tumor grade	1.032	0.479	2.225	0.94

FXR1, FMR1 autosomal homolog 1; KASH, King Abdulaziz Specialist Hospital; HR, hazard ratio; CI, confidence interval.

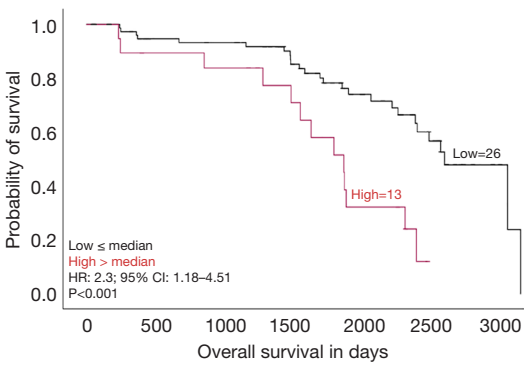

Figure 2 Kaplan-Meier survival plots showing the association between FXR1 protein expression and overall survival in KASH cohort. CI, confidence interval; HR, hazard ratio; KASH, King Abdulaziz Specialist Hospital.

the available data in the KASH cohort, a high FXR1 protein level was significantly associated with TNBC, followed by the luminal A, HER2$^+$, and luminal B subtypes (P<0.001; *Table 2*).

Association of FXR1 protein levels with patient outcomes

In the univariate analysis, a high FXR1 protein level was associated with shorter OS (P<0.001; *Figure 2*). In the Cox regression analysis of the KASH cohort, a high FXR1 protein level was a significant predictor of shorter OS regardless of lymph node status, tumor size, and tumor grade (hazard ratio =3.079, 95% confidence interval: 1.055–8.986, P=0.04; *Table 3*). However, no statistical significance was found when the data was categorized into TNBCs and all non-TNBC (Figure S3).

FXR1 mRNA levels

In order to validate our protein-level results, *FXR1* mRNA levels were determined in all public DNA microarray datasets in the BC Gene Expression Miner database (version 5.0; n=10,872). An exhaustive expression analysis found that *FXR1* mRNA levels were significantly higher in patients who were younger (aged ≤51 years) or had basal-like or TNBC (all P<0.0001). High *FXR1* mRNA levels were also associated with the receptor statuses ER$^-$ (P<0.0001), PR$^-$ (P<0.0001), and HER2$^-$ (P=0.004; *Figure 3*). No significant correlations were observed with the other clinicopathological parameters. Additionally, bc-GenExMiner version 5 (https://bcgenex.centregauducheau.fr), a publicly available dataset, was used as a prognostic

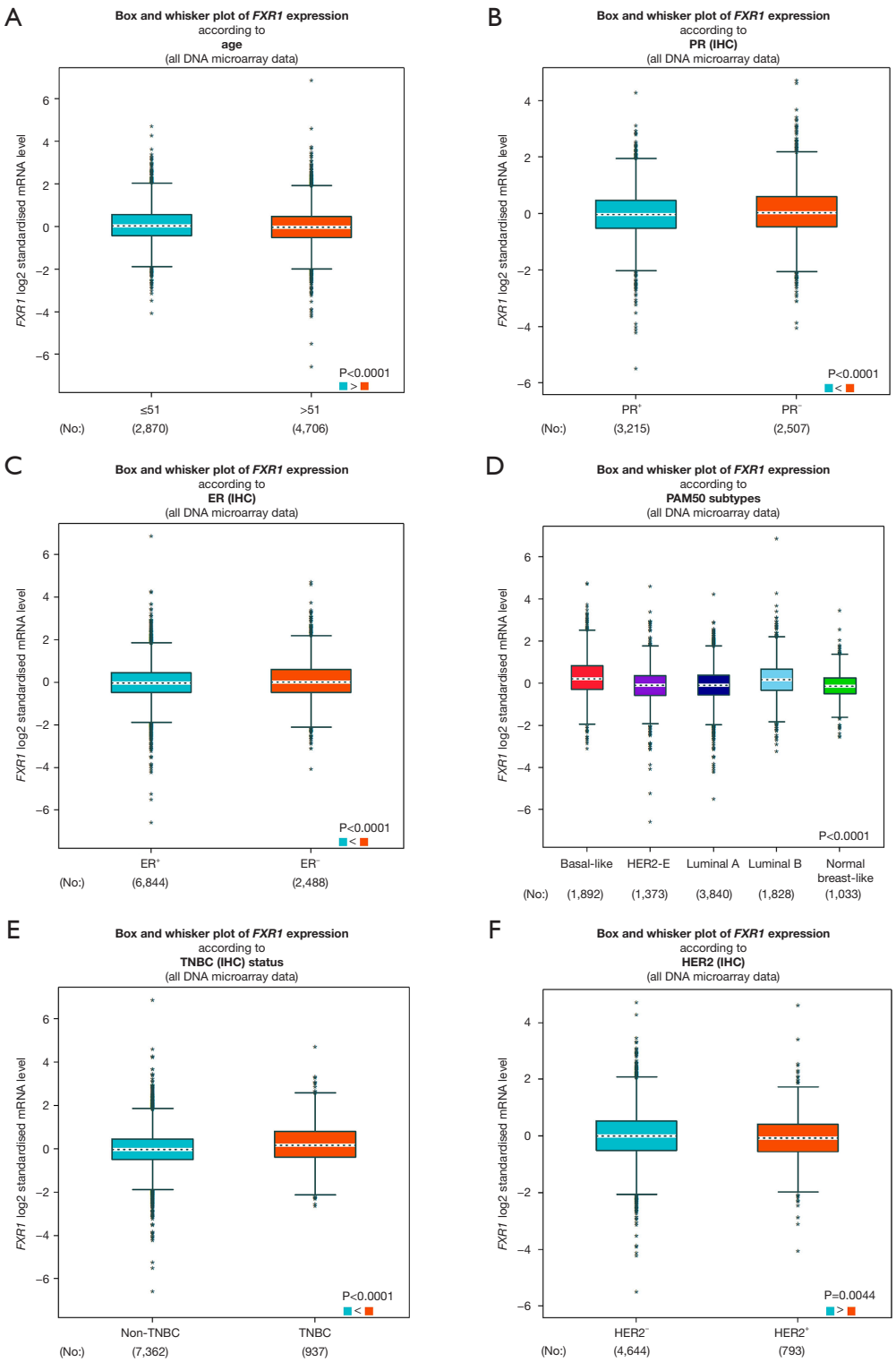

Figure 3 Expression analysis for FXR1 with breast cancer criteria. PR, progesterone receptor; IHC, immunohistochemistry; ER, estrogen receptor; TNBC, triple-negative breast cancer; HER2, human epidermal growth factor 2.

analytical module to validate the prognostic significance of *FXR1*. The results confirmed our findings that high FXR1 was associated with poor prognosis in the whole cohort. However, there is no statistical significance in any BC molecular subtypes (Figure S4).

Discussion

In Saudi Arabia, BC is the leading cancer in women as the number of BC cases in Saudi women has more than tripled during the last 17 years (1). The medical community in Saudi Arabia is quite concerned about this significant increase in BC prevalence. Notably, there is a lack of extensive testing and low knowledge of BC in Saudi Arabia, which has resulted in some instances of delayed detection and more severe stages upon diagnosis. Such delays can limit treatment options and affect outcomes, emphasizing the need for better evaluations of biomarkers associated with BC development and aggressiveness. Detecting novel prognostic and predictive factors could help reduce the risk of metastasis, guide treatment, and, ultimately, improve the quality of life for those with BC.

Previous studies have associated *FXR1* overexpression with poor prognosis in different cancers, such as hepatocellular carcinoma (17-20). An in-silico study by Qian *et al.* (9), identified a 3q-19 amplification-associated gene signature in TNBC and suggested FXR1 as a potential driver. FXR1 plays an important role in the transport, translation, and degradation of mRNAs (10). However, to date, the clinicopathological and prognostic significance of FXR1 in BC remains unclear. Therefore, this study stained a cohort of BC tissue samples for FXR1 using IHC to evaluate its clinicopathological and prognostic significance and potentially improve BC prognostication, monitoring, and personalized therapy.

This study found that high FXR1 protein levels were significantly associated with aggressive BC features, including stage IIB and IIIC, ER^-, PR^-, and $HER2^-$. Additionally, among BC molecular subtypes, high FXR1 protein levels were significantly associated with TNBC. These results are consistent with Qian *et al.* (9), who reported that the 3q-19 gene expression signature, which included the *FXR1* gene, was significantly associated with ER^- and PR^- status as well as with the basal-like, luminal B, and TNBC subtypes. Interestingly, in our study, higher FXR1 protein levels were associated with low Ki-67. The low level of Ki-67 in these patients may be due to the neoadjuvant chemotherapy they may have received (21). A previous study supports this by demonstrating a significant association between elevated FXR1 expression and a pathological complete response (pCR), which is characterised by the absence of residual invasive and *in situ* carcinoma on hematoxylin and eosin assessment of the entirely excised breast specimen and all examined regional lymph nodes after the completion of neoadjuvant therapy. Therefore, FXR1 may be considered an independent predictive biomarker for better response to neoadjuvant chemotherapy in patients with high FXR1 levels (9). However, FXR1 protein levels warrant further analysis in the context of chemotherapy responses and care.

Our result demonstrated that patients with higher FXR1 expression have poor outcomes. The findings of our study suggest that FXR1 has the potential to serve as a prognostic biomarker in BC; however, it is intriguing that our analysis of the entire cohort revealed that a high FXR1 level was associated with a poor outcome but not in a specific molecular subtype. Therefore, categorizing patients according to their molecular subtype appears to invalidate the prognostic value of FXR1. This phenomenon remains questionable and necessitates additional clinical research to be approved. Thus, the publicly accessible data that were used in this study have verified the prognostic value of FXR1. This is in agreement with another study that revealed that FXR1 was associated with worse distant metastasis-free survival (9). Moreover, an *in vivo* and *in vitro* study assessed FXR1 protein and mRNA levels in colorectal cancer, concluding that FXR1 was an independent and substantial factor associated with negative outcomes in patients, revealing that FXR1 acts as an oncogene, stimulating the proliferation, migration, and infiltration of cancer cells (17). Additionally, increased FXR1 expression was found to be associated with a more unfavorable prognosis in patients with hepatocellular carcinoma (18).

In order to validate our protein-level results, we examined *FXR1* mRNA levels in all publically available DNA microarray datasets in the BC Gene Expression Miner database (version 5.0; n=10,872). An exhaustive expression analysis found that *FXR1* mRNA levels were significantly higher in patients who were younger (aged ≤51 years) or had basal-like or TNBC. High *FXR1* mRNA levels were also associated with the receptor statuses ER^-, PR^-, and $HER2^-$. Given the detection of differences in *FXR1* mRNA levels detection with age, subtype, and receptor-negative receptor statuses, they may potentially represent an accurate marker and therapeutic target.

Overall, all these results suggest that FXR1 might

have a vital role in BC behavior, consistent with several *in vitro* studies that revealed that FXR1 overexpression plays a critical role in cancer behavior by regulating the transcription, post-transcription, and translation of several target genes in several pathways (12,21).

While current findings suggest that FXR1 could have a role in BC development, more mechanistic research is needed to demonstrate the potential role of FXR1 in BC progression and metastasis. While our study's results are remarkable, it had some limitations. One of these limitations is the small number of clinical samples. Furthermore, the hospital where we gathered the data did not follow up with some of the 100 patients, making the survival data unavailable. However, the data provided high statistical power and enabled us to identify a novel biomarker associated with aggressive behavior in BC. There are limited studies on FXR1 in the cancer field; however, our study was the first to examine the association of FXR1 with aggressive features in BC and to address a critical gap in the existing literature.

In future research, interrogating FXR1 protein expression in BC tissues with more clinicopathological data (including treatment response) may improve the prediction and treatment of a subset of patients with BC. Future studies examining the mechanism of FXR1 in promoting the aggressive behavior of BC are also critical, as they may offer a new potential therapeutic strategy for BC, particularly a subset of TNBC, and could stratify care in this patient group.

Conclusions

In conclusion, this study found that FXR1 overexpression at the gene and protein levels is associated with aggressive clinicopathological features of BC and poor survival. Therefore, FXR1 can potentially be used as both a prognostic marker and a therapeutic target.

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Footnote

Reporting Checklist: The authors have completed the REMARK reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-1542/rc

Data Sharing Statement: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-1542/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-1542/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. This study was approved by the Institutional Review Board at King Abdulaziz Specialist Hospital (KASH; approval number: HAP-02-T-067) and was conducted according to the Declaration of Helsinki (as revised in 2013). Informed consent was obtained from all individuals prior to surgery to use their tissue materials in research.

References

1. Al-Qahtani S, Zafar MU, Assiri AM, et al. Pattern of Malignant Tumors in Najran, Saudi Arabia: A 5-year Retrospective Study. International Journal of Biomedicine 2021;11:498-504.
2. Spitale A, Mazzola P, Soldini D, et al. Breast cancer classification according to immunohistochemical markers: clinicopathologic features and short-term survival analysis in a population-based study from the South of Switzerland.

Ann Oncol 2009;20:628-35.
3. Sørlie T, Perou CM, Tibshirani R, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci U S A 2001;98:10869-74.
4. Ozsoy A, Barca N, Dolek BA, et al. The Relationship Between Breast Cancer and Risk Factors: A Single-Center Study. Eur J Breast Health 2017;13:145-9.
5. Xiao K, Ullah I, Yang F, et al. Comprehensive bioinformatics analysis of FXR1 across pan-cancer: Unraveling its diagnostic, prognostic, and immunological significance. Medicine (Baltimore) 2023;102:e36456.
6. Tamanini F, Willemsen R, van Unen L, et al. Differential expression of FMR1, FXR1 and FXR2 proteins in human brain and testis. Hum Mol Genet 1997;6:1315-22.
7. Majumder M, Johnson RH, Palanisamy V. Fragile X-related protein family: a double-edged sword in neurodevelopmental disorders and cancer. Crit Rev Biochem Mol Biol 2020;55:409-24.
8. Wang J, Qian J, Hoeksema MD, et al. Integrative genomics analysis identifies candidate drivers at 3q26-29 amplicon in squamous cell carcinoma of the lung. Clin Cancer Res 2013;19:5580-90.
9. Qian J, Chen H, Ji X, et al. A 3q gene signature associated with triple negative breast cancer organ specific metastasis and response to neoadjuvant chemotherapy. Sci Rep 2017;7:45828.
10. Singh B, Stoffel A, Gogineni S, et al. Amplification of the 3q26.3 locus is associated with progression to invasive cancer and is a negative prognostic factor in head and neck squamous cell carcinomas. Am J Pathol 2002;161:365-71.
11. Bechara E, Davidovic L, Melko M, et al. Fragile X related protein 1 isoforms differentially modulate the affinity of fragile X mental retardation protein for G-quartet RNA structure. Nucleic Acids Res 2007;35:299-306.
12. Majumder M, House R, Palanisamy N, et al. RNA-Binding Protein FXR1 Regulates p21 and TERC RNA to Bypass p53-Mediated Cellular Senescence in OSCC. PLoS Genet 2016;12:e1006306.
13. Kunheri B, Raj RV, Vijaykumar DK, et al. Impact of St. Gallen surrogate classification for intrinsic breast cancer sub-types on disease features, recurrence, and survival in South Indian patients. Indian J Cancer 2020;57:49-54.
14. Gradishar WJ, Moran MS, Abraham J, et al. NCCN Guidelines® Insights: Breast Cancer, Version 4.2023. J Natl Compr Canc Netw 2023;21:594-608.
15. McCarty KS, Jr., McCarty KS, Sr. Histochemical approaches to steroid receptor analyses. Semin Diagn Pathol 1984;1:297-308.
16. Jézéquel P, Gouraud W, Ben Azzouz F, et al. bc-GenExMiner 4.5: new mining module computes breast cancer differential gene expression analyses. Database (Oxford) 2021:2021:baab007.
17. Jin X, Zhai B, Fang T, et al. FXR1 is elevated in colorectal cancer and acts as an oncogene. Tumour Biol 2016;37:2683-90.
18. Zhao K, Gao J, Shi J, et al. FXR1 promotes proliferation, invasion and migration of hepatocellular carcinoma in vitro and in vivo. Oncol Lett 2023;25:22.
19. Mavaddat N, Barrowdale D, Andrulis IL, et al. Pathology of breast and ovarian cancers among BRCA1 and BRCA2 mutation carriers: results from the Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA). Cancer Epidemiol Biomarkers Prev 2012;21:134-47.
20. Melchor L, Benítez J. The complex genetic landscape of familial breast cancer. Hum Genet 2013;132:845-63.
21. Majumder M, Palanisamy V. RNA binding protein FXR1-miR301a-3p axis contributes to p21WAF1 degradation in oral cancer. PLoS Genet 2020;16:e1008580.

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