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ORIGINAL RESEARCH

Overexpression of *MTFR2* Predicts Poor Prognosis of Breast Cancer

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Background: *Mitochondrial fission regulator 2* (*MTFR2*) has been reported to promote proliferation, migration and invasion in tumors; however, little is known about its function in breast cancer. Thus, we investigated the effect of *MTFR2* expression on prognosis of breast cancer.

Methods: The expression of *MTFR2* in breast cancer tissues was detected by immunohistochemistry, and overall survival (OS) and recurrence free survival (RFS) were evaluated by the Log rank test and Cox model.

Results: We found that *MTFR2* expression was significantly associated with clinical stage (P<0.001), T classification (P=0.005), N classification (P=0.001), M classification (P=0.041), *HER2* expression (P= 0.001), and molecular subtypes (P=0.002), respectively. Compared with low *MTFR2* expression, the patients with higher expression of *MTFR2* exhibited significantly shorter OS and RFS (All P < 0.001). Both univariate and multivariate analyses showed that *MTFR2* was an independent prognostic factor for OS (HR, 2.8, 95% CI 1.1–6.8, P = 0.023) and RFS (HR, 2.8, 95% CI 1.2–6.4, P = 0.015) in breast cancer patients. Moreover, in *HER2* positive and TNBC subtype, the associations between high *MTFR2* expression and poor OS and RFS were more pronounced.

Conclusion: Taken together, our results demonstrated that high *MTFR2* expression was associated with poor prognosis of breast cancer patients, and such an association was more pronounced in the patients with aggressive tumors. Therefore, *MTFR2* expression might be a potentially important prognostic biomarker and clinical target for patients with breast cancer.

Keywords: *MTFR2*, breast neoplasms, prognosis, biomarker, survival analysis

Introduction

Breast cancer has become the second cancer with high incidence and mortality globally, accounting for approximately 11.6% of all cancer deaths.[1] It is a heterogeneous disease, which can be divided into 25 subtypes according to different histology and molecular profiles.[2] More recently, despite targeted therapy (such as anti-estrogen and anti-*HER2*) has been widely used and improved prognosis, treatment outcomes for breast cancer remain relatively poor. Therefore, it is of great clinical significance to find new biomarkers that can effectively distinguish the patients with good prognosis between those with poor prognosis, and develop a new treatment scheme for patients with breast cancer.[3,4]

MTFR2 is also called *family with sequence similarity 54, member A* (*FAM54A*) and *DUF729 domain containing 1*(*DUFD1*, a 2 kb mRNA). It is located on chromosome *6q23.3* and plays a key role in mitochondria, promoting mitochondrial division and aerobic respiration in eukaryotic cells.[5] Wang et al found that *MTFR2* is one of the genes which are mostly correlated to dual specificity protein kinase *TTK* (*TTK*). It may

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regulate the expression of *TTK* by activating the transcription of *TTK* promoter, thus affecting the occurrence, treatment tolerance and recurrence of glioblastoma.[6]

TTK is located on chromosome *6q13-6q21*.[7] It enhances the activity of *auroral kinase B* through direct phosphorylation in the centromere, which affects cell proliferation and is necessary for chromosome alignment.[8–10] Since mRNA and protein of *TTK* were overexpressed in breast cancer, *MTFR2* might affect prognosis of breast cancer. Thus, we would explore the effect of expression of *MTFR2* in breast cancer on clinical outcome.

Patients and Methods

Study Patients

We collected 139 patient samples with breast cancer from our hospital between January 2010 and December 2011. The median age at surgery was 53 years old (range: 32–91 years). All patients were followed up for 4 to 82 months with a median of follow up of 72 months. We ended our follow-up on July 30, 2017. All patients did not receive radiotherapy or chemotherapy before surgery. We collected clinical data, including age at operation, tumor size, lymph node status, breast grade, molecular subtype status, treatment method, and the time of recurrence and death in breast cancer patients. Stage of tumor was based on the American Joint Committee on Cancer (AJCC), the 8th edition. Written informed consents were given to all patients and this study was approved by the IRB committee of the Affiliated Yantai Yuhuangding Hospital of Qingdao University.

Hormone receptor positivity was confirmed if allred score was above or equal to 3. *HER2*-positive expression was defined as score 3+, and negative expression with a score of 0 or 1+. To confirm gene amplification, the fluorescent in situ hybridization (FISH) was performed on tumors with a score of 2+. Our definition of molecular subtypes was as following: 1) *Luminal/HER2* negative referred to *estrogen receptor (ER)* positive and/or *progesterone receptor (PR)* positive but negative for *HER2*; 2) *HER2* positive represented *HER2* positive rather than related to *ER* or *PR* status; 3) Triple-negative breast cancer (TNBC) was that *ER*, *PR* and, *HER2* status were all negative.[11]

Immunohistochemistry (IHC)

IHC analysis was used to detect *MTFR2* expression in 139 cases of breast cancer tissue samples. The procedures were carried out in a similar manner previously described (12). In a brief step, we cut the paraffin-embedded sample into 4 μm slices, bake at 60 °C for 2 hours, then dewaxed with xylene and rehydrated. The slices were soaked in EDTA antigen repair buffer and microwave for antigen repair. We treated the slices with

Table 1 Clinicopathological Characteristics and *MTFR2* Expression of Patients with Breast Cancer

Variables	Number of Cases (%)
Age(years)	
≤55	82(59.0%)
>55	57(41.0%)
Clinical stage	
I	24(17.3%)
II	79(56.8%)
III	32(23.0%)
IV	4(2.9%)
T classification	
T_1	58(41.7%)
T_2	68(48.9%)
T_3	7(5.1%)
T_4	6(4.3%)
N classification	
N_0	63(45.3%)
N_1	47(33.9%)
N_2	15(10.8%)
N_3	14(10.0%)
Grade	
I, II	111(79.9%)
III	28(20.1%)
Expression of *ER*	
Negative	51(36.7%)
Positive	88 (63.3%)
Expression of *PR*	
Negative	61(43.9%)
Positive	78(56.1%)
Expression of *HER2*	
Negative	105(75.5%)
Positive	34(24.5%)
Expression of *MTFR2*	
Low expression	70(50.4%)
High expression	69(49.6%)
Radiotherapy	
Not done	96(69.1%)
Done	43(30.9%)
Chemotherapy	
Not done	41(29.5%)
Done	98(70.5%)

3% hydrogen peroxide in methanol, and then incubated it with 1% rabbit serum albumin. The slices were incubated overnight with anti-*MTFR2* rabbit polyclonal antibodies at 4 °C. After washing, the tissue sections were stained with DAB and treated with biotin-labeled anti-rabbit secondary antibody. The nucleus was stained by hematoxylin.

According to the proportion of positively stained cancer cells, the samples were divided into 1 to 4 grades, which were <10%, 10–50%, 50–75%, and >75% positive cancer cells, respectively. The intensity of staining was marked with different depth of color: light yellow for weak staining, yellowish brown for moderate staining, and brown for strong staining, recorded as 1 to 3 grades, respectively. The difference of staining index was resolved by consensus. According to the measure of heterogeneity from the Log rank test statistics with respect to overall survival (OS), the cutoff values of high and low expression of *MTFR2* was defined. A staining index score greater than or equal to 6 was defined as the high expression of *MTFR2*, while a score less than 6 was considered the low expression of *MTFR2*.

Statistical Analysis

All statistical analyses were performed using the SPSS 23 software, and the categorical variables (eg, *MTFR2* expression) were analyzed using the Chi-square test or Fisher's exact test. Recurrence free survival (RFS) was defined the time from first therapeutic operation until any recurrence or last follow-up or death from any cause. Overall survival (OS) was defined as the time from first therapeutic operation until death due to any cause or last follow-up. The survival analyses were conducted by the Kaplan–Meier method with the Log rank test and the Cox multivariable proportional hazard model. The stratified analysis of survival was also performed by several potential prognostic confounders. All p-values were two-tailed and a $P< 0.05$ was considered statistically significant.

Results

MTFR2 Expression in Study Patients' Tumors

In this study, we performed the IHC in 139 patients. The clinical stages of these patients from I to IV were 24, 79, 32, and 4, respectively. The high *MTFR2* expression was observed in 70 samples (50.4%) and the weak or no staining was detected in 69 cancer patients (49.6%) (Table 1). *MTFR2* expression was found in the region containing cancer cells; while it was difficult to detect in normal breast or adjacent non-cancerous tissues. In subcellular localization, *MTFR2* expression existed mainly in the cytoplasm as shown in Figure 1.

Association of *MTFR2* Expression with Clinicopathological Characteristics of Study Patients

As shown in Table 2, *MTFR2* expression was significantly associated with clinical stage (P < 0.001), T classification (P = 0.003), N classification (P = 0.001), *HER2* expression (P = 0.002), and molecular subtypes (P = 0.002), respectively and borderline significantly associated with

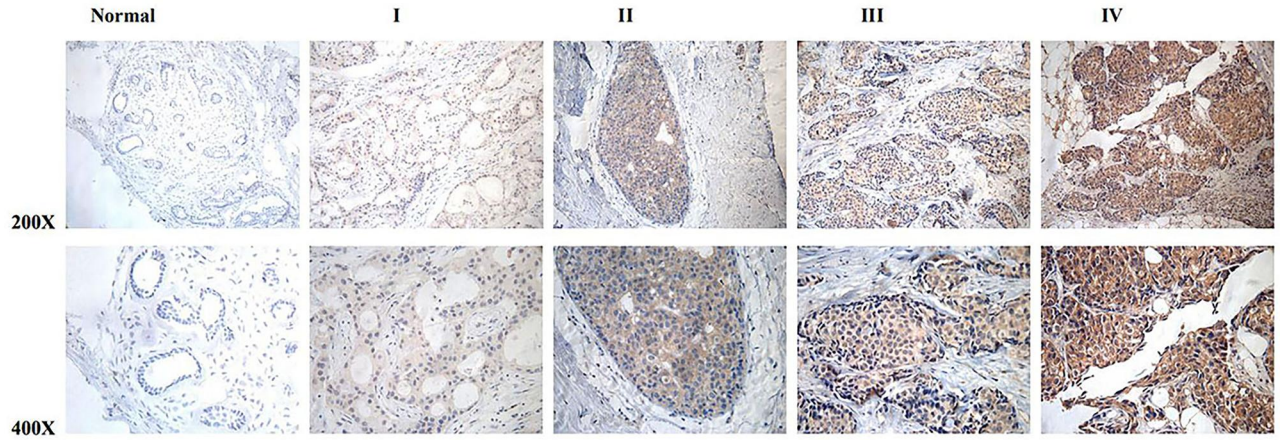

Figure 1 *MTFR2* protein overexpression in archived breast cancer tissues examined by immunohistochemistry. Representative IHC images of *MTFR2* expression in normal human breast *vs* breast cancer tissues at different clinical stages.

Table 2 Associations Between Clinicopathological Characteristics and Expression of *MTFR2* of Patients with Breast Cancer

Characteristics	*MTFR2*		χ^2(P value)	F (P value)
	Low (n=70) n %	High (n=69) n %		
Age(years)			0.919	1.000
≤55	41(29.5%)	41(29.5%)		
>55	29(20.8%)	28(20.2%)		
Clinical stage			<0.001	<0.001
I	18(12.9%)	6(4.3%)		
II	46(33.1%)	33(23.8%)		
III	6(4.3%)	26(18.7%)		
IV	0(0%)	4(2.9%)		
T classification			0.005	0.003
T_1	36(25.9%)	22(15.8%)		
T_2	33(23.8%)	35(25.2%)		
T_3	1(0.7%)	6(4.3%)		
T_4	0(0%)	6(4.3%)		
N classification			0.001	0.001
N_0	40(28.8%)	23(16.5%)		
N_1	24(17.3%)	23(16.5%)		
N_2	5(3.6%)	10(7.2%)		
N_3	1(0.7%)	13(9.4%)		
M classification			0.041	0.058
No	70(50.4%)	65(46.7%)		
Yes	0(0%)	4(2.9%)		
Grade			0.704	0.833
I, II	55(39.6%)	56(40.3%)		
III	15(10.8%)	13(9.3%)		
ER expression			0.345	0.382
Negative	23(16.6%)	28(20.1%)		
Positive	47(33.8%)	41(29.5%)		
PR expression			0.806	0.865
Negative	30(21.6%)	31(22.3%)		
Positive	40(28.8%)	38(27.3%)		
*HER2*expression			0.001	0.002
Negative	61(43.9%)	44(31.6%)		
Positive	9(6.5%)	25(18.0%)		
Subtype			0.002	0.002
Luminal/HER2(-)	47(33.8%)	39(28.0%)		
HER2(+)	9(6.5%)	25(18.0%)		
TNBC	14(10.1%)	5(3.6%)		

M classification (P = 0.058). However, there were no significant associations with other variables including age, breast grade, *ER* status and *PR* status. Moreover, the Spearman correlation analysis showed that *MTFR2* expression level was significantly correlated to clinical stages (r = 0.407, P < 0.001), T classification (r = 0.261, P = 0.002), N classification (r = 0.312, P < 0.001), M classification (r = 0.173, P = 0.041), and *HER2* expression (r = 0.272, P = 0.001), respectively (Table 3). Thus, the IHC results revealed that increase of *MTFR2* staining was positively correlated with advanced tumors, suggesting that high *MTFR2* expression appeared to be associated with progression of breast cancer.

Table 3 Spearman Correlation Between *MTFR2* and Clinical Pathological Factors

Variables	*MTFR2* Expression	
	Spearman Correlation	P value
Clinical stage	0.407	<0.001
T classification	0.261	0.002
N classification	0.312	<0.001
M classification	0.173	0.041
Grade	−0.032	0.706
ER expression	−0.080	0.348
PR expression	−0.021	0.807
HER2 expression	0.272	0.001
Subtype	0.043	0.614

Association Between *MTFR2* Expression and Survival

As shown in Figure 2A and B, the Kaplan–Meier analysis showed an negative association between *MTFR2* expression and both of RFS and OS of patients with breast cancer (both P < 0.001). The cumulative rates of RFS and OS for patients with high *MTFR2* expression were 59.4% and 63.8%, respectively, whereas the rates were 88.6% and 90.0% for patients with low *MTFR2* expression, respectively. After both univariate and multivariate Cox proportional hazard regression analyses were performed, our results showed that N stage (aHR, 1.70, 95% CI, 1.24–2.33), *MTFR2* expression (aHR, 3.85, 95% CI, 1.52–9.77) and *HER2* expression (aHR, 4.81, 95% CI, 1.84–12.6) were independent prognostic factors for RFS. Furthermore, we found that N stage (aHR, 1.81, 95% CI, 1.30–2.52), *MTFR2* expression (aHR, 3.30, 95% CI, 1.23–8.82) and *HER2* expression (aHR, 5.02, 95% CI, 1.91–13.2) were also independent prognostic factors for OS (Table 4). However, we did not find significant associations between the treatment (eg, radiotherapy and chemotherapy) and both RFS and OS as shown in Table 4.

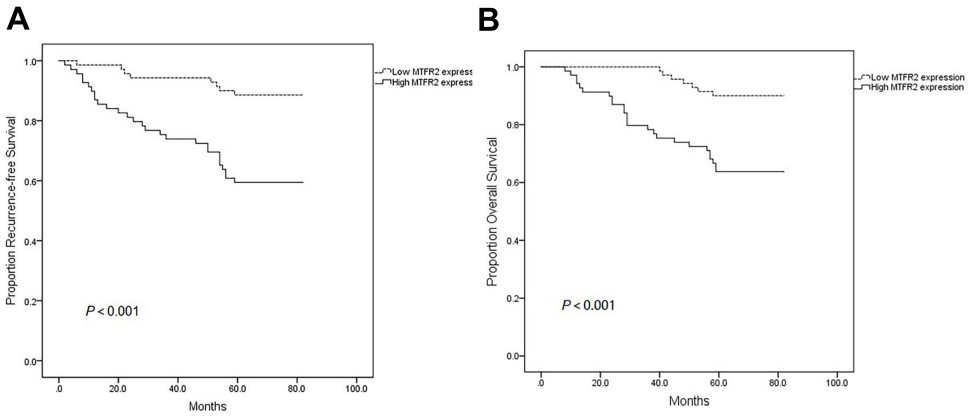

Figure 2 Kaplan–Meier plots of RFS and OS according to *MTFR2* expression level. (**A**) RFS of all patients with high *MTFR2* expression *vs* low *MTFR2* expression. (**B**) OS of all patients with high *MTFR2* expression *vs* low *MTFR2* expression.

Prognostic of *MTFR2* Expression in Aggressive Subtypes

We assessed survival according to *MTFR2* expression in each molecular subtype. The expression of *MTFR2* had no significant effect on survival in the patients with negative expression of *luminal/HER2* (Figure 3A; P=0.074), while the RFS differed significantly in both *HER2* subtype (Figure 3B; P=0.016) and TNBC (Figure 3C; P=0.015), similarly, OS differed significantly in the *HER2* subtype (Figure 3E; P=0.017) and TNBC (Figure 3F; P=0.008), but no significant difference in the patients with *Luminal/HER2* negative expression (Figure 3D; P=0.291).

Discussion

In the present study, *MTFR2* expression levels were relatively higher in cancer lesions than those in normal tissues. *MTFR2* was highly expressed in breast cancer tissues, and it was significantly correlated with clinical stage, T, N, classification and *HER2* expression level of breast cancer. The expression of *MTFR2* increased with the progression of breast cancer, indicating that high expression of *MTFR2* could be related to the progression of breast cancer. Our findings revealed that *MTFR2* was an independent prognostic factor for prognosis of breast cancer patients, and the patients with high *MTFR2* expression had worse RFS and OS than those with corresponding low expression. Lu et al also found that *MTFR2* can promote growth, migration, invasion and tumor progression in breast cancer cells.[12] Thus, it appears that *MTFR2* expression may have clinical significance as a novel predictor of prognosis and one of potential new targets for future targeted therapy of breast cancer.

Previous studies found that *MTFR2* was highly expressed in mice testicular cells.[5] *MTFR2* encodes a protein in the mitochondria and promotes mitochondrial fission and anti-DNA oxidative damage.[13,14] Mitochondria play a key role in induction of intrinsic apoptosis.[15] Compared to those in normal cells, mitochondria in cancer cells express a higher level of reactive oxygen species (ROS) and reductant,[16–18] whereas the excessive ROS damage lipids and DNA.[19,20] In addition, mitochondrial fission can induce glycolysis reprogramming of cancer-related myofibroblasts, accelerating tumor growth and angiogenesis.[21]

Recently, Wang found that *MTFR2* promoted the proliferation, migration, and invasion of oral squamous carcinoma.[22] Wang et al also found that *MTFR2*-dependent regulation of *TTK* was involved in maintaining glioma stem-like cells (GSCs) in glioblastoma and could be a potential new druggable target for glioblastoma.[6] It might regulate the expression of *TTK* by activating the transcription of *TTK* promoter for participation in up-regulation and expression of GSCs in glioblastoma. Besides the effect on cell proliferation, *TTK* also played important roles in centrosome duplication, DNA damage response, and organ development.[8] Daniel et al demonstrated that reduced *TTK* levels could cause abnormal mitoses, induce apoptosis and decrease survival of breast cancer cells.[23] Maire et al found that *TTK* depletion would seriously impair the viability and ability to form colonies of TNBC cell lines.[24] Therefore, *TTK* could be an independent prognostic biomarker and it is biologically plausible that *MTFR2* might activate regulation, promote expression of *TTK* in breast tumor cells, and have an important regulatory role in the occurrence and development of

Table 4 Univariate and Multivariable Analysis on Survival of Patients with Breast Cancer

Characteristics	RFS				OS			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	*P*	aHR (95% CI)	*P*	HR (95% CI)	*P*	aHR (95% CI)	*P*
Age		0.098		0.117		0.226		0.154
≤55	1.00		1.00		1.00		1.00	
>55	1.74 (0.90–3.34)		2.31 (0.98–4.96)		1.53 (0.77–3.07)		1.82 (0.80–4.13)	
T stage		<0.001		0.292		<0.001		0.582
T1/T2	1.00		1.00		1.00		1.00	
T3/T4	5.08 (2.38–10.9)		2.01 (0.55–7.40)		5.26 (2.43–11.4)		1.43 (0.40–5.17)	
N stage		<0.001		0.001		<0.001		<0.001
N0/N1	1.00		1.00		1.00		1.00	
N2/N3	3.32 (1.70–6.45)		1.70 (1.24–2.33)		4.15 (2.07–8.32)		1.81 (1.30–2.52)	
Clinical stage		<0.001		0.567		<0.001		0.286
I/II	1.00		1.00		1.00		1.00	
III/IV	4.96 (2.56–9.61)		1.62 (0.31–8.50)		6.53 (3.18–13.4)		2.44 (0.47–12.58)	
Grade		0.290		0.381		0.927		0.797
I/II	1.00		1.00		1.00		1.00	
III	1.48 (0.72–3.08)		1.47 (0.62–3.44)		1.04 (0.45–2.41)		0.88 (0.34–2.31)	
MTFR2		<0.001		0.005		0.001		0.017
Low	1.00		1.00		1.00		1.00	
High	4.29 (1.96–9.43)		3.85 (1.52–9.77)		4.39 (1.90–10.1)		3.30 (1.23–8.82)	
ER		0.994		0.675		0.903		0.821
Negative	1.00		1.00		1.00		1.00	
Positive	0.99 (0.51–1.97)		1.37 (0.32–5.93)		0.96 (0.47–1.96)		1.18 (0.28–5.06)	
PR		0.807		0.142		0.988		0.259
Negative	1.00		1.00		1.00		1.00	
Positive	1.09 (0.56–2.11)		3.42 (0.66–17.6)		1.01 (0.50–2.02)		2.54 (0.50–12.8)	
HER2		0.001		0.001		<0.001		0.001
Negative	1.00		1.00		1.00		1.00	
Positive	2.91 (1.51–5.62)		4.81 (1.84–12.6)		3.66 (1.83–7.31)		5.02 (1.91–13.2)	
Group		0.897		0.223		0.854		0.972
non-TNBC	1.00		1.00		1.00		1.00	
TNBC	1.06 (0.41–2.74)		1.08 (0.73–3.86)		0.91 (0.32–2.58)		1.02 (0.40–2.59)	
Radiotherapy		0.619		0.122		0.962		0.206
No	1.00		1.00		1.00		1.00	
Yes	0.83 (0.40–1.72)		0.52 (0.23–1.19)		0.98 (0.47–2.07)		0.57 (0.24–1.36)	
Chemotherapy		0.548		0.501		0.692		0.767
No	1.00		1.00		1.00		1.00	
Yes	0.81 (0.40–1.62)		1.32 (0.58–3.00)		0.86 (0.41–1.82)		1.15 (0.47–2.82)	

Abbreviation: aHR, adjusted with the variables listed in this table.

breast cancer. However, the exact mechanisms need further investigation.

Intriguingly, we also found that expression of *MTFR2* was associated with aggressive subtypes, particularly for *HER2*-positive and TNBC subtypes, indicating that *MTFR2* may have clinical significance as a new target for improved outcome and individualized treatment of patients with breast cancer. Furthermore, *MTFR2*

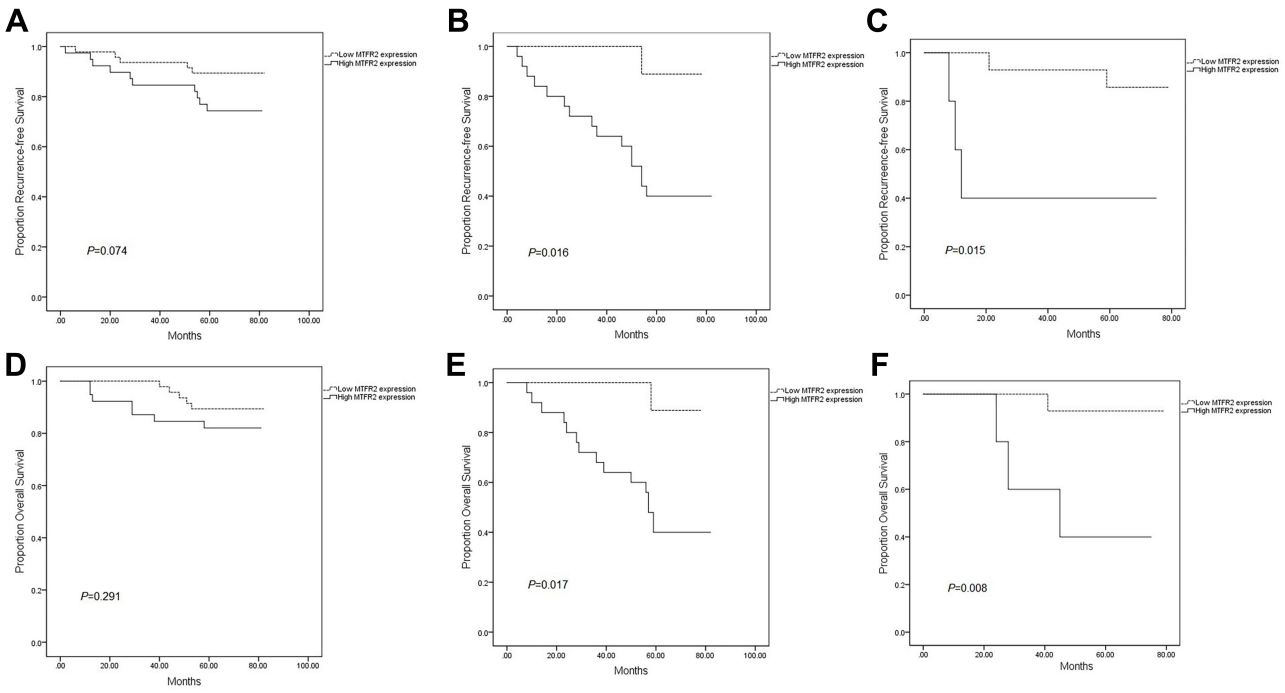

Figure 3 Kaplan–Meier plots of RFS and OS according to *MTFR2* expression level in each subtype. RFS differed significantly according to *MTFR2* expression in the *HER2* and TNBC subtypes (**B** and **C**), but it did not differ in the other subtypes (**A**). OS differed significantly according to *MTFR2* expression in the *HER2*and TNBC subtypes (**E** and **F**), but it did not differ in *luminal*/*HER2* negative (**D**). P values were calculated by Log rank tests.

expression was significantly correlated with *HER2* expression status, implying that *MTFR2* may provide additional effective value for targeted therapy in patients with breast cancer. Therefore, *MTFR2* might be a valuable biomarker for predicting prognosis and guiding future plan of follow up of breast cancer patients.

In this study, several limitations need to be addressed. First, the retrospective review with a small sample size is our main limitation, which may result in biased estimates of association. Moreover, since this is a relatively small study and all patients were recruited from a single hospital, the selection bias may exist. However, our preliminary findings from such a small sample size may help generate a hypothesis for testing or validation in future large prospective studies via consortia or multi-centers. Finally, the exact molecular mechanisms underlying the associations remain unclear, thus, more mechanistic investigation is warranted.

Conclusion

In conclusion, we found that high expression of *MTFR2* is correlated with breast cancer progression, and *MTFR2* expression was significantly associated with survival of breast cancer patients. Moreover, the prognostic effect of *MTFR2* expression was even more pronounced in aggressive tumors. Our results may support that *MTFR2* might serve as an independent prognostic biomarker and a potential therapeutic target for breast cancer.

Data Sharing Statement

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Ethics Committee of the Yantai Yuhuangding Hospital Affiliated Hospital of Qingdao University and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Disclosure

The authors declare that they have no competing interests. These authors contributed equally to the manuscript: Wenjie Lu, Rukun Zang and Yuncheng Li.

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