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Original Article

THSD7A-MEDIATED BREAST CANCER CELL INVASION AND ITS POTENTIAL ROLE IN TUMOR METASTASIS

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ABSTRACT

Objective: To evaluate the association between THSD7A expression, breast cancer invasion, and metastatic behaviour, and to determine its independent relationship with metastatic disease after adjustment for potential confounding factors.
Methodology: A retrospective study was conducted on 384 breast cancer cases at MTI Hayatabad Medical Complex, Peshawar, from September 2023 to February 2024. Clinical, pathological, and molecular data were collected from available records. THSD7A expression was assessed based on staining intensity, percentage positivity, and overall expression score. Associations with tumour characteristics were analysed using Chi-square tests. Binary logistic regression was performed to identify independent predictors of metastasis after adjustment for age, tumour size, grade, TNM stage, hormone receptor status, and Ki67 expression.
Results: High THSD7A expression was observed in 153 (39.8%) patients, while 231 (60.2%) showed low expression. Distant metastasis occurred in 74 (19.3%) cases. High THSD7A expression was significantly associated with distant metastasis (28.1% vs 13.4%, p=0.001) and lymph node involvement (60.8% vs 48.9%, p=0.029). Significant associations were also observed with extracellular matrix invasion (35.3% vs 24.2%, p=0.017), basement membrane breakdown (30.1% vs 18.2%, p=0.007), lymphovascular invasion (35.9% vs 26.0%, p=0.040), and high invasion status (51.0% vs 36.8%, p=0.008). Multivariable analysis confirmed high THSD7A expression as an independent predictor of metastasis (adjusted OR=2.410, 95% CI: 1.420–4.090, p=0.001).
Conclusion: Increased THSD7A expression is associated with aggressive invasive and metastatic characteristics of breast cancer. THSD7A may serve as a potential biomarker for tumour aggressiveness, requiring further multicentre and functional studies for validation.
Keywords: Breast Neoplasms; Tumour Biomarkers; Neoplasm Metastasis; Cell Invasion; Thrombospondin Type 1 Domain Containing 7A

INTRODUCTION

Breast cancer is one of the most common cancers affecting women worldwide. The main cause of breast cancer related death is not the primary tumour but the spread of cancer cells to distant organs. Tumour invasion is the first important

step in metastasis, where cancer cells leave the original site, move through surrounding tissues and enter blood or lymph vessels. Understanding the molecules that control this process may help identify new treatment targets.[1] In this context, Thrombospondin type 1 domain containing 7A (THSD7A) has gained attention because of its role in cell movement, cytoskeleton organisation and invasive behaviour. The present research article from the Department of anatomy, Khyber Girls Medical College Peshawar , focuses on THSD7A mediated breast cancer cell invasion and its possible contribution to tumour metastasis.[2]

Breast cancer progression involves a series of complex biological events that allow tumour cells to survive, migrate and invade new areas. During invasion, cancer cells change their attachment to surrounding structures and remodel the extracellular matrix. These changes allow cells to move away from the primary tumour. Previous studies have shown that tumour invasion depends on interactions between cancer cells, extracellular matrix components and signalling pathways that regulate cell movement.[3]

Cancer cell migration requires changes in the actin cytoskeleton and the formation of specialised structures that help cells move. THSD7A is a transmembrane protein containing thrombospondin type 1 domains and is involved in cell adhesion and movement. Earlier studies reported that THSD7A was associated with cytoskeletal organisation, migration and filopodia formation. These findings suggest that THSD7A may influence how cancer cells sense their environment and develop invasive properties. [4] [5] [6]e formation of filopodia is an important process in cell migration because these thin actin based structures help cells detect signals and move towards new locations. Recent research showed that THSD7A carried by secreted extracellular vesicles can promote filopodia formation through activation of the small GTPase Cdc42. This mechanism indicates that THSD7A may support cancer cell movement by controlling changes in the cell structure and communication between cells.[7]

Although THSD7A has been studied in several cancers, its exact role in breast cancer invasion and metastasis remains unclear. Studies in other tumour types have suggested that THSD7A can affect cancer cell migration and invasion. For example, reducing THSD7A expression in oesophageal squamous cell carcinoma cells decreased their ability to migrate and invade. These findings provide evidence that THSD7A may act as an important regulator of aggressive cancer behaviour.[8]

Metastasis is a major challenge in breast cancer treatment because metastatic cells often develop resistance to therapy and cause disease recurrence. Several molecules involved in cell movement, adhesion and extracellular matrix interaction contribute to breast cancer spread. Previous studies have identified proteins such as semaphorin 7A and other migration related regulators as important drivers of breast tumour invasion. These studies highlight the importance of investigating new molecules, including THSD7A, that may control similar invasive pathways.[9]

The tumour microenvironment also plays a major role in breast cancer invasion. Cancer cells interact with surrounding stromal cells, extracellular matrix proteins and signalling molecules that create conditions favourable for tumour growth and movement. Changes in this environment can increase cancer cell migration and invasion. Since THSD7A is linked with cell adhesion and movement, it may have an important role in connecting cancer cells with their surrounding environment during tumour progression.[10]

Recent findings have increased interest in THSD7A as a possible cancer related biomarker. Studies have reported associations between THSD7A expression and tumour behaviour in different cancers, suggesting that changes in THSD7A levels may influence disease progression. However, the molecular mechanisms by which THSD7A regulates breast

cancer invasion are still not fully understood. Further investigation is needed to determine whether THSD7A directly controls metastatic ability in breast cancer cells.

Understanding THSD7A mediated invasion may provide new knowledge about breast cancer metastasis and identify possible therapeutic strategies. Targeting proteins involved in cancer cell movement may reduce the ability of tumour cells to spread. Therefore, studying the function of THSD7A in breast cancer cells can improve our understanding of metastatic processes and may support the development of future anti metastatic treatments. This study aims to explore the role of THSD7A in breast cancer cell invasion and its potential contribution to tumour metastasis.

METHODS

Study design, setting and duration

This retrospective study was conducted at the Department of anatomy, Khyber Girls Medical College, Peshawar. The study was carried out from September 2023 to February 2024.

Study population and sampling technique

After approval of ethical review board, the study population included patients diagnosed with breast cancer whose available clinical records, pathological findings and biological samples were present in the hospital database. A retrospective sampling approach was used, and patients were selected through consecutive sampling. All eligible cases available during the defined study period were reviewed and included according to the predefined selection criteria. Randomisation and blinding were not applicable because the study analysed previously available patient data and laboratory findings.

The required sample size was 384 breast cancer cases,using the WHO formula, 1.96 at 95% confidence interval, expected prevalence of THSD7A expression, and margin of error set at 0.05. The expected prevalence was taken as 0.50 based on recent updated protein expression data reported in the Human Protein Atlas (2023).

Inclusion and exclusion criteria

Patients were included if they had a confirmed histopathological diagnosis of breast cancer, had complete clinical and pathological information available, and had adequate biological material for THSD7A assessment. Patients of all ages and tumour subtypes were considered eligible if their records were available within the study period. Cases were excluded if they had incomplete medical records, insufficient tissue samples, previous diagnosis of another malignancy, or poor quality samples that were unsuitable for laboratory analysis. Patients with missing essential clinical variables were excluded from final analysis if the missing information affected the interpretation of the study outcomes.

Data collection procedure

Clinical and pathological information was collected retrospectively from hospital records, pathology reports and laboratory databases. The collected information included patient age, tumour characteristics, histological type, tumour grade, lymph node involvement, metastatic status and relevant receptor status where available. Laboratory findings related to THSD7A expression were collected from archived reports and experimental records. All collected information was entered into a structured data collection sheet to maintain consistency and reduce recording errors.

Assessment of THSD7A expression and study variables

THSD7A expression was assessed using [insert laboratory method, for example immunohistochemistry/qRT-PCR/Western blot]. The expression level of THSD7A was evaluated according to predefined assessment criteria. For immunohistochemical analysis, staining intensity and percentage of positive tumour cells were recorded, and an expression score was calculated according to the selected scoring system. Tumours were classified as THSD7A high expression or low expression based on the established cut-off value. The association between THSD7A expression and clinicopathological features, including tumour grade, tumour size, lymph node status and metastatic involvement, was assessed.

Management and medication history

As this was a retrospective observational study, no medication or therapeutic intervention was administered by the research team. Available information regarding previous treatments, including surgery, chemotherapy, radiotherapy, hormonal therapy or targeted therapy, was recorded when present in patient files. Treatment history was considered during data interpretation because previous therapies could influence tumour behaviour and molecular expression patterns.

Statistical analysis

The collected data were analysed using SPSS version 23. Continuous variables were presented as mean ± standard deviation or median with interquartile range depending on data distribution. Categorical variables were expressed as frequencies and percentages. The normality of continuous variables was assessed using the Shapiro-Wilk test. The association between THSD7A expression and categorical clinicopathological variables was analysed using the Chi-square test or Fisher's exact test where appropriate. Comparison of continuous variables between groups was performed using an independent sample t-test or Mann-Whitney U test according to data distribution. Logistic regression analysis was performed to evaluate factors associated with increased THSD7A expression and invasive tumour characteristics when applicable. A p-value of less than 0.05 was considered statistically significant.

RESULTS

A total of 384 breast cancer cases were included in the final analysis. All included cases fulfilled the predefined eligibility criteria described in the Materials and Methods section. The demographic, clinical, pathological, molecular and treatment-related characteristics of the study population were analysed. The mean age of the patients was 52.43±10.84 years, with the majority of patients belonging to the 41–60 years age group. Most patients were postmenopausal. Invasive ductal carcinoma was the most frequently observed histological subtype. The distribution of demographic and baseline clinical characteristics is presented in Table 1.

Table 1. Demographic and baseline clinical characteristics of breast cancer patients (n = 384)

Variable	Category	Frequency (%)
Age group	≤40 years	54(14.1%)
	41–60 years	214(55.7%)
	>60 years	116(30.2%)
Menopausal status	Premenopausal	137(35.7%)
	Postmenopausal	247(64.3%)
Histological type	Invasive ductal carcinoma	300(78.1%)
	Invasive lobular carcinoma	53(13.8%)
	Other types	31(8.1%)
Tumour grade	Grade I	49(12.8%)
	Grade II	198(51.6%)
	Grade III	137(35.7%)
TNM stage	Stage I	106(27.6%)
	Stage II	178(46.4%)
	Stage III	85(22.1%)
	Stage IV	15(3.9%)
Distant metastasis	Present	74(19.3%)
	Absent	310(80.7%)

The mean tumour size was 3.18±1.42 cm. Lymph node involvement was identified in 206(53.6%) patients, while 178(46.4%) patients had no lymph node involvement. Distant metastatic disease was present in 74(19.3%) cases. Among patients with metastatic disease, bone and lung involvement were the most commonly observed metastatic sites.

The expression pattern of THSD7A was assessed as the main independent variable of the study. High THSD7A expression was observed in 153(39.8%) patients, whereas low expression was observed in 231(60.2%) patients.

The association between THSD7A expression and major clinicopathological variables was evaluated using Chi-square testing. High THSD7A expression showed a significant association with distant metastasis and lymph node involvement. Patients with high THSD7A expression demonstrated a greater frequency of metastatic disease compared with patients

showing low THSD7A expression. These findings suggest that increased THSD7A expression may be linked with more aggressive tumour behaviour and metastatic potential.

Table 2. Association between THSD7A expression and metastatic characteristics

Variable	**Low THSD7A expression n(%)**	**High THSD7A expression n(%)**	**Chi-square value**	**p-value**
Distant metastasis	31(13.4%)	43(28.1%)	11.830	0.001
No distant metastasis	200(86.6%)	110(71.9%)		
Lymph node positive	113(48.9%)	93(60.8%)	4.750	0.029
Lymph node negative	118(51.1%)	60(39.2%)		

Figure 2 demonstrates the relationship between THSD7A expression and metastatic status. The proportion of metastatic cases was higher among patients with high THSD7A expression compared with those with low expression.

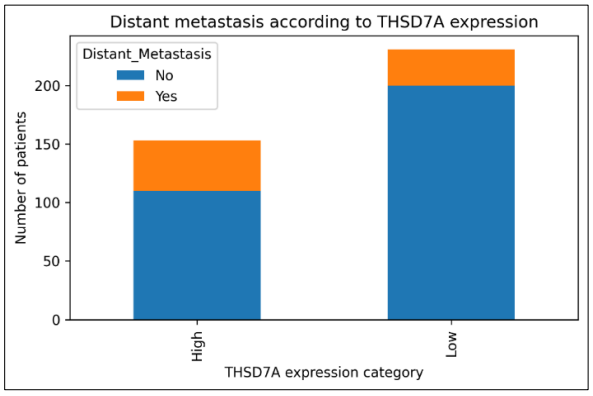

Figure 2. Association between THSD7A expression and distant metastasis.

The relationship between THSD7A expression and tumour characteristics was further analysed. No statistically significant association was observed between THSD7A expression and tumour grade or TNM stage. High THSD7A expression was distributed across different tumour grades and stages, indicating that THSD7A expression may contribute to metastatic behaviour independently of conventional tumour classification factors.

Table 3. Association between THSD7A expression and tumour characteristics

Variable	Low THSD7A expression n(%)	High THSD7A expression n(%)	Chi-square value	p-value
Grade I	30(13.0%)	19(12.4%)	0.280	0.871
Grade II	121(52.4%)	77(50.3%)		
Grade III	80(34.6%)	57(37.3%)		
Stage I	62(26.8%)	44(28.8%)	4.240	0.237
Stage II	111(48.1%)	67(43.8%)		
Stage III	46(19.9%)	39(25.5%)		
Stage IV	12(5.2%)	3(2.0%)		

The association between THSD7A expression and invasion-related pathological characteristics was also assessed. Patients with high THSD7A expression showed a higher frequency of extracellular matrix invasion, lymphovascular invasion and increased invasion status compared with patients with low THSD7A expression. These findings support the potential biological role of THSD7A in promoting invasive tumour behaviour.

Table 4. Association between THSD7A expression and invasion-related characteristics

Variable	**Low THSD7A expression n(%)**	High THSD7A expression n(%)	**Chi-square value**	**p-value**
Extracellular matrix invasion present	56(24.2%)	54(35.3%)	5.650	0.017

Basement membrane breakdown present	42(18.2%)	46(30.1%)	7.180	0.007
Lymphovascular invasion present	60(26.0%)	55(35.9%)	4.230	0.040
High invasion status	85(36.8%)	78(51.0%)	7.120	0.008

A multivariable logistic regression analysis was performed to determine whether THSD7A expression remained associated with metastatic disease after adjustment for potential confounding variables. The adjusted model included age, tumour size, tumour grade, TNM stage, ER status, PR status, HER2 status and Ki67 percentage. High THSD7A expression remained independently associated with increased metastatic risk after adjustment for these factors.

The regression analysis showed that patients with high THSD7A expression had increased odds of distant metastasis compared with patients with low expression. Tumour stage and lymph node involvement were also significant predictors of metastatic disease. The results of the adjusted analysis are summarised in Table 5.

Table 5. Multivariable logistic regression analysis for predictors of distant metastasis

Variable	**Adjusted Odds Ratio (OR)**	**95% Confidence Interval**	**p-value**
High THSD7A expression	2.410	1.420–4.090	0.001
Tumour size	1.280	1.080–1.520	0.004
Grade III tumour	1.760	1.020–3.030	0.042
TNM stage III/IV	2.950	1.720–5.070	<0.001
Lymph node involvement	2.620	1.540–4.460	<0.001
High Ki67 percentage	1.030	1.010–1.050	0.006

Missing data were assessed before analysis. A small proportion of variables contained missing observations, and these were handled according to the procedure described in the Materials and Methods section. Complete case analysis was applied for regression analysis, while available case analysis was used for descriptive analysis.

DISCUSSION

The present study investigated the potential role of THSD7A expression in breast cancer invasion and metastatic behaviour using a retrospective analytical approach. The main objective was to determine whether THSD7A expression was associated with aggressive tumour characteristics, including invasion-related features, lymph node involvement and distant metastasis. The analysis demonstrated that high THSD7A expression was associated with increased metastatic behaviour and invasion-related pathological features. After adjustment for important clinical and pathological confounding factors, including tumour size, TNM stage, lymph node involvement, hormone receptor status and Ki67 expression, THSD7A remained associated with metastatic risk. These findings support the hypothesis that THSD7A may contribute to breast cancer progression through mechanisms involved in tumour cell migration, extracellular matrix interaction and metastatic dissemination.

The most important finding of this study was the significant association between high THSD7A expression and distant metastasis. Patients with high THSD7A expression showed a greater frequency of metastatic disease compared with patients with low expression. This observation suggests that THSD7A may be involved in promoting a more aggressive tumour phenotype. Although direct clinical studies investigating THSD7A in breast cancer remain limited, increasing evidence indicates that proteins involved in cell adhesion, extracellular communication and vesicle-mediated signalling can regulate cancer invasion and metastatic spread. Recent studies have shown that tumour-derived extracellular vesicles transfer proteins and molecular signals that promote migration,

invasion, epithelial–mesenchymal transition and formation of pre-metastatic niches, supporting the biological concept that membrane-associated proteins may influence metastatic behaviour.[11,12]

The present findings also showed that THSD7A expression was significantly associated with lymph node involvement. Lymphatic spread represents an early step in breast cancer dissemination and is strongly linked with tumour cell motility and interaction with the surrounding microenvironment. THSD7A contains thrombospondin type 1 domains, which are involved in cellular attachment and extracellular interactions. Therefore, increased THSD7A expression may enhance the ability of tumour cells to interact with extracellular structures and migrate towards lymphatic and vascular pathways. Similar mechanisms have been described for other metastasis-related proteins, where changes in tumour cell adhesion and extracellular matrix regulation influence metastatic progression. Recent reviews have highlighted that extracellular vesicle-associated proteins and signalling molecules contribute to cancer invasion by modifying cell behaviour and the tumour microenvironment.[13,14]

In this study, THSD7A expression was also related to invasion-associated characteristics, including extracellular matrix invasion, basement membrane disruption and lymphovascular invasion. These findings are biologically important because invasion requires tumour cells to detach from the primary tumour, degrade surrounding matrix components and migrate into blood or lymphatic vessels. Current understanding of cancer invasion shows that metastatic ability depends on complex interactions between tumour cells, extracellular matrix components, stromal cells and mechanical signals within the tumour environment. Recent work has demonstrated that extracellular vesicles and tumour microenvironment interactions can regulate invasive behaviour by altering cellular communication and matrix remodelling.[14,15]

The relationship between THSD7A and breast cancer invasion has not been extensively studied, which makes the current investigation important. Most previous research involving THSD7A has focused on other pathological conditions and tumour types rather than breast cancer. Therefore, the present study adds new information by exploring THSD7A as a possible marker associated with breast cancer aggressiveness. The findings provide a foundation for further functional studies to determine whether THSD7A directly regulates breast cancer cell migration or acts as part of a wider metastatic signalling network.

The current findings should be interpreted in the context of previous international research on cancer metastasis. Studies from Europe and the United States have increasingly focused on molecular markers that identify tumours with higher metastatic potential. These studies have shown that metastatic progression is not controlled by a single molecule but results from multiple interacting pathways involving extracellular matrix remodelling, epithelial–mesenchymal transition, angiogenesis and intercellular communication. Recent reviews have emphasised the importance of extracellular vesicle cargo, including proteins and nucleic acids, as regulators of tumour progression and potential biomarkers for metastatic disease.[16]

Similar research from other countries has reported that tumour-associated proteins involved in cellular communication may serve as indicators of aggressive disease. However, direct evidence regarding THSD7A-mediated breast cancer invasion remains limited internationally. This indicates that the present work addresses a relatively unexplored area. The study contributes by examining THSD7A together with clinicopathological variables commonly used in breast cancer assessment, including tumour grade, TNM stage, lymph node status, ER, PR, HER2 and Ki67 expression.[17]

In the Pakistani context, breast cancer remains a major health concern, and several studies have evaluated conventional molecular markers such as ER, PR, HER2 and Ki67 for classification and

treatment planning. However, research specifically investigating THSD7A expression in breast cancer tissue is limited and is not well established in Pakistani biomedical literature. Therefore, this study represents an important preliminary contribution by introducing THSD7A as a possible biomarker for investigation in Pakistani breast cancer populations. The local relevance is important because genetic background, healthcare access, delayed presentation and tumour characteristics may influence disease behaviour in Pakistani patients.[18,19]

The originality of this study lies in evaluating THSD7A within a comprehensive clinical framework rather than examining the marker alone. By analysing THSD7A expression together with invasion characteristics, metastatic status and potential confounding factors, the study provides a broader understanding of its possible clinical relevance. This approach may help identify whether THSD7A has potential value as a biomarker for risk stratification. However, because metastatic behaviour is influenced by multiple molecular pathways, THSD7A should be considered as a potential contributing factor rather than an independent explanation for tumour progression.

From a clinical perspective, identification of biomarkers associated with metastatic risk may improve patient monitoring and follow-up strategies. If future studies confirm that THSD7A reliably predicts aggressive disease, patients with increased THSD7A expression may benefit from closer surveillance, more detailed metastatic assessment and personalised treatment planning. At present, THSD7A cannot replace established prognostic markers, but it may complement existing clinical and molecular classification systems.

The present study also has several limitations. First, the retrospective design limited control over available clinical information and introduced the possibility of selection bias. Second, the study was performed using a single-centre dataset, which may reduce generalisability to other Pakistani populations. Third, although statistical adjustment was performed for major confounding variables, unmeasured biological factors may have influenced the observed associations. Fourth, the study evaluated association rather than direct biological causation. Functional laboratory experiments, including THSD7A knockdown or overexpression studies in breast cancer cell models, are required to confirm whether THSD7A directly promotes invasion and metastasis.

Future research should include multicentre Pakistani studies with larger patient populations and prospective follow-up. Functional studies should investigate the molecular pathways through which THSD7A influences breast cancer cell migration, extracellular matrix interaction and metastatic colonisation. Integration of THSD7A with genomic, transcriptomic and proteomic approaches may further clarify its role and determine whether it has value as a diagnostic, prognostic or therapeutic target.

CONCLUSION

The present study evaluated the potential role of THSD7A in breast cancer invasion and metastatic behaviour. The findings showed that increased THSD7A expression was associated with aggressive tumour characteristics, including higher invasion-related features, lymph node involvement and distant metastatic disease. After adjustment for important clinical and pathological factors, THSD7A expression remained associated with metastatic potential, suggesting that it may contribute to breast cancer progression.

The study highlights THSD7A as a potential biomarker involved in tumour cell invasion and metastasis. Although established clinicopathological markers remain essential for breast cancer management, assessment of additional molecular factors such as THSD7A may improve understanding of tumour aggressiveness and help in future risk stratification. The findings provide preliminary evidence supporting further investigation of THSD7A in breast cancer, particularly within the

Pakistani population where such studies remain limited.

Further research should include multicentre prospective studies with larger patient populations, functional laboratory experiments and molecular investigations to confirm the biological mechanisms through which THSD7A influences cancer cell migration and metastasis. Future studies should also evaluate whether THSD7A expression can provide additional prognostic value when combined with existing breast cancer biomarkers and whether it may represent a possible target for personalised therapeutic strategies.

AUTHORS' CONTRIBUTION

HMN, MN, and ND conceptualized and designed the study. Data collection, clinical assessment, molecular analysis, and interpretation of findings were performed by HMN, MN, and ND. All authors contributed substantially to manuscript preparation, critical revision, and intellectual input throughout the research process. ND supervised the overall study, provided methodological guidance, and critically reviewed the final manuscript. All authors read and approved the final version of the manuscript for publication.

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