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Prognostic Significance and Metastatic Potential of *MMPs* and *TIMPs* in Breast Cancer; An In-Silico Study

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ABSTRACT

Background: Matrix metalloproteinase (MMP) family and its endogenous tissue inhibitors (TIMPs) play central roles in regulating extracellular matrix (ECM) dynamics, thereby contributing to breast cancer progression and metastatic spread. A thorough genomic analysis of the genes coding for the members of MMPs and TIMPs in breast cancer for their prognosis and metastatic potential is lacking.

Methods: In this study, data from The Cancer Genome Atlas (TCGA) Pan-Cancer Atlas, the Genotype-Tissue Expression (GTEx) and publicly available breast cancer microarray datasets were integrated for comprehensive analysis of genetic alterations, transcriptomic dysregulation, prognostic significance and metastatic potential of MMP and TIMP genes in breast cancer.

Results: The findings revealed marked genetic alterations across *MMP* and *TIMP* genes, with gene amplification being the most prevalent mutation type. In addition to genetic alterations, substantial upregulation of *MMP1, MMP9, MMP11, and TIMP1*, while downregulation of *MMP19, MMP27*, and *TIMP4* were observed. Prognostic evaluation using Kaplan- Meier analysis revealed that overexpression of *TIMP1* and *TIMP4* correlates with better overall survival, whereas high expression of *MMP1*, *MMP8*, *MMP12* and *MMP15* are linked to poor outcomes.

Conclusions: These findings demonstrate potential clinical value of MMPs and TIMPs as biomarkers for breast cancer prognosis and diagnosis. Additionally, the study highlights the therapeutic promise of targeting the MMP-TIMP axis to modulate ECM dynamics and impede tumor progression and metastasis.

EDITORIAL NOTE

Editorial Note on Version of Record

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INTRODUCTION

The extracellular matrix (ECM) is a non- cellular scaffold composed of proteins and carbohydrate- rich macromolecules that surround cells, providing structural support while maintaining tissue architecture and function. In addition to providing essential mechanical scaffold to cells and tissues, ECM relays a plethora of biochemical cues that regulate cell proliferation, differentiation and tissue morphogenesis [1]. It plays a crucial role in mediating appropriate responses to external cellular environment. It provides both structural and biochemical support, influencing cell behavior and regulating various cellular processes. The ECM is essential for tissue development, maintenance, and repair. ECM is composed of several key constituents including proteins (collagen, elastin, fibronectin, laminins), glycosaminoglycans and proteoglycans [2]. Imbalances or abnormalities in the ECM can contribute to various diseases, including fibrosis, cancer, and degenerative disorders [3].

MMPs are a class of zinc- dependent endopeptidases that mediate ECM homeostasis by breaking down ECM proteins. MMPs are defined by two conserved motifs; a cysteine-containing prodomain that inhibits their catalytic activity and a histidine-rich catalytic domain responsible for the endopeptidase function [4]. Since ECM provides structural and biochemical support to the cells, the disintegration of its components by MMPs will affect cellular behavior in a number of physiological processes. MMPs regulate several physiological processes including embryogenesis, ECM remodeling, wound healing, angiogenesis, and immune response [5-8]. Therefore, anomalies in MMP levels can lead to abnormal degradation of the ECM, which is a primary trigger for the development of chronic degenerative diseases [9-11]. Additionally, this dysregulation also correlates with cancer development by regulating tumor microenvironment, cell proliferation, invasion and migration [12-15].

MMPs comprise 23 family members that are categorized according to their sub- cellular localization and substrate preference for the ECM substrates. The major categories comprise membrane-type matrix metalloproteases (MT-MMPs), collagenases, gelatinases, stromelysins, matrilysins, and additional MMPs [16]. MMPs function by cleaving specific peptide bonds in ECM proteins, resulting in their degradation and subsequent tissue remodeling [7].

The in vivo activities of MMPs are regulated by the local equilibrium between them and their physiological inhibitors. Within the ECM, the enzymatic activity of MMPs is modulated by TIMPs, which act as their endogenous inhibitors [17]. TIMPs serve as important regulators of ECM dynamics, contributing to the control of matrix turnover, tissue remodeling and cellular processes. Like MMPs, TIMPs regulate angiogenesis, cellular proliferation and apoptosis. Dysregulation of the equilibrium between MMPs and TIMPs has been recognized as a key factor contributing to the progression of multiple cancer types [12].

In breast cancer, both MMPs and TIMPs have been extensively studied because of their contribution to tumor progression, invasion and metastasis [18, 19]. Specific MMPs, such as MMP2, and MMP9 were found to be overexpressed and correlated with ERBB2 overexpression [20]. MMP9 has been proven to break down type IV collagen, a fundamental structural component of the basement membrane, which is a vital stage in metastatic progression. [21]. Similarly, tumor derived MMP13 correlated with aggressive breast cancer phenotype and poor prognosis [22]. Contrarily, MMP8 has protective role in breast cancer metastasis [23].

Additionally, therapeutic potential of MMPs and TIMPs has been explored in breast cancer [24, 25]. However, a comprehensive study providing a genetic and molecular landscape of *MMPs* and *TIMPs* collectively in breast cancer is lacking. The current research fills the gap by using genomic and transcriptomic datasets and employing systems genomics approaches. Several genes encoding MMPs and TIMPs were found to have genetic alterations and deregulated expression. Importantly, molecules with prognostication value and metastatic potential in breast cancer were also identified.

METHODS

List of Genes Encoding MMPs and TIMPs

Table 1 lists the genes encoding MMPs and TIMPs. The list of genes was generated based on previously published literature [26] in conjunction with HUGO gene nomenclature committee database (https://www.genenames.org/). All *MMP* and *TIMP* genes summarized in table 1 were investigated with respect to mutation status, expression patterns and their association with overall patient survival.

Genomic Alteration Analysis

Alterations in genes encoding MMPs and TIMPs were identified using data from the Cancer Genome Atlas (TCGA) (**https://www.cancer.gov/tcga**, accessed on 10 April 2024) via cBioportal [27]. cBioportal contains breast cancer datasets derived from several studies. For the analysis of genetic alterations, the dataset titled "TCGA Breast Invasive Carcinoma (TCGA, Pan-Cancer Atlas)," comprising 996 patient samples, was selected. This dataset includes the both the copy-number alterations (CNAs) and mutations.

Copy number alterations were obtained from the cBioPortal, where discrete GISTIC-based categories are use. In this classification, "gain" corresponds to low-level copy number increase (+1), while "amplification" represents high-level copy number increase (+2).

Transcriptome Changes

Transcriptomic analysis between normal tissue and breast cancer samples was conducted using Xena platform [28] that integrates data from GTEx [29] and TCGA. The heatmap was produced utilizing the gene set from Table 1. The gene list was copied into the Xena platform for analysis. "Main category" was chosen as the first phenotypic variable and for the second genomic variable, "Gene expression" option was selected. All the *MMP* and *TIMP* genes were copied to create the heatmap. The "view chart" tool was employed to create box plots for comparing gene expression changes of individual genes between GTEx normal breast tissues and TCGA breast cancer patients. Heatmap and box plots were generated using Xena as it employs a standardized pipeline to process TCGA and GTEx datasets, thereby reducing batch-related variability and enabling reliable comparative analysis. Expression values were obtained directly from the UCSC Xena platform, and no additional statistical transformations were applied.

Survival Analysis

The web-based Kaplan-Meier (KM) Plotter platform [30] was utilized for assessing survival outcomes. The platform integrates multiple breast cancer expression datasets to generate KM survival curves and estimates hazard ratios through Cox proportional hazards models, while statistical significance is evaluated using log-rank tests. A cohort of 1879 breast cancer patients was categorized into high and low expression groups according to the median expression level, and overall survival was subsequently calculated. The optimal probes for all the genes were selected using "Jetset", and survival analysis was performed over a follow-up period of 120 months.

Comparative Expression Analysis in Tumor, Normal and Metastasis Tissues

Gene expression differences among tumor, normal and metastasis tissues were assessed using the TNMplot (https://tnmplot.com) [41], an online resource that integrates gene expression data from multiple publicly available datasets, including TCGA, GTEx and gene expression omnibus. Multi-gene option was selected after choosing Breast tissue from the available options. Members of *MMP* and *TIMP* were loaded to generate density and box plots.

RESULTS

Genetic Alterations in Breast Cancer

Genomic alteration analysis of the genes encoding members of MMP and TIMP families

revealed alterations in all the genes examined in breast cancer patients. There were remarkable differences in the frequency of genetic alteration across the genes studied, ranging from 0.3% in *MMP19* to 10% in *MMP16* (Figure 1A). Gene amplification was found to be the most common genetic alteration. The other detected mutations were deep deletions, missense mutations and multiple alterations.

Notably, in 317 (32%) of queried patients, genetic alterations in all the genes in the *MMP* and *TIMP* families were detected, highlighting significance of these ECM molecules (Figure 1A). *CHD1*, *GATA3, PIK3CA* and *TP53*, previously known to be highly mutated, were used as controls. Higher mutation frequency was found in these control genes which validates my analysis (Figure 1A).

In the breast cancer subtypes, both the mutation rates and mutation types were markedly different from each other. Subtypes specific analysis revealed that breast invasive mixed mucinous carcinoma exhibited only amplification and deep deletions. The remaining breast cancer subtypes had representation of mixed genetic alterations in addition to amplification and deletions. (Figure 1B). These differences likely reflect underlying molecular heterogeneity among breast cancer subtypes. Clinically, such variation in alteration profiles may contribute to subtype-specific differences in tumor behavior and response to targeted therapies.

Genetic alterations in *MMPs* and *TIMPs* were identified across multiple cancer types, rather than being confined to breast cancer. Querying combined TCGA Pan-Cancer Atlas cohort of 10,953 patients across 32 cancer studies demonstrated similar mutation patterns across wide spectrum of cancers. These results suggest that genetic alterations in the *MMP* and *TIMP* genes are prevalent across cancer types (Figure 2).

Expression Analysis of *MMP* and *TIMP* family members in Breast Cancer

In addition to analyzing genetic alterations, expression analysis was also performed as transcriptomic anomalies are critical in tumor development. To do so, data from TCGA and GTEX were used and transcripts of all the genes under study were analyzed. As depicted in figure 3A, significant expression dysregulation was observed in breast cancer. Relative to normal breast tissue, several *MMP* and *TIMP* genes exhibited over- or under-expression in breast cancer samples. For example, *MMP1, MMP9, MMP11, MMP12, MMP13,* and *TIMP1* are some of the represented genes that exhibited elevated expression in breast cancer. In contrast, *MMP19, MMP21, MMP27, MMP28, TIMP2, TIMP3,* and *TIMP4* are among the genes with significantly lower expression in breast cancer. Expression alterations in the individual genes are shown in figure 3B. Collectively, these findings suggest substantial expression dysregulation in *MMP* and *TIMP* genes in breast cancer.

MMP and *TIMP* Expression Profiles and Overall Survival in Breast Cancer

Following the identification of widespread genetic alterations and expression changes in breast cancer, the prognostic significance of the observed expression alterations was further evaluated. KM Plotter [30], an online platform that integrates multiple microarray datasets, was used to assess overall survival among breast cancer patients based on the transcript levels of *MMPs* and *TIMPs*. These results showed that overexpression of *TIMP1* and *TIMP4* correlated with improved overall survival, whereas high expression of *MMP1, MMP8, MMP12* and *MMP15* was linked to poor patient survival (Figure 4). To validate the analysis, *TOP2A*, an established marker for poor survival in breast cancer, was analyzed, and the findings were consistent with its known role. No significant association with patient survival was observed for the other genes in the *MMP* and *TIMP* families (Supplementary figure S1). Overall, these findings underscore the role of *MMPs* and *TIMPs* that may serve as potential prognostic biomarkers in breast cancer.

Expression Changes in *MMP* and *TIMP* Genes During Tumor Progression and Metastasis

Following the evaluation of prognostic significance, the expression patters of *MMP* and *TIMP* genes were further investigated across different tissue types to gain deeper insights into their potential involvement in cancer progression and metastasis. The TNMplot platform was employed to assess differences in gene expression among normal, tumor and metastatic tissue samples. Analysis revealed distinct expression profiles of *MMP* and *TIMP* family members

across the three tissue categories (Figure 5A-B). Notably, *MMP1*, *MMP9*, *MMP11*, *MMP14*, *TIMP1* and *TIMP2* showed elevated expression in tumor and metastatic tissues relative to the normal controls, supporting their potential involvement in tumorigenesis and metastasis. Interestingly, *MMP3* and *MMP13* exhibited similar expression patterns in normal and metastatic tissues, which differed from those observed in primary tumor samples.

Figures

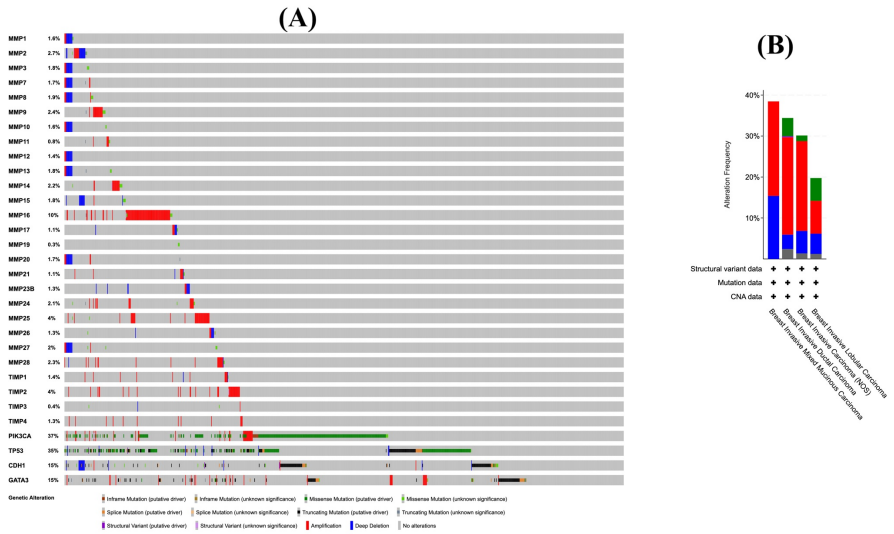


Figure 1: The diagram shows the genetic alterations in genes coding members of MMPs and TIMPs. (A) The distribution of genetic changes in the listed genes is illustrated for 996 in individual patients with the individual grey lines representing breast cancer patients. The color-coded bars represent various types of genetic alterations. Well-established genes like PIK3CA, TP53, CDH1 and GATA3 are used to validate the analysis. (B) The graphs display breast cancer subtypes, highlighting various genetic alterations in MMPs and TIMPs.

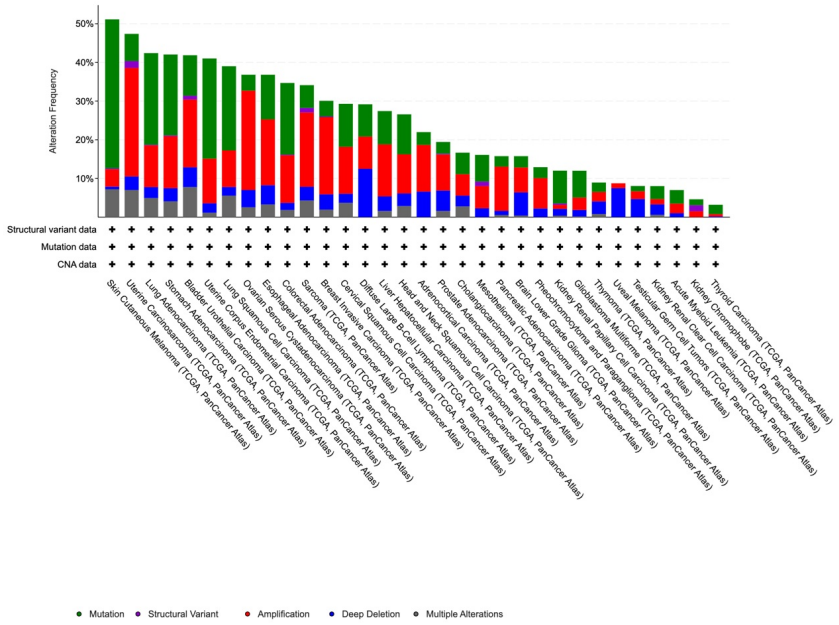


Figure 2: The figure illustrates the prevalence of genetic alterations in MMP and TIMP genes among different cancer types. Data from the TCGA Pan-Cancer Atlas, which includes 10967 samples / 10953 patients from 32 studies, is used.

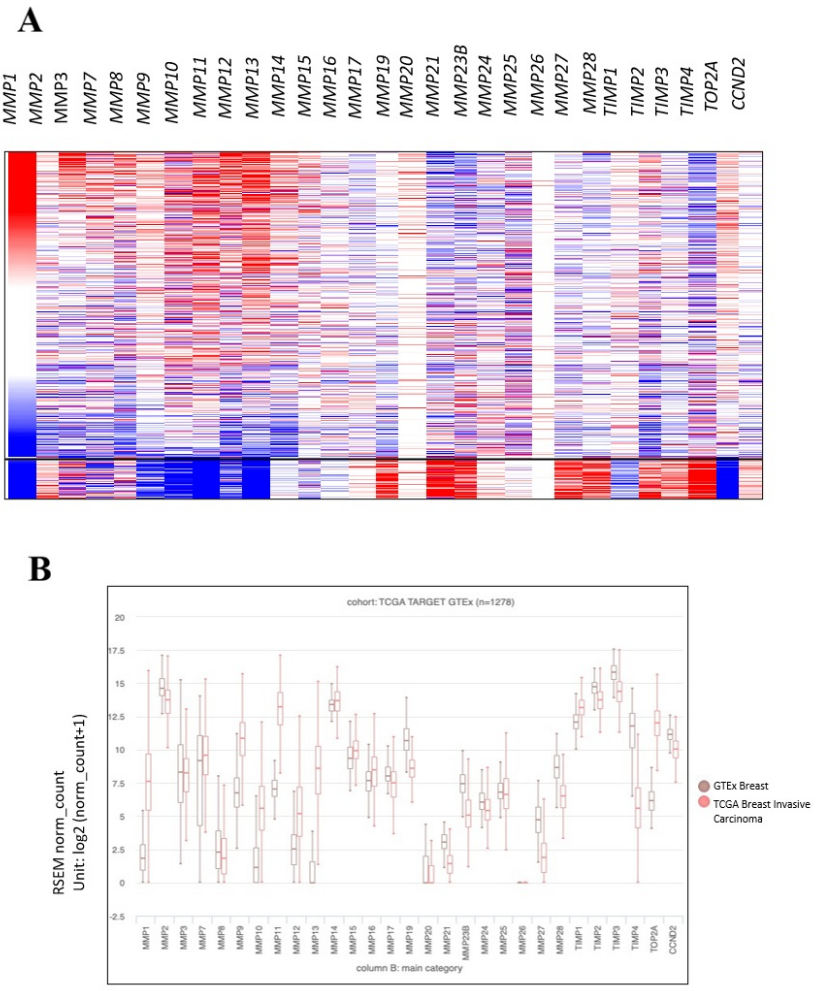


Figure 3: Expression patterns of genes encoding MMPs and TIMPs. (A) Underexpression (blue bars) and overexpression (red bars) of the analyzed genes are shown. Data from TCGA and GTEx were used to compare gene expression between normal and breast cancer samples. (B) Expression levels of individual genes were compared between normal and breast cancer patients. P values for each gene were determined by Xena's built-in Welch's t-test. MMP1 p <0.001 (t = -39.98), MMP2 p <0.001 (t = 14.15), MMP3 p = 0.049 (t = 1.972), MMP7 p <0.001 (t = -5.180), MMP8 p = 0.014 (t = 2.452), MMP9 p <0.001 (t = -25.58), MMP10 p <0.001 (t = -29.10), MMP11 p <0.001 (t = -65.90), MMP12 p <0.001 (t = -18.09), MMP13 p <0.001 (t = -57.46), MMP14 p <0.001 (t = -4.647), MMP15 p <0.001 (t = -7.331), MMP16 p <0.001 (t = -7.138), MMP17 p <0.001 (t = 11.74), MMP19 p <0.001 (t = 24.19), MMP20 p = 0.6181 (t = 0.4990), MMP21 p <0.001 (t = 19.71), MMP23B p <0.001 (t = 22.07), MMP24 p <0.001 (t = 6.515), MMP25 p = 0.2782 (t = 1.086), MMP26 p <0.001 (t = -4.506), MMP27 p <0.001 (t = 23.77), MMP28 p <0.001 (t = 22.69), TIMP1 p <0.001 (t = -16.12), TIMP2 p <0.001 (t = 18.83), TIMP3 p <0.001 (t = 21.38), TIMP4 p <0.001 (t = 36.19), TOP2A p <0.001 (t = -58.62), CCND2 p <0.001 (t = 20.99).

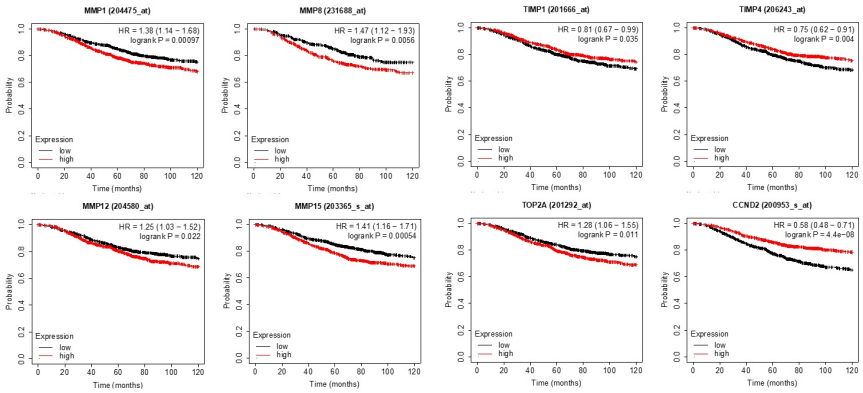


Figure 4: Expression of MMP and TIMP genes and their prognostic significance in breast cancer. KM plots illustrating overall survival in breast cancer patients. X-axis represents the time after diagnosis in months and

Y-axis indicates the overall survival probability. Red and black curves correspond to high- and low-expression group, respectively. The patients were stratified into high and low expression groups using the median expression level as the cutoff. KM survival curves and log-rank P-values were obtained using the KM Plotter online tool, as previously described [30].

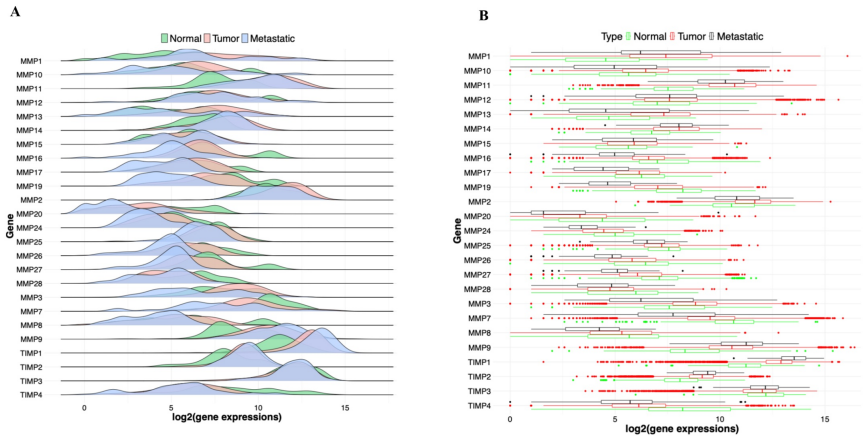


Figure 5: The differential expression of MMPs and TIMPs in breast cancer. (A) Normal, tumor and metastatic samples are shown as green and pink and blue, respectively. (B) Green, red and black box plot correspond to normal, tumor and metastatic samples, respectively.

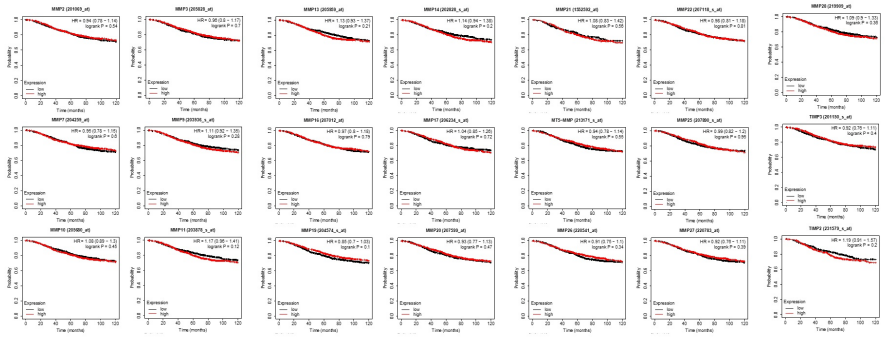


Figure 6 (Supplementary figure): KM plots of MMP and TIMP family members showing no significant association with overall survival in breast cancer patients. X-axis represents the time after diagnosis in months and Y-axis indicates the overall survival probability. Red and black curves correspond to high- and low-expression group, respectively. The patient cohort was grouped according to the median expression level.

Tables

Name	Gene symbol
Matrix metallopeptidase 1	*MMP1*
Matrix metallopeptidase 2	*MMP2*
Matrix metallopeptidase 3	*MMP3*
Matrix metallopeptidase 7	*MMP7*
Matrix metallopeptidase 8	*MMP8*
Matrix metallopeptidase 9	*MMP9*
Matrix metallopeptidase 10	*MMP10*
Matrix metallopeptidase 11	*MMP11*
Matrix metallopeptidase 12	*MMP12*
Matrix metallopeptidase 13	*MMP13*
Matrix metallopeptidase 14	*MMP14*
Matrix metallopeptidase 15	*MMP15*
Matrix metallopeptidase 16	*MMP16*
Matrix metallopeptidase 17	*MMP17*
Matrix metallopeptidase 19	*MMP19*
Matrix metallopeptidase 20	*MMP20*
Matrix metallopeptidase 21	*MMP21*
Matrix metallopeptidase 23B	*MMP23B*
Matrix metallopeptidase 24	*MMP24*
Matrix metallopeptidase 25	*MMP25*
Matrix metallopeptidase 26	*MMP26*
Matrix metallopeptidase 27	*MMP27*
Matrix metallopeptidase 28	*MMP28*
TIMP metallopeptidase inhibitor 1	*TIMP1*
TIMP metallopeptidase inhibitor 2	*TIMP2*
TIMP metallopeptidase inhibitor 3	*TIMP3*
TIMP metallopeptidase inhibitor 4	*TIMP4*

Genes analyzed in the study.

DISCUSSION

This study provides important insights into the mutational landscape, gene expression alterations, and prognostic implications of *MMP* and *TIMP* family members in breast cancer. Integration of TCGA-Pan-Cancer and transcriptome data showed that *MMPs* and *TIMPs* are frequently altered in breast cancer and across other cancer types, underscoring their fundamental roles in tumor biology.

The mutational analysis revealed significant variation in the frequency of genetic alterations across *MMP* and *TIMP* genes, with *MMP16* showing the highest alteration frequency (10%) and *MMP19* the lowest (0.3%). The relatively high alteration frequency observed for *MMP16* compared to other *MMP* family members may reflect its genomic location with the region prone to copy-number alterations in breast cancer. Gene amplification was identified as the predominant alteration type, consistent with previous findings linking the elevated activity of MMPs to tumor aggressiveness and metastasis [31; 40]. Furthermore, genetic alterations in at least one *MMP* or *TIMP* gene were identified in 32% of breast cancer patients, reinforcing the fundamental contribution of ECM remodeling in carcinogenesis. Importantly, the findings were evaluated using well characterized driver genes such as *TP53* and *PIK3CA* [32].

When analyzed across breast cancer subtypes, distinct mutational patterns were observed. For instance, mixed mucinous carcinoma exclusively exhibited amplifications and deep deletions, while other subtypes displayed a broader spectrum of genetic alterations. These findings align with studies emphasizing the molecular heterogeneity of breast cancer and the need for

subtype- specific treatment approaches [33, 34]. For instance, more frequent alterations in certain *MMPs* and *TIMPs* in aggressive subtypes may reflect enhanced extracellular matrix remodeling and invasive potential, which are hallmarks of these tumors. In contrast, breast invasive lobular carcinoma, which is generally slow-growing and hormone receptor-positive, may exhibit distinct alteration profiles associated with more regulated proliferative signaling. These subtype-specific differences suggest that alterations in *MMP* and *TIMP* genes are not uniform across breast cancer but are instead shaped by the underlying molecular context, which may influence disease progression and therapeutic response. Additionally, the pan-cancer analysis revealed that *MMP* and *TIMP* alterations extend beyond breast cancer, highlighting their universal roles in cancer biology. This aligns with earlier reports demonstrating widespread dysregulation across malignancies [13]. This finding also underscores the therapeutic potential of targeting ECM-modifying enzymes in a broad cancer context.

In addition to accumulation of multiple mutations, gene expression anomalies underlie the development of tumorigenesis [32]. Gene expression analysis offered further insights into the dysregulation of *MMPs* and *TIMPs* in tumor dissemination. Gene such as *MMP1*, *MMP9*, and *TIMP1* were significantly overexpressed in tumor tissues, consistent with their roles in promoting ECM degradation, angiogenesis and tumor invasion [26]. Conversely, *MMP19*, *MMP27*, and *TIMP4* were markedly downregulated, potentially reflecting tumor- suppressive roles. This is interesting given the contrasting roles of MMPs and TIMPs in the cells. These results are in agreement with prior reports demonstrating the complex roles of MMPs and TIMPs in tumor biology [35].

Higher expression of *TIMP1* and *TIMP4* was associated with favorable overall survival, as demonstrated by KM survival analysis, while elevated expression of *MMP1*, *MMP8*, *MMP12*, and *MMP15* predicted poorer outcomes. TIMPs, known for their inhibitory activity on MMPs, likely suppress tumor invasion and metastasis, which may explain their positive prognostic value [36]. Conversely, increased expression of certain MMPs is associated with enhanced ECM breakdown, facilitating metastasis and poor prognosis [37-39].

The differential expression analysis across normal, tumor and metastatic tissues further elucidated the functional roles of MMPs and TIMPs in breast cancer. Consistent with the earlier reports, several *MMPs*, including *MMP1*, *MMP9*, *MMP11* and *MMP14* were found to be upregulated in tumor and metastatic tissues [42]. These findings support their contribution to tumor invasion and metastatic dissemination, as increased MMP activity facilitates degradation of structural barriers and promotes cancer cell migration. In parallel, the elevated expression of *TIMP1* and *TIMP2* in tumor and metastatic samples suggests a more complex regulatory paradigm. Although TIMPs are classically described as inhibitors of MMP activity, their increased expression in cancer has been associated with additional MMP- independent functions [43, 44]. Notably, TIMP1 can interact with the cell surface receptor CD63 and integrins, leading to activation of intracellular signaling pathways such as PI3K/ AKT that regulate cell survival and apoptosis [45]. In breast cancer, this signaling axis has been implicated in modulating tumor cell behavior in a context dependent manner [46]. At the same time, elevated TIMP expression may reflect a compensatory response to increased proteolytic activity within the tumor microenvironment, acting to restrain excessive extracellular matrix degradation and metastatic dissemination. Therefore, the net effect of TIMP1 likely depends on the balance between its MMP-inhibitory and signaling mediated functions. This duality may partially explain the seemingly paradoxical observation that TIMP1 is upregulated in tumor and metastatic tissues while being associated with improved overall survival in the present analysis. Interestingly, *MMP3* and *MMP13* did not follow the general trend of tumor associated dysregulation, exhibiting expression patterns more similar to those in normal tissues, highlighting the functional heterogeneity within the MMP family.

Despite these significant findings, functional validation and thorough analysis of the observed genetic and expression changes is required to confirm their mechanistic roles in breast cancer progression. Moreover, integrating multi- omics data, including proteomics and epigenomics, would enable more comprehensive characterization of the regulatory networks involving MMPs and TIMPs. Importantly, the influence of immune cells in tumor microenvironment on ECM in conjunction with MMPs and TIMPs should also be considered. One of the key limitations of this study is its reliance on bulk RNA-seq, which inherently averages transcriptional signals across heterogeneous cell populations, limiting the ability to discern whether *MMP* and *TIMP* expression originates from malignant cells, stromal cells or immune populations within the tumor microenvironment. Single-cell RNA-seq represents a promising avenue to overcome this

limitation, facilitating the deconvolution of cell type specific expression profiles and the characterization of intercellular communication networks. Applying this technology in future investigations will be essential to unravel the spatiotemporal dynamics of *MMP* and *TIMP* regulation and their functional roles in breast cancer progression.

These findings offer a comprehensive genomic and molecular characterization of *MMP* and *TIMP* family members in breast cancer, highlighting their roles as key players in the disease pathogenesis and prognosis, and underscoring their complex and context dependent functions in tumor progression. Notably, patients with elevated expression of *MMP1, MMP8, MMP12* and *MMP15* exhibited poor overall survival, whereas high *TIMP1* and *TIMP4* expression was associated with improved survival, highlighting the functional heterogeneity within these families. The differential expression observed across normal, tumor and metastatic tissues further supports the multifaceted contributions of MMPs and TIMPs to ECM remodeling, tumor invasion and metastasis, extending beyond their classical roles. While these findings provide a valuable framework for understanding ECM- related protease regulation in breast cancer, functional validation and higher-resolution approaches, including single cell RNA-seq and multi-omics integration are warranted to elucidate the cell-type-specific mechanisms underlying their dual roles and develop targeted therapeutic strategies.

CONFLICT OF INTEREST

None

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ETHICS STATEMENT

Disclosure

Portions of this manuscript were edited with the assistance of AI- based language tools to improve clarity, readability and language quality. The author takes full responsibility for the scientific content, interpretation, analyses and conclusions presented in this work.

Ethics Approval and Consent to Participate

The findings presented in this study are based, in part, on data generated by the TCGA Research Network: https://www.cancer.gov/tcga.

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