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Original Article

Clinical Utility of Plasma uPA and PAI-1 as a Prognostic Biomarker in Breast Cancer

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Abstract

Background: Breast cancer represents the most frequently diagnosed form of cancer on a global scale and stands as the primary cause of cancer-related mortality among women. Metastasis of tumors constitutes a significant factor contributing to mortality in breast cancer cases. The urokinase-type plasminogen activator system, including uPA, uPAR, PAI-1 and PAI-2, is crucial for tumor progression and metastasis. Their combination is a validated prognostic marker for both node-negative and node-positive breast cancer, guiding treatment decisions for early breast cancer. This study aims to analyse uPA and PAI-1 levels in breast carcinoma patients and their correlation with disease stage, hormonal status, and potential use as prognostic indicators. ***Objective:*** To estimate the plasma levels of uPA and PAI-1 in patients with breast carcinoma and compare them to those in the control group. To correlate these markers (uPA and PAI-1) with other clinicopathological parameters. ***Methods:*** A cross-sectional analytical study was conducted on 30 biopsy-proven breast cancer patients. Blood samples were collected to analyse uPA and PAI-1 levels and coagulation profiles. The correlation between uPA and PAI-1 levels and other clinicopathological parameters was studied. ***Results:*** Our study observed a statistically significant association of uPA levels with increasing tumor size, higher tumor stage, lymphadenopathy and higher ki67 index (<0.05). On the contrary, the association of uPA levels with ER/PR and HER2/neu receptor status was insignificant. The association of high PAI-1 levels with higher clinical stage and ER-negative status of the tumor was statistically significant. ($p<0.05$). Both uPA and PAI-1 show co-elevation in most breast cancer patients. ***Conclusion:*** Plasma uPA/PAI-1 levels may provide important information in the risk stratification of patients with breast cancer and act as potential prognostic biomarkers.

Keywords: ***PAI-1, uPA, MMP, Breast carcinoma, Her-2/neu.***

Introduction

Breast cancer is the most common cancer in women and a leading cause of cancer-related deaths globally. In 2022, it was the second most diagnosed cancer in women, with approximately 2.3 million new cases, making up about 11.6% of all cancer cases. It also ranked as the fourth highest cause of cancer-related deaths worldwide, claiming 666,000 lives [1]. The World Cancer Report 2020 highlighted that early detection and rapid treatment are the best intervention strategies for managing the menace of breast cancer [2]. While advancements in treatment and early detection are significant, the mortality rates linked to breast cancer remain a concern. Key prognostic factors including tumor stage, grade, lymph node status, and hormone receptor expression are regularly assessed. Continuous research is vital to find more effective predictors, as breast cancer is a complex disease. Notably, malignant tumors metastasise by degrading the extracellular matrix, allowing cancer cells to spread to other parts of the body. Proteolytic enzymes like matrix metalloproteinases, cysteine proteases, and serine proteases, along with the urokinase-type plasminogen activator system, play a crucial role in this process [4]. Urokinase-type plasminogen activator (uPA), its receptor (uPAR), and plasminogen activator inhibitor-1 and -2 (PAI-1 and PAI-2) are principal components of this system. Urokinase-type plasminogen activator (uPA) is a serine protease produced by tumor and normal cells, involved in tissue remodelling. It is regulated by plasminogen activator inhibitor type-1 (PAI-1). Both uPA and PAI-1 play important roles in tumor invasion and metastases in breast cancer and can be used as prognostic markers [7].

The combination of uPA and PAI-1 serves as a promising biomarker that has recently intrigued researchers. This complex is essential for degrading the extracellular matrix (ECM), releasing growth and angiogenetic factors, and spreading cancer cells, all of which contribute to a poor prognosis in breast cancer [5,6].

This study aims to investigate the levels of uPA and PAI-1 in breast cancer patients and their correlation with disease stage and

hormonal status. It also explores the potential use of uPA and PAI-1 as prognostic indicators. Additionally, the study includes an analysis of the coagulation profile associated with breast cancer.

Material and Methods

A cross-sectional analytical study at Lady Hardinge Medical College from January 2022 to June 2023 compared plasma uPA and PAI-1 levels in 30 biopsy-proven breast carcinoma cases with a control group of 30 healthy female healthcare workers. The study excluded patients with prior chemotherapy, recurrence, and male breast cancer. It also examined the correlation between uPA and PAI-1 levels and clinicopathological parameters.

Informed written consent was obtained from all participants. Detailed history and examination findings were recorded using a pre-designed form. Blood samples were collected in vacutainer tubes (EDTA & Citrate vial) for analysis of uPA and PAI-1 levels, as well as coagulation profiles.

Determination of uPA and PAI-1 Levels

The uPA levels were analyzed using the Human PLAU/uPA ELISA Kit from Fine Test, Wuhan Fine Biotech Co., Ltd. The PAI-1 levels were analyzed using the BOSTER PicokineTM ELISA kit.

Determination of Coagulation Profile

The levels of Prothrombin time (PT) activated partial thromboplastin time (aPTT), and D-dimer were measured in each case of breast cancer. The quantitative determination of D-dimer was performed using the STA-Lia test D-Di PLUS kit on a fully automated coagulation analyser photo-optical STA-Compact (Stago, France). Plasma prothrombin time (PT) was determined using the STA-Neoplastine Cl Plus kit, while APTT was determined using the STA-C.K. Prest kit. The STA-Lia test D-Di PLUS kit was also used for the quantitative determination of D-dimer.

H&E-stained slides were used to study the tumour's morphological characteristics and histopathological findings. Immunohistochemistry for ER, PR, HER-2/neu and Ki-67 was studied in each case. ASCO/CAP Guidelines 2019 were followed for immunohistochemical interpretation.

The results were tabulated and analysed. Statistical Package for Social Sciences (SPSS) version 18.0 was used for statistical analysis. Pearson correlation was applied to see the relationship between the variables. A p-value of <0.05 was considered statistically significant at a 95% confidence level.

Results

In this study, 30 cases of breast carcinoma were diagnosed using FNAC and confirmed through histopathological examination. The age range for breast cancer patients was 28-69 years, and for controls, it was 24-70 years. Tumor sizes ranged from 2 cm to 8.5 cm, with the majority (56.6%) falling in the range of 2.1-5 cm.

In our study, 56.6% of cases were T2, 20% were T3, and only 2 were T1. Lymph node involvement was observed in 66.7% of cases. Among the different stages of breast cancer, Stage II cases had the highest incidence at 56.7%, followed by Stage III at 33.3%, and Stage I at 10%. No cases in our study were at Stage IV. Histological grading was done using the Nottingham modification of the Bloom & Richardson method and was scored as Grade I, II, or III. Grade II cases had the highest incidence at 63.3%, Grade III at 30%, and Grade I at 6.7%.

Among the breast cancer patients, 60% were ER-positive, while 40% were ER-negative. Additionally, 57.7% of the patients were PR-positive, and 43.3% were PR-negative. There was a higher incidence of HER-2/NEU-negative breast cancer cases at 66.7% compared to HER-2/NEU-positive cases at 33.3%. Furthermore, Ki-67 levels ≥20% were found in 86.7% of cases, while levels below 20% were found in 13.3%.

The uPA levels in breast cancer patients were significantly higher ($p<0.05$) than in controls, with a mean of 3.82 ng/ml and a range of 0.85 ng/ml to 5.66 ng/ml. The ROC curve, created using the uPA values of both breast cancer patients and controls as the observed variable and the presence or absence of cancer as the classifier variable, indicated that uPA values were generally higher in breast cancer patients A uPA level > 3 ng/ml had a sensitivity of 83.33% and specificity of 93.33%, indicating its diagnostic utility in breast cancer patients [**Graph 1**].

The PAI-1 levels in breast cancer patients were significantly higher ($p<0.05$) compared to controls, with a mean of 17.49 ng/ml and a median of 17.28 ng/ml. A ROC curve, based on the PAI-1 values of breast cancer patients and controls, showed that PAI-1 values greater than 14 ng/ml had a sensitivity and specificity of 86.67% for diagnosing breast cancer [**Graph 2**]. This suggests that PAI-1 levels may be useful for diagnosing breast cancer.

The criteria for determining positive levels of uPA and PAI-1 were set at ≥3 ng/ml and ≥14 ng/ml, respectively. uPA tested positive in 25 cases, with significantly elevated levels found in breast cancer patients (83.3%) compared to healthy subjects [**Table 1**]. Similarly, PAI-1 was positive in 26 cases of breast carcinoma, with uPA levels being notably raised in breast cancer patients (86.7%) in comparison to normal healthy individuals [**Table 2**].

In the majority of breast cancer patients (80%), both uPA and PAI-1 levels were elevated [**Table 3**].

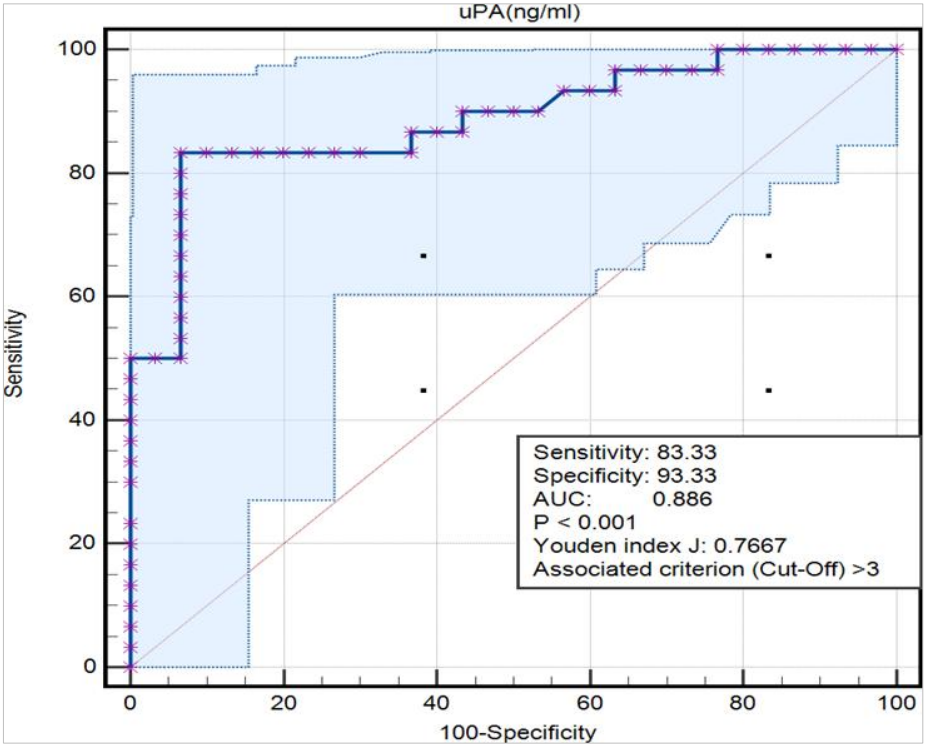
The Prothrombin time (PT) range for breast cancer patients was 12.3s to 14.7s, with a mean of 13.25s. The PT range for controls was 11.1s to 15.0s, with a mean of 12.88s. All observed PT values were within the limit of 16.9s for both controls and breast cancer cases.

The Activated Partial Thromboplastin time (APTT) range for breast cancer patients was 22.8s to 30.9s, with a mean of 28.04s. The APTT range for controls was 25.5s to 32.0s, with a mean of 29.45s. All observed APTT values were within the limit of 36.6s for both control and breast cancer cases.

The Plasma D-dimer range for breast cancer patients was 0.12 µg/ml to 1.07 µg/ml, with a mean of 0.72 µg/ml. The Plasma D-dimer range for controls was 0.1 µg/ml to 0.83 µg/ml, with a mean of 0.32 µg/ml. The difference in Plasma D-dimer between cases and controls was significant ($p<0.05$), with a p-value of 0.001. Most breast cancer patients had elevated plasma D-dimer levels.

Relationship of uPA and PAI-1 with other clinicopathological parameters [**Table 3 & 4**]

Our study observed a statistically significant association between uPA levels and tumor size ($p<0.05$). A statistically significant was found between higher uPA levels and higher stage, lymphadenopathy ($p<0.05$) and higher ki67 index. On the contrary, the association of uPA levels with histological grade, ER/PR and HER2/neu receptor status was insignificant. We observed that the association of high PAI-1 levels with higher clinical stage and ER-negative status of the tumor was statistically significant. ($p<0.05$). The association of PAI-1 levels with tumor size, lymph node involvement status, histological grade, PR, HER-2/NEU receptor status, and the Proliferative index (Ki 67) value were not significant. ($p>0.05$). The association between uPA and PAI-1 levels with plasma D-dimer levels in breast cancer patients was not statistically significant. ($p>0.05$).

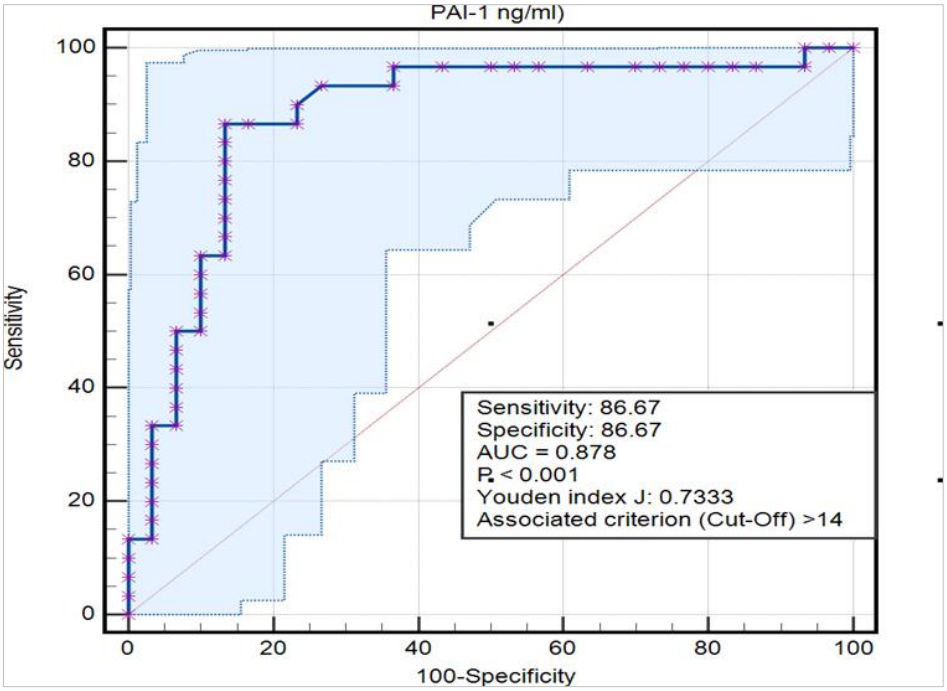


Graph 1: Roc analysis of uPA as variable and presence/absence of breast cancer as classification variable

The area under the ROC curve (AUC)	0.886
Standard Error [a]	0.0444
95% Confidence interval [b]	0.778 to 0.954
z statistic	8.695
Significance level P (Area=0.5)	<0.0001

[a] *DeLong et al., 1988*

[b] *Binomial exact*



Graph 2: Roc analysis of pai-1 as variable and presence/absence of breast cancer as classification variable

The area under the ROC curve (AUC)	0.878
Standard Error [a]	0.0491
95% Confidence interval [b]	0.768 to 0.948
z statistic	7.700
Significance level P (Area=0.5)	<0.0001

[a] DeLong *et al.*, 1988

[b] Binomial exact

Table 1: Distribution of uPA in breast cancer cases and controls.

uPA (ng/ml)	Number of Cases	
	Control	Breast Cancer
Non-elevated (< 3 ng/ml)	28 (93.3%)	5 (16.7%)
Elevated (≥ 3 ng/ml)	2 (6.7%)	25 (83.3%)
Total	30 (100%)	30 (100%)

Table 2: Distribution of PAI-1 in breast cancer cases and controls.

PAI-1 (ng/ml)	Number of Cases	
	Control	Breast Cancer
Non-elevated (<14 ng/ml)	25 (83.3%)	4(13.3%)
Elevated (≥ 14 ng/ml)	5(16.7%)	26(86.7%)
Total	30 (100%)	30 (100%)

Table 3: Relationship between the elevation of uPA and PAI-1 in breast cancer.

Total Cases (N = 30)	uPA Positive (≥3 ng/ml)	uPA Negative (<3 ng/ml)
PAI-1 Positive (≥14 ng/ml)	24 (80 %)	2 (6.7 %)
PAI-1 Negative (<14 ng/ml)	1 (3.3 %)	3 (10%)

Table 4: Relationship of uPA with other clinicopathological parameters.

Clinicopathological Factors	Category	Number of Patients	uPA (ng/ml)				*p* Value
			Min.	Max.	Mean	SD	
Tumor Size/ Stage	T1	02 (6.7%)	1.92	3.25	2.59	0.94	0.014
	T2	17 (56.6%)	1.29	5.06	3.50	1.07	
	T3	06 (20.0%)	0.85	5.56	4.06	1.76	
	T4	05 (16.7%)	4.66	5.66	5.14	0.39	
Histological Grade	I	2 ((6.7%)	1.92	3.19	2.56	0.90	0.28
	II	19 (63.3%)	0.85	5.66	3.81	1.47	
	III	09 (30%)	3.09	5.18	4.13	0.82	
Lymph Node Involvement	Uninvolved	10 (33.3%)	0.85	5.66	4.08	1.35	0.043
	Involved	20 (66.7%)	1.29	4.73	3.31	1.08	
ER	Negative	12 (40%)	1.29	5.66	4.11	1.49	0.20
	Positive	18 (60%)	0.85	5.19	3.63	1.16	
PR	Negative	13 (43.3%)	1.29	5.66	4.01	1.40	0.40
	Positive	17 (57.7%)	0.85	5.19	3.68	1.24	
Her-2/neu	Negative	20 (66.7%)	1.29	5.66	4.0	1.26	0.33
	Positive	10 (33.3%)	0.85	5.31	3.47	1.37	
Ki-67	< 20%	04 (13.3%)	2.18	3.62	3.02	0.605	0.023
	≥ 20%	26 (86.7%)	0.85	5.66	3.95	1.34	
D-Dimer	< 0.50	5 (16.7%)	1.29	5.56	3.32	1.77	0.452
	≥0.50	25 (83.3%)	0.85	5.66	3.92	1.21	

Discussion

Breast cancer is the most prevalent type of cancer and the leading cause of cancer-related deaths among women worldwide [9]. Breast cancer remains a major global health concern, with 2.3 million women diagnosed worldwide in 2020. Variations in incidence rates are due to differences in risk factors, screening strategies, and access to treatment. Molecular biomarkers are now used to stratify patients and provide a range of treatment options, including targeted therapies. These biomarkers include immunohistochemical markers (e.g., ER, PR, HER-2/neu and proliferation marker Ki-67), genetic markers (e.g., BRCA 1, BRCA 2) and immunologic markers (e.g., immune checkpoint proteins such as PDL-1 and tumour-infiltrating lymphocytes) [10]. Tumor metastasis accounts for 90% of cancer-related deaths. Therefore, early detection of breast cancer metastasis is crucial. A delayed diagnosis of metastatic disease leads to a poorer prognosis and survival, highlighting the necessity for improved approaches [7,11].

The metastatic spread of cancer involves key stages, beginning with cancer cells detaching from their primary site and migrating into nearby tissues. This process requires the activation of proteolytic enzymes that degrade the extracellular matrix (ECM) and basement membranes. A primary focus of research is on plasminogen activators (PAs), particularly tissue-type (tPA) and urokinase-type plasminogen activator (uPA).

While tPA is mainly associated with thrombolysis, uPA is critical in cancer metastasis. Encoded by the PLAUR gene, uPA facilitates plasminogen activation, proteolysis, signal transduction, and cellular adhesion. Typically expressed at low levels, uPA increases during tissue remodelling, wound healing, inflammation, and embryogenesis, playing a significant role in ECM degradation, cell invasion, and migration. The zymogen form of uPA (pro-uPA) acts on the uPA receptor and triggers a cascade of proteolytic events that leads to the degradation of ECM. Once pro-uPA is activated to uPA, it converts plasminogen to its active form, plasmin [12].

Plasmin, a potent proteolytic enzyme, effectively degrades or remodels ECM proteins, such as fibrin, fibronectin, laminin, and vitronectin, thereby creating a localized microenvironment conducive to matrix degradation. This process facilitates the migration and invasion of cancer cells. Plasmin, in turn, activates

downstream proteases such as pro-matrix metalloproteinase (MMP)-3 and MMP-3, pro-MMP-9 and MMP-9, leading to ECM remodelling. Additionally, plasmin can release ECM-bound growth factors that contribute to tumor progression. Urokinase plasminogen activator (uPA) is regulated by a negative feedback loop involving plasminogen activator inhibitors 1 and 2 (PAI-1 and PAI-2). High levels of uPA in tumors compared to normal tissues suggest it could be a therapeutic target for cancer. Most studies on uPA and PAI-1 have focused on frozen tissue extracts and found elevated levels. However, few studies have examined these markers in serum or plasma in breast cancer, with many reporting increased levels.

Ferroni P *et al.* studied PAI-1 levels in 187 cases of breast carcinoma patients and 187 healthy controls. Plasma levels of PAI-1 were found to be higher in cases as compared to the controls ($p<0.001$) [13]. Pusina *et al.* studied 66 breast cancer patients and found the uPA/PAI-1 complex to be raised in serum in 30 % of cases of breast carcinoma [14]. Paluchowski MB *et al.* investigated 252 cases of metastatic breast carcinoma and their uPA levels in serum using ELISA. They found that 26% of patients had elevated uPA levels. However, they did not find any correlation between uPA levels and tumor subtypes or grading [15].

Nafakh *et al.* studied 55 cases of breast cancer and found a significant increase ($p < 0.05$) in PAI-1 levels in the serum of women with breast cancer as compared to controls [16]. In 2022, Wrzeszcz K and colleagues conducted a study on 41 breast cancer patients to analyse the levels of uPA and PAI-1 in their plasma. Contrary to most studies, their findings showed a significantly lower level of PAI-1 antigen in patients with lymph node involvement [17].

McGowan *et al.* in their study showed that breast cancer patients who have tested negative for lymph nodes and have undergone uPA/PAI-1 measurements, do not require adjuvant chemotherapy. These patients have shown to have outstanding outcomes despite not receiving chemotherapy. After a 10-year follow-up, only 10% of these patients succumbed to the disease and 13% developed a recurrence/metastasis. It's worth noting that if these patients had received hormone therapy, their overall 10-year survival rate would have likely exceeded 90% [18].

Sobocan *et al.* studied levels of uPA and PAI-1 in 67 cases of triple-negative breast cancer. They discovered no significant correlation between these biomarkers and tumor size, lymph node status, or age at diagnosis. Additionally, they found no association between these biomarkers and recurrence or disease-specific survival [19].

This study comprising 30 breast cancer patients examined the levels of urokinase-type plasminogen activator (uPA) and plasminogen activator inhibitor-1 (PAI-1) as potential biomarkers. Elevated levels of both uPA and PAI-1 were observed in the majority (80%) of the breast cancer patients. This indicates the potential diagnostic utility of measuring uPA and PAI-1 levels. A statistically significant correlation was observed between higher uPA levels and advanced stage, lymph node involvement, higher histological grade, and a higher ki67 index (<0.05). However, no significant association was found between uPA levels and the status of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2/neu).

The significance of uPA and PAI-1 in the dissemination of cancer has been substantiated by both retrospective and prospective studies. Elevated levels of uPA and PAI-1 in breast tumor tissue serve as independent prognostic indicators of unfavourable patient outcomes, particularly in cases of lymph node-negative breast cancer. Furthermore, these biomarkers can anticipate the efficacy of adjuvant chemotherapy in the early stages of breast cancer. Notably, uPA and PAI-1 stand out as highly validated predictive biomarkers for lymph node-negative breast cancer, particularly in the identification of patients who may be spared the toxicity and financial burden associated with adjuvant chemotherapy [18].

Recently, a prospective multicentre study involving 93 lymph node-negative and ER-positive breast cancer patients provided direct evidence that uPA/PAI-1 measurement is cost-effective and cost-saving [20].

Study Limitations

The smaller sample size of the study population limits the application of study findings which need to be validated in their relationship to the outcome of a larger study population.

Conclusion

The uPA, along with its receptor and PAI-1, has been shown to play a significant role in various stages of cancer. It is frequently found to be abnormal in multiple types of cancer, including breast cancer, and has become a potential target for cancer prognosis, diagnosis, and treatment. Preclinical data suggests that targeting uPA and PAI-1 can suppress tumours and reduce metastasis. Our study underscores the importance of measuring levels of uPA and PAI-1 in all breast cancer cases to reduce cancer-related morbidity and mortality associated with metastasis.

Declarations

Ethical Consideration

The research ethics committees of Lady Hardinge Medical College approved this study. All participants provided informed consent.

Acknowledgment

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Financial Disclosure

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