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Original Article

Analysis of Coagulation Parameters in Patients with Breast Pathology and Their Possible Relevance to a Hypercoagulable State

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Abstract

Background: To study the alteration in coagulation parameters such as activated partial thromboplastin time (APTT), prothrombin time (PT), thrombin time (TT), D-dimer and fibrinogen among patients with benign and malignant breast lesions when compared to normal controls.

Materials and methods: The present study was a prospective cross-sectional study conducted among 50 cases diagnosed with benign and malignant breast cancer and comparing them with 20 age-matched controls. Coagulation parameters such as PT, TT, APTT, fibrinogen, and D-dimer were collected and compared between the malignant cases, benign cases, and age-matched control groups based on clinical and demographic details, the status of Progesterone receptor, Estrogen receptor, Her2 Neu, side and grading of cancer.

Results: Significant difference was reported with regard to mean age (p=0.0103) between malignant and benign tumor group (p=0.0103). Mean fibrinogen (p<0.001), thrombin time (p=0.007), and D-dimer (p<0.001) between the three groups also showed a statistically significant difference.

Conclusion: Of the biological parameters assessed in the present study; thrombin time, D-dimer and fibrinogen levels show significant differences in patients with benign and malignant breast diseases. This may serve as a biological marker to evaluate the beginning of Cancer-associated venous thrombosis (CAT) in breast cancer patients.

1. INTRODUCTION

A prothrombotic state is brought on by malignancy, and venous or arterial thrombotic episodes frequently which results in complications during cancer treatment. Thrombosis is reported among 15% to 20% of all cancer patients at some time during their disease. Patients with gynaecological and breast malignancies are more likely to develop venous thromboembolism (VTE) than people in the general population. The prevalence of cancer-associated thrombosis fluctuates according on the main site (1).

Breast cancer, now the most often diagnosed disease globally, has overtaken lung cancer, representing 1 in 8 cancer diagnoses, and totalling 2.3 million new cases across both genders (2). In 2020, it was the most often diagnosed cancer in women, representing a quarter of all female

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cancer cases (3). The prevalence of this disease has been rising worldwide, particularly in developing countries. In 2020, around 685,000 women succumbed to breast cancer, accounting for 16% of all female cancer fatalities (4). Breast cancer has been reported to show an incidence of 28.8% among Indian women (5). During the progression of the disease, 1% of patients experience problems from thromboembolic events, which exacerbates their clinical condition and increases morbidity and mortality (1). Cancer-associated venous thrombosis (CAT) occurrence in any anatomical site correlates with heightened all-cause mortality across various malignancies, with research indicating that patients with CAT and uterine, breast, or prostate cancer exhibit a three-to-five-fold elevated risk of mortality compared to those without CAT (6).

Literature indicates that individuals with malignant tumors have micro-inflammatory states that lead to inflammatory responses associated with the dysfunction of the blood coagulation system. The increased secretion of inflammatory mediators may be associated with endothelial cell dysfunction and indirect activation of the coagulation pathway, leading to an accelerated release of inflammatory factors from neutrophils and mononuclear cells, so establishing a detrimental cycle of coagulation activation (1,7,8,9).

The relationship between coagulation-related haematological factors and cancer-associated thrombosis in breast cancer patients has not been investigated, and this study was conceived and executed to address this deficiency. The authors evaluated the specified coagulation indices, as well as D-dimer and fibrinogen levels, which are crucial for clot formation. The chosen characteristics were compared among the three groups and analysed for correlation with hormone receptors, including progesterone receptors, estrogen receptors, Her2 Neu, and cancer grade.

2. MATERIALS AND METHODS

The present study was of prospective cross-sectional design and was conducted at a tertiary healthcare center. Department of Pathology, Surgery and Oncology were involved in the study. Breast cancer patients of both sexes who fulfilled the inclusion criteria included in the study. Ethical approval was secured from the Institutional Human Ethics Committee (Reference no: PSH/IHEC/2022/Appr/FB/026).

A sample size was calculated considering the prevalence of breast cancer in India (25.8%) and an approximate sample size of 72 was considered for the study (10).

formula = $\frac{p(100-p)Z^2}{E^2} = \frac{25.8(100-25.8)1.96^2}{10^2} = 73$

2.1. Patient selection

Biopsy-proven breast cancer of all histological subtypes, biopsy-proven preinvasive breast cancers, and cases with radiological diagnoses of benign (preinvasive) / invasive breast cancers were involved in the present study. Breast cancer patients on inadequate biopsy, chemotherapy, recurrence, patients whose coagulation parameters are not sent as a part of pre-treatment workup, and patients who did not consent to the study were not included in the study.

2.2. Procedure

The study samples were taken solely after acquiring patient consent. Clinical characteristics, histopathology diagnosis, and Hormone status (ER, PR, Her2Neu, Ki67) were obtained from the hospital database. Coagulation parameters assay (PT, APTT, TT, fibrinogen, D-dimer, and platelet count) was performed as a pre-therapeutic workup and the results were retrieved from the hospital information system (HSIS). The parameters considered had the following normal value range: Activated partial thromboplastin time – 25-34 sec (Photo optical detection of clot), Thrombin time – 14-21 sec (Photo optical detection of clot), Claus fibrinogen – 200- 400mg/dl (Photo optical detection of clot), D-dimer - <0.5mg/L (Immunoassay).

2.3. Statistical analysis:

The gathered data was examined utilizing statistical software R version 4.2.1 and Microsoft Excel. Categorical variables were represented as frequencies and percentages. Continuous variables were expressed as Mean ± SD / Median (Min, Max).The normality of the variable was assessed using the Shapiro-Wilk test and QQ plot, and a two-sample t-test was employed to compare the means of various variables among clinicopathological statuses. Mann-Whitney The U test was employed to examine the distribution of various factors concerning clinicopathological status, while the chi-square test was utilized to assess the dependency between categorical variables. Welch's ANOVA was employed to compare the means of variables between groups, and the Games-Howell test was utilized for post hoc analysis. The Kruskal-Wallis test was employed to compare the distribution of variables across the groups. Dunn's test was employed as a post hoc analysis. A p-value of 0.05 or lower signifies statistical significance.

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3. RESULTS

3.1. Comparison of different variables between the benign and malignant groups

The research comprised a total of 70 participants and data acquired included measures from 25 benign, 25 malignant, and 20 normal control patients. **Table 1** examined various factors between benign and malignant groups; a two-sample t-test revealed a significant difference in mean age between the groups (p=0.0288). Chi-square test revealed a significant difference in symptom distribution (p=0.022), mammogram results across the groups (p<0.0008), and extra comorbidities between groups (p=0.0016). No notable disparity was observed in the distribution of breast cancer by side. Mann-Whitney U test indicated no significant difference in platelet count distribution across the groups.

3.2. Distribution of different variables among malignant cases

The distribution of different variables in malignant cases was shown in **Table 2**, majority participants in the malignant group presented with grade 2, (n=16, 64%) cancer followed by 16% presenting with grade 1 cancer. The majorityofparticipants tested negative for ER (64%), PR (80%), and Her2 Neu (56%). When the level of Ki67 was assessed, the majority ofparticipants showed 20-30% (20%) and 60-70% (16%) expression. Most of the participants did not show lymph node involvement (96%) and the most common TNM staging seen among the participants was T2N0M0 (24%) followed by T3N0M0 (20%).

3.3. Comparison of coagulation parameters based on the cancer side

The comparison of coagulation parameters between right and left-sided breast cancer is presented in **Table 3**, revealing no significant variation in the mean PT, TT, and fibrinogen levels between the two patient groups. Mann-Whitney U test revealed no significant difference in the distribution of APTT (p=0.127) and D-dimer (p=0.193) based on the diagnosis in cancer patients.

3.4. Comparison of coagulation parameters based on ER, PR and Her2 Neu status

Table 4 analyzed coagulation parameters in relation to estrogen receptor (ER), progesterone receptor (PR), Her2 Neu status, and vascular metastasis in malignant patients. The two-sample t-test indicates no significant difference in the mean PT, APTT, TT, and D-dimer relative to the ER status of malignant patients. Fibrinogen levels exhibited a statistically significant change (p=0.0341). Regarding PR, Her 2 Neu status, and vascular metastases, no significant differences were seen depending on any of the variables.

3.5. Comparison of coagulation parameters based on the cancer grading

Table 5 evaluated coagulation parameters according to cancer grading, revealing no significant change in their distribution. **Table 6** compares the coagulation parameters among the three groups (benign, malignant, and control). Welch's ANOVA indicates a significant difference in the mean fibrinogen levels between the groups (p<0.001). The Kruskal-Wallis test revealed a statistically significant difference in thrombin time (p=0.007) and D-dimer levels (p<0.001) among the groups.

3.6. Comparison of coagulation parameters between the three groups

Post hoc analysis revealed a significant difference in the mean fibrinogen levels between the malignant group and both the benign (p-value=0.0466) and control (p-value=0.0001) groups. Post hoc analysis revealed a significant difference in the distribution of TT between the control group and the malignant group (p=0.0192). A notable disparity in D-dimer distribution was seen when contrasting the malignant group with both the benign (p<0.001) and control (p<0.001) groups (**Figure 1**). Prothrombin time and APTT did not show any significant different between the groups (**Figure 2**).

4. DISCUSSION

The development of distant metastases is the primary cause of elevated mortality among women with breast cancer, attributed to the proximity of axillary lymph nodes, which increases the likelihood of metastases. This factor serves as a significant predictor of survival in patients with infiltrative breast cancer and is linked to the individual's coagulation status (11). A state of increased hypercoagulation among patients can result in the incidence of CAT and there is a gap in knowledge related to parameters that can be used to assess this worsened condition. Prior literature indicates that patients exhibiting markedly elevated mortality rates linked to CAT were those with colorectal, upper gastrointestinal malignancies, and breast cancers; individuals in advanced stages of breast cancer also face an augmented risk of Recurrent Venous

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Table 1. Studies evaluating the alteration of Ikaros in hematologic malignancies.

Variables	Sub Category	Benign	Malignant	p-value
Age (years)	Mean ± SD	41.8 ± 13.8	50.52 ± 13.54	0.0288t*
	Median (Min, Max)	42 (19, 65)	50 (24, 73)	
Clinical presentation	Cyst	4 (16%)	0	0.022MC*
	Lump	19 (76%)	25 (100%)	
	Pain	2 (8%)	0	
Side	Bilateral	4 (16%)	0	0.0644MC
	Left	12 (48%)	10 (40%)	
	Right	9 (36%)	15 (60%)	
Mammogram	BIRADS II	10 (40%)	1 (4%)	< 0.0008MC*
	BI RADS – III	1 (4%)	1 (4%)	
	BIRADS -IV	3 (12%)	4 (16%)	
	BI RADS -IV A	1 (4%)	0 (0%)	
	BI RADS -IV B	0 (0%)	1 (4%)	
	BIRADS- IV C	0	1 (4%)	
	BIRADS V	0	8 (32%)	
	Not available	10 (40%)	9 (36%)	
Other comorbidities/ symptoms	K/c/o dermatomyositis	0	1 (4%)	0.0016MC
	Hypertension	0	1 (4%)	
	Retroviral positive on ART	0	2 (8%)	
	Thyroid Surgery done	0	1 (4%)	
	Hypothyroidism	0	2 (8%)	
	Type 2 DM	0	1 (4%)	
	Multiple morbidities	0	1 (4%)	
	Nil	25 (100%)	16 (64%)	
Platelet count	Mean ± SD	294.913 ± 66.72	299.25 ± 70.22	0.829MW
	Median (Min, Max)	286 (211, 495)	296 (161, 430)	

Abbreviation: t – Two sample t-test, MC – Chi-square test with Monte Carlo simulation, MW – Mann Whitney U test, * indicates statistical significance.

Thrombosis (RVT) and fluctuations in heart rate (12,13,14). Activated partial thromboplastin time (APTT), thrombin time (TT), and prothrombin time (PT) are common indicators of a person's coagulation status. Levels of D-dimer (D-D) are another useful indicator of the fibrinolytic system (15), high blood coagulation system activity, which is linked to advanced cancer stages and a high incidence of venous thromboembolism (VTE), is indicated by elevated D-dimer levels, which are caused by coagulation cascade activation (16).

In a study by Mandoj C et al., the activation of coagulation was examined in patients with early-stage breast cancer who had a mean age of 60.3±13.4 years at diagnosis and a follow-up period of 6 to 112 months. This contrasts with the current study's findings, which show that participants' mean ages were much lower in both the benign and malignant tumor groups. The same study also found that majority of patients belonged to the grade 2 cancer stage and reported a negative Her2 status (83.4%) andthese results align with that of the present study. Other results such as the proportion of participants reporting as ER-positive (79.1%), PR positive (69.8%), and % Ki-67 was ≤15% (60.4%) contrasted the results obtained in the present study (17). The difference in results could be due to the large sample size employed alongside the long follow-up of the patients.

In a study by Pang M et al., biological parameters related to platelet count were compared between the two groups that underwent mastectomy with and without deep vein thrombosis (DVT). In contrast to the findings of the current investigation, which indicated that there was no significant difference in the platelet count between the two groups, the results indicated that there were significant differences in platelet count levels between the two groups ($p<0.05$) (15).

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Table 2. Distribution of different variables in malignant cases.

Variables	Sub Category	Number of subjects (%)
Grade	Grade 1	4 (16%)
	Grade 2	16 (64%)
	Grade 3	5 (20%)
ER (Estrogen Receptor)	Negative	16 (64%)
	Positive	9 (36%)
PR (Progesterone Receptor)	Negative	20 (80%)
	Positive	5 (20%)
Her2 Neu	Negative	14 (56%)
	Positive	11 (44%)
Ki67 %	10-20	2 (8%)
	15-20	3 (12%)
	20-30	5 (20%)
	25-30	1 (4%)
	30-40	4 (16%)
	40-50	1 (4%)
	50-60	1 (4%)
	60-70	4 (16%)
	70-80	1 (4%)
	80-90	1 (4%)
	90	2 (8%)
Lymph node	Positive	1 (4%)
	Negative	24 (96%)
Staging	T1N0M0	2 (8%)
	T1N1M0	1 (4%)
	T2N0M0	6 (24%)
	T2N1M0	3 (12%)
	T2N1M1	1 (4%)
	T2N2M0	1 (4%)
	T3N0M0	5 (20%)
	T3N1A	1 (4%)
	T3N1M1	1 (4%)
	T3N2AM0	1 (4%)
	T3N3BM1	1 (4%)
	T4BN0	1 (4%)
	T4BN0M0	1 (4%)

Circulating tumor cells (CTCs) and common coagulation tests, such as fibrinogen level, D-dimers, prothrombin time, and APTT, were evaluated in a study by Dirix LY et al. The findings indicated that a higher CTC count was linked to a lower platelet count. The results of the present study contrasted this withthe platelet count being higher in the malignant tumor group, but this difference was not statistically significant (18). This discrepancy can be explained by the two studies' different sample sizes and disparate research approaches.

When considering changes in coagulation markers based on cancer grading, Mi XK et al assessed level of various circulating plasmamicroparticle tissue factors (MP-TF) among breast cancer patients (observation group) and patients with benign breast lesions (control group). PT, APTT, fibrinogen, and D-dimer levels were among the parameters that were examined. The findings demonstrated that the observation group had higher overall MP-TF levels, and that this difference grew as cancer staging progressed ($p<0.05$) (19). This result was not that of the present study as no difference was seen in the parameters among the participants based on the staging of cancer.

Participants in the thrombus group had considerably greater levels of PT than those in the control group, according to the findings of a prior study that evaluated biological characteristics between two groups that had mastectomy with and without DVT ($p<0.05$) (15). PT levels were found to be lower among participants in the observation group, and this difference was statistically significant ($p<0.05$) in another study that compared MP-TF levels between patients with breast cancer (observation group) and patients with benign breast lesions (control group) (19). The findings of the current study, which revealed no differences between the groups, were at odds with the findings of these two investigations.

Regarding APTT levels, a prior study that included APTT levels was carried out to evaluate MP-TF levels between patients with benign breast lesions (control group) and patients with breast cancer (observation group). According to the study's findings, the observation group's APTT values were lower, and this difference was statistically significant ($p<0.05$) (19). This was at odds with the current study's findings, which indicated that there was no variation in the groups' APTT scores.

A prior study comparing fibrinogen levels between patients with breast cancer (observation group) and patients with benign breast lesions (control group) revealed that fibrinogen levels increased statistically significantly ($p<0.05$) in the observation group. This finding was entirely consistent with the findings of the current study (19).

When considering D-dimer levels, the results of a previously conducted study that compared biological parameters between 2 groups that underwent mastectomy with and without DVT showed that D-dimer levels of participants in thrombus group were higher than that observed in control group ($p<0.05$) (15). This was consistent with the current study's findings, which showed a statistically significant variation in the groups' D-dimer levels.The present study's findings were entirely consistent with another study by Mi XK et al. that compared MP-TF levels between patients with breast cancer (observation

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Table 3. Comparison of coagulation parameters based on side of the breast cancer.

Coagulation parameters	Side of the lesion		p-value
	Left breast (n=10)	Right breast (n=15)	
PT (Prothrombin Time)	10.26± 0.45 10.3 (9.6, 11.2)	10.52± 0.66 10.4 (9.7, 11.3)	0.247t
TT (Thrombin Time)	17.32± 0.98 17.1 (15.9, 19.3)	16.8± 0.66 17 (13.6, 19.7)	0.301
APTT (Activated Partial Thromboplastin Time)	21.88 ± 2.99 22.75 (13.9, 24.4)	24.36± 3.09 24.2 (19.5, 30.3)	0.127
Fibrinogen	353.77± 56.95 356.4 (271, 467.1)	333.26± 94.13 348.8 (188.4, 494.3)	0.505t
D-dimer	2.56± 4.99 0.66 (0.34, 16.5)	0.72± 0.61 0.53 (0.21, 2.5)	0.193MW

Abbreviation: t – Two sample t-test, MW – Mann Whitney U test, * indicates statistical significance.

Table 4. Comparison of coagulation parameters basedon ER, PR, and Her2 Neu status.

ER (Estrogen Receptor)			
Coagulation parameters	**Negative**	**Positive**	**p-value**
PT (Prothrombin Time)	10.45± 0.70 10.4 (9.6, 12)	10.35± 0.35 10.3 (9.9, 11.1)	0.64t
TT (Thrombin Time)	17.23± 1.27 17.2 (15.7, 19.7)	16.6± 1.31 17 (13.6, 18.2)	0.257t
APTT (Activated Partial Thromboplastin Time)	23± 3.46 23.1 (13.9, 30.3)	24± 2.86 23.4 (19.5, 29.5)	0.437t
Fibrinogen	313.97± 66.42 306.4 (188.4, 424.1)	390.34± 83.67 380.4 (216, 494.3)	0.0341t*
D-dimer	1.8± 4.01 0.57 (0.21, 16.5)	0.84± 0.53 0.54 (0.35, 2.5)	0.363MW
PR (Progesterone Receptor)			
PT (Prothrombin Time)	10.42± 0.634 10.4 (9.6, 12.4)	10.4 ± 0.469 10.3 (9.9, 11.1)	0.924t
TT (Thrombin Time)	16.92± 1.42 16.85 (13.6, 19.7)	17.34± 0.545 17.2 (16.8, 18.2)	0.316t
APTT (Activated Partial Thromboplastin Time)	23.29± 3.6 23.1 (13.9, 30.3)	23.68± 1.08 23.4 (22.7, 25.3)	0.682t
Fibrinogen	336.76± 77.35 346 (188.4, 467.1)	360.28± 99.83 373 (216, 494.3)	0.643t
D-dimer	1.67± 3.59 0.615 (0.21, 16.5)	0.584± 0.318 0.48 (0.35, 1.14)	0.196MW
Her2 Neu			
PT (Prothrombin Time)	10.4 ± 0.431 10.4 (9.6, 11.2)	10.44± 0.781 10.3 (9.7, 12.4)	0.865t
TT (Thrombin Time)	17.1± 1.08 17.1 (15.8, 19.7)	16.88± 1.58 17 (13.6, 19.3)	0.692t
APTT (Activated Partial Thromboplastin Time)	24.22 ± 2.83 23.3 (20.3, 30.3)	22.28± 3.52 22.5 (13.9, 26.5)	0.153t
Fibrinogen	354.4± 80.46 354.8 (224.5, 494.3)	325± 81.42 348.8 (188.4, 429.8)	0.378t
D-dimer	1.7± 4.26 0.53 (0.21, 16.5)	1.14± 1.08 0.64 (0.32, 3.68)	0.644MW
Vascular Metastasis			
PT (Prothrombin Time)	10.33 ± 0.46 10.3 (9.6, 11.2)	10.64 ± 0.852 10.4 (9.7, 12.4)	0.392
TT (Thrombin Time)	16.81 ± 1.17 17 (13.6, 19.3)	17.5 ± 1.56 17.3 (15.7, 19.7)	0.324

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APTT (Activated Partial Thromboplastin Time)	22.61 ± 2.84 23.1 (13.9, 26.6)	25.3 ± 3.58 24.5 (21, 30.3)	0.11
Fibrinogen	350.43 ± 79.23 361.35 (216, 494.3)	318.4 ± 85.51 308.8 (188.4, 449.8)	0.41
D-dimer	1.71 ± 3.79 0.54 (0.21, 16.5)	0.79 ± 0.5 0.69 (0.37, 1.71)	0.328

Abbreviation: t – Two sample t-test, MW – Mann Whitney U test, * indicates statistical significance.

Table 5. Comparison of coagulation parameters based on grading of cancer.

Coagulation parameters	Grade			p-value
	Grade 1	Grade 2	Grade 3	
PT (Prothrombin Time)	10.15± 0.31 10.05 (9.9, 10.6)	10.34± 0.421 10.35 (9.7, 11.2)	10.88± 1.01 10.88 (9.6, 12.4)	0.26K
TT (Thrombin Time)	15.9± 1.70 16.25 (13.6, 17.5)	17.28± 1.14 17.2 (15.7, 19.7)	17± 1.25 16.6 (15.8, 19.1)	0.2675K
APTT (Activated Partial Thromboplastin Time)	22.92± 2.71 23.05 (19.5, 26.1)	23.13± 3.34 23.1 (13.9, 30.3)	24.46± 3.67 24.46 (20.3, 29.5)	0.8686K
Fibrinogen	401.87± 29.19 402.25 (373.2, 429.8)	324.97± 82.6 320.75 (188.4, 494.3)	345.92± 89.2 357.7 (216, 449.8)	0.1214K
D-dimer	1.19± 0.917 0.89 (0.48, 2.5)	1.73± 4.02 0.535 (0.21, 16.5)	0.78± 0.54 0.69 (0.35, 1.71)	0.4559K

Abbreviation: K – Kruskal Wallis test.

Table 6. Comparison of coagulation parameters between the three groups.

Coagulation parameters	Groups			p-value
	Benign	Malignant	Control	
PT (Prothrombin Time)	10.37± 0.199 10.4 (9.9, 10.7)	10.46± 0.431 10.5 (9.7, 11.4)	10.42± 0.596 10.4 (9.6, 12.4)	0.6731WA
TT (Thrombin Time)	19.7± 2.34 18.75 (16.1, 22.4)	18.15± 2.13 17.7 (14.1, 25.1)	17± 1.30 17 (13.6, 19.7)	0.007K*
APTT (Activated Partial Thromboplastin Time)	23.91± 0.634 23.75 (22.8, 25.6)	24.14± 2.31 24.1 (21, 30.4)	23.36± 3.23 23.36 (13.9, 30.3)	0.6271WA
Fibrinogen	268.31± 21.56 268.31 (236.9, 320.4)	302.9± 59.98 302.9 (203, 475.4)	341.46± 80.56 348.8 (188.4, 494.3)	< 0.001WA*
D-dimer	0.317± 0.018 0.315 (0.29, 0.36)	0.461± 0.435 0.33 (0.16, 2.18)	1.457± 3.22 0.55 (0.21, 16.5)	< 0.001K*

Abbreviation: WA – Welch's ANOVA, K – Kruskal Wallis test, * indicates statistical significance.

group) and patients with benign breast lesions (control group). The observation group's D-dimer levels showed a statistically significant increase ($p<0.05$) (19). Dirix LY et al studied assessed the relationship between CTCs and standard coagulation tests and the results showed that an increased CTC count was associated with increased D-dimer levels (18). This was in complete alignment with the results obtained where levels of D-dimer were significantly increased in the malignant group. According to a study by Gochhait S et al., D-dimer levels were considerably elevated with $p<0.001$ in patients with operable breast cancer who also had lymph node metastases, indicating a connection between the fibrinolytic pathway and the carcinogenesis of breast cancer (11). This finding was in line with the current study's findings and may offer compelling proof that D-dimer levels are a valuable metric for determining a patient's hypercoagulation status in cases of breast cancer. The comparison between the benign and malignant groups, as well as the amount of parameters evaluated, was the study's strongest point. The patients included in the study came from a single hospital rather than a multicenter approach, and the study's restrictions were met. Khan UT et al.'s comprehensive review and meta-analysis also showed that the impact on long-term mortality was less clear if breast cancer patients had survived the initial VTE (20). Because determining the likelihood of developing the initial VTE is crucial, the findings of this study are crucial. Further research is warranted on the use of other parameters as well as the management of the altered coagulation state to reduce mortality associated with breast cancer-induced thrombosis.

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Figure 1. Mean plot of D-dimer, thrombin time and fibrinogen between the malignant, benign and control groups.

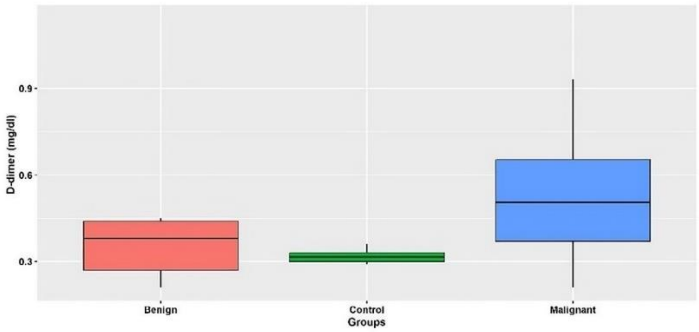

Figure 1A. Mean plot of D-dimer over groups.

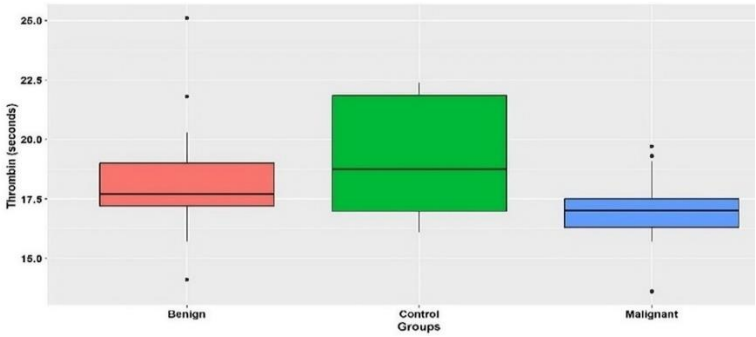

Figure 1B. Mean plot of thrombin time over groups.

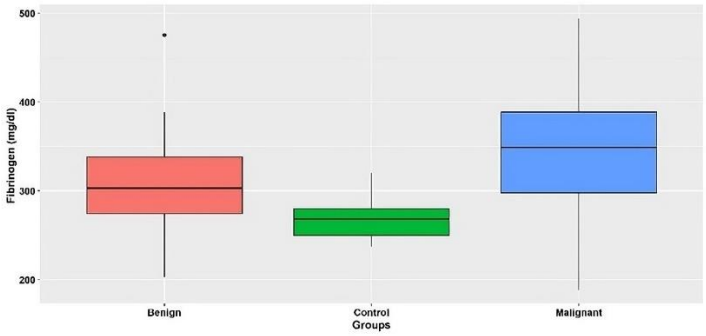

Figure 1C. Mean plot of fibrinogen over groups.

Figure 2. Mean plot of prothrombin time and APTT between the malignant, benign and control groups.

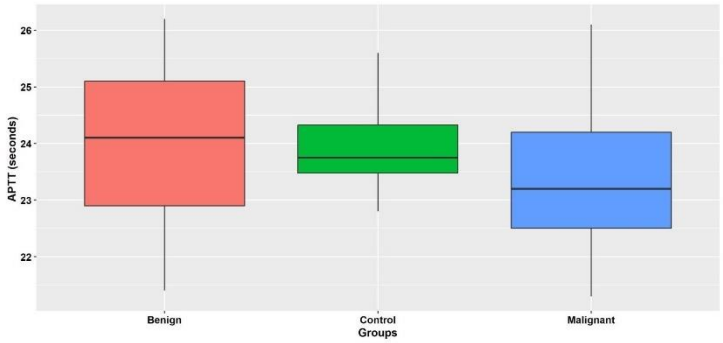

Figure 2A. Mean plot of prothrombin time over groups.

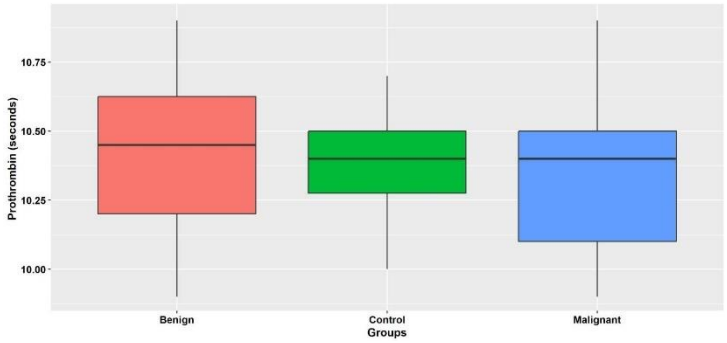

Figure 2B. Mean plot of APTT over groups.

5. CONCLUSION

The current study's findings demonstrated that there was no discernible variation in the platelet counts across the groups. Fibrinogen levels showed a statistically significant difference based on ER status as well as between benign and malignant groups of patients. The present study concludes that parameters like fibrinogen along with thrombin time and D-dimer levels can serve as indicators of the extent of hypercoagulation status in patients suffering from breast cancer.

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Conflicts of interest

The authors report there are no competing interests to declare

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Ethical statement

Ethical approval for the study was obtained from the Institutional ethics committee and it was carried out in concordance with Declaration of Helsinki.

References

1. Kyriazi V. Breast cancer as an acquired thrombophilic state. J Breast Cancer. 2012 Jun;15(2):148-56.

2. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA A Cancer J Clin. 2021 May;71:209–49.

3. Heer E, Harper A, Escandor N, Sung H, McCormack V, Fidler-Benaoudia MM. Global burden and trends in premenopausal and postmenopausal breast cancer: a population-based study. Lancet Glob Health. 2020 Aug;8(8):e1027–37.

4. Arnold M, Morgan E, Rumgay H, Mafra A, Singh D, Laversanne M, et al. Current and future burden of breast cancer: Global statistics for 2020 and 2040. Breast. 2022 Dec; 66:15-23.

5. Sathishkumar K, Chaturvedi M, Das P, Stephen S, Mathur P. Cancer incidence estimates for 2022 & projection for 2025: Result from National Cancer Registry Programme, India. Indian J Med Res. 2022 Oct-Nov;156(4&5):598-607.

6. Beinse G, Berger F, Cottu P, Dujaric ME, Kriegel I, Guilhaume MN, et al. Circulating tumor cell count and thrombosis in metastatic breast cancer. J Thromb Haemost. 2017 Oct;15(10):1981-1988.

7. Rückerl R, Schneider A, Hampel R, Breitner S, Cyrys J, Kraus U, et al. Association of novel metrics of particulate matter with vascular markers of inflammation and coagulation in susceptible populations -results from a panel study. Environ Res. 2016 Oct; 150:337-347.

8. Campello E, Spiezia L, Radu CM, Simioni P. Microparticles as biomarkers of venous thromboembolic events. Biomark Med. 2016 Jul;10(7):743-55.

9. Snoderly HT, Boone BA, Bennewitz MF. Neutrophil extracellular traps in breast cancer and beyond: current perspectives on NET stimuli, thrombosis and metastasis, and clinical utility for diagnosis and treatment. Breast Cancer Res. 2019 Dec;21(1):145.

10. Madhav MR, Nayagam SG, Biyani K, Pandey V, Kamal DG, Sabarimurugan S, et al. Epidemiologic analysis of breast cancer incidence, prevalence, and mortality in India: Protocol for a systematic review and meta-analyses. Medicine (Baltimore). 2018 Dec;97(52):e13680.

11. Gochhait S, Sahoo SS, Chhabra G, Mukhopahay AK, Sharma S. Role of D-dimer in patients of operable breast cancer withlymph node metastases: A matched cross-sectional study. Oncol J India. 2020 May-Aug;4(2):39-42.

12. Okello CD, Mulumba Y, Omoding A, Ddungu H, Orem J. Survival of patients with cancer associated thrombosis at the Uganda Cancer Institute. Ecancermedicalscience. 2021 Mar; 15:1212.

13. Kovac M, Kovac Z, Tomasevic Z, Tomic B, Gvozdenov M, Radojkovic D. Breast cancer and recurrent thrombosis - Results from prospective single center study. Breast J. 2019 Jul;25(4):783-785.

14. Wang L, Wang J, Li P, Wang X, Wu S, Shi B. Association between short-term heart rate variability and blood coagulation in patients with breast cancer. Sci Rep. 2021 Jul;11(1):15414.

15. Pang M, Zhao F, Yu P, Zhang X, Xiao H, Qiang W, et al. The significance of coagulation and fibrinolysis-related parameters in predicting postoperative venous thrombosis in patients with breast cancer. Gland Surg. 2021 Apr;10(4):1439-1446.

16. Hill CN, Hernández-Cáceres MP, Asencio C, Torres B, Solis B, Owen GI. Deciphering the Role of the Coagulation Cascade and Autophagy in Cancer-Related Thrombosis and Metastasis. Front Oncol. 2020 Dec;10:605314.

17. Mandoj C, Pizzuti L, Sergi D, Sperduti I, Mazzotta M, Lauro LD, et al. Observational study of coagulation activation in early breast cancer: Development of a prognostic model based on data from the real-world setting. J Transl Med. 2018 May;16(1):129.

18. Dirix LY, Oeyen S, Buys A, Liégois V, Prové A, Van De Mooter T, et al. Coagulation/fibrinolysis and circulating tumor cells in patients with advanced breast cancer. Breast Cancer Res Treat. 2022 Apr;192(3):583-591.

19. Mi XK, Liu QR, Zhu L, Sang MX, Guo LR, Shan BE. Mechanism of the high coagulation state of breast cancer tissue factor. Eur Rev Med Pharmacol Sci. 2017 May;21(9):2167-2171.

20. Khan UT, Walker AJ, Baig S, Card TR, Kirwan CC, Grainge MJ. Venous thromboembolism and mortality in breast cancer: cohort study with systematic review and meta-analysis. BMC Cancer. 2017 Nov;17(1):747.

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