CORRELATION OF COAGULATION MARKERS (PT, INR, D-dimer & Factor VIII) WITH AXILLARY LYMPH NODE METASTASIS IN CARCINOMA BREAST

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ABSTRACT:
Introduction: The extracellular matrix remodeling is an important step in primary tumor growth, and metastasis. Many studies regarding carcinomas, including breast carcinoma, have suggested elevated levels of procoagulant factors and fibrinogen and fibrin degradation factors and associated fall in coagulation system inactivators. In the current study we try and correlate the coagulation markers D-dimer, Factor VIII, PT & INR in carcinoma breast patients, with advancing stages of the disease and lymph node metastasis and to look for the relation of these coagulation markers with know prognostic factors in carcinoma breast.
Methods: A total of 100 subjects (Diagnosed cases of operable carcinoma breast) were enrolled in the study from the Department of Surgery, Krishna Hospital, Karad, over the period December 2020 to July 2022.
Results: The above study had a mean age of 53.33yrs, with marority of the cases being of left sided breast carcinoma (58%), with majority of them belonging to the stage IIA (33%). There was a statistically significant correlation between the coagulation markers D-dimer, Factor VIII, PT and INR; with progressive stage of carcinoma breast with p value= 0.024, p value= 0.05, p value= 0.023 respectively. There was a statistically significant decrease in the coagulation markers that were noticed postoperatively (PT p value= 0.03, INR p value=0.0008, D-Dimer p value= 0.016, and Factor VIII p value=0.001 respectively.)
Conclusion: There is a statistically significant correlation between the coagulation markers D-dimer, Factor VIII, PT and INR; with progressive stage of carcinoma breast .

INTRODUCTION

Breast cancer is one of the most commonly occurring cancers in Indian women and every 4 mins a woman is diagnosed with carcinoma breast in India, and one woman dies of carcinoma breast in every 13 mins in India. Considering the magnitude of the disease, the tumor characteristics and the lymph node status are important characteristics to be considered before formulating a plan of management for patients.

The important factor for formulating an effective surgical and postoperative therapy in carcinoma breast patients, is the lymph node metastatic status. In a clinically node negative carcinoma breast, axillary sampling or sentinel lymph node metastasis are the standard procedure to perform to assess lymph node metastasis.

There are many proven theories suggesting the important role of coagulation and fibrinolytic systems in cancer biology and angiogenesis. The extracellular matrix remodeling is an important step in primary tumor growth, and metastasis. Many studies regarding carcinomas, including breast carcinoma, have suggested elevated levels of procoagulant factors including Factors V, VII, VIII, IX, XI levels and fibrinogen and fibrin degradation factors, like D-dimer and associated fall in coagulation system inactivators like decrease in antithrombin III was noticed..

In the current study we try and correlate the coagulation markers D-dimer, Factor VIII, PT & INR in carcinoma breast patients, with advancing stages of the disease and lymph node metastasis and to look for the relation of these coagulation markers with know prognostic factors in carcinoma breast.

AIM: To evaluate the role of coagulation markers in patients of carcinoma breast and lymph node metastasis, their relationship with histopathologic parameters, as predictive and prognostic factors.

OBJECTIVES
1. To correlate plasma level of coagulation markers with clinico-pathological stage of carcinoma breast.
2. To assess the role of coagulation markers value as predictive markers of lymph node metastasis in breast cancer.
3. To assess changes in D-dimer values according to the advancing stage of breast carcinoma and lymph node metastasis.

MATERIAL AND METHODS

Study Site:
Department of General Surgery, Krishna Institute of Medical Sciences, Tertiary Level Hospital.

Study Duration:
December 2020 to July 2022

Study Design:
Prospective observational study.

Sample Size:
A total of 100 subjects were enrolled in the study from the Department of Surgery, Krishna Hospital, Karad.
We took n=50 + 50 in each group of lymph node involvement and with node negative disease.

$$n = (2SD^2)(Z_{1-\alpha/2} + Z_{1-\beta})^2 \div d^2$$

SD= Standard Deviation

$Z_{1-\alpha/2}$= Critical value and a standard value for the corresponding level of confidence

$Z_{1-\beta}$ = the desired power

d   = difference in means of two group (effect size)
n   = Sample Size

Study Criteria:
Inclusion Criteria: All diagnosed patients of operable carcinoma breast admitted in the surgical ward of Krishna hospital, Karad from December 2020 to July 2022.

Exclusion Criteria: Patients having
1. Disorders of coagulation
2. Hematological disorders, thromboembolic events, cardiac conditions, any other medical factors that cause derangement in coagulation markers.
3. Any other syndromic tumors
4. Only operable stages of carcinoma breast (Stage IA to Stage IIIC) were taken up for the study.
5. No male Carcinoma breast patients were taken up for the study.

Source of Data:
In this study 100 patients diagnosed with carcinoma breast admitted in Krishna Hospital, karad during the period of December 2020 to July 2022 were included.

Methodology:
● Patients who satisfied the inclusion criteria were taken up for the study after obtaining informed consent. Those patients having the exclusion criteria were excluded from the study.
● A detailed history was recorded in accordance with standard case record proforma.
● A complete physical examination including the local examination of bilateral beasts, along with axilla and supraclavicular fossa examination was done to assess the lymph node status. A thorough systemic examination was done of Cardiovascular system, Respiratory system, Central Nervous system and Abdominal examination was done including pervaginal examination and Per-rectal examination were done to evaluate the presence of any concomitant disease and rule out any evidence of metastasis, or syndromic tumors.
● The patient's general condition and fitness to withstand general anesthesia and the surgery was assessed with required investigations complete blood counts, renal function tests, liver function tests, blood sugars, serum electrolytes, urine routine, chest x-rays. USG Abdo-pelvis and Chest x-ray were also used to rule out metastasis.
● Patients underwent mammography and usg of b/l breast and axilla for the radiological evidence of the breast carcinoma and the axillary lymphadenopathy, and presence of contralateral breast disease.
● The patients were taken up for FNAC (Fine needle aspiration cytology) and whenever required excision biopsy for the histological proof of carcinoma.
● The patients with proven Carcinoma breast, coagulation markers PT/INR, D-Dimer, and Factor VIII were investigated.
● The study subjects were divided into two groups - one group with clinical lymph node positive disease and the second group with clinical and radiological node negative disease.
● The first group were taken up for modified radical mastectomy with axillary dissection of level I and level II lymph nodes. The second group was taken up for modified radical mastectomy with axillary sampling.
● The Histological subtypes of the excised specimens of each patient were followed up , with the size of the tumor , margins, and the number of positive lymph nodes in the axillary dissection were recorded, and TNM staging was done accordingly. The patients

were subsequently the patients in the study were staged according to the AJCC anatomical staging.

● The patients were followed up on an outpatient basis while POD 10 and postoperative coagulation markers PT/INR, D-Dimer, and Factor VIII were investigated, subsequently the variation of the coagulation markers with relation with stage of disease, lymph node involvement, and postoperative variations were compared.

STATISTICAL ANALYSIS
● The data was collected using the case record proforma described above.
● The data was entered and analyzed using Microsoft Excel Data sheets software.
● The data was represented in tables, charts, for analysis and was analyzed using t-test

OBSERVATION & RESULTS
Age distribution of patients taken up for the study

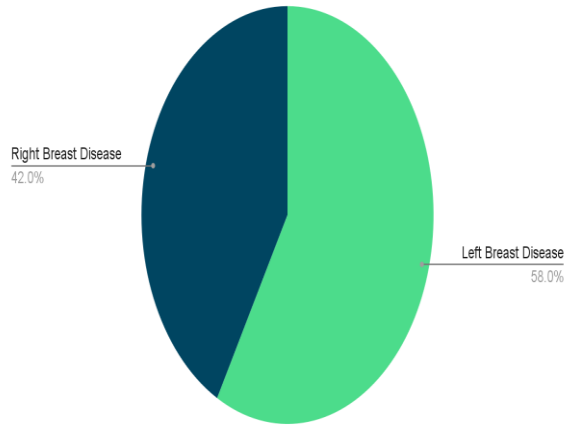| Age Range	No.of patients	Percentage
30-40yrs	12	12
41-50yrs	27	27
51-60yrs	33	33
61-70yrs	22	22
>70yrs	6	6
Total	100	100
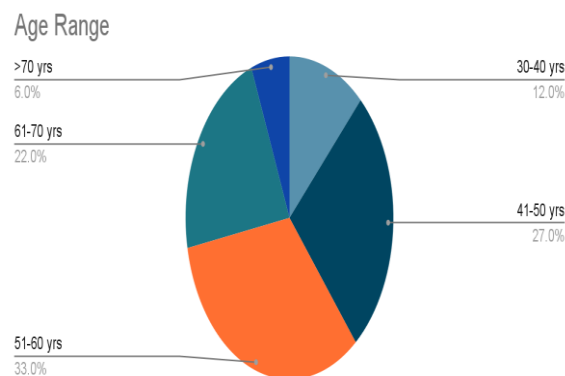
The age distribution of patients taken up for the study majority belonged to the age group of 51-60 yrs with a mean age group being 53.33yrs

Patients distribution according to the side of disease

Side of Disease	No. of patients	Percentage
Left side	58	58
Right side	42	42

Distribution of patients according to side of disease
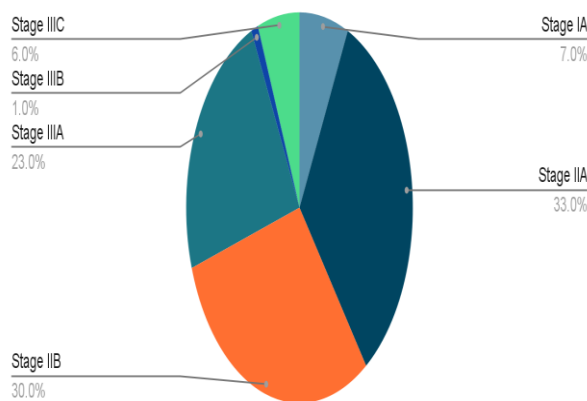

Among the patients taken up for the present study 58% had carcinoma of the left breast and 42% had carcinoma of the right breast.

Patients distribution according to TNM stage of Diseases

| TNM Stage	Number of Patients	Percentage
IA	7	7
IIA	33	33
IIB	30	30
IIIA	23	23
IIIB	1	1
IIIC	6	6
Total	100	100

TNM Staging

The patients taken up for the study majority belonged to stage IIA (33%), 30% of the patients in the study belong to Stage IIB 23% of the patients in the study belong to Stage IIIA, 7% of the

patients in the study belong to Stage IA, 6% of the patients in the study belong to Stage IIIC, 1% of the patients in the study belong to Stage IIIB.

Distribution of patients with relation of tumor size with nodal involvement

Tumor Size	N0	N1	N2	N3
Tis	3	0	0	0
T1	4	2	1	0
T2	31	18	15	2
T3	12	5	3	4

Tumor Size with Nodal involvement
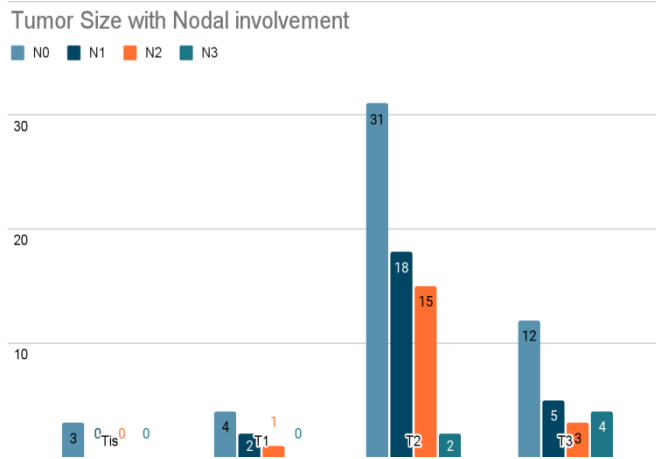
The current study the distribution of patients of same Tumor size (T) staging according to TNM staging compared to various stages of Nodal involvement was done(N). Majority of patients were in the T2N0 making up 31% of the total study group, followed by the T2N1 group of 18% of patients. 15% of patients were in the T2N3 group, 12% in T3N0 group, 5% in the T3N1 group, 4% in T3N3 and T1N0 groups each, 3% in T3N2 and TisN0 groups each and 1% in T1N2 group respectively.
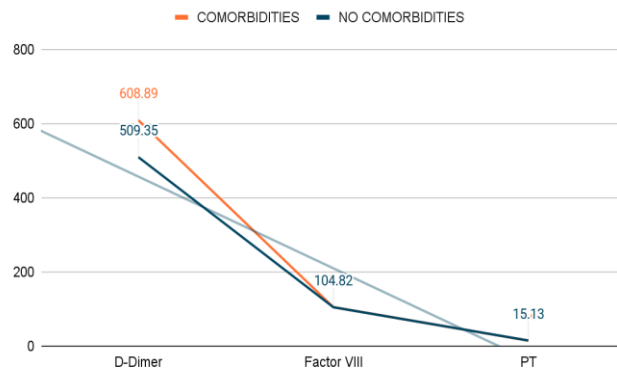
Comorbidities

Total No. Of Patients- 10

Mean of	Comorbidities (DM, HTN, Epilepsy, Hypothyroidism)				No Comorbidities			
	Stage IIA	Stage IIB	Stage IIIA	Mean	Stage IIA	Stage IIB	Stage IIIA	Mean
D-dimer	530	516.67	780	608.89	376.97	514	653.75	509.35

Factor VIII	101.33	104.67	109.33	105.11	101.67	105.93	106.87	104.82
PT	14	14.67	16	14.89	14.75	15.17	15.48	15.13

Variation f the mean of coagulation factors with comorbidities

The present study vehicle comparing the patients in the same groups with and without comorbidities, there was a 16% increase in mean values of D-dimer was noticed in the group with comorbidity compared to the group with no comorbidity. No much difference was noticed in the Factor VIII and PT values.

Variation of D-Dimer values in advancing stages of lymph node involvement (Pre-op)

Tumor size(T)	N0	N1	N2	N3
Tis	166.67	-	-	-
T1	162.5	505	450	-
T2	357.5	424.44	605	1753
T3	663.33	698	753.33	2031.5

D-Dimer Variation with T&N stages (pre-op)
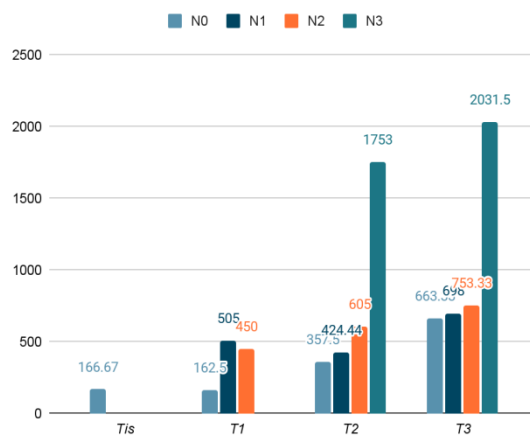
In the present study we have assessed the variation of D-Dimer values with different TNM staging of the patient preoperatively. There was an increase in the mean D-dimer values noted with increasing tumor size and nodal stage in the patient. This was found to be statistically significant with p value of 0.024.

Variation of D-Dimer values in advancing stages of lymph node involvement (Post-op)

| Tumor Size(T)	N0	N1	N2	N3
Tis	62.5	-	-	-
T1	65	66.67	130	-
T2	132.125	169.44	208.75	715
T3	203.08	213	185	977.5

In the present study we have assessed the variation of D-Dimer values with different TNM staging of the patient postoperatively. There was an increase in the mean D-dimer values noted with increasing tumor size and nodal stage in the patient, but there was a significant drop in the D-dimer values compared to the preoperative values of the same group of patients. This was found to be statistically significant with p value of 0.054.

D-Dimer values comparison pre-op and post-op according to the advancing TNM staging of Ca. Breast

| TNM stage	No. of patients	Pre-op Mean D-Dimer (ng/ml)	Post-op Mean D-Dimer (ng/ml)
IA	7	151.67	72.86
IIA	33	376.97	134.94
IIB	30	514	186
IIIA	23	653.75	215.43
IIIB	1	590	320
IIIC	6	1933.33	890
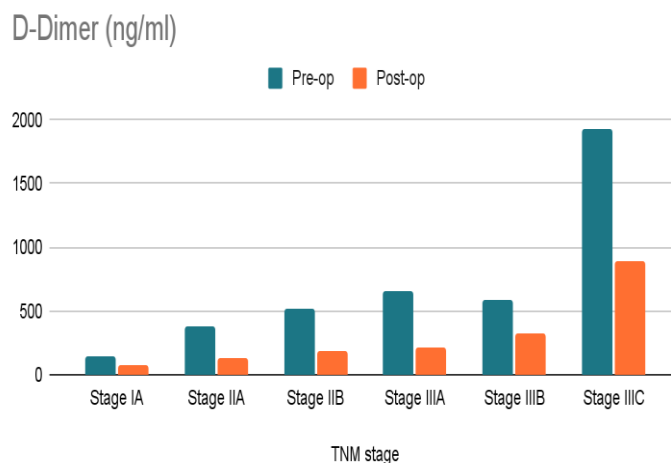
D-Dimer Variation with T&N stages (post-op)
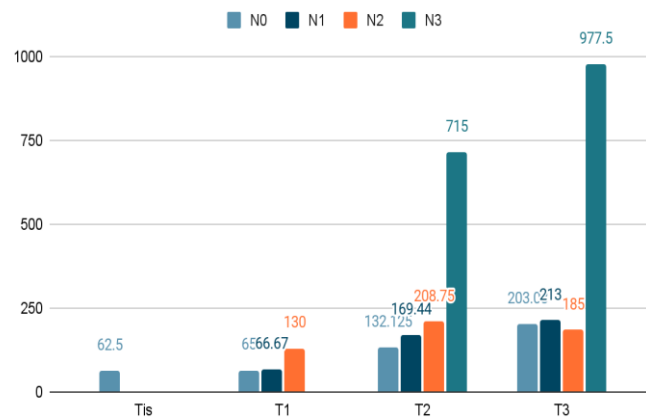
The current study there was a comparison of the mean D-dimer values of the TNM stage group of patients preoperatively and postoperatively, there was a statistically significant drop in the D-dimer values post-operatively, with p value of 0.016.

Variation of Prothrombin Time values in advancing stages of lymph node involvement (Pre-op)

| Tumor size(T)	N0	N1	N2	N3
Tis	12.33	-	-	-
T1	12.5	15	16	-
T2	14.34	14.67	15.4	17
T3	16.08	16	14	16.5

PT Variation with T & N stages (pre-op)
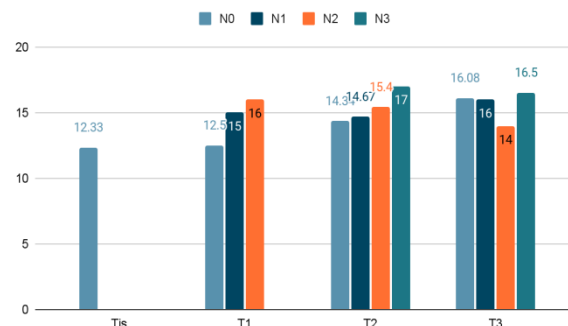
In the present study we have assessed the variation of Prothrombin Time values with different TNM staging of the patient preoperatively. There was an increase in the mean PT values noted with increasing tumor size and nodal stage in the patient. This was found to be statistically significant with p value of 0.023

Variation of Prothrombin Time values in advancing stages of lymph node involvement (Post-op)

| Tumor Size (T)	N0	N1	N2	N3
Tis	12	-	-	-
T1	12	12.5	13	-
T2	11.5	12.39	12.6	14
T3	12.8	12.8	12.33	13

PT variation with T & N stages (post-op)
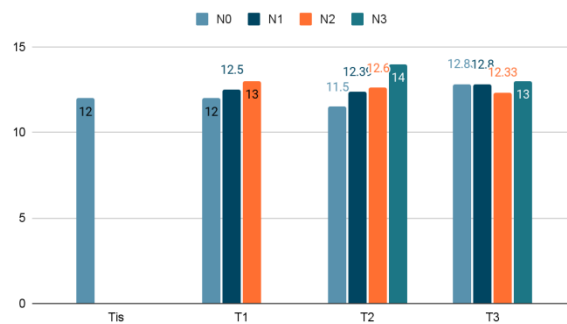
In the present study we have assessed the variation of Prothrombin Time values with different TNM staging of the patient preoperatively. There was an increase in the mean PT values noted with increasing tumor size and nodal stage in the patient. This was found to be statistically significant with p value of 0.034.

PT value variation with the advance in TNM staging of Ca. breast

| TNM Stage	No. of. patients	Pre-op PT Mean	Post-op PT Mean
IA	7	12.33	12
IIA	33	14.75	11.85
IIB	30	15.17	12.5
IIIA	23	15.48	12.61
IIIB	1	17	14
IIIC	6	16.67	13.33

Prothrombin Time (PT) Sec
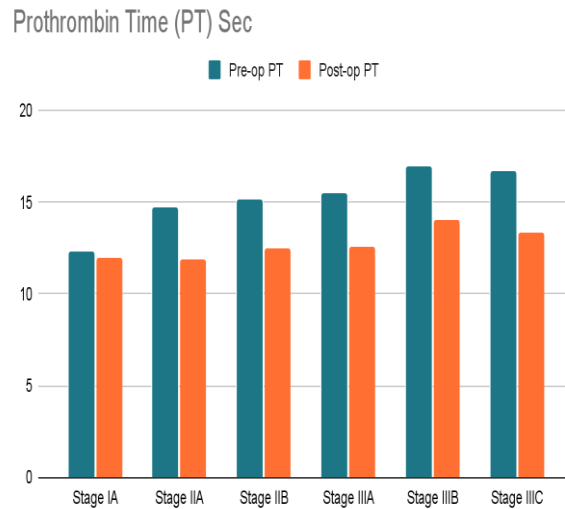
The current study there was a comparison of the mean PT values of the TNM stage group of patients preoperatively and postoperatively, there was a statistically significant drop in the PT values post-operatively, with p value of 0.003.

INR value variation with advancing TNM stage of ca. Breast

| TNM Stage	No.of patients	Pre-op Mean INR	Post-op Mean INR
IA	7	0.9	0.8
IIA	33	1.2	0.8
IIB	30	1.2	0.9
IIIA	23	1.3	0.9
IIIB	1	1.4	1
IIIC	6	1.4	0.9

INR
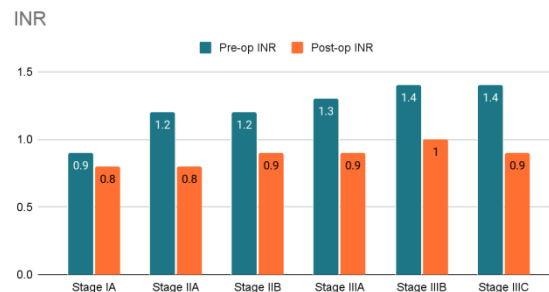
The current study there was a comparison of the mean INR values of the TNM stage group of patients preoperatively and postoperatively, there was a statistically significant drop in the INR values post-operatively, with p value of 0.0008.

Variation of Factor VIII values in advancing stages of lymph node involvement (Pre-op)

Tumor Size (T)	N0	N1	N2	N3
Tis	95.67	-	-	-
T1	97.25	99	100	-
T2	98.5	104	106.87	116.5
T3	109.33	106.4	108.67	115.5

Factor VIII variation with T & N stages (pre-op)
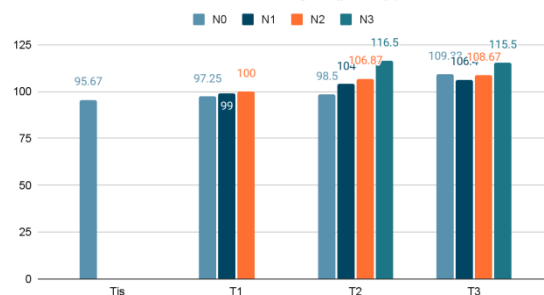
In the present study we have assessed the variation of Factor VIII values with different TNM staging of the patient preoperatively. There was an increase in the mean Factor VIII values noted with increasing tumor size and nodal stage in the patient. This was found to be statistically significant with p value of 0.05.

Variation of Factor VIII values in advancing stages of lymph node involvement (post-op)

Tumor Size (T)	N0	N1	N2	N3
Tis	86.33	-	-	-
T1	77	76.5	78	-
T2	86.12	88.78	91.6	98.5
T3	97.58	90	93	98.25

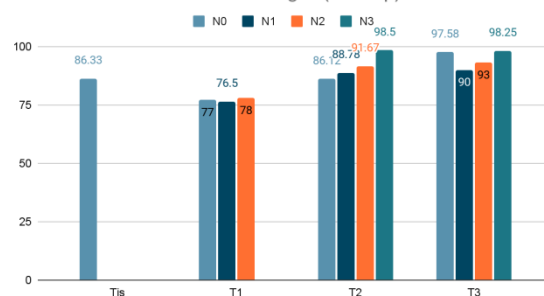Factor VIII variation with T&N stages (Post-op)

In the present study we have assessed the variation of Factor VIII values with different TNM staging of the patient postoperatively. There was an increase in the mean Factor VIII values noted

with increasing tumor size and nodal stage in the patient. This was found to be statistically significant with p value of 0.03.

Factor VIII values with advancing TNM staging of Ca. Breast

TNM Stage	No.of Patients	Pre-op Factor VIII	Post-op Factor VIII
IA	7	95.67	79.83
IIA	33	101.67	88.48
IIB	30	105.93	92.1
IIIA	23	106.87	90.78
IIIB	1	103	94
IIIC	6	115.83	98.33
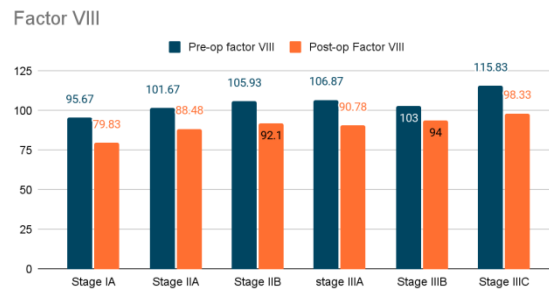
The current study there was a comparison of the mean Factor VIII values of the TNM stage group of patients preoperatively and postoperatively, there was a statistically significant drop in the Factor VIII values postoperatively, with p value of 0.0016

DISCUSSION

With the high prevalence of breast cancer 25.8 per 1 lakh, and the high incidence of mortality and morbidity associated, it has become a paramount importance to take up various tumor characteristics and patients variables into consideration while the treatment plan is being made. Involvement of the axillary lymph nodes is the most important prognostic factor, with direct relationship between no. of lymph nodes involved and the prognosis of the patient, and the risk of recurrence.

Demographic Characteristics

Gender is the most important risk factor with the incidence of breast carcinoma in males being less than 1% of the incidence in women. Masses in male patients are more likely to be benign and the result of gynaecomastia rather than carcinoma breast.

In the current study 100 female patients with carcinoma breast were taken up for the study.

According to the American Cancer Society, Breast Cancer Facts & Figures, the incidence of breast cancer is <2% of total cases in women younger than 20yrs. Thereafter there is an increase

in incidence to 1 in 225 from ages 30-39 yrs, 1 in 69 from ages 40-49, 1 in 44 from ages 50-59 yrs, 1 in 29 from ages 60-69 yrs and 1 in 8 by age 80 yrs.

In the current study the age distribution among the subjects were majorly distributed in the age group of 51-60yrs with a mean age of 53.33, followed by 41-50yrs (27%), 61-70yrs (22%), 30-40yrs (12%) and >70yrs (6%) respectively.

Choudhary, Ganpat Singh, et al and the group in their study observed that the majority of the patients were in the age group of 31-40 yrs (33%) of their study subjects. **Sergi, D. et al.** and the group in their study observed that Mean age at diagnosis was 60.3 ± 13.4 years of their study subjects.

The chances of a patient developing carcinoma is higher in the left breast by 5-10% compared to the right breast. In the current study 58% of the patients had left breast carcinoma and 42% of the patients had right breast carcinoma, showing 16% increase in the left breast carcinoma.

D-Dimer

The extracellular matrix remodeling occurring during tumor growth, tumor cell invasion into the surrounding tissue and distant metastasis is associated with activation of coagulation and fibrinolytic systems, D-Dimer being the product of fibrin degradation, is reported to be elevated in cancer patients compared to normal control subjects.

In the present study D-Dimer levels are measured at the beginning of evaluation of the patient, and POD 10 after Modified Radical Mastectomy, and axillary clearance or axillary sampling.The study was an attempt to relate the D-Dimer to lymph node status in carcinoma Breast, and predict lymph node metastasis in clinically node negative Breast cancer. Our study showed a significant progressive increase inD-Dimer level with increased stage of disease, and significant relationship between D-Dimer levels and the level of lymph nodes involved pathologically. There is a significant decrease in the D-Dimer levels post surgery observed in the study.

Choudhary, Ganpat Singh, et al and the group in their study found a statistically significant rise in the mean values of D-Dimer with increase in tumor size(p value 0.014), and with progressive stage of axillary lymph nodes involvement(p value 0.004).

Yan Lu et al. and the group in their study found statistical significance between the lymph node metastasis staging and the D-dimer values. (n=11,SMD=0.82; 95% CI=-0.44- -0.05). **Sergi, D. et al** and the group in their study observed there was an increased D-Dimer levels (63; 27.0%) in Carcinoma Breast patients, and D-Dimer levels were prognostically relevant for the overall survival rate of the patients.**Shyamveer Singh,et al** and his group observed in their study that there were significant increase in D-Dimer levels in carcinoma patients, significantly more in patients with invasion of lymphovascular and adipose tissue compared to localized tumor; they have also observed significant drop in D-Dimer levels after surgery (p value=0.000).

Factor VIII

The extracellular matrix remodeling occurring during tumor growth, tumor cell invasion into the surrounding tissue and distant metastasis is associated with activation of coagulation and fibrinolytic systems,Factor VIII is reported to be elevated in cancer patients compared to normal control subjects.

In the present study Factor VIII levels are measured at the beginning of evaluation of the patient, and POD 10 after Modified Radical Mastectomy, and axillary clearance or axillary sampling.The study was an attempt to relate the Factor VIII to lymph node status in carcinoma Breast, and predict lymph node metastasis in clinically node negative Breast cancer. Our study showed a significant progressive increase in Factor VIII levels with increased stage of disease, and

significant relationship between Factor VIII levels and the level of lymph nodes involved pathologically. There is a significant decrease in the Factor VIII levels post surgery observed in the study.

Sergi, D. et al and the group in their study observed there was an increased Factor VIII levels (29; 12.3%) in Carcinoma Breast patients, and Factor VIII levels were prognostically relevant for the overall survival rate of the patients.**Shyamveer Singh,et al** and his group observed in their study that there were significant increase in Factor VIII levels in carcinoma patients, significantly more in patients with invasion of lymphovascular and adipose tissue compared to localized tumor; they have also observed significant drop in Factor VIII values after surgery (p value=0.000).

Prothrombin Time & INR
The extracellular matrix remodeling occurring during tumor growth, tumor cell invasion into the surrounding tissue and distant metastasis is associated with activation of coagulation and fibrinolytic systems.

In the present study Prothrombin Time & INR levels are measured at the beginning of evaluation of the patient, and POD 10 after Modified Radical Mastectomy, and axillary clearance or axillary sampling.The study was an attempt to relate the Prothrombin Time to lymph node status in carcinoma Breast, and predict lymph node metastasis in clinically node negative Breast cancer. Our study showed a significant progressive increase in Prothrombin Time levels with increased stage of disease, and significant relationship between Prothrombin Time levels and the level of lymph nodes involved pathologically. There is a significant decrease in the Prothrombin Time levels and INR post surgery observed in the study.

Sergi, D. et al and the group in their study observed there was an increased Prothrombin Time values in Carcinoma Breast patients, and Prothrombin Time levels were prognostically relevant for the overall survival rate of the patient (p value=0.001).**Tas, Faruk, et al**. and the group observed higher levels of INR (p = 0.042) and that prolongation of PT and INR had statistically significant adverse effect on survival (p = 0.05 and p = 0.014, respectively).

SUMMARY
Breast Cancer is the second leading cause of cancer-related deaths, preceded by lung cancer, and the axillary lymph node involvement is the greatest prognostic factor of the patient's recovery post Modified Radical Mastectomy. It is reported in many studies that procoagulant and fibrin degradation factors are found to be increased in patients with malignant disease compared to normal control subjects.

In the current study, 100 patients that were histologically proven cases of breast cancer, were included in the study. The age groups of patients taken up for the study were included in the age range of 30 to >70yrs, the maximum 33% in the 51-60 yrs age group. With 58% of patients having left sided breast disease and 42% having right breast disease.
The maximum percentage of patients were in stage IIA which is 33%, with 30% in StageIIB, with 23% in Stage IIIA, with 7% in stage IA, with 6% in Stage IIIC, and 1% in Stage IIIB, in accordance to AJCC anatomic staging.
In the current study there was a 16% increase in the mean D-dimer levels observed in patients with comorbidities with the mean of patients without any comorbidities.

In the present study the we assessed the variation of D-dimer values with the advancing stage of nodal involvement with comparison with the tumor size with no nodal involvement there was a

statistically significant increase in the d-dimer values noticed with pre-operative p value= 0.024, and post-op p value= 0.054, and the fall in D-dimer values post Modified Radical mastectomy with axillary clearance of level I and level II or axillary sampling on POD-10 were found to be statistically significant with p value=0.016.

In the present study the we assessed the variation of PT values with the advancing stage of nodal involvement with comparison with the tumor size with no nodal involvement there was a statistically significant increase in the PT values noticed with pre-operative p value= 0.023, and post-op p value= 0.034, and the fall in PT values post Modified Radical mastectomy with axillary clearance of level I and level II or axillary sampling on POD-10 were found to be statistically significant with p value=0.003. The fall in INR values post Modified Radical mastectomy with axillary clearance of level I and level II or axillary sampling on POD-10 were found to be statistically significant with p value=0.0008.

In the present study the we assessed the variation of Factor VIII values with the advancing stage of nodal involvement with comparison with the tumor size with no nodal involvement there was a statistically significant increase in the d-dimer values noticed with pre-operative p value= 0.05, and post-op p value= 0.03, and the fall in Factor VIII values post Modified Radical mastectomy with axillary clearance of level I and level II or axillary sampling on POD-10 were found to be statistically significant with p value=0.001.

CONCLUSIONS
1. The Mean value of D-dimer and the advancing stage of disease were found to be correlated significantly with a p value of 0.024.
2. The Mean value of Factor VIII and the advancing stage of disease were found to be correlated significantly with a p value of 0.05
3. The Mean value of PT and the advancing stage of disease were found to be correlated significantly with a p value of 0.023
4. There was a statistically significant decrease in the coagulation markers that were noticed postoperatively (PT p value= 0.03, INR p value=0.0008, D-Dimer p value= 0.016, and Factor VIII p value=0.001 respectively.)
5. In the current study the presence of comorbidities in patients was associated with elevated levels of D-dimer of 16%.

References
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