EVALUATION OF IL-6 AND IL-8 IN CANCER BREAST PATIENTS AND CORRELATION WITH TNM STAGING

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KEYWORDS

IL-6, IL-8, BREAST CANCER , TNM STAGE

ABSTRACT

Introduction: Breast cancer is a global health concern, with one in eight women dying by age 90. Management involves age, menopausal status, tumor size, and estrogen levels. Estrogen and Progesterone receptor status are crucial for optimal prognosis. IL-6 and IL-8 concentrations could serve as biomarkers for disease progression and prognosis. **Aims:** This study aims to develop a feasible method for diagnosing and managing breast cancer, considering the strong association between elevated IL-6 and IL-8 serum concentrations. **Methodology:** The study analyzed data from breast cancer patients admitted to the Krishna Institute of Medical Sciences in Karad, focusing on their clinical stages, pre-operative evaluations, and inflammatory processes. **Results:** The study involved 70 participants aged 52.2 years and found that 40.0% had lesions in the Upper Outer Quadrant. The majority (62.9%) had T2 stage lesions. The study also showed a strong correlation between interleukin-6 and IL-8 levels with different T stages of a disease, with the highest levels observed in the N2 stage. **Discussion:** The study reveals elevated serum IL-6 and IL-8 levels in breast cancer patients, particularly advanced-stage cases, and a significant association with metastasis, potentially aiding in clinical management. **Conclusion:** The study explores the role of interleukin-6 and IL-8 levels in breast cancer patients, revealing their association with tumor, node, and metastasis staging, suggesting potential biomarkers.

INTRODUCTION

Breast cancer is a global health concern, leading to one in eight women dying by age 90, with incidence rates increasing, particularly in developing nations, with a mean age of 42 years.[1,2]

Breast cancer is a multifaceted disease with diverse natural history and biological subtypes, presenting clinical, pathological, and molecular features. Prognosis and management involve age, menopausal status, histological type, tumor size, and estrogen levels.[3]

Breast cancer management has evolved, favoring conservative surgery over mastectomy. Immunohistochemistry and hormone status testing are crucial for treatment planning, with Estrogen and Progesterone receptor status being crucial for optimal prognosis.[4]

Estrogen receptors play a crucial role in breast cancer, influencing cell proliferation through the Estrogen receptor (ER) and progesterone receptor (PR). Patients with ER-positive or PR-positive tumors have better prognosis and response to endocrine therapy, leading to routine hormone receptor testing for recurrence prevention.[5]

The tumor microenvironment (TME) is crucial for cancer development and progression, involving cancer cells, stromal cells, immune cells, and the extracellular matrix. Chronic

inflammation, characterized by pro-inflammatory cytokines, can promote genetic instability, angiogenesis, and apoptosis resistance.

Interleukins, pleiotropic cytokines, contribute to cancer progression. IL-6 and IL-8 stimulate cell proliferation and tumor angiogenesis in cancer cells. Treatment effectiveness and prognosis are influenced by disease stage and immune system processes controlled by interleukins.[6]

The study evaluates the correlation between IL-6 and IL-8 concentrations in breast cancer patients' blood serum and their clinical stage, suggesting that these cytokines could serve as biomarkers for disease progression and prognosis, potentially aiding treatment decisions.

AIM & OBJECTIVES

Elevated IL-6 and IL-8 serum concentrations are strongly associated with breast cancer and correlate with disease stage. This study aims to develop a feasible method for diagnosing and managing breast cancer, alongside other methods.

MATERIALS & METHODS

The study included patients diagnosed with breast cancer and hospitalized to the general surgery department of the Krishna Institute of Medical Sciences in Karad.

Study design

Observational Prospective type of Study

Place of study

KVVDU, Karad hospital

Study period

MARCH 2022 to SEPTEMBER 2024

This prospective hospital-based study included all cases satisfying inclusion criteria, collected data from detailed history, clinical examination, pre-operative evaluation of IL-6 and IL-8, and patients evaluated at diagnosis.

Inclusion criteria: The study included patients in clinical stages IIA, IIB, IIIA, and IIIB according to TNM classification, aged 25-79 years.

Exclusion criteria: Patients aged 25-79 years, with inflammatory breast carcinoma, or showing clinically overt active inflammatory process, are excluded from the study.

The study recorded patient information after hospital admission, analyzed categorical and continuous variables using Chi square test/Fisher Exact test, and entered data into MS EXCEL spreadsheet using SPSS version 21.0.

RESULTS

The study involved participants aged 52.2 years with an average of 13.6 years.

Table 1: Age (in years) distribution of study participants

Mean	52.186
Median	51.000
Std. Deviation	13.5607
Minimum	28.0
Maximum	87.0

The study involved 70 participants, with 22 aged 51-60 years and 19 aged 41-50 years.

Table:2Distributionofstudyparticipantsaccordingtoagegroup:

Agegroup	Frequency	Percent
Upto40years	14	20.0
41-50years	19	27.1
51-60years	22	31.4
>60 years	15	21.4
Total	70	100.0

The study found that 40.0% of participants (40.0%) had lesions in the Upper Outer Quadrant (UOQ), followed by 24.3% in the Retro- Areolar site, with lower frequencies in the Lower Outer Quadrant, Upper Inner Quadrant, and multifocal sites.

Table 3: Distribution of study participants according to site lesion:

Site	Frequency	Percent
Lower Inner Quadrant	4	5.7
Lower Outer Quadrant	10	14.3
Multifocal	2	2.9
Retro-Areolar	17	24.3
Upper Inner Quadrant	9	12.9
Upper Outer Quadrant	28	40.0
Total	70	100.0

The study's participants were categorized based on their T-stage of lesions, with the majority (62.9%) having T2 stage lesions.

Table :4 Distribution of study participants according to T staging:

T-stage	Frequency	Percent
T1	7	10.0
T2	44	62.9
T3	11	15.7
T4	8	11.4
Total	70	100.0

The table provides the distribution of study participants according to the N-staging, which represents the extent of lymph node involvement. The majority of participants, 33 out of 70 (47.1%), had N0 stage lesions, indicating no lymph node involvement. The remaining participants had varying degrees of lymph node involvement, with 19 participants (27.1%) classified as N1 stage and 18 participants (25.7%) classified as N2 stage.

Table :5 Distribution of study participants according to N staging:

N-stage	Frequency	Percent
N0	33	47.1
N1	19	27.1
N2	18	25.7
Total	70	100.0

The table shows study participant distribution based on TNM staging, with majority (51.4%) in stage IIA, followed by advanced stages (21.4%) in stage IIIA, 15.7% in stage IIB, and 11.4% in stage IIIB.

Table 6: Distribution of study participants according to overall TNM staging:

TNM-stage	Frequency	Percent
IIA	36	51.4
IIB	11	15.7

IIIA	15	21.4
IIIB	8	11.4
Total	70	100.0

The study's table shows moderate variability in IL6 levels (13.31), with a median of 12.00, and higher variability in IL8 (41.21), with a range of 20 to 104.

Table 7: Distribution of IL among the breast carcinoma patients:

	IL6	IL8
Mean	13.31	41.21
Median	12.00	34.00
Std. Deviation	5.757	17.893
Minimum	6	20
Maximum	32	104

The table shows a strong correlation between interleukin-6 and IL-8 levels with different T stages of a disease. In the T1 stage, IL-6 levels are 9.29, IL-8 levels 31.14, and 11.34 respectively. In the T2 stage, IL-6 and IL-8 levels increase to 11.34, 35.30, 47.18, and 24.50 respectively, indicating a significant correlation.

Table 8: Association of IL-6 and IL-8 with T stage:

Stage		IL6	IL8
T1	Mean	9.29	31.14
	SD	3.498	8.764
T2	Mean	11.34	35.30
	SD	3.698	11.185
T3	Mean	15.64	47.18
	SD	3.585	13.688
T4	Mean	24.50	74.38
	SD	4.660	20.480
p-value		0.0001	0.0001

The table shows a significant association between increasing nodal stage and elevated levels of interleukin-6 and IL-8, with the highest levels observed in the N2 stage. IL-6 levels are highest in N0, while IL-8 levels are highest in N1.

Table 9: Association of IL-6 and IL-8 with N stage

Stage		IL6	IL8
No	Mean	10.88	35.18
	SD	5.510	18.632
N1	Mean	12.32	40.79
	SD	4.460	14.505
N2	Mean	18.83	52.72
	SD	3.382	14.563
p-value		0.0001	0.0001

The table explains the correlation between tumor stage, nodal involvement, and metastasis (TNM stage) and the levels of interleukin-6 and IL-8.

Table 10: Association of IL-6 and IL-8 with TNM stage

Stage		IL6	IL8
	Mean	9.17	29.50

IIA	SD	2.007	3.621
IIB	Mean	12.82	43.18
	SD	1.601	10.741
IIIA	Mean	17.67	50.20
	SD	2.093	13.497
IIIB	Mean	24.50	74.38
	SD	4.660	20.480
p-value		0.0001	0.0001

DISCUSSION

Breast cancer is a prevalent and challenging disease, with the TNM staging system being crucial for determining prognosis and treatment strategies. Inflammatory cytokines, IL-6 and IL-8, have been linked to cancer progression and may serve as biomarkers for early diagnosis and treatment response. This study aims to evaluate serum IL-6 and IL-8 levels in breast cancer patients and investigate their correlation with TNM staging, aiming to understand their potential role as biomarkers for disease progression and their clinical utility in breast cancer management.

The study's age distribution aligns with previous research on breast cancer patients, with a mean age of 52.46 compared to 56 years in Elkablawy et al[7].'s index study, possibly due to varied histopathology.

Rampal et al'[8]s study revealed that 23% of patients were in stage IV of breast cancer, indicating a diverse age range for the study population.

The study found that the majority of participants (40.0%) had breast cancer lesions in the Upper Outer Quadrant (UOQ), followed by the Retro-Areolar site (24.3%). This distribution aligns with the general epidemiology of breast cancer, as the UOQ is the most common location for tumors. Previous studies have found higher tumor placement in the UOQ, with the incidence of female breast cancer increasing from 47.9% in 1979 to 53.3% in 2010, primarily due to a larger proportion of target epithelial tissue in that region.[9]

The study analyzed the distribution of lesion sites in breast cancer patients, focusing on the association between biomarkers and overall stage or metastatic status. The majority of participants (62.9%) had T2 stage lesions, while 47.1% had N0 stage lesions. The majority (51.4%) were classified as stage IIA, representing an early stage of the disease, with the remaining participants distributed across more advanced stages. The findings align with previous studies on breast cancer epidemiology and patient evaluation and management.

The present study focuses on the detailed staging of breast cancer, assessing the T-stage, N-stage, and overall TNM-stage, providing valuable information for treatment planning, prognosis, and interpretation of associations between biomarkers and disease stage. It also evaluates the levels of IL-6 and IL-8 in breast cancer patients and their association with T-stage, N-stage, and overall TNM-stage.[11]

The study found moderate variability in IL-6 levels, with a significant positive association with T-stage, N-stage, and overall TNM-stage. As disease stage increased, IL-6 levels also increased. Higher IL-8 levels were found in more advanced stages of the disease. These findings align with Rampal et al.[9]'s previous research, which found increased serum IL-6 associated with metastasis.

Studies show that IL-6 and IL-8 levels are significantly higher in breast cancer patients compared to healthy controls, with higher levels in advanced-stage breast cancer. These findings suggest that these cytokines may be involved in the pathological processes driving tumor growth and dissemination. Understanding the relationships between IL-6, IL-8, and different staging parameters can help improve clinical management of breast cancer patients.[11]

The study compares IL-6 levels with previous research on breast cancer staging, finding a progressively increasing trend with each stage. It also found a significant association between elevated serum IL-6 and metastasis. The study also found higher IL-6 levels in advanced-stage breast cancer compared to earlier stages.[8,10]
Mishra et al.[11]'s study highlights serum ferritin's role in breast cancer metastasis prediction, highlighting the potential utility of serum biomarkers in disease management.
Kumari et al.[12]'s study found that serum IL-6, IL-8, and TNF-α levels are significantly higher in breast cancer patients compared to healthy controls, correlated with clinical tumor stage and lymph node metastasis. These interleukins may serve as potential biomarkers for disease progression and metastasis, providing valuable information for clinical decision-making and risk stratification in breast cancer management.

CONCLUSIONS

The study evaluates serum levels of interleukin-6 and IL-8 in breast cancer patients and their association with tumor, node, and metastasis staging. Most participants had lesions in the UOQ and RA sites, with most in early stages. IL-6 and IL-8 levels were significantly associated with T-stage, N-stage, and overall TNM-stage, suggesting potential as biomarkers for disease progression and metastasis.

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