Section: Miscellaneous

Original Research Article

A CLINICO PATHOLOGICAL STUDY OF PRE-OPERATIVE SERUM INTERLEUKIN-6 AND C-REACTIVE PROTEIN LEVELS IN BREAST CANCER PATIENTS

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Abstract

Background: Despite remarkable improvements in cancer treatment approaches, breast cancer is still the main cause of cancer related death in women. Recently an association between breast cancer & inflammation has emerged as the seventh hallmark of cancer. Chronic inflammation is a key contributor in the development & progression of carcinogenesis. IL-6& CRP are found to be elevated in various inflammatory & malignant diseases. Elevated levels of both markers at the time of diagnosis of breast cancer indicate aggressiveness of the tumor. Breast cancer survivors with association of Chronic inflammation are at risk of recurrence and metabolic disturbances. The present study is aimed to strengthen the relationship between serum IL-6 and CRP levels with breast carcinoma staging and its relation to clinical outcome. **Materials and Methods:** A total number of 100 females who all are cytologically and histopathologically proven breast cancer patients were selected for the study & were Subjected to thorough evaluation. Serum levels of IL-6 were assessed via Enzyme- Linked immuno-sorbent assay & CRP was measured via immuno-turbidimetry. Histological findings included tumor size, lymph node, metastasis & tumor staging correlated with serum levels of IL-6 &CRP in all cases. Statistical analysis of the data was then processed. **Results:** Increase in cancer invasion & Staging are associated with increase in pre-operative serum IL-6 & CRP levels correlated with TNM staging (IL-6; P-0.010, CRP; P-0.011). It interpreted that serum Levels of IL-6 & CRP increases with subsequent stage of breast Cancer. **Conclusion:** This study strengthens the positive correlation of serum IL-6 & CRP levels with TNM staging of breast cancer,hence indirectly correlating with the prognosis of the patient. Thus, breast cancer patients with pre-operative raised levels of CRP& IL-6 should be paid a special attention for better patient management and survival outcome.

INTRODUCTION

Breast cancer is a disease affecting millions of women, as well as men, all over the world. The Tumor-Node-Metastasis (TNM) system of classification is used for staging of the disease, which has a strong influence on the prognosis of the patient.[1] IL-6 as major mediator of the inflammatory response, plays a primary role in the pathophysiology of cancer.[2-5] IL-6 has a role in cancer; IL-6 regulates chronic inflammation, which can create a cellular microenvironment beneficial to cancer growth.[6] One of the hallmarks of cancer is angiogenesis in conjunction with systemic and local inflammation.[7] IL-6 is a pleiotropic cytokine with a wide range of functions. IL-6 binds to the IL-6 receptor, activates the Janus kinase (JAK), and subsequently phosphorylates the signal transducers and activators of transcription (STAT). The phosphorylated STAT gene translocates into the nucleus and activates the target genes like VEGF and rho which increases the aggressiveness of the tumor. This involvement of IL-6 at a cellular level with the processes of cancer control is reflected by

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the results of serum studies of cancer patients, where IL-6 may reflect prognosis and tumor load. Elevated IL-6 levels have been associated with advanced-stage and metastasis-related morbidity.[8-10] Increase levels of IL-6 in the serum and tumor site have been demonstrated in several cancers and including breast cancer.[11]While this increases poor prognosis and is usually accompanied by poor prognosis and lower survival in breast cancer patients, downregulation of IL-6 is related to a better response to patients.[12,13] C-reactive protein (CRP) is a representative marker for inflammatory conditions, and performs a crucial anti-infection function in the immune system. In many cancers, it has been reported that chronic inflammation is involved with malignant change, and the risks of cancer are increased when pre-diagnostic CRP levels are high.[14] Cancer invasion begins with inflammation around cancer cells. Thus, it has been reported that serum CRP levels are higher in cases of invasive cancer than in cases of non-invasive cancer. [15,16]

The principal objective of this study was to determine the relationship between serum IL-6 and CRP levels with staging and prognosis in breast cancer patients.

MATERIALS AND METHODS

This prospective study was carried out at Department of Pathology, B.R.D Medical College and included 100 cytologically and histopathologically proven breast cancer patients, with their age range from 26 to 85 years. In addition, 12 apparently healthy age -matched and sex-matched individuals were involved in this study as a control group for a duration of one year from July 2021 to June 2022.

All cytologically and histopathologically proven breast cancer patients who have attending the surgical OPD/IPD were selected for the study and their basic investigations, chest X-ray(mammography) report, FNAC reports, biopsy reports were analyzed thoroughly and Blood samples were drawn for the levels of IL-6 and CRP assessment. After reviewing clinico-radiological and cytological reports patients were assessed according to (AJCC 8th edition of TNM staging of breast cancer)

1. Primary tumour (T1=≤2 cm, T2=2-5 cm, T3=>5 cm, T4=Chest wall or skin infiltration.
2. Nodal staging (N1=1-3 nodes, N2=4-9 nodes, N3=>10 nodes.
3. Presence(M1) or Absence(M0) of distant metastasis.

All mastectomy specimens of previously reviewed cases received in the department of pathology, were grossed thoroughly and were assessed for tumor size, extension, margins and lymph nodes status.

Sections from tumor mass, margins and all lymph nodes were assessed thoroughly for staging of breast cancer. Histopathology slides was studied for confirmation of diagnosis of carcinoma breast and for its lymph node metastasis. Patients were asked for follow up every 3 months for a period of one year and for re-estimation of serum IL-6 and CRP levels.

Assay For Serum Il-6 And CRP

The blood sample for IL-6 were collected in EDTA tubes and were analysed using ELISA technique (Enzyme linked immunosorbent assay) and normal value for IL-6 in a healthy individual is expected to be <7 pg/ml. CRP were measured using immunoturbidimetric method by Selectropro -M machine. samples were taken in plain vials for serum separation and normal value of CRP up to 6 mg/L is taken as standard. The results were tabulated and statistically analyzed using SPSS. A p value < 0.05 was considered as statistically significant. The IL-6 and CRP levels were correlated with tumor size, status of lymph node metastasis, presence or absence of metastasis and TNM staging.

RESULTS

Patient characteristics

In this study, 100 breast cancer patients included, out of which 98 was female of median age of 54.74 years (range, 26-85 years). In all, 8 patients had stage IIa disease (8%), 26 patients belong to stage IIb (26%), 18 patients belong to stage IIIa (18%),20 belongs to stage IIIb (20%), 15 patients to stage IIIc (15%) and 13 to stage IV(13%). The other patient characteristics are summarized in Table 1.

Clinicopathological significance of IL-6 and CRP in breast cancer

We noted that IL-6 levels were significantly correlated with the tumor size as highest level (25.8±11.3) in T4 stage and lowest in T1 (8.2±5.5).In cases of lymph node metastasis, level of IL-6 also correlated with lymph node metastasis as highest in N3 stage(32.5±10.5).In this study level of IL-6 also correlated with distant metastasis, as higher level (39.5±9.4) were seen in cases where metastasis present while lower levels (16.9±8.0) were seen in cases without metastasis.

As levels of CRP were also significantly correlated with tumor size as highest levels of CRP were seen in T4(16.4±2.9), while lowest levels were seen in T1(8.2±3.5). level of CRP also correlated with Lymph node metastasis status as highest levels were seen in N3(29.7±15.1), while lowest were seen in N1(9.2±4.3). CRP levels also correlated with presence of distant metastasis. Higher levels of CRP (9.2±4.3) were seen in cases where metastasis has occurred while lower levels (10.4±6.8) were seen in cases without metastasis. In this study, serum IL-6 levels increased according to TNM Staging as highest levels of IL-6 were noted in stage IV (39.4±9.8) followed by stage IIIc (26.6±6.8), followed by stage IIIb (18.7±5.2), followed by stage IIIa (16.7±4.8) and stage IIb (11.2±4.6) while lowest

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levels were in stage IIa (5.8±1.3). This difference was statistically significant(P<0.05).

Serum CRP also increases according to TNM Staging as highest levels of CRP were noted in stage IV (38.4±10.2) followed by in stage IIIc (20.9±8.4), in stage IIIb (12.5±8.8), in stage IIIa (13.4±7.6), in stage IIb (10.3±3.6) and lowest in stage IIa (8.8±4.2). This difference was also statistically significant(P<0.05). It interprets that Serum CRP Levels increases with subsequent stage of breast cancer.

RESULTS

Table 1: Statistical comparison between cases and controls as regards Serum IL-6 and CRP levels

Variables	Study group		P value
	Median±SD	CASE(N=100)	CONTROL=12)
IL-6 Level	12.2±11.46	5.52±3.78	0.03
CRP Level	20.61±9.52	10.32±7.48	0.001

Table 2: Patient characteristics

	No. of patients	%
Total number of patients	100	
Age		
Median (Range)	54.74(26-85)	
Tumor Size		
T1	12	12
T2	26	26
T3	24	24
T4	38	38
LN Metastasis		
N1	29	29
N2	35	35
N3	27	27
Distant Metastasis		
Metastasis present	87	87
Metastasis absent	13	13

Table 3: Correlation between the IL-6, CRP and clinicopathological parameters

IL-6	CRP	
Median±SDMedian±SD		
Total	(pg/ml)	(mg/dl)
Tumor size		
T1	8.2±5.5	8.2±3.5
T2	17.6±8.4	10.8±2.4
T3	19.5±9.8	9.3±2.2
T4	25.8±11.3	16.4±2.9
LN Metastasis		
N1	11.7±4.5	9.2±4.3
N2	20.9±6.5	14.9±9.4
N3	32.5±10.5	29.7±15.1
Distant Metastasis		
Metastasis present	39.5±9.4	37.6±15.8
Metastasis absent	16.9±8.0	10.4±6.8
TNM Stage		
IIa	5.8±1.3	8.8±4.2
IIb	11.2±4.6	10.3±3.6
IIIa	16.7±4.8	13.4±7.6
IIIb	18.7±5.2	12.5±8.8
IIIc	26.6±6.8	20.9±8.4
IV	39.4±9.8	38.4±10.2
P value	0.010	0.011

DISCUSSION

The mean age of present study population was found to be 54.74(26-85) years which was in accordance to Ravishankaran and karunanithi where mean age was 59.11(36-85) years. This study was comparable to Ravishankaran and karunanithi et al, (2011) as well as Gehan et al, (2016),Where higher levels of IL-6 found in stage IV (39.4±9.8, 39.8±9.4 and 38.2±4.82 respectively) followed by stage IIIc (26.6±6.8, 26.3±7.0 and 27.08±3.67 respectively) followed by stage IIIb (18.7±5.2, 19.1±4.8 and 20.25±2.70 respectively) followed by stage IIIa (16.7±4.8, 16.9±4.7 and 16.57±4.64) followed by stage IIb (11.2±4.6, 11.7±4.4 and 11.54±5.14 respectively) and lower levels in stage IIa (5.8±1.3, 5.6±1.5 and 8.0±4.44 respectively)

This study was comparable to Ravishankaran and karunanithi et al, (2011) as well as Gehan et al,

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(2016),Where highest level of CRP found in stage IV (38.4±10.2, 37.5±16.0 and 36.4±13.57 respectively) followed by stage IIIc (20.9±8.4, 21.5±9.9 and 17.33±7.17 respectively) followed by stage IIIb (12.5±8.8, 12.8±9.2 and 5.5±2.45 respectively) followed by stage IIIa (13.4±7.6, 13.8±7.2 and7.43±3.60) followed by stage IIb (8.8±4.2, 9.2±4.6 and 6.5±2.07 respectively) and lowest in stage IIa (10.3±3.6, 10.1±3.9 and7.0±0.0 respectively). Thus, the levels of IL-6 correlate with all the aspects of breast cancer like tumors size, lymph node involvement, distant metastasis and the final TNM staging of the disease. The overall survival of the patient also seems to be affected in patients with elevated levels of IL-6. levels of CRP also correlated with tumor size, lymph node metastasis and distant metastasis. It has been proved that TNM staging correlates with the prognosis of patients with breast cancer. As IL-6 has a direct correlation with the stage of the disease it may indirectly correlate with the prognosis of the patients.

CONCLUSION

In this study, P-value of IL-6 levels according to TNM staging was 0.010 which is statistically significant (P<0.05) which showed that serum Level of IL-6 increases with subsequent stage of breast cancer and P-value of CRP levels according to TNM staging, was 0.011 which is statistically significant (P<0.05) which showed that serum CRP Levels increases with subsequent stage of breast cancer. This study strengthens the positive correlation of serum IL-6 levels and CRP levels with TNM staging of breast cancer, hence, indirectly correlating with the prognosis of patients. Assessing preoperative CRP levels in invasive breast carcinoma patients could be the more accurate prognostic factor, compared with those already established. So, we concluded that particular attention should be paid to patients with higher preoperative IL-6 and/or CRP expression levels during preoperative follow-up for breast cancer.

Limitations of the study

1. A larger sample size needs to be evaluated to reach a definite conclusion.
2. A longer follow up of the patient is also essential for completeness.

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