Research Article

Role of Inflammatory markers in patients with breast carcinoma and their correlation with Tumor markers

Soma Gupta[1*], Sukanya Mukherjee[2], Sukla Nath [3]

[1*]Department of Biochemistry, Midnapore Medical College, Paschim Medinipur, West Bengal, India
[2] Specialised Medical Officer, Jhargram Medical College, Jhargram, West Bengal, India
[3]Department of Biochemistry, NRS Medical College, Kolkata 14, West Bengal, India

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Corresponding Author: ***Soma Gupta*** Email: ***docsomagupta@gmail.com***

ABSTRACT

Background: Breast carcinoma remains a serious global health concern, with over 2.3 million women diagnosed annually and significant mortality rates persisting despite improvements in screening and treatment protocols.

Aim: This is an observational, case control, hospital-based study which was carried out to find the role of inflammatory markers in patients with breast carcinoma and their correlation with tumour markers.

Metrials & Methods: The study population consists of (3) three distinct study groups, Group A: patients diagnosed with breast carcinoma (n=70), Group B: healthy controls (n=70) and Group C: patients with benign breast disease (n=70). Patients suffering from any tumor of breast identified for the first time were included in this study population. Recurrent cases were excluded from the study. Serum level of CRP and IL-6 were measured as inflammatory marker whereas CEA and CA 15 - 3 were measured as tumour markers in this study population.

Results: There was significant elevation of inflammatory markers in patients with breast carcinoma when compared to healthy control. The inflammatory markers were found to be positively correlated with patients with breast carcinoma but this correlation was not significant.

Conclusion: Early detection of elevated inflammatory markers could serve as a predictive tool for breast cancer prognosis. Integrating CRP and IL-6 screening in routine diagnostics may help identify high-risk patients earlier.

Keywords: CRP**,** IL 6, Breast Carcinoma, Early Diagnosis, correlation, Tumour marker

1. INTRODUCTION

Breast carcinoma remains a serious global health concern, with over 2.3 million women diagnosed annually and significant mortality rates persisting despite improvements in screening and treatment protocols. In many regions, including India, breast cancer is the most prevalent cancer affecting women and represents approximately 23% of all female cancers. Additionally, a rising proportion of younger women are diagnosed with breast cancer, presenting unique challenges to healthcare systems and necessitating further investigation into early detection and effective treatment strategies. While strides have been made in understanding the molecular basis of breast cancer, the disease continues to impose a substantial health burden due to its complex etiology, which involves an interplay of genetic, hormonal, inflammatory, and environmental factors [1,2]. Among the various biological factors implicated in breast cancer, inflammatory markers, and tumor markers have been increasingly recognized for their roles in the disease onset, progression, and prognosis. Tumor markers such as cancer antigen 15-3 (CA 15-3) and carcinoembryonic antigen (CEA) have shown utility in monitoring disease progression and recurrence. However, the involvement of inflammatory processes in breast carcinoma adds a relatively novel dimension to this cancer's

pathology and underscores the importance of examining inflammatory biomarkers as both contributors to and indicators of disease state [3, 4]. Chronic inflammation has long been recognized as a critical component of various malignancies, including colorectal, lung, and gastric cancers. In these cancers, inflammatory markers not only play a role in early disease progression but also correlate with metastasis, treatment resistance, and survival rates. In breast cancer, however, the specific role of inflammation is less clearly defined, and studies have shown conflicting results regarding its impact on prognosis and progression. Key inflammatory biomarkers, such as C-reactive protein (CRP) and interleukin-6 (IL-6), are frequently elevated in breast carcinoma patients, suggesting that inflammation may contribute to the tumor microenvironment in ways that promote cancer cell proliferation, invasion, and metastasis. For instance, IL-6 has been shown to foster a pro-inflammatory milieu that supports tumor growth and metastatic spread by enhancing cell motility and aiding the immune evasion of cancer cells. Additionally, the elevated CRP levels observed in many breast cancer patients may reflect an acute-phase response associated with a poorer prognosis. As such, these inflammatory biomarkers may serve as valuable indicators of disease activity and patient outcomes in breast carcinoma, providing potential tools for diagnosis, prognosis, and monitoring response to treatment [5]. This study aims to bridge this knowledge gap by evaluating associations among inflammatory markers and tumor markers in breast carcinoma patients compared to those with benign breast disease and healthy controls. The insights gained from this research could contribute to the development of biomarker-based diagnostic and prognostic tools, potentially improving patient management in clinical practice.

2. MATERIALS AND METHODS

The Hospital based, observational, case control study focuses on a cohort of 210 patients suspected of breast carcinoma, referred to the Department of Pathology at NRSMC&H from various outpatient departments for Fine Needle Aspiration Cytology (FNAC). Based on FNAC results, patients with positive findings were classified as breast carcinoma cases, while those with negative findings will undergo biopsy for confirmation. Among them, those with biopsy-positive results were included in the breast carcinoma group, while biopsy-negative results were classified as benign breast disease. Additionally, to establish a robust comparative baseline, age- and gender-matched healthy controls were included, creating three distinct study groups: healthy controls (n=70), patients with benign breast disease (n=70), and patients diagnosed with breast carcinoma (n=70). Only patients suffering from any tumor of breast identified for the first time were included in the study population. Recurrent cases were excluded from the study. This study was approved by Institutional Ethics Committee. The selected patients were brought to Department of Biochemistry. For each participant, a comprehensive medical history was recorded comprising of age, religion, education (Illiterate, school education up to 12th class, college goers and above), occupation (Housewife/unemployed, Service/Self employed and Students) and marital status (unmarried/ Married. Widowed or divorced or separated). Relevant presenting clinical symptoms were also recorded in terms of breast mass, breast pain, nipple discharge, skin retaction, axillary mass and axillary pain. Patients presented with one or multiple symptoms. Then 2ml venous blood samples was collected from each participant. These samples were centrifuged to separate serum, which were then analyzed for levels of C-reactive protein (CRP) and interleukin-6 (IL-6) (inflammatory markers), and carcinoembryonic antigen (CEA) and cancer antigen 15-3 (CA 15-3) (tumor markers). CRP was estimated by Particle enhanced turbidimetric immunoassay (PETIA) method. In this method, human CRP agglutinates with latex particles coated with monoclonal anti- CRP antibodies. The precipitate is determined turbidimetrically at 552nm, using Cobas Integra 400 Plus System. IL6 and CA 15.3 were estimated by one step direct immunoassay method using chemiluminescent technology on Advia Centaur.

CEA was estimated by Electrochemiluminescence Immunoassay (ECLIA) using Sandwich Principle on Cobas E 601 Immunoassay Analyzer. Data analysis incorporated Student's T-Test to evaluate statistical significance across the groups, with Pearson's correlation coefficient employed to investigate associations between the inflammatory and tumor markers. To assess the diagnostic efficacy of each marker in identifying breast carcinoma, Receiver Operating Characteristics (ROC) curves were used to measure sensitivity and specificity. Area under the ROC curve was found out with 95% CI. The optimum cut off value was found out from associated criterion calculated from Youden Index J, which is the measure of maximum potential effectiveness of a biomarker. Considering the cutoff point, sensitivity and specificity of the individual parameter was calculated. Positive and Negative predictive value was also calculated using appropriate formula. All these statistical analyses was done using MedCalc Statistical Software version 16.4.3 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2016).

3. RESULTS

Table 1: Biochemical parameters among study population

Parameter	**A Carcinoma Breast (n =70)**	**B Healthy Control (n =70)**	**C Benign Breast Disease (n =70)**	**T value (A vs B)**	**P value (A vs B)**
CEA (ng/ml)	3.6 ±2.4	2.1 ± 0.9	2.4 ± 0.4	4.896	P < 0.0001
CA 15-3(U/ml)	20.06 ±5.9	5.9 ± 3.3	10.2 ± 0.3	17.525	P < 0.0001
CRP (mg/L)	4.5 ± 3.9	2.6 ± 1.6	7.5 ± 0.6	3.771	P = 0.0002
IL6 (pg/ml)	2.04 ± 0.8	1.6 ± 1.5	3.01 ± 0.4	2.165	P = 0.0321

All biochemical parameters are expressed in mean ± SD

Table 2: Correlation Between Inflammatory Markers and Tumor Markers

GROUP	CEA & CRP		CA15.3 & CRP		CEA & IL6		CA15.3 & IL6	
	r	p	r	p	r	p	r	p
Breast Carcinoma	0.025	0.86	0.19	0.11	0.12	0.32	0.05	0.67
Benign Breast Disease	0.012	0.594	0.084	0.488	0.07	0.52	0.09	0.44

r = correlation coefficient, p Value < 0.05 is considered as significant

Table 3: Predictive value of CRP and IL 6 to differentiate benign breast disease and breast carcinoma

Parameter	CRP	IL 6
Area under curve (AUC)	0.671 (95% CI: 0.60, 0.74)	0.726 (95% CI: 0.68, 0.76)
Sensitivity	78.57%	81%
Specificity	58.57%	61%
Positive predictive value	26.53%	28%
Negative predictive value	93.48%	94%
Cut off value	0.37mg/L	0.95 pg/ml

CI: Confidence Interval

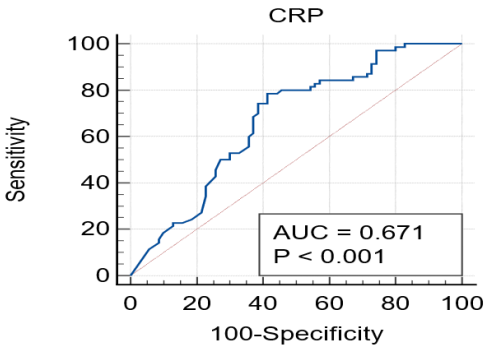

Fig. 1: ROC curve for CRP

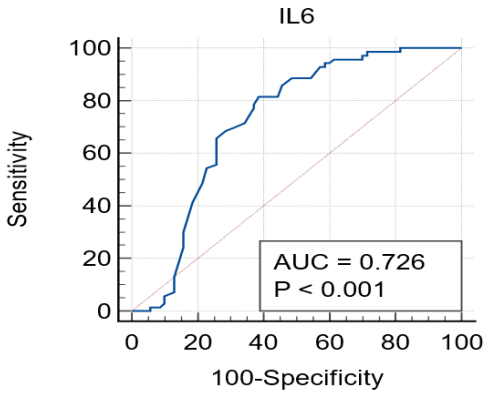

Fig. 2: ROC curve for IL 6

4. DISCUSSION

In breast cancer, carcinoembryonic antigen (CEA) and cancer antigen 15–3 (CA15-3) are the two most widely used serum tumor markers. CEA is normally produced in gastrointestinal tissue during fetal development, but the production stops before birth. Consequently, CEA is usually present at very low levels in the blood of healthy adults (about 2-4 ng/mL). CA 15-3 is a carbohydrate-containing protein antigen called mucin (MUC). In recent years, the parameters are used for assessing prognosis, the early detection of disease progression, and

treatment monitoring in breast cancer. This study shows an elevated serum level of Tumor markers like CEA and CA15.3 in breast cancer patients compared to the healthy control group, which tallies with the findings obtained in the studies conducted by several other studies [6 to 9], (Table 1). Inflammation leads to cancerous growth by several mechanisms. Inflammation creates a tissue microenvironment where the reactive oxygen and nitrogen species released by inflammatory cells could cause potentially malignant DNA alterations and that some inflammatory cytokines and proteins in chronic inflammation promote tumour growth [4]. In this study, CRP and IL 6 were analysed. Serum CRP and IL 6 levels are found to be higher in breast carcinoma patients compared to healthy controls (Table 1). This finding coincides with other study [10, 11] Table 2 shows correlation between Inflammatory Markers and Tumor Markers. Though a positive correlation was obtained in each case, none of them were found to be significant. Cytokine IL-6 is known to be a key player in systemic inflammation. Tumor cells and tumor-associated fibroblasts are the major sources of IL-6, which in turn induce the production of CRP [12]. Moreover, Tumour growth can cause tissue inflammation and hence increase CRP levels. These mechanisms imply that increased CRP is a response to the neoplastic process and that CRP concentrations could thus provide a marker for identifying people with cancer at an early stage when treatment might be more effective. A study by Kumari *et al.*, explains a strong association between inflammation and tumorigenesis and that is reflected by the elevated level of IL6 in the tumor microenvironment [13]. Table 3 shows predictive value of CRP and IL 6 to differentiate benign breast disease and breast carcinoma. Fig. 1 and 2 show ROC curve for CRP and IL 6 respectively. The positive predictive value of IL6 in the above study is 28% with a sensitivity of 81% which signifies it to be a relevant inflammatory biomarker in the pathogenesis of breast cancer. This finding is similar to the findings of the study by Masjedi *et al.*, [14].

LIMITATION

The study did not explore whether early detection of elevated inflammatory markers could serve as a predictive tool for breast cancer prognosis. It did not explore also whether CRP and IL-6 screening in routine diagnostics can help to identify high-risk patients earlier. Multivariate or regression analysis have not been applied to find out whether predictors influence outcomes. These can be considered as limitation of the study.

5. CONCLUSION

CRP and IL-6 levels were significantly elevated in breast cancer patients compared to those with benign breast diseases and healthy controls. These markers were positively correlated with advanced disease stages. There is no significant correlation found between the tumor markers (CEA and CA15-3) and the inflammatory markers (CRP and IL-6) between the breast cancer patients and the patients with benign breast disease.

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CONFLICT OF INTEREST

"We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome."

FUNDING INFORMATION

No Funding was received for this research work.

ETHICAL INFORMATION

Though the study is not concerned with any ethical issue, A written Informed consent was obtained from the patient. Patient anonymity was carefully maintained. Ethical Clearance was also obtained from the IEC.

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