

Original Article

Post-operative outcome & disease-free survival among patients of breast cancer with raised C - reactive protein

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Abstract

Background: Cancer and inflammation have a bidirectional association; chronic inflammation is considered a major contributor to carcinogenesis. C - reactive protein (CRP), an inflammatory protein produced by the liver, has been identified as an important prognostic marker among breast cancer patients. This study aimed to elucidate the role of C-reactive protein as an inflammatory prognostic predictor in breast cancer patients and its impact on disease-free survival (DFS).

Methodology: This prospective cohort study included 80 locally advanced breast cancer (stage II and III) patients presenting at the Department of General Surgery (Unit II), Liaquat University Hospital - Jamshoro/Hyderabad. Patient data, including demographics, stage and hormone status of breast cancer, metastatic workup, pre-operative CRP, post-operative complications and DFS on follow-ups including recurrence, metastasis and post-surgery skin manifestation, were recorded using a structured questionnaire. The statistical analysis was conducted on SPSS version 22.0.

Results: Pre-operatively, a mildly raised serum CRP level was observed in 71.25% of patients and highly raised in 28.5%. The post-operative complications were observed in 12 participants with wound infection in 8, wound dehiscence in 3 and sepsis in only 1 participant. The DFS, including recurrence-free and metastatic-free survival, were observed in 69 participants

Conclusion: After thorough observation, it can be concluded that the raised CRP level is a significant predictor for post-operative complications (wound infection, dehiscence, and sepsis) and disease-free survival among patients with locally advanced breast cancer.

Keywords

C - reactive protein (CRP), Advanced Breast Cancer, Disease Free Survival (DFS), Post-Operative Wound Infection, Dehiscence.

Introduction

Breast cancer is the most common cancer among women¹, with the prevalence of 22% of all female cancers worldwide and 42% cases in developing countries^{2,3}. Previously it was thought to be the 3rd leading cause of cancer-associated mortality. Still, now with the ongoing trends of new research and developing treatment modalities, it has become the treatable one⁴⁻⁶. Mastectomy and chemotherapy have been proved to have better survival among breast cancer patients⁷.

There is a cross-linkage between the inflammatory process and the pathogenesis of cancer^{8,9}, inflammation being the seventh hallmark of cancer⁵. Serum CRP, interleukins and tumour necrosis factor- α ^{4,10} has a critical value as the prognostic biomarker¹¹. There is an increased association of CRP with breast cancer, especially in the post-menopausal group, due to differences in the site of estrogen production¹². The high level of serum CRP favours metastasis, recurrence and increased mortality rate¹³, as it is a good indicator of disease-free survival. In response to stress and surgery, there is an increased surge in catecholamine and prostaglandins during the perioperative period and suggested promoting tumour metastasis¹⁴ and bone metastasis believed to be the commonest site¹⁵.

Serum CRP (>10 mg/L) is considered a useful indicator of poor outcome independent of treatment in patients with metastatic breast cancer; its role in cancer prognosis is crucial, contributing to its clinical utility¹¹. The risk of cancer recurrence is highest among patients with raised inflammatory markers, including CRP, Interleukins-3, 6, and 8 (IL-3, IL-6, IL-8), and Tumor Necrosis Factor (TNF)- α ¹⁶. CRP was significantly raised among patients with metastatic breast cancer, and it has the worst prognosis for the overall survival of the patient^{17,18}. Despite being clean surgery, the post-mastectomy infection rates are observed at 3% and 15%¹⁹. The present study aimed to elucidate the role of C-reactive protein as an inflammatory prognostic predictor in breast cancer patients and its impact on disease-free survival (DFS).

Methodology

This prospective cohort was conducted from January 2018 to March 2020 at the Department of General Surgery (Unit II), Liaquat University Hospital Jamshoro/Hyderabad seeking treatment. A total of 80 consenting patients with locally advanced breast cancer (stage II and III - t2, t2, n1, n2, n3) and raised CRP levels were recruited via non-probability, consecutive sampling. While females presenting with stage I or IV cancer, proven metastatic disease, pregnant or lactating women and those who lost to follow-up were excluded from the study sample.

Patient data comprising of the demographic characteristics, breast cancer stage, hormonal status, pre-operative CRP levels, post-operative complications (wound infection, dehiscence, sepsis), and disease-free survival (DFS) were collected using a structured questionnaire. Patients were followed up for 2 years with the interval of 6 months to assess DFS concerning recurrence at the operated site, skin manifestation and metastasis.

Patient confidentiality was maintained, and the risk and benefits of the study were discussed in detail with the patient or their attendants before inclusion in the study. The collected data were analyzed using SPSS version 22.0, continuous variables were presented as mean \pm standard deviation, and categorical variables were given as frequencies and percentages.

Results

The enrolled patients were between 35-55 years of age, and the calculated mean age of the study sample was 39 ± 2.0 years. Of the total, 22 (27.5%) patients were diagnosed with stage II breast cancer, while 58 (72.5%) had stage III breast cancer. The hormone receptor status showed that out of 80 breast cancer cases, 17 were estrogen receptor (ER) positive, progesterone receptors (PR) positive in 6 cases, HER2 neu positive in 12 patients, both ER PR positive in 13 cases, triple positive in 15 cases and triple-negative in 17 cases.

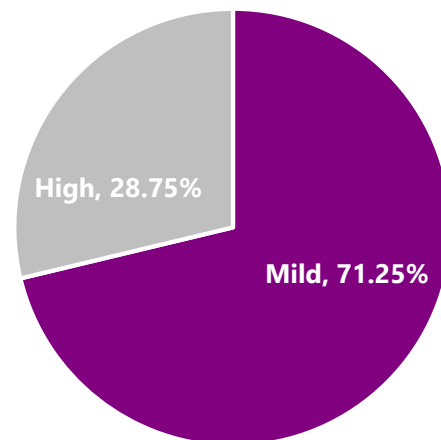


Figure 1: Pre-operative CRP status of the enrolled breast cancer patients.

The pre-operative raised CRP level were categorized as Mild (0.5-6.0 mg/dl) and High (6.1-12.0 mg/dl). Most of the study patients (71.25%) had a mild elevation in the serum CRP levels.

The post-operative complications noted among the study subjects are given in table 3. Of the total, 10% of patients were observed with a wound infection after surgery and recurrence was observed in 5% of patients.

Table 1: Post-operative outcomes among breast cancer patients.

Outcomes	n(%)	
Complications	Wound Infection	08(10)
	Wound Dehiscence	03(3.75)
	Sepsis	01(1.25)
Recurrence	04(5.0)	
Skin Manifestations	02(2.5)	

Disease-Free Survival was observed in 69 patients; 57 of them had mildly raised CRP levels while 23 were observed with highly raised CRP levels.

Discussion

Emerging evidence suggests that the raised levels of serum CRP are independently associated with an increased risk of breast cancer recurrence, relapse, and metastasis. Hence, it is used as the metastatic predictor in the healthcare settings²⁰. According to Livanainen et al., the raised CRP levels (> 10 mg/mL) indicated poor progression-free survival (PFS) ($p < 0.01$), and there was a significant difference between patients with $CRP \leq 10$ and $CRP > 10$ ²¹. Our findings are comparable to this; we observed poor survival in patients with raised CRP levels.

According to a meta-analysis, the CRP levels directly associate with breast cancer risk, i.e. increased CRP levels increase the risk of breast cancer²². Supporting the hypothesis, Pierce et al. conducted a study including 700 early stage breast cancer patients who had elevated CRP levels after treatment. Furthermore, they had reduced disease-free survival²³. A similar study reports reduced disease free survival and high mortality among the breast cancer subjects with elevated CRP levels at the time of breast cancer diagnosis²⁴. In the present study, 71.25% of patients had a mild elevation in

the serum CRP levels at the time of diagnosis, while 28.75% had highly raised serum CRP levels.

The patient's follow-up data showed that the complication rate wasn't very high; 10% had wound infections, 3.75% cases with wound dehiscence, and 1.25% had sepsis. Furthermore, recurrence was observed in only 5.0% of cases which is very low compared to the published literature. Disease-free survival was observed in 86.25% of the patients after 2 years of follow-up. In contrast, an Indian study reported the recurrence followed by death among 28% of breast cancer patients after surgery and disease-free survival in 76% of their patients after 1 year of follow-up¹³.

Conclusion

In conclusion, the present study indicates that the raised CRP level is a significant predictor for post-operative complications (wound infection, dehiscence, and sepsis) and disease-free survival among patients with locally advanced breast cancer.

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