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Comparison of Erythrocyte Sedimentation Rate and C-Reactive Protein levels between breast Cancer Patients

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Abstract:

Background: Inflammatory response plays an essential role in the initiation and progression of several cancers, including breast cancer. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are two inflammatory indicators that increase in many pathologic and physiologic conditions. The objectives of this study were to estimate and compare the levels of these inflammatory markers in breast cancer patients with those of apparently healthy subjects without the disease. **Methods:** This is a case study conducted at the National Cancer Institute, Sabratha Hospital and Medical Research Center in Zawiya, during 2019. The study population includes 80 subjects (30 healthy women and 50 confirmed breast cancer cases). The levels of ESR and CRP were investigated using standardized laboratory methods. **Results:** The obtained results showed that the ESR levels of the participants with breast cancer were highly significant compared to that of the controls, but there was no significant difference in levels of CRP. The levels of ESR in all stages of BC were statistically significant compared to control individuals. In contrast, no significant difference in CRP in BC patients with stage III and VI and in controls, despite the significant difference in levels of CRP noticed between BC patient with stage II and controls. There were no differences between the levels of ESR in patients with and without chronic diseases. The levels of CRP showed significant differences between patients with chronic diseases and controls. ESR levels remained elevated despite the course of BC treatment and the levels of CRP in patients, who had combination of chemotherapy and radiotherapy, were increased. In conclusion, this study suggests that ESR is significantly raised in breast cancer patients, whereas, there is no association between of CRP and breast cancer.

Keywords :Erythrocyte Sedimentation Rate, C-Reactive Protein, Breast Cancer

1. Introduction

Breast cancer (BC) is the most frequent kind of malignant disease in women and the main cause of cancer-associated death worldwide. The exact cause of BC is not completely known [1,2]. The etiologyof BC is multifactorial and includes both environmental and genetic factors, as well as genetic and epigenetic changes during progression. After diagnosing cancer, a stage is assigned to it, based on how advanced it is. Knowing the stage of breast cancer is an important factor in making decisions about BC treatment. Breast cancer stage is usually expressed as a number on a scale of 0 through IV[3]. Most women with breast cancer in stages I,

II, or III are treated with surgery, often followed by radiation therapy. Several women also get various types of drug therapy such as chemotherapy, hormone therapy and HER2 targeted drugs.

leukemia, colorectal cancer and prostate [12,13].

CRP is raised in circulation in acute inflammation, infection and tissue damage. CRP is a sensitive but nonspecific marker of acute and chronic inflammatory conditions like infections, rheumatoid arthritis, and chronic obstructive pulmonary disease. The concentration of CRP is raised in large amount in bacterial infection, it is also useful in differentiating between bacterial and viral infections [14].

Previous epidemiologic studies have reported that elevated CRP levels may be associated with a poor prognosis of several types of solid cancers, including endometrial, cervical, colorectal, pancreatic, hepatocellular, esophageal, renal cell, bladder, prostate, ovarian and non-small cell lung cancer [15-19]. Moreover, several studies reviewed association of CRP with breast cancer risk. However, not all studies have found a significant association between CRP and breast cancer risk[6-21].

Systemic inflammation is regarded as a crucial long-term prognostic factor for breast cancer.Elevated concentrations of inflammatory markersare associated with reduced survival among BC Patients[4-6]. Previousstudies reported that inflammatory pathways play an important role in BC progression[7,8]. Acute and chronic inflammation cause cytokines, mainly interleukin-6, to be released into the bloodstream. The liver responds to this by producing acute phase reactants. There are two methods in common use for detecting the acute phase response: the ESR and the more specific measurement of CRP concentration [9]. CRP and ESR are commonly increased in acute inflammatory disorders. Nevertheless, patterns of response are diverse for each test. CRP increases within hours of beginning of an infection or inflammatory disorder and returns to normal within 3-7 days if the acute process is resolved. ESR, in contrast, rises in a slower way and remains high for a longer period of time. ESR is a simple inexpensive index of measurement of inflammation frequently ordered in clinical medicine [10,11]. The test actually measures the rate of sedimentation of erythrocytes in a sample of blood that has been placed into a tall, thin, vertical tube. The erythrocytes settle at a faster rate in the presence of an increased level of proteins, particularly proteins called acute phase reactants as mentioned above. The level of acute phase reactants (such as CRP, haptoglobin, caeruloplasmin and fibrinogen) increases in the blood in response to inflammation. In cancer nagement, a high ESR level has been found to correlate with the prognosis of BC and other types of cancer such as

Hodgkin's disease, gastric carcinoma,

2. Materials and Methods

This is a case study conducted at the National Cancer Institute, Sabratha Hospital and Medical Research Center in Zawiya, over a 5 months period (20th march, 2019 to 21st august, 2019). The study was carried out on 50 females diagnosed with Breast Cancer (Case group) with stages I to IV and 30 apparently healthy women from Medical Research Centerof Zawiyaas Controls. The mean age of the patients was 53 years (Range40-85) and that of control was 45 years (Range 40-60). Demographic data related to age, family history of breast cancer, use of chemotherapy, radiotherapy, chronic disease, type ,stage of breast cancer and menopausal status were recorded through standard questionnaire.

TheBloodsamples were collected from participants after obtaining their consent to participate in the study. ESR levels were measured using a Westergren method and CRP was measured using Qualitative and Semi-Quantitative Agglutination Latex (Meridian Healthcare®).

2.1 Statistical analysis

renal cell carcinoma, chronic lymphocytic

Data in this study was analysed using Graph Pad Prism 5.01 software (Graph Pad software Inc). Results were viewed as statistically significant when the P value < 0.05.

3. Results

3.1 Patient characteristics:

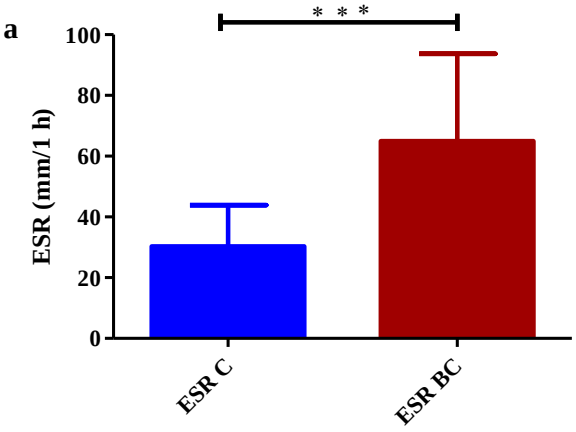
A total of 50 breast cancer and 30 healthy women were enrolled in this project. The mean age of all patients was 52 years (range:32-88), while that of the controls was 45 years (range:40-60).

Consistent with the results from other studies [6,20,22].we observed that the ESR level of the participants with breast cancer was highly significant compared to that of the controls (*P*< 0.0001; figure 1a). However, there was no significant difference in levels of CRP of the patients comparing to controls (P=0.1 figure 1b). In general, 4 patients (8%) had normal ESR levels, 46 (92%) had elevated ESR. Assessment of CRP showed that 37 (74%) had negative CRP results and 13 (26%) had positive CRP results (Table 1)

Table 1 Inflammatory marker levels

ESR	N	%
Normal level	4	8%
High (>25mm/h)	46	92%
CRP		
Normal level	37	74%
Low(< 0.5 mg/dL)	13	26%

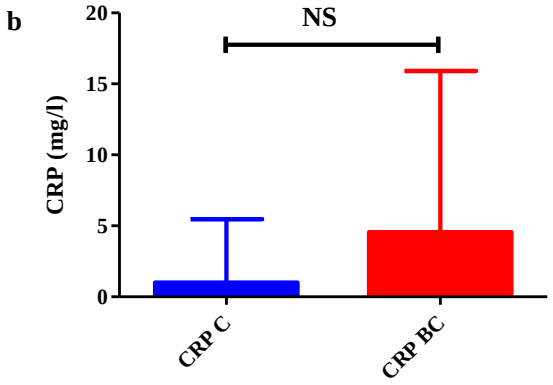
Figure.1 Bar graphs show the levels of ESR (a) and CRP (b) of BC patients comparing to control participants. Data expressed as mean, error bars



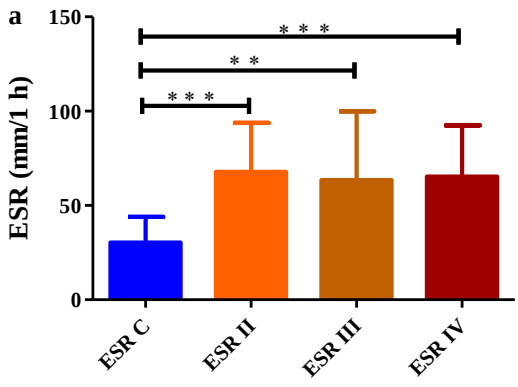
demonstrate SEM, ***=P<0.001.

3.2 Breast cancer stages and inflammatory markers levels

In this study, we estimated the levels of inflammatory markers in different stages of BC. Out of 50 cases of breast cancer, 1 was in stage I , 16 in stage II, 11 in stage III, and 22 in stage IV. The results demonstrated that the levels of ESR in all



stages were statistically significant (P=< 0.0001 in stage II and IV; P=0.0084 in stage III) compared to control individuals (figure 3.2 a). In contrast, the statistical analysis shows no significant difference in CRP in BC patients with stage II and IV than in controls, despite the significant difference in levels of CRP noticed between BC patient with stage III and controls (figure 2 b).



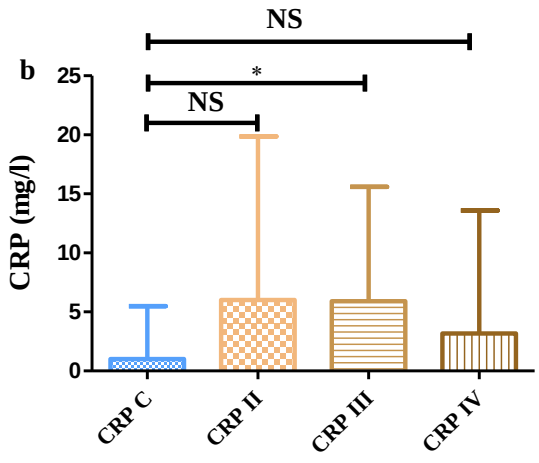


Figure 3.2 Comparison of levels of inflammatory (ESR & CRP) markers in different BC stages. Data expressed as mean, error bars demonstrate SEM, *= p< 0.05; **=p<0.01; ***=p<0.001

3.3 ESR and CRP levels in BC patients with and without chronic diseases

The data shows, 23 (46%) patients had chronic diseases, whereas 27 (54%) had no history of any chronic disease. Evaluation of serum inflammatory markers in patients illustrated high serum CRP and ESR. The levels of ESR observed highly significant differences between patients with and without chronic diseases and controls (P= < 0.000; figure 3a).The levels of CRP also showed significant differences between patients with chronic diseases and controls (P= 0.03; figure 3b).

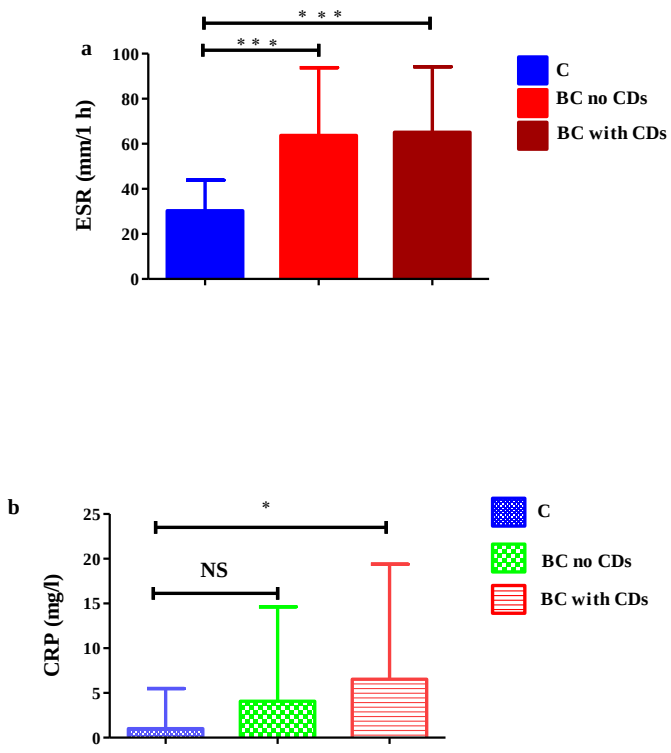


Figure .3 ESR and CRP levels in BC patients with and without chronic diseases.

3.4 Effect of cancer therapy on the levels of ESR and CRP

In this part of our study we sought to investigate the effect of BC therapy (which included chemotherapy only and/or in combination with radiotherapy) on levels of the inflammatory markers. Out of 50 cases of breast cancer, 11(22%) had chemotherapy only, 35 (70%) had combination of chemotherapy and radiotherapy, 1 (2%) had radiotherapy only and 3(6%) had no treatment. The results demonstrated that the levels of ESR in patients who had chemotherapy only, and in combination of chemotherapy and radiotherapy, were significantly higher (***=< 0.0002; ***=p<0.0001 respectively; figure 4a) than that of control individuals but there was no difference between the levels of ESR in patients who had chemotherapy only and the patients treated by combination of chemotherapy and radiotherapy. Figure .4b illustrates a significant difference in the levels of CRP in patients who treated with combination of chemotherapy and radiotherapy compared to control individuals (p<0.001; figure .4b). Nevertheless, the patients who had chemotherapy only showed negative

results for CRP.

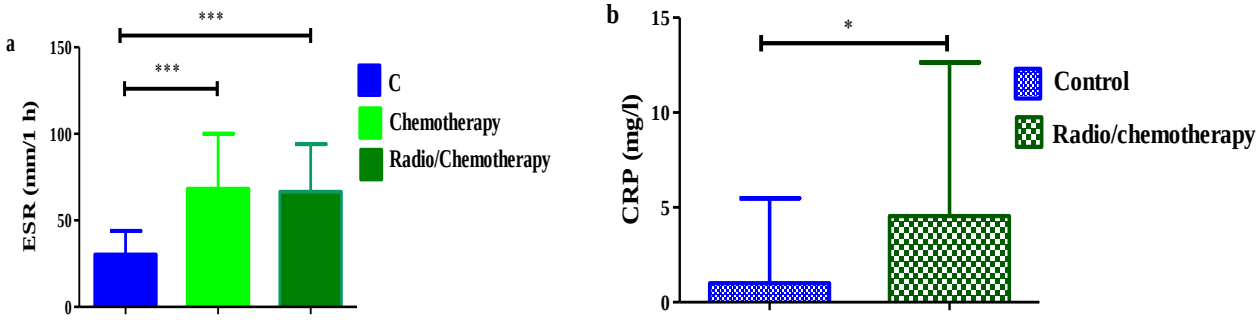


Figure .4 effect of BC therapy on levels of the inflammatory markers. patients . Data expressed as mean, error bars demonstrate SEM, ***= p< 0.001; **=p<0.01; *=p<0.05

4. Discussion

BC is defined as a malignant tumor beginning in the cells of the breast that may metastasize to distant parts of the body or invade nearby tissues. Inflammation and immune response may play an important role in the initiation and progression of several cancers, including breast cancer [2]. The ESR and CRP are two commonly ordered laboratory tests widely used as diagnostic tests for detecting inflammatory conditions that may be caused by infection, autoimmune disorders, malignancies, or tissue necrosis [23].

In the present study, our data enhances the earlier finding that the ESR levels of the participants with breast cancer were highly significant compared to that of the controls [24-25].Nevertheless, there was no significant difference in levels of CRP of the BC patients comparing to controls. The relations between elevated CRP and cancer risk have been described for many years, but the results from prospective cohort studies remain controversial. Results from previous prospective epidemiologic studies are conflicting, with several studies showing an association between raised CRP levels and poor prognosis and others showing no such association[22,24,25,6,20].

The ESR is widely used as a laboratory marker of systemic inflammation, while it is a non-specific parameter. It reflects the tendency of red blood cells to settle more rapidly in the face of some disease states, usually because of increases in plasma fibrinogen, immunoglobulins and other acute-phase reaction proteins. Changes in red cell shape or number may also affect the ESR. CRP is an acute-phase protein of hepatic origin produced under transcriptional control by the cytokine IL‑6 originating from the site of pathology [26].Due to the long half-life of some plasma proteins and perhaps a longer amplified response time, the ESR does not change rapidly at the beginning of the inflammatory process and normalizes more slowly than that of other acute phase reactants. The half-life of CRP is constant, so a raised level is generally determined by

the degree of production and, therefore, the severity of the precipitating cause. In the first day of a disease process, the ESR may be normal and CRP raised. The CRP will return to normal within a 24 hours or so, if the focus of inflammation is removed. The ESR will continue raised for several days until excess fibrinogen is removed from the serum [27].

Our results illustrate that high levels of ESR in all stages compared to control individuals. In contrast, the levels of CRP in BC patients with stage II and IV were higher than that in control, but the difference was not statistically significant, despite the significant difference in levels of CRP noticed between BC patient with stage III and controls. This indicates that the levels of some plasma proteins remained high during stages of BC whereas the level of CRP was increased only in stage III or because the presence of variation between samples in other stages.

A previous study by Shilpa*et al.*, 2014 has demonstrated that the serum hsCRP (High sensitivity CRP) levels were associated with advanced stage. In stage I, association of hsCRP was not significant with disease while in stage II and III there was significant association [28]. In stage IV patients with distant metastasis, serum hsCRP values were highly significantly raised compared to stage II and III. O'Hanlon DM *et al.*, 2002 reported that the level of CRP were significantly higher in patients with Stage IV disease compared with controls. The conflicting result between our data and these studies may be attributable to the methods used or the health status of participant[29]..

Several chronic disorders and breast cancer share common risk factors (e.g. excessive alcohol consumption, obesity and physical inactivity). The greater incidence of chronic disorders may reflect greater awareness and increased health care use associated with the treatment of BC. Cancer treatment may also contribute to developing chronic disorders [30]. Diabetes has been recognized as a major factor contributing to the development of solid organ cancers, such as liver, pancreatic, colorectal, breast, endometrial, uterine and bladder cancers [31].In this study we evaluated the levels of serum inflammatory markers in BC patients with some chronic diseases. The results observed that no differences between the levels of ESR in patients with and without chronic diseases. The levels of CRP also showed no significant differences between patients with chronic and without chronic diseases but there was significant differences in the levels of CRP between patients with chronic diseases and controls. Previous study carried out by Jeong H *et al.*,2019 proposed that plasma CRP was associated with an increased risk of chronic disease in the general population. Anotherstudy by Kirsten Erickson *et al*indicated that chronic hyperglycemia is statistically significantly associated with reduced overall survival in patients of early-stage BC[32,33].

In the last part of this study, we investigated the effect of BC therapy (which included chemotherapy only and/or in combination with radiotherapy) on levels of the ESR and CRP. The results show that the levels of ESR were remained elevated despite the course of treatment. Furthermore, there was no difference

between the levels of ESR in patients who had chemotherapy only and the patients treated by combination of chemotherapy and radiotherapy. The data showed that the levels of CRP in patients who had combination of chemotherapy and radiotherapywere significantly higher compared to control individuals, but the patients who had chemotherapy only showed negative results for CRP (the data is not shown). These results suggest that chemotherapy and radiotherapy may stimulate the production of CRP. Previous studies have shown that irradiation increases immune/inflammatory responses [34,35].

Conclusion

In summary, our results indicatedthat the ESR levels of the participants with breast cancer were highly significant compared to that of the controls, but there was no significant difference in levels of CRP of the patients compared to controls. Combined with previous research, further investigations with a longer follow-up are to be performed to find out whether CRP, as a marker of inflammation, plays a direct role in breast carcinogenesis.

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