

Review Article

Study of Some biochemical markers associated with prognosis of Breast cancer in Iraqi women

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Background

The prediction of treatment outcome in patients with advanced breast cancer remains a challenge. Even within the same stage, survival and response vary, so the goal of this study was to evaluate the prognostic value of systemic inflammatory markers available in the general laboratory including: C-reactive protein, D-dimer, Procalcitonin and Erythrocyte sedimentation rate in patients with breast cancer.

Methods:

Retrospective cohort study carried out between January 1, 2022 and May 31, 2023 with a total of 98 patients with different stages of breast cancer. From which the levels of the inflammatory markers C-reactive protein, D-dimer, Procalcitonin and Erythrocyte sedimentation rate were obtained prior to the first line of chemotherapy, the study evaluates the correlation of basal levels and their variation with the response to treatment, the value of CRP and ESR in prognosis was also assessed.

Results:

Ninghty eight patients with a mean age of 55 years ($SD \pm 12$) were included; 70% were women, 83% had adenocarcinoma, 47% had more than two organs involved by metastasis and 89% had an $IK > 70\%$. At the start of chemotherapy, 52%, 43%, 53% and 34% had abnormal levels of PC, DD, ESR and CRP, respectively. Patients with low ESR ($p = 0.004$), high DD ($p = 0.012$) and abnormal CRP ($p = 0.040$) had a worse overall response rate to first line chemotherapy.

Conclusions: CRP and Procalcitonin levels are independent prognostic factors for survival in patients with advanced breast cancer receiving chemotherapy

Introduction:

The future of breast cancer depends on genetic identity and finding the reason for this genetic alteration. Diagnosis and decision making are currently based on histopathology and immunohistochemistry. Recently, several predictive and prognostic tools have been developed that use the information and technology obtained from the Human Genome Project, and are useful for predicting the recurrence of early-stage breast cancer, and anticipating the benefits of chemotherapy in those patients (1). Several biochemical parameters can provide predictive and prognostic information about the tumor and its potential behavior. Most predictive and prognostic techniques are based on the analysis of the level of biochemical parameters responsible for tumor cells. C-reactive protein (CRP)

levels increase in response to acute inflammation, infection, and tissue damage. There are also reports that CRP levels are elevated due to cancer. C-reactive protein is produced by the liver, in response to infection or injury, when stimulated by the cytokine IL-6. Tumor sites are often associated with inflammation and this inflammation contributes to tumor growth, invasion, and metastasis (2).

Materials and methods:

Patients with a recent diagnosis of breast cancer a single cancer center with stage I/IV were included from January 1, 2023 to May 13, 2023, at the time of diagnosis from Warith International Cancer Institut/ Kerbala city , they were graded according to the Nottingham criteria for breast cancer (7), the histological type was established, and functional status according to the ECOG scale (Eastern Cooperative Oncology Group) (8). They were obtained demographic identification data, age, sex, and the values of CRP, Erythrocyte sedimentation rate, Calcitonin and D-dimer were recorded by using turbidimetric assays.

An Immunochemical method was used to measure CRP. In accordance with CRP, ESR and D-dimer values were classified patients in

The elevated CRP has been found to be associated with an unfavorable outcome for many solid tumors, including endometrial, cervical, prostate, and colorectal cancer, whether this is true for breast cancer has been debated (3). Researchers from Denmark analyzed data from more than 2,000 breast cancer patients and followed their progress for up to seven years from diagnosis; the average follow-up

was three years (4). The researchers found that regardless of lifestyle, menopausal status, and the presence of cardiovascular disease, increasing CRP levels resulted in an increasingly unfavorable prognosis (5). An elevated of CRP at diagnosis remained predictive of overall survival rates regardless of patient age, tumor size, lymph node status or presence of metastases, and whether or not the patient was estrogen receptor positive. It remained true even when we excluded patients who we believed had bacterial infections because of their very high CRP levels (6). While measuring CRP levels offers a general indication of health and longevity, measuring CRP levels in breast cancer patients

appears to be an easy way to predict disease severity; the aim of study was to determine some biochemical markers responsible for occurrence of breast cancer in Iraqi women.

three groups. They all received management with platinum-based chemotherapy or targeted therapy

according to the presence of sensitive mutations. The description of the categorical variables was made in terms of the absolute frequency distribution. The estimates of survival were performed using the model parametric product limit (Kaplan Meier method), their differences were evaluated through a log-rank test, The Kaplan-Meier estimate is a straightforward method used to calculate survival probabilities over time, even when dealing with challenging subjects or situations. It involves determining the survival probability for each time interval by dividing the number of surviving subjects by the number of patients at risk during that interval (9). A multivariate analysis was carried out using the proportional hazard

model (Cox), to estimate the predictive ability of the PI. The baseline potential prognostic factors included in the model were: age, sex, CRP, Calcitonin, D-dimer, weight loss, tobacco consumption (smokers and ex-

Statistical analysis

All the Statistical analyzes were performed using the package SPSS software (SPSS,

Results

Ninety-eight patients diagnosed between the 1st January 2023 and May 31, 2023. The middle age of the study subjects was 55 years old (SD ± 12), of the which, women represented 70% of the cases. 64% of patients did not have weight loss >10% in the previous six months. The Karnofsky index (KI) was greater than 70% in 88 patients, the index is represented as a numerical scale ranging from 0 to 100, with higher scores indicating better functional ability and overall health. It is commonly used in clinical settings,

smokers vs. non-smokers), the likelihood ratio was used to test the contribution of each variable to the model when the last one is added.

Chicago, IL, USA). All The tests were two-tailed and the statistical significance was accepted at p values of 0.05 or less.

particularly in oncology, to evaluate and communicate a patient's performance status and their ability to carry out daily activities (10), Tobacco consumption (current or previous) was referred by 53% of the cases. The main diagnosis was adenocarcinoma present in 83% of cases, followed by Ductal Carcinoma with 14% . 47% of patients had more than two types involved by metastasis, being bone lesions the most frequent (43%), followed by pleural/pulmonary and nervous system lesions central (35% and 30%, respectively) table (1).

Table (1): No.(%) of patient have breast cancer with some variables

Variables	No.	Percentage	
Age, average 55 (+/- 12.2)	< 70% K.I.	10	10.2
	> 70% K.I.	88	89.8
Weight loss > 10% in the previous six months	No	24	24.5
	Yes	63	64.3
	NA	11	11.2
Histology	adenocarcinoma	82	83.7
	Ductal carcinoma	16	16.3
Tobacco use	Yes	36	36.7
	No	62	63.3
Number of metastasis sites (at diagnosis)	1	52	53.2
	2	34	34.7
	3	6	6.1
	4	6	6.1
Bone metastases	Yes	42	42.9
	No	56	57.1
Liver metastases	Yes	7	7.1
	No	91	92.9

K.I. : Karnofsky index; NA: not applicable

The different serum markers used in the study are summarized in table 2. At the beginning of the chemotherapy, 34% of patients showed

levels high ESR defined as more than 30 mm/hr. and 46%, abnormal CRP levels > 3 mg/dl

Table (2): No. (%) of some serum markers in breast cancer patients

Serum markers	No.	Percentage	
CRP (mg/l)	< 1	24	24.5
	1-3	18	18.4
	> 3	56	57.1
ESR	Less than 30 mm/hr	29	29.8
	More than 30 mm/hr	69	70.2
Procalcitonin (mg/ml)	< 40 mg/dl	37	37.8
	> 40 mg/dl	61	62.2
	NA	11	11.2
D-dimer (mg/L FEU)	Normal	39	39.8
	Abnormal	52	60.2

E.S.R : erythrocyte sedimentation rate

Patients with low AS ($p = 0.004$), high DD ($p = 0.012$) and abnormal CRP ($p = 0.040$) had a lower overall survival. In the bivariate analysis, the elevation of CRP (HR 1.67; 95%

CI: 1.28-2.69; $p = 0.008$) and DD (HR 2.56, 95% CI: 1.05-3.04, $p = 0.006$) were factors associated with bone and liver metastasis.

Discussion

Breast cancer can potentially spread to various parts of the body through a process known as metastasis; It's important to note that not all breast cancers will metastasize, and the likelihood of metastasis can vary depending on various factors, including the stage and characteristics of the tumor. The study found 53.2% of Iraqi women had infected with metastasis I, followed by 34.7 Metastasis type 2 Regular follow-up appointments and surveillance imaging are important for detecting and monitoring the spread of breast cancer. Treatment options for metastatic breast cancer focus on controlling the disease, relieving symptoms, and improving quality of life (11).

C-reactive protein (CRP) is an acute-phase protein that is produced by the liver in response to inflammation in the body. It is often used as a marker of inflammation and infection. While CRP levels can be elevated in various conditions, including infections,

autoimmune disorders, and cardiovascular diseases, its role in breast cancer is not as well-established (10). Some of studies have suggested that elevated CRP levels may be associated with an increased risk of developing breast cancer, as well as poorer prognosis and outcomes in individuals with breast cancer.

The incidence of breast cancer can vary based on various factors, including age, gender, geographic location, ethnicity, and socioeconomic status. It is influenced by both genetic and environmental factors, as well as lifestyle choices and hormonal factors (9). However, it's important to note that CRP is not specific to breast cancer and can be influenced by various factors, including age, gender, body mass index, and other comorbidities (12).

Several studies have investigated the relationship between CRP and breast cancer. Some have suggested that elevated CRP levels may be associated with an increased

risk of developing breast cancer (13), while others have found no significant association. Additionally, elevated CRP levels have been associated

with larger tumor size, lymph node involvement, and advanced stages of breast cancer, indicating a potential link between inflammation and tumor progression (14). It's worth mentioning that CRP is not used as a routine diagnostic tool for breast cancer. The primary methods for diagnosing breast cancer include mammography, ultrasound, and biopsy.

While CRP may have some associations with breast cancer, it is not a specific or sensitive marker for the disease. Other biomarkers, such as estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2), are commonly used for breast cancer diagnosis, prognosis, and treatment decisions (15).

Table (1) showed Chronic inflammation has been implicated in the development and progression of various types of cancer, including breast cancer. Inflammatory processes can promote tumor growth, invasion, and metastasis. CRP, as an acute-phase reactant, is an indicator of systemic inflammation.

Our result was found increased in the ESR levels in patient as 70.2% in patients with breast cancer more than 30 mm/hr; The erythrocyte sedimentation rate (ESR) is a measurement of how quickly red blood cells sink to the bottom of a tube over a given time frame. It is a popular screening tool for a wide range of diseases since it is a non-specific indicator of systemic inflammation, an elevated ESR levels are not substantially impacted by breast cancer (16). Nevertheless, additional variables linked to breast cancer or

its treatment can impact ESR. An increased ESR may be the result of an inflammatory condition, such as a breast infection or inflammation. Furthermore, elevated ESR levels can be a side effect of radiation therapy and some forms of chemotherapy used to treat breast cancer (17).

Procalcitonin levels are typically low in healthy individuals but can significantly increase in response to bacterial infections, particularly severe systemic infections. While procalcitonin is not typically associated with breast cancer, it may have some relevance in specific contexts related to breast cancer treatment and complications (18).

The study found increased in the marker D-dimer in patient as 62% more 0.50 mg/l FEU than normal D-Dimer patient; D-dimer is a tiny protein fragment formed when a blood clot breaks down in the body, it is frequently employed as a diagnostic marker for different medical disorders, including the presence of blood clots and certain kinds of cancer (19). On the other hand, one of the most causes of D-Dimer play important in breast cancer is the risk of venous thromboembolism (VTE), a disorder characterized by the formation of blood clots, is increased in cancer patients. This can happen for a number of reasons, including when tumors release chemicals that promote blood clotting or as a side effect of chemotherapy (20). Elevated D-dimer levels can be caused by blood clots associated with breast cancer, even though the illness itself may not directly cause them. Breast cancer treatment-related variables that might increase D-dimer levels include surgery, immobilization, and the use of specific drugs (21,22).

undergo chemotherapy. Additionally, other biomarkers such as D-dimer (DD) and erythrocyte sedimentation rate (ESR) have been considered as well

Conclusion

The levels of C-reactive protein (CRP) and procalcitonin (PC) have been identified as separate prognostic indicators for the survival of patients with advanced breast cancer who

Recommendations

Healthcare providers should consider regularly monitoring CRP and PC levels in

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