

ESTROGEN AND PROGESTERONE HORMONE RECEPTORS FOR BREAST CANCER TREATMENT

Ali. M. Alremalli ✉ Ali 23312ramliee@gmail.com

Nabiha Elhadi Etumi ✉ Nabiha49.ly@gmail.com

Department of Medical Laboratory, College of Sciences and Medical Technology, Tripoli, Libya , December 2023.

Abstract:

Background: Breast cancer is a heterogeneous and hormone-dependent disease. Screening for the estrogen receptor (ER) and progesterone receptor (PgR) is critical for prognosis assessment and treatment selection for breast cancer for clinical practice. The purpose of this study was to evaluate the expression and distribution of hormonal receptors and their association with clinical diagnostic criteria to improve the treatment of patients in Libya.

Methods: A total study included 114 Libyan female breast carcinoma. who were diagnosed between January 2020 to July 2022 in the hospital medical laboratory in Tripoli. Where it, the paraffin-embedded blocks of these patients were examined by immunohistochemistry to assess ER and PgR status. Microsoft Excel was used to analyze the data.

Results:

Mean age of the cases was 45 years ranging from women 54.4% cases had positive history of breast cancers in first degree, were as patients more than years old. Out of 114 Libyan female breast carcinoma, 45 patient have right side, while left side detected in 69 cases, more over from recorded breast carcinoma there were 9

patient in the 1st stage breast carcinoma, 73 patients in the 2ed stage, 31 patients in the 3th stage breast carcinoma. Out of 114 patients, 28 patients have metastatic breast carcinoma, while 86 patient of them were not. The ER+PgR+ group was dominant with 86(75%) cases, followed by 28(24.6%) ER-PgR-. As for progressed diseases 13 cases (11.4%).

Conclusion:

The ER+PgR+ and ER-PgR- are the most common subgroups in women with breast cancer in Libya. The hormonal receptor status is associated with the age and the histologic grade in breast cancer patients. The systematic use of hormonal treatment should be reevaluated. A further study should be done to investigate the reasons of high rate of ER- PgR- in breast cancer patients in Libya.

Keywords: Breast cancer, Estrogen receptor (ER), Progesterone receptor (PR), hormonal receptor (HR), Immunohistochemistry, Clinicopathologic factors, Libyan female breast carcinoma.

Introduction:

Breast cancer is the most frequent malignant tumor and the most common cause of cancer-related death among women in the developed countries. Breast cancer is increasing in the developing countries, including Libya, where it ranks at the first cancer in women after cervical cancer. Breast cancer is a hormone-dependent disease, and thus, resulting from the mitogenic effects of estrogen and progesterone. ⁽¹⁾ Steroid hormones and their receptors play multiple roles in the regulation of biological functions, including sex organ development, pregnancy, bone density, cholesterol mobilization, brain function, cardiovascular system, and more. ⁽¹⁻⁵⁾

They play an important role in breast cancer development and progression. Almost 70% of breast cancers are hormone receptor-positive. ⁽⁶⁾ Their cells have positive expression of ER and/or PR, which are related to cancer cell growth and spread. Estrogen and its receptor, ER, play a critical role in the development and progression of breast cancer. ⁽⁷⁾ PR is an upregulated target gene of ER, its expression is dependent on estrogen, and PR can modulate ER action. ⁽⁸⁾ PR is also a valuable prognostic biomarker of overall survival or disease-free survival (DFS) in breast cancer.

The positivity of the ER is generally more than 70% in women with breast cancer than that of PgR, 50%. ⁽⁹⁾ The ER/PgR status is essential for clinical and therapeutic care of the breast cancer patients. The ER has well-established prognostic and predictive values, while the PgR has a

controversial additional predictive value. The presence or not of ER and PgR helps determine a possible relapse of breast cancer. The hormonal receptor status allows to distinguish four subgroups of breast cancers: ER+PgR+, ER.

ER+PgR-, ER-PgR+, and ER-PgR-. This classification helps to decide hormonal treatment for ER/PgR positive patients and chemotherapy for the ER/PgR negative patients. Although the immunohistochemical evaluation of ER and PgR is a routine clinical practice in the diagnosis and treatment of breast cancer management worldwide, the clinical utility of ER and PgR testing in breast cancer is currently performed since June 2013 in Libya

The current research is essential to update the immunohistochemical activity of ER/PgR in primary breast cancers. Herein, the aim of this study was to evaluate the expression of ER and PgR, their distribution, and their correlation with classic clinicopathologic prognostic parameters (age, breast feeding, family history, anatomical site, grade, metastasis, ER&PR Receptor) to enhance the breast cancer patient's medical care. ⁽¹⁰⁻¹⁵⁾ Signal transducer and activator of transcription 1 (STAT1) appears to be directly involved in the step of recognize and destroy developing tumors, ⁽¹⁷⁾ PR can down regulate the STAT1 mediated interferon-alpha signal to escape innate immune surveillance by phosphorylation of STAT1. ⁽¹⁸⁾ PR exists as two predominant isoforms, PR-A and PR-B, which are transcribed from the same gene located on 11q22-q23 by two distinct promoters and exhibit different transcriptional and biological activities as ligand-activated transcription factors. ^(19,20) In this study, will

contribute to classify patients into different subgroups based on their hormonal receptor status in order to determine the better treatment strategies for women with breast cancer in Libya.

Materials and Methods:

Study Site and Design :

This retrospective study reviews the medical records of the oncology department of the Tripoli Central Hospital located in Tripoli and considered one of the major hospitals in Libya.

Patients were screened at first admission by specialist physicians. This included demographic information for the examination, age and medical history, as well as the location of breast cancer, the extent of disease progression, the stage of breast cancer, and data on the hormones progesterone and estrogen and their receptors.

Sample size and study population:

The sample size was determined from patients who underwent breast tumor surgery in the Oncology Department of Tripoli Central Hospital, from January 2020 to July 2022. The sample size was 114 patients who underwent complete or partial mastectomy and part of them took a breast sample.

Tumor sample :

All tumor specimens were samples from either a complete mastectomy or a partial mastectomy or a biopsy of the breast. The tumor sample was routinely fixed in 10% buffered formalin and embedded in paraffin. Paraffin blocks were cut into sections with a thickness of 4 μm . The histological diagnosis was confirmed by review of the original section

stained with hematoxylin and eosin (H&E) by histopathologists. The tumor was reclassified and classified according to the current WHO classification ⁽¹⁶⁾. Microscopic venous invasion (MVI), sarcomatoid characteristics, tumor necrosis, and cystic structure were also evaluated.

Multiple tissue blocks:

The tumor region most representative of a BCC tumor was identified and labeled on an H&E STAINED section. Selected regions were perforated from the original blocks and re-stained into multi-tissue blocks. A 4 µm thick section was cut from these embedded paraffin blocks and mounted on pre-coated slides (microarray technology version, TMA).

Staining assessment of ER/PgR

The visual analysis through the optic microscope allowed to evaluate the staining intensity (weak, moderate, intense) and the percentage of tumor cells showing a nuclear immunostaining for ER and PgR (range: 0- 100%). Breast tissue sections were considered positive for the ER and PgR if $\geq 1\%$ of tumor cells displayed a positive nuclear staining in accordance with the recommendations of the American Society of Clinical Oncology/College of American Pathologist. The immunostaining intensity and the percentages of stained cells for ER and PgR were reviewed independently by two pathologists. For the purpose of this study, the percentages of tumor cell nuclei positively stained for ER and PgR were considered.

Statistical analysis Data :

was collected in an Excel database from Windows 8. The difference between subgroups based on ER/PgR status and mean age was evaluated by way analysis of variance. The Chi-Square test was used to analyze associations between classical clinicopathological parameters (menopausal status, histological type, and tumor grade) and combined ER/PgR status. Data were reported as frequencies for disease history, histologic type, tumor grade, and ER/PgR status and as frequencies for age of patients.

Results:

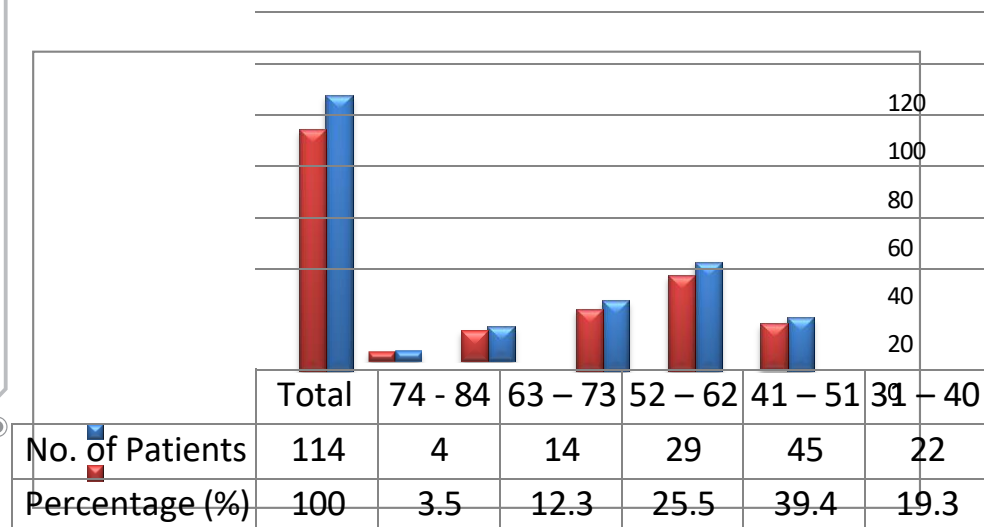
Data for a total of 114 female Libyan patients with breast cancer, diagnosed at hospital medical laboratory in Tripoli. Were collected their age, breast feeding, family history, anatomical site, grade of cancer and receptor status. The results of the study analysis are summarized in Table 1.

Table 1: Characteristics of the study Sample

Variables	Total (N)	Percentage(%)
Age Group (years)		
31 – 40	22	19.3 %
41 – 51	45	39.4 %
52 – 62	29	25.5 %
63 – 73	14	12.3 %
74 - 84	4	3.5 %
Breast Feeding		
Yes	64	56.1 %
No	50	43.9 %
Family History		
Yes	45	56.1 %
No	69	43.9 %
Anatomical site		

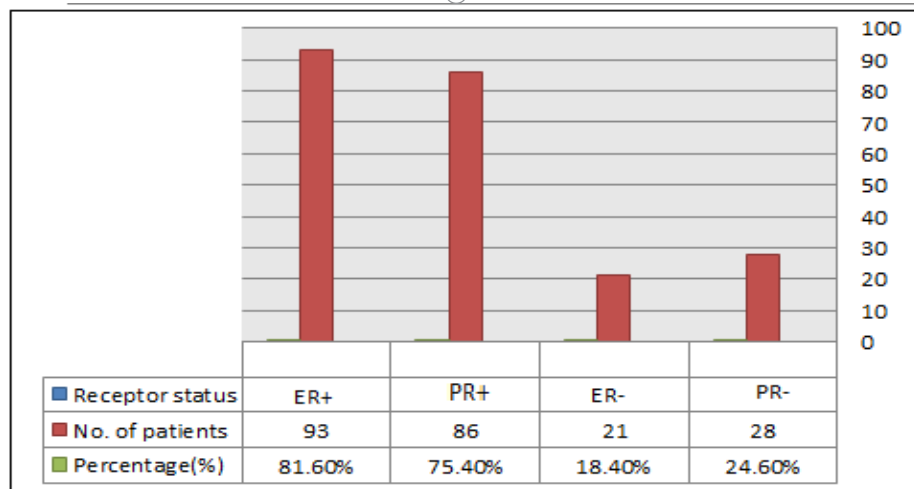
Variables	Total (N)	Percentage(%)
Left	62	54.4 %
Right	52	45.6 %
Grade		
Grade I	9	7.9 %
Grade II	73	64.01 %
Grade III	31	27.2 %
Receptor status		
Estrogen receptor status		
Positive	93	81.6 %
Negative	21	18.4 %
Progesterone receptor status		
Positive	86	75.4 %
Negative	28	24.6 %
Total	114	100 %

The mean age of the participants was 37.82 years $\pm$ 17.428 SD (range: 31-84 years). The average age of the cases was 45 years. The ages of the cases were divided into five age groups. The largest number of cases was in the age group (41-51), 39.4%, as shows in Graph 1.



Graph (1) Shows the relationship between Age distribution, Number of patients and its percentage in 114 Libyan female breast carcinoma.

Out of 114 Libyan female breast carcinoma, the rate of women who breastfeeding during their lifetime was 64 cases (65.1%), the rate of women with a history of breast cancer was 45 cases (39.5%), 52 cases have right breast (45.6%), while left breast detected in 62 cases with (54.45%). More over from recorded breast carcinoma there were 9 patient in the 1st stage breast carcinoma, 73 patients in the 2ed stage, and 31 patients in the 3th stage breast carcinoma, as shows in (Table 1). The ER+PgR+ group was dominant with 86 cases (75%), followed by 28 (24.6%) ER-PgR-. As for progressed diseases 13 cases (11.4% as shows in (Graph 2).



Graph (2) Shows the relationship between Number of patients,its percentage and estrogen and progestrone receptor status in 114 Libyan female breast carcinoma.

Discussion:

For decades, samples of Libyan female breast carcinoma diagnosed with invasive breast carcinomas were sent to laboratories equipped with immunohistochemical techniques in the developed countries for ER and PgR examination.

This study aimed at determining the hormonal receptor status to better characterize breast cancer subtypes and to assess the association of the hormonal receptor with age, menopausal status, histologic type, and tumor grade. In the present study, several significant observations have been identified.

The mean age of all patients at the diagnostic was 48 years, indicating that breast cancer appears early. This finding is similar to several studies conducted in Africa ^(16,19-22) and in the Middle East ⁽²³⁾. However, the mean age of our patients is different from that of the developed countries ^(2,6,24), where breast cancer

commonly occurs at the advanced age or at the postmenopausal period. The early occurrence of breast cancer in women in Libya could be due to the relative short life expectancy (45 years), the multiparity, and the early age at first childbirth, found that the multiparity increased the risk of breast cancer before 45 years in a study in Zimbabwe ⁽²⁵⁾. Moreover, the multiparity^(26,27) and the early age at first childbirth⁽²⁸⁾ were the main risk factors for breast cancer in black American women .

These results are in agreement with data of other studies^(7,29), suggesting that clinical prognostic factors of breast cancer are worse in the African women, including Ivorian women. In contrast, the histologic type and the tumor grade have insufficient prognostic and predictive implications with limited clinical utility⁽³⁰⁾. Therefore, it is valuable to detect ER and PgR status immunohistochemically in the current study to evaluate the survival of patients and to select their treatment.

The proportion of patients expressing ER is superior to those of PgR+. The same finding was reported by different authors in Europe, ^(29,31,32), in the USA^(7,8), and in Africa^(21,33). In addition, ER+PgR+ and ERPgR- were the most frequent subtypes in the current study. Our remarks corroborate with results of several studies^(18, 13, 27, 33), suggesting that ER+PgR+ patients should be considered for hormonal therapy, and ERPgR- patients should benefit from chemotherapy. Previously, a large number of breast cancer women underwent a systematic hormonal treatment in a blind manner in Libya.

However, 38% of the study patients may not suitable for hormonal therapy, tamoxifen, since they do not express ER and

PgR. As a result, they will not benefit from hormonal therapy, and the chemotherapy remains the only systematic treatment^(33, 34, 35).

Conclusion:

ER+PgR+ and ER-PgR- are the most common subtypes. Hormone receptor status correlates with age and tumor grade in breast cancer patients. Taken together, the results of this study help eliminate the regular use of hormone therapy. The increased proportion of ER-PgR- patients should be carefully considered in a future study. The ER/PgR status is no longer sufficient for the treatment of breast cancer patients in Libya.

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