Prognostic impact of hormone and HER2 status on the prognosis of breast cancer in Mosul

Alya A. Al Zobair ¹, Bassam I. Jasim ², Barrak F. Al Obeidy³, Nazar M. T. Jawher⁴.

¹College of Medicine, Mosul University, Mosul, Iraq
²College of Medicine, Nineveh University, Mosul, Iraq
³Department of Molecular Genetics, Ibn Altheer Teaching Hospital/Iraq.
⁴Department of pathology, College of Medicine, Nineveh University/Iraq.

Corresponding Author
Alya A. Al Zobair
College of Medicine, Mosul University, Mosul, Iraq
Mosul Oncology Hospital
alyaa7azizz@gmail.com
Phone: 009647737112114
Postal address: Mosul University, College of Medicine, Mosul, Iraq.

Abstract
Currant molecular classification of breast cancer based on Estrogen receptor (ER), Progesterone receptor (PR) and HER2 for gene expression is widely used for determining treatment approach for patients with breast cancer, our aims were to discover whether the molecular classification of breast cancer provides more information regarding survival compared to conventional histopathological prognostic factors. In this study we analyze the prognostic impact of ER, PR and HER2 expression using immunohistochemical study in breast cancer patients (n=152) independently and combined to gather. Survival analysis was done using Kaplan-Meier and Cox proportional hazards models adjusting for patient age, stage of the breast cancer. Molecular classification of breast cancer based on the pattern of expression of ER, PR, and HER2 was done. ER+/PR+/HER2 – a subtype of breast cancer was found in 40.7% of cases, ER+/PR+/HER2 + was observed in 28% of the cases, ER-/PR-/HER+ was found in 12.5% and finally, triple-negative subtype was found in 17.7% of the cases. Our result demonstrated that patients with different expressions of ER, PR, and HER2 have a different clinical outcome with different responses to treatment. Patients with ER+/PR+/HER2 – tumor have a favorable prognosis while patients with triple-negative tumors have the worst prognosis. Therefore, we recommend using this molecular classification in all patients with breast cancer for selecting the appropriate treatment approach.

Key words: Estrogen receptor, HER2, Breast cancer, Molecular classification, Mosul


Introduction
The cancer burden is increasing in the world including Eastern Mediterranean region EMR (¹). Breast and lung cancers are the most common (exclude non-melanoma skin cancer) cancers in the world (²). According to WHO there is an annual increase of breast cancer from 1% to 5% in EMR (³). In Nineveh Province and according to Mosul cancer registry, the most common cancer is carcinoma of the breast (⁴).

Histopathological properties of breast cancer, personal properties of the patient and preferences of chemotherapy regimens were used previously in predicting the recurrence rate of the disease. Estrogen receptor (ER) positive breast cancers comprise 80% of all breast cancer and it is a practical indicator of normal breast development in addition to the progress of cancer, moreover, ER positivity would predict response to endocrine therapy, while Progesterone receptor (PR) has a weak predictive value (⁵). It has been found that combined positivity of ER/PR breast cancer has improved disease-free survival compared to similarly staged patients with ER/PR negative tumors at 5 years, but this difference is less apparent at 10 years (⁶).

HER2 is an oncogene located on chromosome 17q. It is a part of the epidermal growth factor family along with 3 other EGR receptors (HER1, HER2, HER3, and HER4). It is also named NEU2 & ERBB2. Normally HER2
receptors help control the growth and division of breast cells. HER2 was found to be overexpressed in 20-30% of breast cancer and it is associated with more aggressive disease, higher recurrence rate, and increased mortality and this poor prognostic effect is independent of other factors like tumor size, age, and others. At the same time, there are many antiHER2 immunotherapeutic agents that were developed for the treatment of metastatic and early breast cancer and have led to improved survival and decreased relapse rates (7).

Immunohistochemical assessment of ER, PR, and HER2 markers is widely used along with histopathological grading and staging in determining the therapeutic approach in the treatment of breast cancer patients (6, 7). In this study, we identified breast cancers with (or without) this receptor and followed their impact on recurrence and survival in Nineveh province and its nearby regions to discover whether the molecular classification of breast cancer provides more information regarding survival compared to conventional histopathological prognostic factors.

**Patients and Method**

This prospective follow up study was conducted on women who were diagnosed with primary breast cancer at Mosul Oncology hospital in 2013, 393 new cases were diagnosed with breast cancer in Mosul Oncology Hospital in this year, according to cancer registry in Iraq (8). We prospectively followed up those patients tell July 2019. The criteria of inclusion in this study were Patients who (1) had invasive breast cancer (2) had undergone breast-conserving surgery or mastectomy; (3) had no severe concomitant diseases; (4) had complete immunohistochemistry result for ER, PR, and HER2 and (5) follow up period more than 59 months. Only 152 patients were included in this study because of the migration and unstable condition of Mosul city before and during the ISIS invasion.

The American Joint Committee on Cancer (AJCC) pathologic tumor-node-metastasis (TNM) classification of Breast tumors was used for tumor staging (9) and the patients were treated according to the international guidelines (10). This study was conducted in conformity to the Helsinki Declaration and was approved by the Ethics Committee of Mosul Medical College and Nineveh ministry of the health office. Clinical features and patients characteristics including, age of the patient, stage of the disease, tumor characteristics (grade, lymph node status, tumor size, and histology), treatment type and evidence of recurrence were obtained from hospital records.

Patients follow up were carried out on an outpatient basis, at three months interval in the first five years and then annually. The follow-up evaluation consisted of clinical interrogation and annual mammography. Further evaluation including a blood test for serum calcium, Alkaline phosphatase, tumor marker, CT scan of the chest and abdomen and bone scan were done when any clinical evidence of recurrence or metastasis were suggested. Patients on Tamoxifen have referred annually for gynecological assessment and patients on Aromatase inhibitor were periodically monitored for bone mineral density.

ER, PR and HER2 expression status were evaluated by immunohistochemistry and done on the surgical specimen. Nuclear (not cytoplasmic) staining was scored for ER and PR. Nuclear staining greater than or equal to 1% of tumor cells was regarded as a positive test and Nuclear staining of less than 1% of tumor cells was regarded as a negative test (8). According to the American Society of Clinical Oncology/College of American Pathologists recommendation, HER2 membrane pattern and staining intensity were evaluated and the expression was scored as 0, 1+, 2+, or 3+. A staining score of 3+ was regarded as positive test and tumors with 2+ score (equivocal) were further analyzed by fluorescence in situ hybridization (FISH) test according to the Nottingham modification of the Bloom - Richardson grading scheme and the WHO classification system (11, 12).

According to the pattern of ER, PR and HER2 expression, cases were divided into 4 group: first group; ER +ve, PR +ve and HER2 –ve, second group; ER +ve, PR +ve and HER2 +ve, third group; ER-ve, PR-ve and HER2 +ve and fourth group; ER-ve, PR-ve and HER2 –ve (triple negative) (13).

**Statistical analysis**

The data management and statistical analysis were conducted using SPSS (Version 20; SPSS). For assessment the significant differences between patients in different groups, χ² test was used. The overall survival duration was calculated from the date of the first diagnosis of the disease to the date of death or the last follow-up visit. Disease-free survival is the period after mastectomy or lumpectomy without any clinical evidence of recurrence or metastasis. Kaplan-Meier test was used to verify the survival differences between the four groups and Cox proportional hazards models were performed to evaluate the prognostic impact of ER, PR, and HER2 in breast cancer patients. Significant prognostic variables such as patient age and tumor stage were included in these models. Cox regression plots were constructed for different groups of patients.
Result:

Population description
The mean age of all breast cancer patients included in this study at the time of diagnosis was 49.2 years (SD= 11.1, range 25-80 years), out of 152 patients, 97 patients (63.8%) were between 40-59 years, 25 patients (16.4%) were ≤39 years and 30 patients (19.7%) were ≥ 60 years old.

Histopathological characteristics
The distribution of the histological types were as follow: 132(86%) were ductal carcinoma, 16 patients (10.2%) were lobular carcinoma, 2 patients (1.25%) were mixed lobuloductal carcinoma and 2 patients (1.25%) were other histological types. Regarding grade of the tumor; 5 tumors (3.2%) were grade I, 63 tumors (41.4%) were grade II and 84 tumors (55.4%) were grade III.

Distribution pattern of ER, PR and HER2 expression in breast cancer samples and its relation with clinicopathological features
Based on immunohistochemical analysis; out of 152 cases, 106 (69.7%) cases showed positive expression of ER and 46 (30.3%) cases were negative. For HER2 receptor; 63 (41.4%) showed overexpression of HER2 and 89 (58.6%) cases showed negative expression. The distribution of the pattern of expression of ER, PR and HER2 markers in the present study was as follows: First group 62/152 (40.78%) showed (ER+, PR+, and HER2 -), Second group 44/152 (28.9%) showed (ER+, PR+, and HER2 +), Third group 19/152(12.5%) showed (ER-, PR- and HER2+) and lastly the fourth group 27/152(17.7%) showed (ER-, PR- and HER2-).

The mean age of patients in the first group (ER+, PR+, and HER2 -) was 54 years (SD 10.7), mean age for the Second group (ER+, PR+, and HER2 +) was 45 (SD 8.8), mean age for Third group (ER-, PR- and HER2+) was 44 years (SD 8.8) and mean age for patients with fourth group (ER-, PR- and HER2-) was 46 (SD10.1). There was a statistically significant association between the age of the patients and the pattern of expression of ER, PR, and HER2. The p-value was 0.000 (Fig 1).

![Figure 1](image-url): Age distribution according to ER, PR & HER2 expression pattern.

A significant association was found between tumor grade and pattern of expression of ER, PR and HER2, the first group of patients (ER+, PR+, and HER2 -) had a higher proportion of grade I and grade II tumors compared with other groups of patients with p value=0.000. (Table 1)

Table 1: Correlation of pattern of expression of ER, PR and HER2 with clinicopathological features of 152 breast cancer cases.

<table>
<thead>
<tr>
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<th>ER+,PR+, HER2-</th>
<th>ER+, PR+ &amp; HER2+</th>
<th>ER-, PR- &amp; HER2+</th>
<th>ER-, PR- &amp; HER2-</th>
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A significant association was found between the pattern of expression of ER, PR and HER2 with lymph node status of breast cancer (p value=0.005) in which higher number of lymph node metastasis was found among patients in the third group (ER-, PR- and HER2 +) and the fourth group (ER-, PR- and HER2 -) compared with other groups of patients (Table 1).

Furthermore, a significant association was found between the pattern of expression of ER, PR and HER2 with stage of the breast cancer with (p value=0.000), the third group (ER-, PR- and HER2 +) and the fourth group (ER-, PR- and HER2 -) of the patients had higher percentage of advanced stage of breast cancer compared with first and second groups of breast cancer patients.No significant association between the pattern of expression of ER, PR and HER2 and the histopathological types, and tumor size (Table 1).

Survival analysis:
Out of 152 patients who were included in this study, 58 patients (38.1%) had died of breast cancer while 94 (61.8%) were still alive at the end of the observation period. Tumor stage and grade showed a significant association with the overall survival of the patients with breast cancer. (Fig 2) shows that patients with histological grade I and II tumor had statistically longer overall survival compared with grade III tumors with (p value=0.000). Disease-free survival was found.

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<th>Survival analysis:</th>
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| Out of 152 patients who were included in this study, 58 patients (38.1%) had died of breast cancer while 94 (61.8%) were still alive at the end of the observation period. Tumor stage and grade showed a significant association with the overall survival of the patients with breast cancer. (Fig 2) shows that patients with histological grade I and II tumor had statistically longer overall survival compared with grade III tumors with (p value=0.000). Disease-free survival was found.
Figure 2: Kaplan–Meier plot, breast cancer survival according to grade of tumor. P-value from long-rank test was 0.000.

The mean survival time for those patients with ER-positive was 59 months (SD 18), while for patients with ER− was 37 months (SD 21). The mean survival for patients with HER2 + was 47 months (SD 19) while the mean survival for patients with HER2− was 59 months (SD 29). Patients with ER-positive tumors had statistically significant longer overall survival when compared with patients with ER-negative tumors with p-value 0.000 (Fig 3).

Figure 3: Kaplan-Meier plot. Breast cancer survival according to the expression of ERP-value from long-rank test was 0.000.

Moreover, those patients with ER-positive tumors had a statistically lower cumulative incidence of cancer-related death than those patients with ER-negative tumors (HR=0.408) (Fig 4).
Figure 4: Cox proportional hazards estimate for overall survival among patients with ER + VS ER- tumor. (HR=0.408).

Whereas those patients with HER2 + tumor had shorter but not significant overall survival compared with HER2 – tumor with p value=0.10 as shown in (Fig 5).

The different expression patterns for ER, PR, and HER2 receptors were also compared, the mean survival time for patients with the first group (ER+, PR+, and HER2 -) was 66 months (SD=15.4), for the second group (ER+, PR+, and HER2 +) was 49 months (SD=18), for the third group of patients (ER+, PR+, and HER2 -) was 41 months (SD=19) and for the fourth group of patients (ER+, PR+, and HER2 -) was 32 months (SD=21).

The first group of patients (ER+, PR+ and HER2 -) had significantly longer survival rate with p value= 0.000, followed by the second group of patients (ER+, PR+ and HER2 +), while the fourth group of patients (ER-, PR- and HER2 -) had significantly the shorter overall survival with p value0.001 (Fig 6).
Figure 6: Kaplan-Meier plot. Breast cancer survival according to pattern of expression of ER, PR & HER2. P-value from long-rank test was 0.001

The cumulative incidence of death was significantly lower in the first group of patients (ER+, PR+ and HER2 -) compared with the other groups (HR=0.361, 95% CI 0.210-0.621), there was also significant increase in the risk of death (HR= 2.381 95% CI 1.48-4.505) in the fourth group of patients (ER-, PR- and HER2-) when compared with other groups of patients with breast cancer. The estimated risk of death for these four groups of breast cancer patients adjusted for patient’s age at the diagnosis and tumor stage is shown in Table 2 and fig 7.

Table 2: Estimated risk of death associated with different pattern of expression of ER, PR & HER2.

<table>
<thead>
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<th>Hazard ratio</th>
<th>Confidence Interval</th>
<th>P value</th>
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<td>ER+ vs ER-</td>
<td>0.408</td>
<td>0.249-0.668</td>
<td>0.000</td>
</tr>
<tr>
<td>HER+ vs HER-</td>
<td>1.485</td>
<td>0.918-2.401</td>
<td>0.107</td>
</tr>
<tr>
<td>ER+, PR+, HER- vs others</td>
<td>0.361</td>
<td>0.210-0.621</td>
<td>0.00</td>
</tr>
<tr>
<td>ER+, PR+, HER+ vs others</td>
<td>1.256</td>
<td>0.754-2.092</td>
<td>0.381</td>
</tr>
<tr>
<td>ER-, PR-, HER+ vs others</td>
<td>1.559</td>
<td>0.794-3.060</td>
<td>1.97</td>
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<tr>
<td>ER-, PR-, HER- vs others</td>
<td>2.589</td>
<td>1.488-4.505</td>
<td>0.001</td>
</tr>
</tbody>
</table>
Furthermore, disease-free survival has been found significantly shorter in the third and fourth groups of patients with p-value 0.005 (Fig 8).

Discussion:
Carcinoma of the Breast is a heterogeneous disease with varied molecular features, morphological appearance, behavior, and response to therapeutic approaches\[(14, 15)\]. For many decades, histological grade, lymph node status and tumor size were regarded as the only established prognostic factors in clinical practice with limiting impact.
on therapeutic decision making\textsuperscript{(14, 15)}. However, current molecular classification of breast cancer based on ER, PR and HER2 for gene expression is widely used for determining treatment approach for the patient with breast cancer. In this study, we analyze the prognostic impact of ER, PR and HER2 markers in breast cancer patients independently and combined to gather.

Several studies have shown survival advantages of ER receptor in breast cancer, data from SEER program study showed that ER was an independent prognostic factor in a large cohort study of breast cancer women, furthermore, it has been found that this survival advantages is substantially enhanced by adjuvant hormonal therapy which was given to patient with ER positive tumor by reducing the recurrence rate not only during treatment period but throughout the first decade and reducing breast cancer mortality by about a third during the first 15 years, therefore ER expression status is regarded as both a good prognostic factor and predictor factor for response to endocrine therapy\textsuperscript{(3,16,17,18)}.

In accordance with the previous studies\textsuperscript{(16, 17, 18)}, the results of this study showed that patients with ER-positive tumor had superior survival compared with patients with ER-negative tumor and the estimated risk of death was significantly higher in patients with ER-negative tumor compared with patients with ER-positive tumor, in addition to that we observed that there was an increase in the proportion of ER-positive breast cancer with increasing age.

It is well known that overexpression of HER2 gene is a significant predictor of both short overall survival and time to relapse in breast cancer patient, since 1998 Trastuzumab (Herceptin), which is humanized monoclonal antibodies against extracellular domain of HER2, became the standard adjuvant treatment in early-stage breast cancer who showed overexpression of HER2 with appropriate cardiac monitoring. It has been proven that trastuzumab is an effective drug in improving survival for patients with early HER2 positive breast cancer as well as metastatic HER2 positive breast cancer\textsuperscript{(19, 20, 21, 22)}.

Our result showed that patients with HER2 overexpression have shorter overall survival than patients with low expression of HER2 and patients with HER2 overexpression has higher estimated risk of death (HR =1.4) but this not reach the degree of significance, it is quite reasonable to assume this result as most of the patients who included in our study have received adjuvant trastuzumab every 3 weeks after loco-regional treatment and completed planned one year.

In this study, the molecular classification of breast cancer, based on immunohistochemical analysis of ER, PR, and HER2, was done. ER+/ PR+/ HER2 – a subtype of breast cancer was found in 40.7\% of cases, ER+/ PR+/ HER2 + was observed in 28\% of the cases, ER-/ PR-/ HER2+ was found in 12.5\% and finally, triple-negative subtype was found in 17.7\% of the cases. This pattern of expression of these markers are more or less within the expression rate of other studies in Iraq and another study abroad\textsuperscript{(23, 24, 25, 26, 27)}, although there is wide detection rate in the pattern of expression of these markers, this may be contributed to the variation of genetic predisposition, diversity of risk factors, immunohistochemical methodology and difference in the number of case studies.

Additionally, we found that patients with ER+/PR+/ Her2 – breast tumor have lower grading, less number of lymph nodes metastasis and lower final staging, in controversy to those breast cancer patients with ER-/ PR-/ Her2 + and those patients with triple-negative tumor who have high grade, larger tumor size, higher percentages of lymph nodes metastasis and higher clinical stage. These results are found to be inconsistent with the result of other studies\textsuperscript{(28, 13)}.

Survival analysis using the Kaplan-Meier test revealed that patients with ER+/ PR+ / Her2 -ve breast tumors have substantially better survival compared with other groups of patients. Additionally, we found that patients with ER+/PR+/ HER2+ have better survival and lower estimated risk of death compared with patients with ER-/ PR-/ HER2+ patients supporting the significance of ER and PR status in determining overall survival in HER2 positive breast cancer adding to this, the survival benefit of adjuvant endocrine therapy that was given to all patients with ER+ tumor who were included in our study.

While patients with triple-negative tumor have the worse survival and higher estimated risk of death and this result is quite reasonable due to aggressive nature of this subgroup of breast cancer and the lack of current target therapy, in addition to that, it has been found that triple negative breast cancer patients have different pattern of metastatic spread with higher likelihood of lung and brain metastasis and less bone metastasis and this may contribute to shorter survival in this group of patients\textsuperscript{(24, 29, 30, 31, 32)}.
Our result is more or less similar to the result of other studies, although some of the patient’s population who included in their study have not received adjuvant hormonal. In contrary, all ER+ breast cancer patients who were included in our study have received adjuvant therapy, additionally, some of these studies have incorporated CK5, 6 and/or EGFR markers in their subtyping which is not supported by the St Gallen Consensus Discussion 2013. The 2015 St Gallen’s consensus meeting (International Expert Consensus on the Primary Therapy of Early Breast Cancer) recommended the assessment of Ki67, which is a nuclear marker of cell proliferation that is expressed in all cell cycle phases, except G0, for the distinction between strongly endocrine responsive, low proliferation, good prognosis ‘luminal A-like’ and less endocrine responsive, higher proliferation, poorer prognosis ‘luminal B-like’ (HER2-negative) tumors, and defined luminal A as ER+/PR+/HER2- tumors with a Ki67 index ≤ 14%.

In conclusion, our result demonstrated that patients with different expressions of ER, PR, and HER2 have different clinical survival with different responses to treatment. Patients with ER+/PR+/HER2+ tumor have favorable prognosis while patient with triple-negative tumor have the worst prognosis and these survival results are comparable to that of other studies, therefore, we recommend to use this molecular classification in all patients with breast cancer for selecting the appropriate treatment approach, however, we need to do further wider survival studies which include the assessment of Ki67 to provide additional information for selected subgroup of patients with breast cancer.

Acknowledgment: This study was supported from Medical College, Mosul University.

References: