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The molecular subtypes configuration of metastatic breast cancer in Basrah city

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SUMMARY

Globally, breast cancer (BC) is the second and the first of the top ten cancers in the world and Iraq, respectively. The configuration of molecular subtypes on metastatic BC (MBC) for rebuilding the implications on the management. This study aimed to describe the clinicopathologic properties and metastatic configuration of molecular BC subtypes. This is a retrospective study of 500 MBC females from Basrah city, Iraq. The study was conducted at Basrah Oncology Center, for a period from June 2010 to June 2021. The HR expression status and HER2 gene amplification were evaluated by IHC. The associations of molecular subtypes and distant metastases are modelled by regression analysis. The most common age group belonged to 41years-50 years in (144, 28.8%). A total of 59 of 500 women have a positive family history of cancer. The most common histology in this study is IDC (430, 86%). The intermediate grade was recorded in most patients (311, 62.2%). Bone was the most common site of secondaries in (174, 34.8%) of patients. The ER was positive in 294(58.8%), and PR positive in 328(65.6%). The HER 2neu negative more than positive [298(59.6%) vs. 202(40.4%)]. The HR+/Her2neu– (Luminal A) was the prevalent molecular subtypes. None of the variables was significantly associated with metastasis to bone, pulmonary, liver, brain, chest wall, LN, or pleura, except the age of patients, BMI, HR+ and HER 2 neu (P=0.02), (P=0.05), (P=0.01), and (P=0.01), respectively, showed strong affection with the metastatic pattern. The commonest age of BC in our locality is more than fifty years. High BMI has high infinity on the development of BC. The bone is the most common site of secondaries. All metastasis sites are strongly associated with molecular phenotypes patterns. Molecular phenotypes show different behaviour of metastasis concerning the sites.

Key words: Breast cancer, HER 2neu, Molecular phenotypes, ER, PR

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INTRODUCTION

In 2011, the Iraqi cancer registry board documented 3845 cases of BC [1], yet, this number rose to 4542 cases of BC in 2014 [2]. The American Cancer Society (ACS) recorded 232,340 new cases of invasive BC in 2013 and 39,620 deaths happened in that year [3,4]. According to GLOBCAN 2020, the new cases of BC were 2,261,419 (11.7%), with 684,996 (6.9%) dead cases overall at all sites [5]. In terms of histopathology, BC has a heterogeneous collection with several histological subsets, clinical manifestations, responses to management, and prognosis [6]. Different clinical and histological factors influence the prognosis of BC, like the presence and extent of lymph node metastasis, age at diagnosis, tumour grade, and histology, size of the primary tumour, Hormonal Receptors (HR), and Her 2neu status [6]. These factors cause to elaborate on about 15 distinct histopathologic forms according to the classification recognized by the American Joint Committee on Cancer (AJCC) [7]. In addition, further microscopic cellular features of heterogeneity of BC may be present such as nuclear pleomorphic, tubule formation, and mitotic index [8]. The DNA microarray expression profiles also express to lead to another subtype of molecular classification which corresponds to prognostic groups based on the biological and aggressiveness of the BC, that strongly affected by the genes controlling expression of the ER and HER2/neu receptor status [3]. The National Surgical Adjuvant Breast Project (NSABP) B-06 trial concluded that patients with ER and PR negative, have a worse prognosis than those patients with ER or PR positive [9]. Approximately, all normal cells, carry two copies of the human epidermal growth factor receptor-2 gene (HER2 or HER 2neu; also known as the c-erbB2 gene), but about 20% of BC have multiple copies of the gene amplification [10], hence this gene has the ability to increased expression of the products, and cause activation of the HER2 kinase, leading to increased proliferation, survival, and tumour cells metastasis [11, 12]. HER2 overexpression is infinite to metastasize earlier and to have a poor prognosis [3, 11, 12].

The American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP) published 2010 the recommendations from an international expert panel to develop the optimal IHC ER/PR testing performance and the optimal HER2 testing [13]. Multiple datasets have confirmed the molecular BC subtypes, including Two luminal subtypes

(luminal A and B); a Basal-like subtype; and a HER2-enriched subtype [6, 7].

Here, we discuss the clinicopathologic properties, and metastatic configuration concerning molecular BC subtypes in Basrah city, Iraq.

METHODS

Design and setting of the study

A retrospective study of 500 MBC female patients was enrolled and identified. The patient's demographic data, pathologic properties, and molecular subtypes were reported. The study was conducted in Basrah Oncology Centre, Basrah, Iraq, in the period from June 2010 and June 2021.

Data collection

Retrospectively, data were collected with the preview of medical records. The following data were studied: age, TNM staging, grades, histopathology, ER and PR status, HER 2neu status, molecular subtypes, BMI, and metastatic sites.

Hormonal receptors

The ER, PR, and HER2 protein status were examined by IHC. ER and PR positivity was defined as 1% or more of tumour cell nuclei with immunoreactivity. HER2 positivity was defined as either a 3+ immunohistochemistry score (uniform and intensity membrane staining of >10% of tumour cells) or a positive in situ hybridization result [13]. The luminal cancers classify into luminal A (ER+ and PR+/HER2–, Nottingham grades I-II) and luminal B (ER+ and/or PR+/HER2–, grade III or ER+ and/or PR+/HER2+). Triple-negative (basal-like) tumours were defined as tumours that were ER, PR, and HER2 negative [13].

Ethical considerations

Written informed consent was obtained from all patients participating in this study. The Medical Ethical Committee of the College of the Medicine/University of Basrah approved this study.

Statistical analysis

All analyses were conducted by using SPSS version 24.0 for Windows (SPSS Inc., Chicago, Illinois, USA). The association of clinicopathologic patterns, molecular subtypes, and distant metastases modelled with univariate and multivariate regression analysis were calculated for each model. A two-sided P value of 0.05 or less was considered statistically significant for Fisher's exact, and Pearson chi-square tests.

RESULTS

The most common age group belonged to 41-50 years (144,

Tab. 1. Patients demographic (n=500).

Variables	Range	No. (%)
Age (years)	<20	28 (5.6%)
	21-30	79 (15.8%)
	31-40	98 (19.6%)
	41-50	144 (28.8%)
	51-60	121 (24.2%)
	>60	30 (6%)
Residence	Urban	255 (51%)
	Rural	245 (49%)
Family history	Yes	59 (11.8%)
	No	441 (88.2%)
BMI (m^2/Kg)	Underweight (<18.5)	9 (1.8%)
	Normal (18.6-24.9)	111 (22.2%)
	Overweight (25-29.9)	146 (29.2%)
	Moderate obesity (30-34.9)	151 (30.2%)
	Severe (35-39.9)	62 (12.4%)
	Malignant (>40)	21 (4.2%)
Patients number each year	2010	13 (2.6%)
	2011	16 (3.2%)
	2012	25 (5%)
	2013	22 (4.4%)
	2014	31 (6.2%)
	2015	38 (7.6%)
	2016	48 (9.6%)
	2017	53 (10.6%)
	2018	78 (15.6%)
	2019	80 (16%)
	2020	39 (7.8%)
	2021	57 (11.4%)

28.8%), whereas 28(5.6%) of women were below the age of 20. We documented that 255(51%) of patients lived in urban sites, while 245(49%) of the where lived in rural regions. A total of 59 of 500 women have a positive family history of cancer. Regarding body mass index (BMI), moderate obesity was prevalent in 151(30.2%), while the underweight women were 9(1.8%), as shown in (Table 1).

The most common histology in this study is IDC (430, 86%) patients. The T2 stage was frequent 249(49.8%). The N1 staging was common in (198, 39.6%) of patients. In addition, all women were MBC. The intermediate grading was recorded in most patients (311, 62.2%), followed by high in 180(36%), and the rest as the low grade in 9(1.8%). Multiple secondaries were documented in 140(28%) of the sample. Finally, bone was the most common site of secondaries in (174, 34.8%) of patients. The last site of MBC was LN (24, 4.8%). The ER-positive in 294(58.8%), and PR positive in 328(65.6%). The HER 2neu negative more than positive [298(59.6%) vs. 202(40.4%)]. The HR+/Her2neu– (Luminal A) was the prevalent molecular subtype 252(50.4%), while the least was triple-negative/basal-like 80(16%) of patients, as shown in (Table 2).

The correlation between metastasis sites and study variables was investigated by a univariate regression model in (Table 3). None of the variables was significantly associated with spreading to, except age, BMI, HR+, and HER 2 neu (P=0.02; 0.05; 0.01 and 0.01), respectively.

As shown in (Table 4), BC subtypes were statistically significant

Tab. 2. MBC features (n=500)

Variables		No. (%)
Histology	Carcinoma in situ (CIS)	10 (2%)
	Invasive ductal carcinoma (IDC)	430 (86%)
	Invasive lobular carcinoma (ILC)	52 (10.4%)
	Mixed	5 (1%)
	Medullary carcinoma	3 (0.6%)
T	T0	5 (1%)
	T1	88 (17.6%)
	T2	249 (49.8%)
	T3	92 (18.4%)
	T4	66 (13.2%)
N	N0	106 (21.2%)
	N1	198 (39.6%)
	N2	100 (20%)
	N3	96 (19.2%)
M	M0	0 (0%)
	M1	500 (100%)
Grade	Low	9 (1.8%)
	Intermediate	311 (62.2%)
	High	180 (36%)
Metastasis sites	Bone	174 (34.8%)
	Lung	94 (18.8)
	Liver	112 (22.4)
	Brain	44 (8.8%)
	Chest wall	50 (10%)
	Lymph nodes (LN)	24 (4.8%)
	Pleura	36 (7.2%)
	Multi secondaries	140 (28%)
ER	Positive	294 (58.8%)
	Negative	206 (41.2%)
PR	Positive	328 (65.6%)
	Negative	172 (34.4%)
HER 2neu	Positive	202 (40.4%)
	Negative	298 (59.6%)
Molecular subtypes	HR+/Her 2neu–	252 (50.4%)
	HER2-enriched	168 (33.6%)
	Triple-negative/basal-like	80 (16%)

Tab. 3. Univariate analysis of MBC correlation with variables of the study

Variables	Metastasis								
	Bone	Pulmonary	Liver	Brain	Chest wall	LN	Pleura	Multi sites	*P*-value*
	Odds ratio								
Age (50.4± 16.4) years	9.2	7.1	3.3	4.1	4.3	5.2	2.1	4.5	0.02
Residence	1.8	0.6	0.6	0.9	0.6	0.6	1.7	1.3	0.06
Family history (positive)	1.5	0.3	0.9	0.9	0.9	0.9	0.9	0.9	0.4
BMI (26.9± 10.5) m^2/Kg	8.8	6.4	4.3	2.2	1.2	2.9	0.7	3.6	0.05
IDC	2.5	1.8	1	4.2	1.2	2.3	3.3	3.1	0.2
T stags	2.1	1.4	2.4	0.9	0.9	2.2	2.2	2.2	0.8
N stags	1.4	1.5	3.3	1.9	1.3	1.5	0.1	0.6	0.4
Intermediate grade	0.6	1.7	2.5	0.8	1.1	1.4	1.1	1.4	0.8
ER/PR+	7.2	5.3	4.5	5.9	4.4	3.9	1.9	5.3	0.01
HER 2neu -	9.3	7.4	8.1	6.4	2.5	2.2	3.8	5.9	0.01

Tab. 4. Multivariate analysis for BC subtypes, and metastasis sites

BC subtypes	Metastasis sites								
	Bone	Pulmonary	Liver	Brain	Chest wall	LN	Pleura	Multi sites	P-value
	Odds ratio								
HR+/Her 2neu –	9.44	6.33	4.45	6.75	4.42	3.74	2.42	5.22	0.01
HER2-enriched	8.35	8.07	4.45	6.41	4.32	3.54	2.44	6.51	0.01
Triple-negative	9.24	5.89	4.92	5.88	4.22	3.55	1.78	5.84	0.01

with all sites of secondaries as HR+/HER2neu– (P=0.01), HER2-enriched (P=0.01), and triple-negative (P=0.01).

DISCUSSION

Our findings regarding demographic and tumour characteristics resemble data from previous studies conducted in Iraq like Al-Naqqash et al., [14, 15], Al-Alwan et al., [16], and Al-Rawaq, [17]. The age of patients with BC is an important factor in the occurrence and treatment [8]. The mean age reported in a comparative study done between Iraqi and British women was more than fifteen years than that demonstrated by our results [18], while among US females, authors reported that BC is in the sixth decades of life [19], which is higher than we documented. In Arabian countries, BC is more commonly detected in women below the age of 50, which is consistence with our findings, unlike in the USA, where women aged 50 years and older are most commonly reported [19]. Among residents, the results showed no significant differences between urban, and rural areas. All previous and recent studies [14-18, 20, 21], were conducted in Iraq didn't mention interesting data about residence in their results, but in particular, cancer screening and healthcare centres explained geographic disparities in cancer incidence among residents, however, in the US, the burden of BC is not distributed equally which is higher in urban regions compared to rural [22], but two other recent studies reported that rates of BC in rural was higher than urban area [23, 24]. Several papers published by Al-Alwan et al., 2017–2019 [16, 25, 26], discussed BC concerning family history in Iraq, in 2019 the percentage was 25.6%; in 2018 the percentage was 51.1%; in 2017 the percentage was 20.2%, respectively, with no significant differences [25, 26]. We estimated only 11.8% of patients had a positive family history. These discrepancies between our data and other studies may be due to there being no perfect cancer registry program, no accurate screening modalities, and may be related to socioeconomic-educational causes. Globally, between 20–25% of BC cases have a positive family history, and approximately 10% of them have an autosomal dominant inheritance pattern [24].

Overall studies that discussed BMI as a risk factor, our data agreed with Al-Naqqash et al., [14, 15, 21], Al-Alwan et al., [16], and Al-Rawaq, [17]. The inherent complex interaction between body mass, interpreting by epidemiologic studies correlating these factors with the risk of BC [24]. A pooled analysis of prospective studies documented the risk to be 30% higher with high BMI (>31 m^2/Kg), that explained by higher estradiol levels correlated with increased adipose tissue [3, 11]. Some other studies differ from our findings as Goldhirsch et al., [27]. The tumour size rank among the strongest predictors of distant metastasis, disease-free survival, and overall survival, that strongly associated with the presence of axillary lymph nodes [9, 11].

The bone is the commonest site of secondaries. These are as same as the studies of Soni et al., 2015 and Hess et al., 2006, who reported that the skeletal was the most commonly seen and it is the first site of spreading [28, 29]. Inversely, Al-Naqqash et al. documented the recurrence of the chest wall was a common

metastatic site [14]. Many factors influencing the development of metastases mainly include tumour size, grade, LVI, LN involvement, and hormonal receptors [9-11, 24, 28].

The data of ER+/PR+ was highly reported, whereas the HER 2neu negative was more frequently. These are supported by Al-Naqqash [14], and Cheang [30], while disliked by Al-Sarraf, [31], El-Fatemi, and Chahbounil, [32].

The association between molecular BC subtypes and secondary relapse is of significant clinical interest, which has been well demonstrated by this study. All molecular BC subtypes were significantly associated with bone metastasis by regression models. In terms of evidence, the bone secondaries are the most abundant nearly in all molecular subtypes, although all patients may develop visceral secondaries in one or more organs, as noticed in the current study.

Many studies have documented that patients with ER+ tumours are more likely to have bone metastases, whereas patients with TNBC have a predilection for visceral secondaries [24, 28, 30]. Another study has shown that the luminal-A phenotype significantly dropped the risk of hepatic recurrence [33]. Luminal A and B rarely spread to the lung compared with TNBC and the HER2 subtype [28, 30, 33].

By determining a large population of MBC patients, I can demonstrate that phenotypes show a strong implication to site-specific distant-organ recurs independent of other clinic-pathologic features. All these data articulate that phenotypes change in their metastatic behaviour, thus largely elevating the probabilities that this information could potentially use in choosing the appropriate management and follow-up methods.

CONCLUSION

The commonest age of BC in our locality is more than fifty years. High BMI has high infinity on the development of BC. The bone is the most common site of secondaries. All metastasis sites are strongly associated with molecular phenotypes patterns. Molecular phenotypes show different behaviour of metastasis concerning the sites. National computerization of cancer registration is mandatory, not only for BC but for all other types of cancer.

Competing interests

I (author) declare that we have no conflict of interest.

Consent

All authors declare that written informed consent was obtained from the patient (or other approved parties) for the publication of this article.

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