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CUTOFF VALUE OF KI-67 BIOMARKER AS PROGNOSTIC MARKER IN FEMALE BREAST CANCER

(Retrospective Study)

By

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ABSTRACT

Background: Cancer breast (BC) is the commonest worldwide malignancy in females. KI-67 one of prognostic biomarker in breast cancer.

Objective: Assessing KI-67% expression in relationship with disease free survival (DFS), over-all survival (OS) and various clinic-pathological parameters of the disease (age, menopausal status, tumor size, nodal status, histological type/ grade, Estrogen receptors Progesterone receptors (ER, PR) status and Human Epidermal Growth Factor Receptor (HER2neu) status.

Patients and Methods: This study included 115 female breast cancer patients were done KI-67% biomarker. Our cases at Clinical Oncology Department, Al-Hussein University Hospital during the period between January 2014 and December 2017.

Results: Cutoff value of KI-67% was significance (P-value < 0.01) with (ER, PR and HER2neu), significance (P-value < 0.05) with DFS and insignificance (P-value > 0.05) with OS, age, menopausal status, tumor size, nodal status, histological type/ grade).

Conclusion: Patients with high KI-67% showed significantly poorer prognosis than those with low KI-67%. This may show that KI-67% was the most robust independent prognostic factor in multivariate prognostic analysis, despite having very strong correlations with other biomarkers such as hormone receptor status (ER & PR) and HER2neu. KI-67% might be helpful in identifying patients who have a favorable diagnosis and in preventing unnecessary treatment for these women.

Keywords: KI-67%, DFS, OS, ER, PR and Her2neu.

INTRODUCTION

BC is the most frequently diagnosed cancer among women worldwide about 25% of all new cancer diagnosis in women globally and 29% in Egyptian's females *(Jemal et al., 2011).*

It is well recognized that BC is a heterogeneous disease, and that the biological nature of the disease and clinical outcome are closely interlinked *(Brandt et al., 2017).*

Discussion of malignant breast patients is now carefully using a variety of

prognostic and predictive factors. Rating of these factors has become a requisite section of the pathologists mapping and practice, and only with this information available can the clinical team select the most appropriate treatment for the individual patient *(Giuliano, et al., 2017).*

However, a few of these factors found their way into routine clinical application as established prognostic tools. These primarily include: Nodal status, neoplasm size, histological type/ grade, (ER, PR) status, (HER2neu) status and KI-67 proliferation index *(Gonzalez-Angulo et al., 2011).*

Several other investigational ingredients have been proposed for prognostic and predictive determination including, for instance: proliferative markers, cell cycle regulatory proteins, bone marrow micro metastases, circulating tumor cells and multi-gene assays. None of these ingredients, however, made its way into clinical routine practice *(Schmidt et al., 2012).*

Prognostic and predictive breast cancer markers are imperative in predicting patient survival and relapse, as well as in deciding their treatment protocols. Although a multitude of supposed prognostic and predictive markers have been examined, only routine histopathological and immunohistochemically markers have proven useful *(Taneja et al., 2014).*

Only MAI and KI-67 labelling index appear too applied in routine use. KI-67 has also become established in medicine-based practice. KI-67 is present in all phases of the cell cycle, with its maximum during mitosis. The percentage of cell that changed color positively for KI-67 IHC stain has been used as a measure of growth and spread as well as prediction of outcome in many trials *(Pinto AC et al., 2011).*

The present work aimed to assess KI-67% expression in relationship with disease free survival, over-all survival and various clinic-pathological parameters of the disease (age, menopausal status, tumor size, nodal status, histological type/ grade, Estrogen receptors Progesterone receptors (ER, PR) status and Her-2/Neu status).

PATIENTS AND METHODS

This were a retrospective study that included the 115 female patients with the diagnosis of BC registered at the archive of Clinical Oncology and Nuclear Medicine Department, Al-Hussein University Hospital during the period between January 2014 and December 2017. The patients were diagnosed of all stages of BC (Tis, T1, T2, T3, and T4), and all histological types (IDC, ILC, Mixed, Mucinous, Medullary carcinoma, and DCIS). All patients were subjected to an IHC examination for KI-67% expression. All of patients were given one or more types of adjuvant or neoadjuvant chemotherapy, hormonal treatment and or radiotherapy following primary surgery.

Statistical Methods:

Data were collected, revised, coded and entered to the Statistical Package for the Social Science (IBM SPSS) version 23. The quantitative data were presented as mean, standard deviations and ranges when their distribution found parametric and median with inter-quartile range (IQR) when their distribution found non parametric. Also, qualitative variables were presented as number and

percentages. The comparison between groups with qualitative data was done by using Chi-square test. The comparison between two groups with quantitative data and parametric distribution were done by using Independent t-test while for non-parametric data were done by using Mann-Whitney test. Kaplan Meier curve (Log Rank test) was used to assess the relation between KI67 and DFS and also OS of the studied cases the confidence interval was set to 95% and the margin of error accepted were set to 5%. So, the p-value was considered significant as the following: (P-value > 0.05: Non significant (NS), P-value < 0.05: Significant (S) and P-value < 0.01: Highly significant (HS).

Ethical Approval:

The current data were collected from patient's files from archive of Clinical Oncology Department, Al Hussein Hospital, and had been approved by the ethical committee, Faculty of Medicine, Al-Azhar University, Cairo, Egypt, before the start of this study.

RESULTS

The association between different clinic pathological parameters, including age menopausal status at diagnosis, tumor size, histological types, grade, nodal status ER, PR, her2neu status and type of surgery and KI-67 is show in **Table (1)**.

The patients' age at diagnosis ranged from 30 to 76 years with a mean 45.41years and SD ± 8.49 years. In the low KI-67<20% patients' group, the median age at diagnosis was 46.58 ± 9.01 years compared with high KI-67>20% patient group 44.40 ± 7.96 years. The difference between low and high KI-67 ratio as regard the age was statically non-significant (P=0.171) **(Figure 1)**.

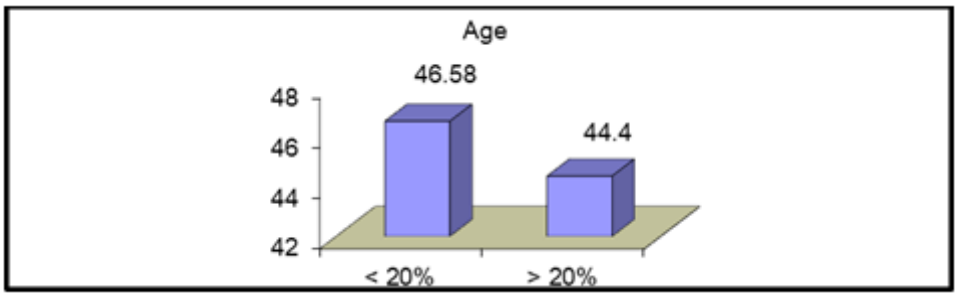

Figure (1): Relation between KI-67 percentage and mean age of our patients 45years

According to menopausal status of patients at diagnosis, there were no statistically significant differences in KI-67 neither in premenopausal nor postmenopausal groups (P= 0.677). In the KI-67 low group< 20%, there were 27(50.9%) premenopausal patients and 26(49.1%) postmenopausal patients. While in the high KI-67 group >20%, there were 34(54.8%) premenopausal and 28(45.2%) postmenopausal patients **(Figure 2)**.

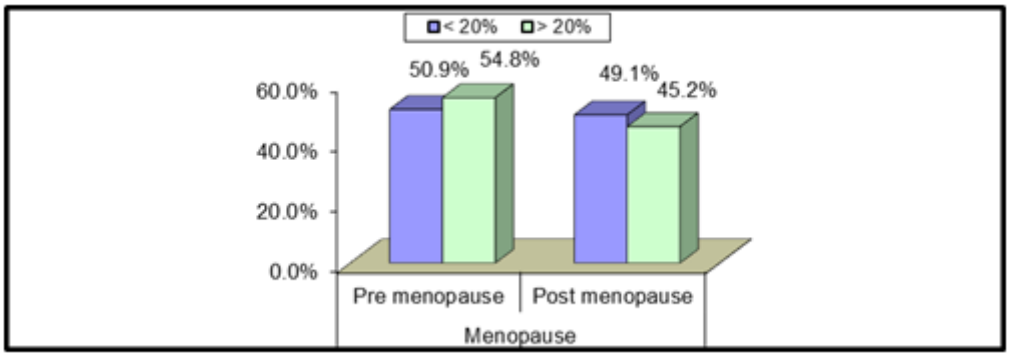

Figure (2): Relation between KI-67 percentage and menopausal status of our patients

All tumor histopathological types have no statistically significant difference for low and high KI-67(P=0.534). In low KI-67<20% {IDC 47(88.7%), ILC 3(5.7%), mixed 0(0.0%), Mucinous 1(1.9%), DCIS 2(3.8%) and medullary carcinoma 0(0.0%)} and in high KI-67>20% {IDC 56(90.3%), ILC 3(4.8%), Mixed 1(1.6%), Mucinous 1(1.6%), DCIS 0(0.0%) and Medullary carcinoma 1(1.6%)} **(Figure 3)**.

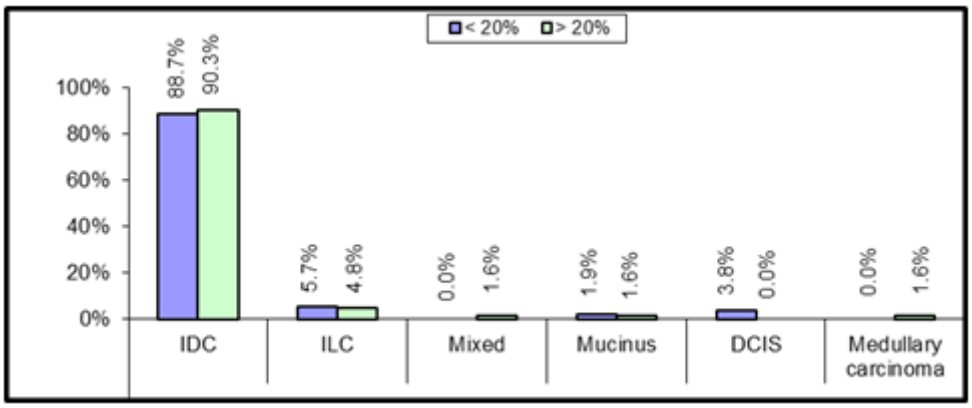

Figure (3): Relation between KI-67 percentage and pathological types of our patients

Difference size of BC has no statistically significance (P=0.382). In low KI-67<20% [TIS 2(3.8%), T1 8(15.1%), T 2 29(54.7%), T3 9(17.0%) and T4 5(9.4%)] patients. In high KI-67>20% [TIS 0(0.0%), T1 7(11.3%), T2 38(61.3%), T3 14(22.6%) and T4 3(4.8%)] patients.

The low KI-67 patient group<20% contained 18(34.0%) patients with negative LNs, 17(32.1%) patients with N1, 12(22.6%) patients with N2 and 6(11.3%) patients with N3. On the other hand, the high KI-67% patient group >20% contained 17(27.4%) patients with negative LNs, 20(32.3%) patients with N1, 15(24%) patients with N2 and 10(16.1%) patients with N3. Correlation analysis revealed no statistically significance between KI-67 expression and nodal status (P=0.824) **(Figure 4)**.

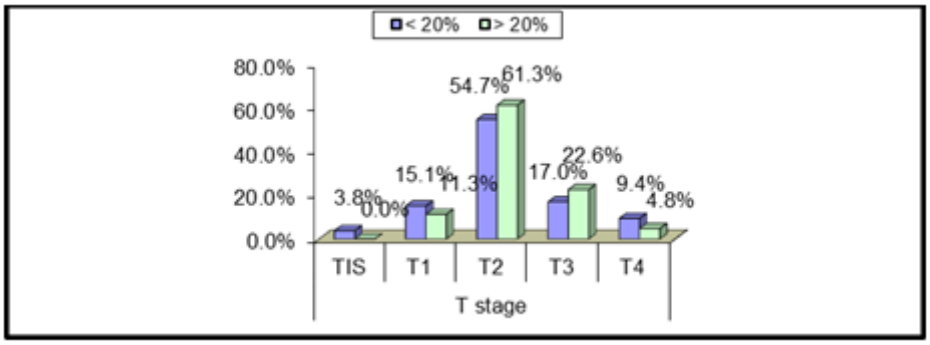

Figure (4): Relation between KI-67 percentage and tumor size staging of our patients

In the low KI-67 group<20%, there were 0(0.0%) patients with G1 tumors, 49(92.5%) patients with G2 tumors and 4(7.5%) patients with G3 tumors. While in the high KI-67 group >20%, there were 1(1.6%) patient with G1 tumors, 49 (78.0%) patients with G2 tumors and 12(19.4%) patients with G3 tumors. That is to say that there is no statistically significance between KI-67 expression and histological grade (P=0.115) **(Figure 5)**.

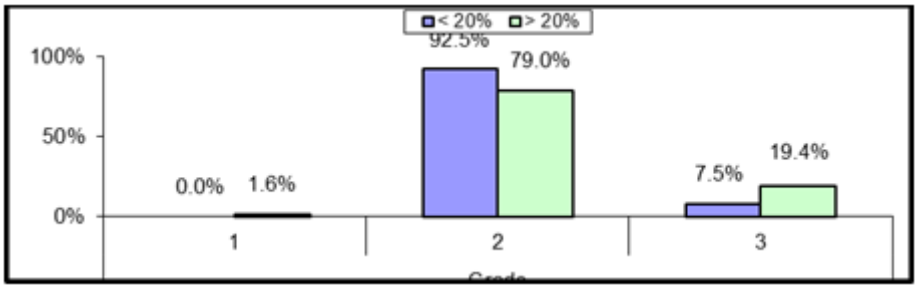

Figure (5): Relation between KI-67 percentage and tumor grading of our patients

As regard the impact of hormonal [ER] status on KI-67 expression, there is a high statistically significance in association between KI-67 expression and ER status (P=0.001). That is to say that KI-67 expressing breast cancer was frequently associated with negative ER tumors. In low KI-67 patients' group<20% showed 2(3.8%) ER negative patients and 51(96.2%) ER positive patients. In high KI-67 patients' group>20% showed 16(25.8%) ER negative patients and 46(74.2%) ER positive patients. Also as regard the association of [PR] hormonal status and KI-67 expression, there is also high statistically significance in association between KI-67 expression and PR status (P=0.001). That is to say that KI-67 expression breast cancer was frequently associated with negative PR tumors. In low KI-67 patients' group <20% showed 4(7.5%) PR negative patients and 49(92.2%) PR positive patients. In high KI-67 patients' group >20% showed 21(33.9%) PR negative patients and 41(66.1%) PR positive patients. As regard the association between HER2/NEU status and KI-67 expression, in low KI-67 patient group<20% showed 50(94.3%) HER2/NEU negative patients and 3(5.7%) HER2/NEU positive patients, in high KI-67 patients' group >20% showed 39(62.9%) HER2/NEU negative patients and 23(37.1%) HER2/NEU positive patients. Correlation analysis revealed high statistically significance between KI-67 and HER2/NEU status (P<0.001). That is to say KI-67expressing breast cancers were frequently associated with HER2/NEU expressing tumors **(Figure 6)**.

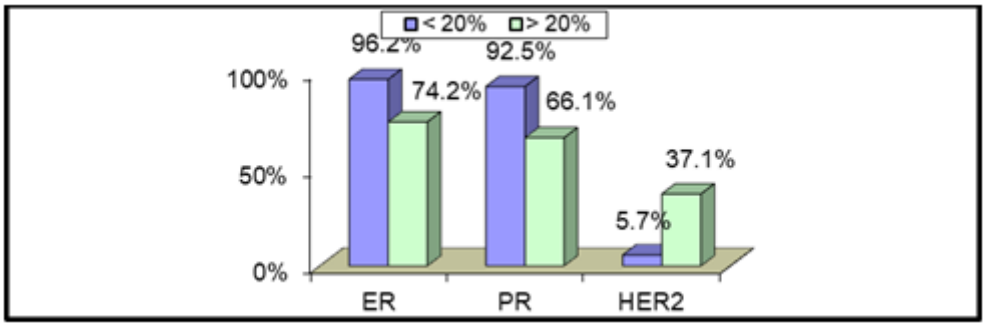

Figure (6): Relation between KI-67 percentage and hormonal status and HER2/NEU of our patients

Ratio of KI-67 and its relation with age, menopausal status, family history, type of surgery, tumor size, histological types and grade showed no significance association between KI-67 and previous parameters on the other hand, Relation between KI-67 and (ER, PR and HER2neu) showed high significance associations between KI-67 and previous parameters, and no significance association between KI-67 and number of metastatic axillary lymph nodes **(Table 1)**.

Table (1): Association between KI-67 and all parameters in our patients

Parameters \ Association		**< 20%**	**> 20%**	**P-value**
		No. %	**No. %**	
Age	Mean±SD	46.58 ± 9.01	44.40 ± 7.96	0.171
	Range	31 – 76	30 – 63	
Menopause	Pre menopause	27 (50.9%)	34 (54.8%)	0.677
	Post menopause	26 (49.1%)	28 (45.2%)	
MRM	No	22 (41.5%)	24 (38.7%)	0.760
	Yes	31 (58.5%)	38 (61.3%)	
BCS	No	31 (58.5%)	38 (61.3%)	0.760
	Yes	22 (41.5%)	24 (38.7%)	
T stage	TIS	2 (3.8%)	0 (0.0%)	0.382
	T1	8 (15.1%)	7 (11.3%)	
	T2	29 (54.7%)	38 (61.3%)	
	T3	9 (17.0%)	14 (22.6%)	
	T4	5 (9.4%)	3 (4.8%)	
Histology	IDC	47 (88.7%)	56 (90.3%)	0.534
	ILC	3 (5.7%)	3 (4.8%)	
	Mixed	0 (0.0%)	1 (1.6%)	
	Mucinus	1 (1.9%)	1 (1.6%)	
	DCIS	2 (3.8%)	0 (0.0%)	
	Medullary carcinoma	0 (0.0%)	1 (1.6%)	
Grade	1	0 (0.0%)	1 (1.6%)	0.115
	2	49 (92.5%)	49 (79.0%)	
	3	4 (7.5%)	12 (19.4%)	
ER	Negative	2 (3.8%)	16 (25.8%)	< 0.001
	Positive	51 (96.2%)	46 (74.2%)	
PR	Negative	4 (7.5%)	21 (33.9%)	< 0.001
	Positive	49 (92.5%)	41 (66.1%)	

HER2	Negative	50 (94.3%)	39 (62.9%)	< 0.001
	Positive	3 (5.7%)	23 (37.1%)	
Dissected LN	Median (IQR)	17 (13 – 20)	18 (15 – 22)	0.091
	Range	2 – 36	5 – 30	
Positive LN	Median (IQR)	2 (0 – 5)	2 (0 – 6)	0.440
	Range	0 – 25	0 – 29	
N stage	No	18 (34.0%)	17 (27.4%)	0.824
	N1	17 (32.1%)	20 (32.3%)	
	N2	12 (22.6%)	15 (24.2%)	
	N3	6 (11.3%)	10 (16.1%)	

Disease recurrence was reported in 13(21.0%) patients with high KI-67 compared with only 4(7.5%) patients with low KI-67, so the effect of KI-67 expression was statistically significant (P=0.043) saying that high KI-67 expressing tumors are more liable for disease progression.

Among the progressed patients with high KI-67 expression >20% there were 6(9.7%) patients with bone metastasis, 3(4.8%) patients with liver metastasis, 2(3.2%) patients with lung metastasis, 2(3.2%) patients with local recurrence and 0.(0.0%) patients in brain metastasis, compared with low KI-67 expression <20% there were 1(1.9%) patients with bone metastasis,1(1.9%) patients with liver metastasis, 2(3.8%) patients with lung metastasis, 0(0.0%) patients with local recurrence and 1(1.9%) patients with brain metastasis. Correlation analysis revealed no statistically significance between KI-67 expression and site of metastasis (P=0.227) (Table 2).

Table (2): Associations between KI-67 and patient's outcome

Parameters \ Associations		**< 20%**	**> 20%**	**P-value**
		No. %	**No. %**	
Relapse	No	49 (92.5%)	49 (79.0%)	0.043
	Yes	4 (7.5%)	13 (21.0%)	
Site	No	48 (90.6%)	49 (79.0%)	0.227
	Lung	2 (3.8%)	2 (3.2%)	
	Liver	1 (1.9%)	3 (4.8%)	
	Bone	1 (1.9%)	6 (9.7%)	
	Brain	1 (1.9%)	0 (0.0%)	
	Local	0 (0.0%)	2 (3.2%)	
Status	Alive	31 (58.5%)	33 (53.2%)	0.689
	Died	3 (5.7%)	6 (9.7%)	
	Lost FU	19 (35.8%)	23 (37.1%)	

As regard the effect of KI-67 expression and overall survival, there are no statistically significance for low and high KI-67 (P=0.390) **(Table 3** and **Figure 7)**.

Table (3): Association between KI-67 expression and patients' survival

KI	**Total N**	**N of Events**	**Mean**	**SE**	**95% CI**		**P-value**
					Lower	**Upper**	
< 20%	34	3	74.054	2.808	68.551	79.558	
> 20%	39	6	67.410	3.286	60.969	73.852	0.390

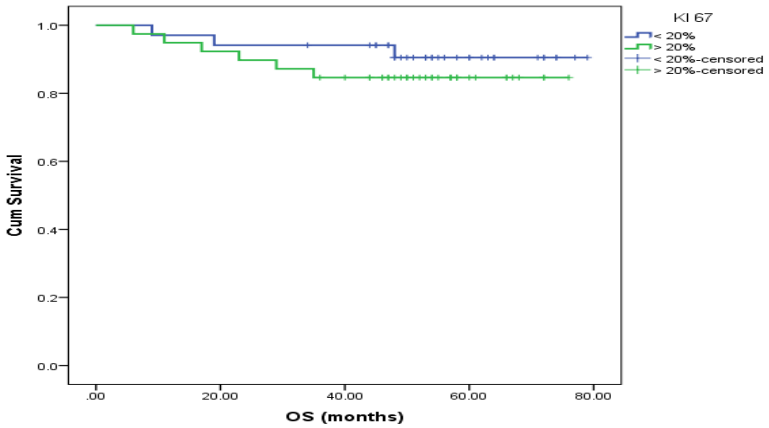

Figure (7): OS Kaplan-Meier curve

As regard the effect of KI-67 expression and patients' survival, we found that KI-67 is statistically significance with disease free survival with (P=0.036) ensuring its prognostic importance in breast cancer patient (Table 4 and Fig 8).

Table (4): Association between KI-67 expression and DFS

KI	Total N	N of Events	Mean	SE	95% CI		P-value
					Lower	Upper	
< 20%	53	4	75.295	2.283	70.82	79.769	
> 20%	62	13	57.431	2.86	51.825	63.038	0.036

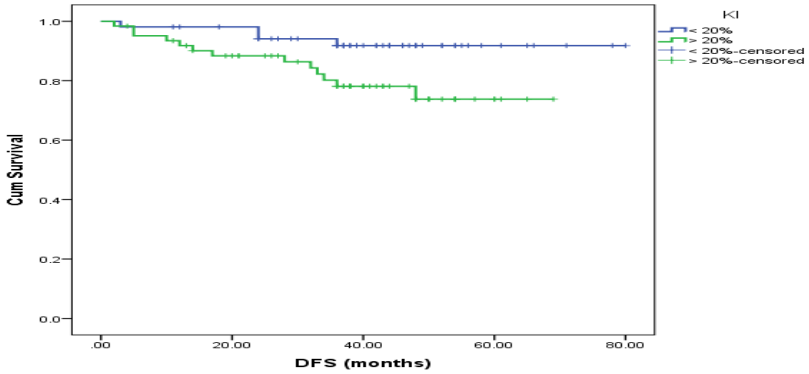

Figure (8): DFS Kaplan-Meier curve

All clinical and histopathological data were tested for their prognostic value in a multivariate analysis for disease free survival. The disease-free survival probabilities were calculated by Kaplan-Meier Estimates (P-value for log rank test). All parameters were of significant correlation for DFS. The overall survival probabilities calculated by Kaplan-Meier Estimates (P-value for log rank test). All parameters showed non-significant correlation for OS.

DISCUSSION

It is well acknowledged that state-of-the-art treatment of breast cancer is most dependent on optimal assessment of involved prognostic factors. Though in excess of a hundred factors have been reported in the literature, only a few evidently succeeded to make their way into routine practice as established prognostic tools *(Seema et al., 2017).*

In this study, our aim was to clarify the association between KI-67 expression and other clinical and pathological parameters and to show its effect on patients' outcome. We compared KI-67 staining frequency according to the various prognostic factors. KI-67 positivity was more frequently found in patients with high grade tumors, hormonal negative and HER2/NEU positive tumors, suggesting that KI-67 was involved in aggressive breast cancer. Moreover, patients with positive KI-67 >20% showed significantly poorer prognosis than those with negative KI-67<20%.

We found no association between KI-67 expression and age nor with menopausal status. The relationship between KI-67 expression with age and menopausal status has been previously explored in number of studies. The prognostic factor KI-67 was statistically significant with age *(Nishimiya et al., 2014).*

We found no association between KI-67 expression and tumor size. The relationship between KI-67expression with tumor size has been previously explored in number of studies. In one of this study done on BC patients, there were no correlations between KI-67 with tumor size *(Mirmalek et al., 2016).*

We found no association between KI-67 expression and histological type. The relationship between KI-67 expression and histological type has been explored in only a small number of studies.

We found no significance between KI-67 and tumor grade. On the contrary, a study found a significance correlation between KI-67 and grade *(Mirmalek et al., 2016).*

We found that KI-67 expression had no significance with positive lymph nodes metastasis. Another study also found no correlation between nodal metastasis and KI-67 expression *(Cheng-Har et al., 2016).* On the contrary, a study was done on BC and found a significant association between KI-67 and lymph nodes metastasis *(Mirmalek et al., 2016).*

We found a high significance relation between KI-67 and hormonal receptors status. A study found a significant correlation between KI-67 and ER, PR status which concluded that KI-67 in breast malignancies has proved its prognostic value, particularly in subgrouping HR-positive breast cancer *(Krishnanz, 2015).* Another study failed to reveal any significance between KI-67 and hormone receptors. The difference may be due to different cut-of as they used *(Awadeikarim et al., 2012).*

In our study, we found that KI-67 expressing tumors were strongly associated with Her-2/neu. This associated was evaluated in many studies. A study found a strong association with Her-2/neu status *(Saroona et al., 2013).* On the contrary, a study failed to reveal any significant association of KI-67 with Her-2/neu this difference may be due to

different cut off values *(Awadeikarim et al., 2012).*

We were able to prove a significant correlation between KI-67expression and earlier onset of recurrence and proved a significant correlation between KI-67 expressions and DFS, that high KI-67 expressing tumors were more liable for disease progression. As regard the association between KI-67 and death rates, there was no significant difference between low and high KI-67 group patients found in our study. A study found also a strong significance between KI-67 and DFS and OS for both. Overall survival was evaluated in 10 years follow up *(Nishimiya et al., 2014).*

The discrepancy among the results of different studies concerning the correlation of KI-67 with patient and disease characteristics and with recurrence and survival outcomes may originate, from different types of studied female BC samples or sample size population characteristics, different methods for assaying KI-67, differences in scoring method or different cutoff to designate high or low KI-67. Our study may provide insights into a probable predictive value for KI-67 in breast cancer treatment.

CONCLUSION

Patients with positive KI-67% showed significantly poorer prognosis than those with negative KI-67%. This may show that KI-67% was the most robust independent prognostic factor in multivariate prognostic analysis, despite having very strong correlations with other biomarkers such as hormone receptor status (ER & PR) and HER2neu.

Competing interests:

The authors declare that they have no competing interests.

Authors' contributions:

All authors involved in design, writing, revising the manuscript and approval of final version, involved in conception design, data collection, literature review, writing the manuscript, and approval of final version, in design, data collection, literature review, writing, revising the manuscript, and approval of final version of manuscript. Additionally, all authors have read and approved the final manuscript.

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القيمة الحدية للمعامل البيولوجى KI-67 للتنبوء بالتطور المرضى لسرطان الثدى عند السيدات (دراسة إسترجاعية)

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خلفيـــة البحـــث: الأورام الغيـــر حميـــده فـــي الثـــدي أكثـــر الأورام النســـائية إنتشـــارا فـــي العـــالم, والمعـــاملات البيولوجيـــه لهـــا دور قـــوي فـــي تحديـــد مـــدي تطور المرض ويعد أهمها هو المعامل البيولوجي KI-67.

الهـــدف مـــن البحـــث: تقيـــيم المعامـــل البيولـــوجي KI-67 وعلاقتـــه بمـــدي تطـــور أو إنتشـــار الـــورم وعلاقتـــه بالعلامـــات الباثولوجيـــة (مســـتقبلات الاســـتروجين والبروجســـتيرون و HER2NEU) وعلاقتـــه بحالـــة الطمـــث والعمر ونوع وحجم الورم ومراحل الورم المتعددة.

المريضـــات وطـــرق البحـــث: تضـــمن البحـــث115 مريضـــات بالغـــات عـــانين مـــن ورم غيـــر حميـــد بالثـــدي يظهـــر فـــي ملفـــات المرضـــي التحليـــل البيولـــوجي KI-67 مـــع تحديـــد قيمتـــه الحديـــة و جميـــع الحـــالات مـــن ارشـــيف قســـم عـــلاج الاورم و الطـــب النـــووي مستشـــفي الحســـين الجـــامعي وقـــد تـــم تشخيصـــهن وعلاجهن في الفترة من يناير 2014 الي ديسمبر2017.

نتـــائج البحـــث: القيمـــة الحديـــة للمعامـــل البيولـــوجي KI-67 لهـــا علاقـــة وطيـــدة بمـــدي تطـــور الـــورم وانتشـــاره, ولـــيس لـــه علاقـــة بأمـــاكن الإنتشـــار. كـــذلك، يوجـــد إرتبـــاط وثيـــق بـــين المعامـــل البيولـــوجي KI-67 والمســـتقبلات الباثولوجيـــة للاســـتروجين والبروجيســـترون و HER2neu، ولـــيس لـــه

علاقة بزيادة نسبة الوفاه من الورم, كما أنه ليس له علاقة بالعوامل الأخري مثل حجم الورم ودرجة وأنواع الخلايا الهيستولوجيه بالورم.

الاستنتاج: المريضات ذوات القيمة الحدية للمعامل البيولوجي KI-67 عالية أكثر من 20%، والتطور المرضي وفرصة انشار الورم أكثر من المريضات ذوات القيمة الحدية للمعامل البيولوجي KI-67 اقل من 20%. و كذلك قوة العلاقة بين المعامل البيولوجي KI-67 وإيجابية أو سلبية مستقبلات الاستروجين والبروجستيرون و HER2neu يساعد علي تحديد وتقييم العلاج المختار مع توقع مدي الاستجابة للعلاج.

الكلمات الدالة: معامل التكاثر البيولوجي، مستقبلات الاستروجين والبروجيستيرون Her2neu، معدل ارتجاع الورم، معدل الوفيات من الورم.