

The Role of Ki-67 in HR+/HER2- Breast Cancer: A Real-World Study of 956 Patients

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Objective: This study determined the cut-off value of Ki-67 expression and discussed the interaction between Ki-67 and histological grade, further explored the prognostic role of Ki-67 in hormone receptor-positive and human epidermal growth factor receptor 2 negative (HR+/HER2-) breast cancer;.

Materials and Methods: We assessed the Ki-67 expression of 956 patients with HR+/HER2 breast cancer diagnosed in the General Hospital of Ningxia Medical University from 2015 to 2019 by immunohistochemistry (IHC). The disease-free survival (DFS) was defined as the time from postoperative to the first local recurrence, distant metastasis or death of the disease. The follow-up by means of inpatient or outpatient medical records and telephone.

Results: 22.5% was used as the cut-off for low/high Ki-67 expression in HR+/HER2- breast cancer. Compared with the value of 14%, which is commonly used in clinic at present, the consistency of the two values is moderate (Kappa = 0.484, $P < 0.001$). The expression of Ki-67 was increased with the grade. (Median: G1:10%; G2:20%; G3:40%. Mean: G1:13%; G2:23%; G3:39%, $P < 0.001$). Survival analysis was based on all patients for a median of 51 months (24–89 months), 63 cases had recurrence or metastasis during the follow-up, which 21 cases had low expression of Ki-67 and 42 cases had high expression. The patients with Ki-67 $\geq 22.5\%$ had a 2.969 higher risk of early recurrence and metastasis than the patients with Ki-67 $< 22.5\%$. There were 4 cases of local recurrence, 7 cases of regional lymph node metastasis, and 52 cases of distant metastasis in all patients, the common distant metastases were bone, liver, and lung, and rare metastases were adrenal gland, bone marrow, and pericardium.

Conclusion: In HR+/HER2- breast cancer, patients with Ki-67 $> 22.5\%$ have a worse prognosis and are more likely to have early recurrence and metastasis.

Keywords: Ki-67, breast cancer, cut-off value, histological grade, recurrence and metastasis

Introduction

According to the Global Cancer Statistics report in 2020, there are about 2.26 million new women with breast cancer worldwide, accounting for 11.7% of all new cancer cases, surpassing lung cancer as the most common tumor in the world for the first time.^{1,2} Breast cancer is divided into four molecular subtypes with different characteristics and prognoses, The most common type of breast cancer in clinic is HR+ breast cancer, accounting for about 75%.³ HR+/HER2- breast cancer accounts for 65% of breast cancer in women under the age of 50 and 75% of breast cancer in elderly women.⁴ In HR+/HER2- breast cancer, gene expression analysis can be divided into two different subtypes-luminal A and luminal B (HER2-).⁵ Ki-67 is an important index that is often used to distinguish between luminal A and luminal B (HER2-) in clinics, and it is also one of the important indexes to define the prognosis of patients with HR+/HER2- early breast cancer. It is located on the long arm of human chromosome 10 (10q25).⁶ The positive rate of expression is different in different stages of the cell cycle, the positive rate of Ki-67 expression is low in the G1 and early S phase, increases gradually during mitosis, reaches the peak in the M stage, decreases rapidly in the late and terminal stage of mitosis, and does not express in G0 stage.⁷ The expression of Ki-67 in breast cancer is related to luminal B (HER2-), high risk of recurrence and good response to neoadjuvant chemotherapy.⁸ In 2011, the

International Breast Cancer Working Group pointed out that due to the lack of standardized evaluation methods of Ki-67 expression, there is still no unified “gold standard” for the evaluation of the Ki-67 proliferation index.⁹ Although the consistency of Ki-67 testing in the same laboratory may be high, in different laboratories it still varies greatly because the consistency and repeatability of Ki-67 expression evaluation are low between observers. Different cut-off values may bring different treatment options to patients, and lack of chemotherapy or over-treatment may lead to different prognoses. Therefore, to guide the standardized treatment of breast cancer patients, clinicians must understand the distribution characteristics of Ki-67 and determine the most suitable cut-off value of Ki-67 for HR+/HER2- breast cancer in our laboratory. Patients with high expression of Ki-67 are prone to early recurrence and metastasis. We should find patients with high risk of recurrence and metastasis and strengthen treatment.

Material and Methods

Patients

The study, of 956 patients with HR+/HER2- breast cancer diagnosed by operation and pathology, from 25 to 80 years old between 2015 to 2019 in the General Hospital of Ningxia Medical University, all patients are female. Tumour samples were collected from the tumour tissue blocks used for routine pathologic evaluation. All patients accordance with the following standard: (1) No distant metastasis before operation; (2) Standardized chemotherapy, radiotherapy and endocrine therapy were performed after operation; (3) The clinical medical records are complete. We collect and organize the following parameters: age, IHC results, tumor stage (the TNM stage of AJCC 7th edition), histological grade, lymph node metastasis, vascular/nerve invasion, transfer time, etc. Patients with stage IV, neoadjuvant therapy, triple-negative, or HER2-positive breast carcinoma were excluded from the study.

Ki-67 Evaluation

The Ki-67 index was detected by IHC in all patients, which was evaluated and determined by two experienced pathologists. The yellow deposition in the nucleus is Ki-67 positive cells, and the expression rate of Ki-67 is the percentage of Ki-67 positive cells in the total number of tumor cells.

IHC Standard

The expression of estrogen receptor (ER), progesterone receptor (PR), and HER2 in all HR+/HER2- breast cancers were detected by immunohistochemical method. The positive of ER and PR is defined as the staining of tumor cells $\geq 1\%$. The expression level of HER2 was divided into 0~3+, and the cases with HER2 expression of 2+ were further detected by fluorescence in situ hybridization (FISH). HER2 negative was defined as (0), (1 +), or negative by the FISH test, HER2 positive was defined as (3 +), or positive by the FISH test.

Follow-Up

The follow-up by means of inpatient or outpatient medical records or telephone. The starting time is the date of operation, and the deadline is December 31, 2021. The endpoint of follow-up is the deadline for disease progression, death, or loss of follow-up. DFS is defined as the time from postoperative to the first local recurrence, distant metastasis, or death of breast cancer. The patients that had recurrent and metastatic must be confirmed by pathological.

Statistical Analysis

The data were analyzed by SPSS 25.0 and GraphPad Prism 8.0.1. The receiver operating characteristic curve (ROC) was used to determine the cut-off value of Ki-67 expression, The relationship between Ki-67 expression and pathological was analyzed by χ^2 test, Kaplan-Meier method was used to draw the survival curve, significant level was set as 0.05.

Result

The expression range of Ki-67 in HR+/HER2- breast cancer of 956 patients is 1%-90%, the most common range is 10%-30%, the median of Ki-67 expression is 20%, and the average is 25% (Figures 1 and 2).

With the statistical analysis of the ROC curve, the cut-off value of Ki-67 is 22.5% (Figure 3). All patients were divided into two groups, compared with the value of 14%, which is commonly used in clinic at present, the consistency of the two values is moderate ($\text{Kappa} = 0.484$, $P < 0.001$) (Table 1). Histological grade, PR expression, T stage, and vascular/nerve invasion were correlated with the Ki-67 (Table 2). The expression of Ki-67 is increased with the grade (Figure 4).

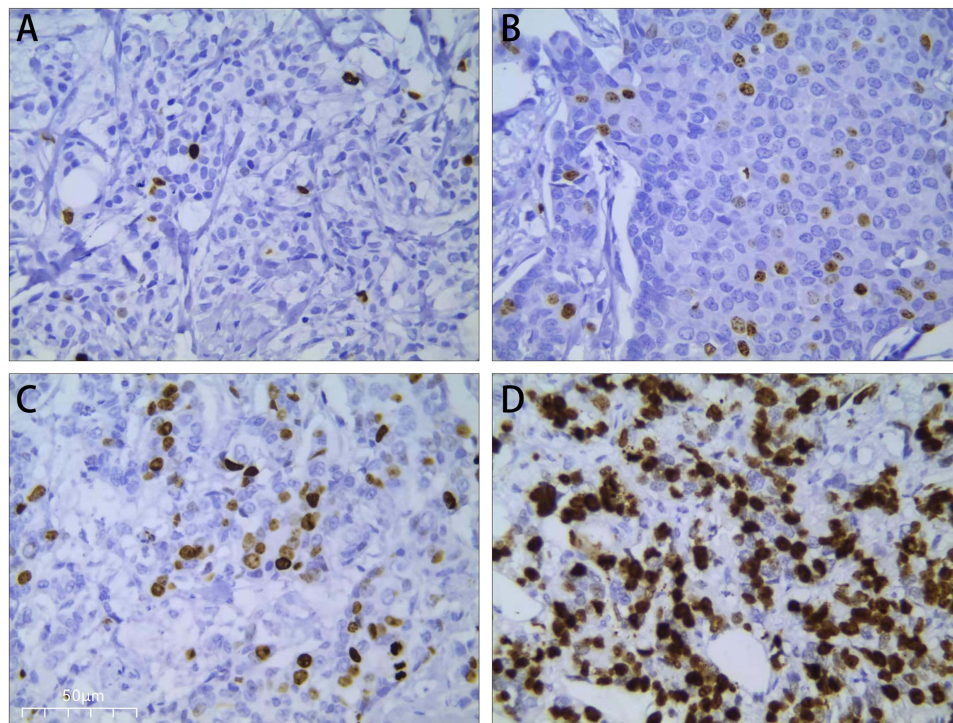


Figure 1 The different expression of Ki-67 in breast cancer of tumor tissues. ((A) 5%; (B) 20%; (C) 30%; (D) 60%; SP x400).

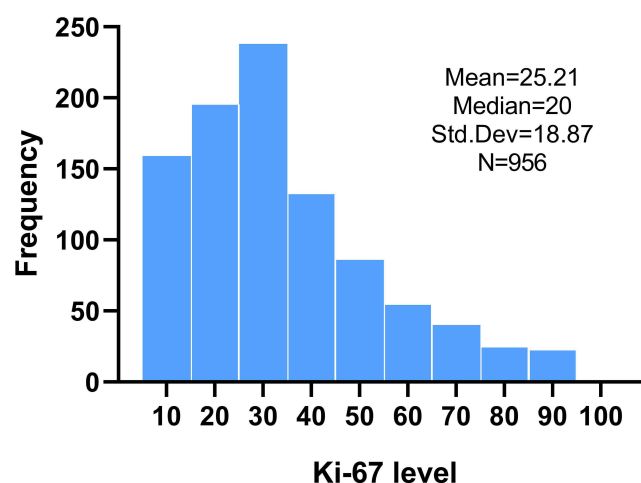


Figure 2 The frequency distribution of Ki-67 value in 2015–2019.

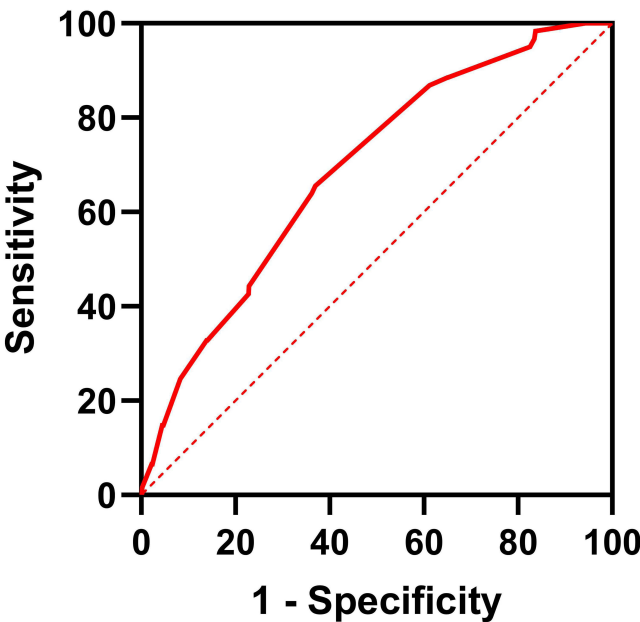


Figure 3 The ROC curve of Ki-67 expression (Area under ROC curve: 0.689; Sensitivity: 63.02%; Specificity: 65.57%; Youden Index: 0.286; 95% CI: [0.626–0.754]; $P < 0.001$).

Survival analysis was based on all patients for a median of 51 months (24–89 months), 63 cases had recurrence or metastasis during the follow-up, which 21 cases had low expression of Ki-67 and 42 cases had high expression. The patients with $Ki-67 \geq 22.5\%$ had a 2.969 higher risk of early recurrence and metastasis than the patients with $Ki-67 < 22.5\%$ (Figure 5, Table 3). Ki-67 was an independent risk factor for HR+/HER2 breast cancer (Table 4). There were 4 cases of local recurrence, 7 cases of regional lymph node metastasis, and 52 cases of distant metastasis in all patients. The common positions of distant metastasis were bone, liver, and lung, and rare metastases were adrenal gland, bone marrow, and pericardium. (Figure 6)

Table 1 HR+/HER2- Breast Cancer at Different Cut-off Values

Type/Cut-Off Value	14%	22.5%	Kappa	P
Luminal A	320 (33.5%)	585 (61.2%)	0.484	<0.001
Luminal B (HER2-)	636 (66.5%)	371 (38.8%)		

Table 2 Correlation of Ki-67 with Pathological for the Different Cut-off Values

Pathological	Ki-67		χ^2	P	Ki-67		χ^2	P
	<14%	≥14%			<22.5%	≥22.5%		
Age			1.458	0.227			8.508	0.004
≤40	40	98			69	69		
>40	280	538			516	302		
Grade			119.975	<0.001			6.019	0.049
G1	101	54			82	73		
G2	196	390			363	223		
G3	23	192			140	75		
PR expression*			10.046	0.002			27.05	<0.001
≤ 20%	56	170			105	121		
>20%	264	466			480	250		

(Continued)

Table 2 (Continued).

Pathological	Ki-67		χ^2	P	Ki-67		χ^2	P
	<14%	≥14%			<22.5%	≥22.5%		
T stage			6.468	0.039			7.811	0.020
T1	201	336			352	185		
T2	119	282			233	168		
T3	5	13			8	10		
N stage			5.957	0.114			8.567	0.036
N0	179	310			319	170		
N1	89	201			170	120		
N2	41	87			72	56		
N3	11	38			24	25		
Vehicle			5.969	0.015			5.704	0.017
Yes	24	81			53	52		
No	296	555			532	319		

Note: *References with a PR threshold of 20%.¹⁰

Abbreviations: PR, Progesterone Receptor; χ^2 , Chi-Square Value; P, Probability-value.

Discussion

Ki-67 index is a common parameter for the molecular type of HR+/HER2- breast cancer by IHC instead of gene detection. To determine the threshold value of Ki-67 in HR+/HER2- breast cancer, we can detect multiple genes in all samples, and then compare the results of gene detection with IHC to get the best threshold value, but this method is expensive and difficult in clinical. Ki-67 was detected by IHC, and the percentage of positive expression was calculated by pathologist with artificial vision. Despite its nearly universal use in pathology laboratories worldwide, no internationally accepted consensus has yet been achieved for some methodological details related to Ki67. Controversial issues refer to choice of IHC antibody clones, scoring methods, inter-laboratory reproducibility, and the potential value of computer-assisted imaging analysis and/or artificial intelligence for Ki67 assessment.¹¹ The individual differences in the judgment of Ki-67 positive cells by different pathologists lead to poor consistency of Ki-67 positive expression, so its reliability is reduced due to the variability between observers. At the same time, although there is a high consistency of Ki-67 testing in the laboratory, the consistency of Ki-67 testing among different laboratories is still lack of comparison. The factors leading to the inconsistency among laboratories include tumor region selection, counting methods and subjective evaluation of positive staining.¹² In recent years, the effectiveness and methods of Ki-67 detection has been a research hotspot. The development of digital image analysis system makes more choices for the evaluation of Ki-67 proliferation index.¹³ It is found that after zoning according to staining distribution, compared with visual quantitative or

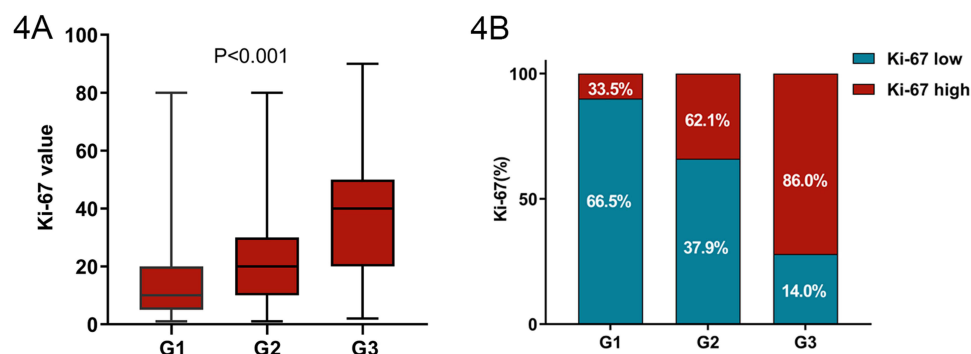


Figure 4 The relationship between Ki-67 expression and histological grade. (Median: G1:10%; G2:20%; G3:40%. Mean: G1:13%; G2:23%; G3:39%, $P < 0.001$).

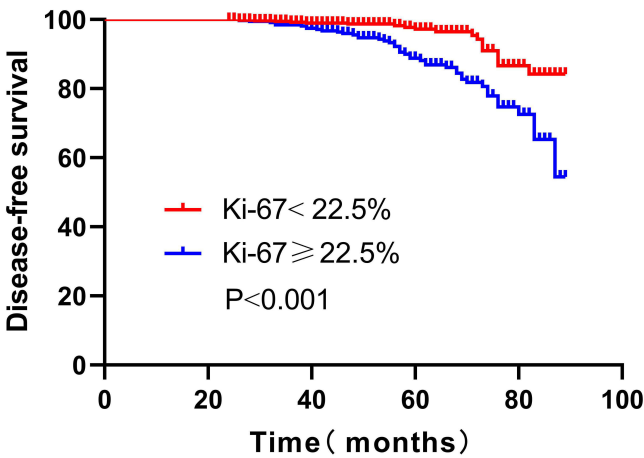


Figure 5 Kaplan-Meier survival curve with the expression of Ki-67.

digital image analysis, different observers have satisfactory consistency in Ki-67 quantification, or it may be a candidate standardized method for Ki-67 index quantification of breast cancer or other malignant tumors.¹⁴

The cut-off value that distinguishes the low/high Ki-67 expression in HR+/HER2- breast cancer is constantly changing. The consensus of experts at the 2009 St Gallen International Breast Cancer Conference recommended that Ki-67 should be used as a proliferative marker for the selection of appropriate systemic treatment, classified according to three levels: low level ($\leq 15\%$), medium level (16–30%) or high level ($> 30\%$).¹⁵ Through the study of the PAM50 gene expression profile and comparison of IHC results, Cheang found that the best cut-off value to distinguish Luminal A and Luminal B (HER2-) breast cancer was 13.25%.¹⁶ Based on this result, the 2011 St Gallen meeting determined the cut-off value of Ki-67 to distinguish these two subtypes at 14%.¹⁷ The 2013 St Gallen meeting raised the cut-off value of Ki-67

Table 3 Univariate Analysis of Prognosis with HR+/HER2- Breast Cancer

Pathological	n	HR	95% CI	χ^2	P
Age		1.773	0.9266~3.392	2.992	0.084
≤40	138				
>40	818				
Ki-67		2.969	1.799~4.901	18.12	<0.0001
Ki-67<22.5%	355				
Ki-67≥22.5%	601				
Grade		2.220	1.164~4.231	5.867	0.0154
G1	155				
G2-3	801				
PR expression		0.6075	0.3439~1.073	2.948	0.086
≤ 20%	226				
>20%	730				
T stage		2.767	1.651~4.635	14.94	0.0001
T1	537				
T2-T3	419				
N stage		2.464	1.496~4.085	12.55	0.0004
N0	489				
N1-N3	467				
Vehicle		2.188	1.115~4.294	5.186	0.0228
Yes	851				
NO	105				

Abbreviations: PR, Progesterone Receptor; HR, Hazard Ratio; CI, Confidence Interval; χ^2 , Chi-Square Value; P, Probability-value.

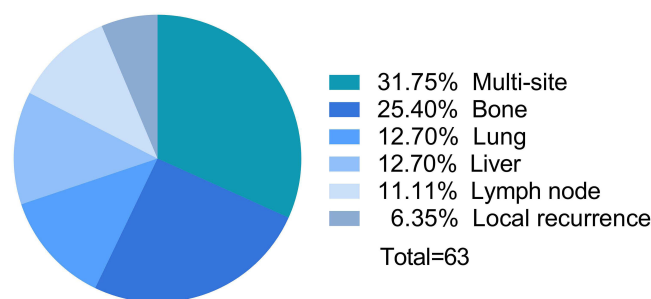
Table 4 Multivariate Analysis of Prognosis with HR+/HER2- Breast Cancer

Factors	β	SE	Wald	P	HR	95% CI
T stage	0.806	0.264	9.350	0.002	2.239	1.336~3.753
N stage	0.687	0.276	6.198	0.013	1.9889	1.157~3.415
Vehicle	0.456	0.293	2.416	0.120	1.578	0.888~2.805
Grade	0.835	0.537	2.416	0.120	2.306	0.084~6.610
Ki-67	0.866	0.287	9.089	0.003	2.378	1.354~4.178

Abbreviations: β , Beta; SE, Standard Error; P, Probability-value; HR, Hazard Ratio; CI, Confidence Interval.

expression to 20%.¹⁸ In 2015, the expert group of the St Gallen meeting suggested that Ki-67 should be explained according to the values of the local laboratory.¹⁹ At the latest St Gallen meeting in 2021, 42.4% of the experts suggested the threshold for Ki-67 to recommend adjuvant chemotherapy in ER+, HER2-, node-negative breast cancer is 30%.²⁰ Many studies have taken different thresholds to explore the effect of Ki-67 expression on the prognosis, including 14%,²¹ 15%,²² 20%,²³ 22%,²⁴ 25%.²⁵ Meta-analysis shows that the threshold value of Ki-67 is between 5% and 30%.²⁶ The guidelines and norms for breast cancer diagnosis and treatment of the Chinese Anti-Cancer Association point out that the value of the Ki-67 proliferation index may be different in different pathological centers, 20–30% can be used as the cut-off value of Ki-67.²⁷ We determined the cut-off value of Ki-67 expression is 22.5% through the analysis of ROC in this study, which means the patients with Ki-67 \geq 22.5% have a poor prognosis and are more likely to have early recurrence and metastasis. In order to compare with the Ki-67 critical value of 14% which is the most commonly used in clinic, we used the Ki-67 cutoff value of 14% and 22.5% respectively to classify all HR+/HER2- breast cancers, and the results were moderately consistent, which means that the Ki-67 cut-off value of 22.5% is more instructive in clinical diagnosis, treatment and prognosis of breast cancer patients. So we should use the Ki-67 threshold in our laboratory instead of continuing to use 14%, which allows some patients to avoid chemotherapy.

HR+/HER2- breast cancer is a heterogeneous tumor, there are differences in PR expression, histological grade, Ki-67 proliferation, and so on, and these characteristics are highly correlated.²⁸ Studies have shown that the expression of Ki-67 is related to the clinicopathological features of breast cancer, such as tumor size, histological grade, PR status, vascular nerve invasion, and so on.² In this study, we found that histological grade, PR expression, T stage, and vascular/nerve invasion are all related to Ki-67 expression. The consensus of experts at the 2017 St Gallen conference pointed out for the first time that histological grade can be used to distinguish the molecular type of HR+/HER2- breast cancer.²⁹ The histological grade is mainly evaluated from three aspects: the degree of glandular duct formation, nuclear pleomorphism, and mitosis count. The expression of Ki-67 increases gradually during mitosis, so the tumor grade may be indirectly related to the expression of Ki-67 according to mitotic cell count. Liang Qin found that Ki-67 is related to tumor grade, and can predict histological grade to some extent.³⁰ Mohammed found that the expression level of Ki-67 was positively correlated with histological grade, the higher the tumor grade, the higher the Ki-67 expression, Ki-67 can predict tumor invasiveness and higher histological grade.²⁹ Professor Fu Li pointed out that the positive rate of Ki-67 in ER+ breast

**Figure 6** The common metastatic sites of HR+/HER2- breast cancer.

cancer varies widely, the expression of Ki-67 in high differentiated and G1 can be less than 5% but more than 20% in high histological grade breast cancer.³¹ It has been reported that luminal-type breast cancer is at opposite ends in histological grade, G1 conforms to luminal A, G3 conforms to luminal B type, and G2 is between them.²⁸ In this study, we analyzed the relationship between Ki-67 expression and histological grade, and the results showed that the expression of Ki-67 is closely related to histological grade, the expression of Ki-67 was increased with the increase of grade. Both histological grade and Ki-67 value can distinguish the molecular type of luminal breast cancer, but the study found that the consistency between them is low, the consistency can be improved when these two factors are combined.³² It is reported that the risk of recurrence of HR+/HER2- breast cancer has remained relatively stable for many years, at least half of the patients with recurrence and metastasis occurred 5 years after diagnosis, and even some patients developed recurrence and metastasis for more than 10 years.²⁸ To improve the survival rate of patients with early recurrence and metastasis, clinicians need to identify high-risk patients with early recurrence and metastasis and strengthen treatment and follow-up. Our study found that the patients with Ki-67 $\geq 22.5\%$ had a 2.969 higher risk of early recurrence and metastasis than the patients with Ki-67 $< 22.5\%$. Studies have found that the common sites of recurrence and metastasis of HR+/HER2- breast cancer include bone, lymph nodes, pleura or lung, liver, and skin.²⁸ We found the most common metastatic site of HR+/HER2- breast cancer is bone (vertebra is the most common), followed by viscera (liver, lung), regional lymph nodes, local chest wall skin, and multi-site metastasis is more common, which is consistent with the literature report. In this study, we also found that three patients had rare metastases of the adrenal gland, bone marrow, and pericardium, which occurred at the same time or successively with the common metastatic sites mentioned above.

Abbreviations

HR, Hormone receptor; HER2, Human epidermal growth factor receptor; DFS, Disease-free survival; ER, Estrogen receptor; PR, Progesterone receptor; FISH, Fluorescence in situ hybridization; AJCC, American Joint Committee on Cancer.

Data Sharing Statement

Available upon request to maqin9304@163.com.

Ethical Statement

This study approval was granted by the Ethics Committee of the General Hospital of Ningxia Medical University (No: KYLL-2021- 610). This study was conducted in accordance with the Declaration of Helsinki. The lead researcher was presenting the purpose of the study, the benefit, and the risk of the procedure taken by the research participant to the ethical committee board prior to approval. Each research participant was given detailed information regarding the purpose, benefit, and risk of the study. Each research participant signed an informed consent form before participating in the study.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All authors declare that they have no competing interests in this work.

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