Distinct outcomes in patients with different molecular subtypes of inflammatory breast cancer

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ABSTRACT

الأهداف: تحديد نتائج المرضى اللمعي A، واللمعي B، ومستقبلات عامل النمو البشري الإيجابي والنوع الفرعي السلبي الثلاثي الجزئيي لسرطان الثدي الالتهابي باستخدام التحليل بأثر رجعي.

الطريقة: أجريت هذه الدراسة خلال الفترة من فبراير 2004م وفبراير 2010م في 3 مستشفيات مختلفة في الصين. قمنا بتحليل النتائج الإكلينيكية والخصائص المرضية واستراتيجيات العلاج في 67 حالة IBC بدون أي نقائل مختلفة. استخدم اختبار مربع كاي وأنوفا لتصميم تقيم النتائج بين الأنواع الفرعية المختلفة. تم تحليل معدل البقاء العام باستخدام طريقة كابلن ميرير وأجري تحليل متعدد المتغيرات باستخدام نموذج كوكس للانحدار.

النتائج: كان معدل البقاء العام لعامين 55% للدراسة الكلية. بلغ متوسط مدة البقاء العام لمرضى لمعي A 35 شهر، واللمعي B 30 شهر، و HER-2 الايجابي 24 شهر، والنوع الفرعي السلبي الإيجابي 20 شهر واختلفت بشكل إحصائي عن بعضها البعض باستخدام التحليل متعدد المتغيرات لمرضى لمعي A 76%، ولمعي B 54%، و HER-2 الايجابي 47%، وانخفضت الوفاة بالمقارنة مع النوع الإيجابي الثلاثي. إضافة إلى ذلك، ارتبط علامة Ki-67 المرتفعة بزيادة خطورة الوفاة. في حين تحسن بقاء المرضى بشكل إحصائي بعد العلاج الجراحي.

الخاتمة: ارتبط نوع سرطان الثدي مع نتائج مختلفة لمرضى IBC. أظهرت الدراسة أن المرضى مع IBC السلبي الثلاثي نتائج ضعيفة أكثر من لمعي A، ولمعي B والنوع الفرعي HER-2. تشير النتائج أن IBC مرض متغاير مشابه لسرطان الثدي التقليدي.

Objectives: To determine the outcome of patients with luminal A, luminal B, human epidermal growth factor receptor-2 (HER-2) positive, and triple negative molecular subtypes of inflammatory breast cancer (IBC) using a retrospective analysis.

Methods: This study was conducted between February 2004 and February 2010 in 3 different hospitals in China. The clinical outcomes, pathological features, and treatment strategies were analyzed in 67 cases of IBC without distant metastases. A chi-square test and one-way ANOVA were used to assess outcomes between different subtypes. Overall survival (OS) was analyzed using the Kaplan-Meier method and multivariate analysis was conducted using the Cox regression model.

Results: The 2-year OS rate was 55% for the entire cohort. Median OS time among patients with luminal A was 35 months, luminal B was 30 months, HER-2 positive was 24 months, and triple negative subtypes was 20 months, and they were significantly different from each other (p=0.001). Using multivariate analysis, luminal A had 76% (p=0.037), luminal B had 54% (p=0.048), and HER-2 positive subtypes had 47% (p=0.032) decreased risk of death compared with the triple negative subtype. Furthermore, elevated Ki-67 labeling was associated with increased risk of death, while the surgical treatment significantly improved patient survival.

Conclusion: Breast cancer subtypes are associated with distinct outcomes in IBC patients. Patients that presented with triple negative IBC had poorer outcome than luminal A, luminal B, and HER-2 subtypes. These results indicate that IBC is a heterogeneous disease similar to the conventional breast cancer.

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Inflammatory breast cancer (IBC) is the most aggressive and fatal form of locally advanced breast cancer, and accounts for approximately 1-6% of all breast tumors.[1] Like conventional breast cancer, IBC is a heterogeneous disease that has been stratified into different subtypes, mainly based on gene expression array data.[2] These distinguishing subtypes of IBC show different clinical features and are associated with survival. However, array-based classification is limited in the clinic due to technical and budget constraints. For prognostic purposes, clinicians need more economical and practical methods, other than DNA array analysis to define subtypes of breast cancer. In 2011,[3] the St. Gallen International Breast Cancer Conference Expert Panel adopted a new approach in defining alternative subtypes of breast cancer. These guidelines were based on the expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (HER-2), and the Ki67 labeling index (LI), a cell proliferation marker.[3] According to the new classification system, the 4 clinical subtypes are defined as follows: luminal A (ER and/or PR positive, HER-2 negative, Ki-67 LI ≤14%); luminal B (ER and/or PR positive, HER-2 negative, Ki-67 LI >14%; or ER and/or PR positive, HER-2 positive); HER-2 positive (ER and PR negative, HER-2 positive); and triple negative (ER, PR, HER-2 negative). The prognostic value of this newly defined subtyping has only been measured in patients with early stages of breast cancer. However, this subtyping approach has not been investigated in patients with IBC. Therefore, in the present study, these new clinical subtypes, clinicopathological characteristics, and prognoses in IBC patients were analyzed retrospectively.

Methods.

Patients. This study was conducted between February 2004 and February 2010 in 3 different hospitals in China. The complete clinical, pathological, and therapeutic records were retrospectively collected from 67 female patients treated at Xiangya Hospital (54 cases), Hunan Provincial People's Hospital (7 cases), and Hunan Provincial Tumor Hospital (6 cases), Changsha, Hunan, China. Patients who presented with metastases at their first diagnosis were excluded. Written informed consent to participate in the study was obtained from all patients. The study protocol was approved by the hospital review board. Clinical data obtained from patients included age, body mass index (BMI), menstrual status, and tumor presentation and stage. Pathological information obtained included histological grade, presence of lymph node (LN) metastasis, and status of ER, PR, HER-2, and Ki-67. Therapeutic regimens and effects were also analyzed.

Pathological analysis. All pathological diagnoses were confirmed by analysis of core needle biopsies by 2 pathologists before treatment. The status of ER, PR, HER-2, and Ki-67 were obtained by immunohistochemical (IHC) staining of paraffin-embedded tissues using the monoclonal antibodies SP1 (α-ER), SP3 (α-HER-2), and SP6 (α-Ki-67) from ThermoFisher Scientific (Fremont, CA, USA) and 1E2 (α-PR) from Ventana (Tucson, AZ, USA). The tissue samples were classified as positive for ER and PR when ≥1% of the tumor cells showed positive nuclear staining. The Ki-67 LI was defined as the percentage of tumor cells showing definite nuclear staining determined by a pathologists. The HER-2 status was evaluated using IHC staining or fluorescence in situ hybridization (FISH). The HER-2 positivity was defined as 3+ receptor overexpression with strong membranous staining in ≥30% of cells, or gene amplification with a gene copy ratio of HER-2/CEP-17 >2.0 using FISH analysis.

Therapeutic methodology. Most patients received neoadjuvant chemotherapy, modified radical mastectomy, or postmastectomy radiation of the chest wall and draining lymphatics. Neoadjuvant chemotherapy regimens included treatment with doxorubicin (Pharmorubicin RD, Pfizer, New York, USA), and taxane (Docetaxel, Sanofi-Aventis, Paris, France). After every cycle of neoadjuvant chemotherapy, an evaluation of the objective response was made using the Response Evaluation Criteria in Solid Tumors (RECIST) 1.0 standard.[4] The objective response rate (ORR) included both the complete and partial responses. Tamoxifen (Yangzijiang Co, Taizhou, China), or the aromatase inhibitor, Femara (Novartis, Basel, Switzerland) were used in patients with hormone receptor (HR)-positive IBC. The HER-2 targeted therapy using Trastuzumab (Roche, Basel, Switzerland) was recommended for HER-2-positive patients. All of the therapeutic regimens were in compliance with the newest National Comprehensive Cancer network (NCCN) guidelines in the corresponding year.

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Follow-up. All cases were followed-up by telephone every 6 months. Data obtained included recurrence, metastasis, and death related to IBC. The follow-up end date was October 2013. The endpoint of this study was overall survival (OS). Patients were included until the last follow-up date, and then censored if follow-up information were unavailable due to fatality, or losing touch.

Statistical analysis. To compare the distribution of clinical and pathological characteristics among the 4 subtypes, a chi-square test and one-way ANOVA were used. The OS was estimated using the Kaplan-Meier method, and the log-rank test was used to assess differences between groups. Prognostic factors with a $p<0.10$ using a univariate analysis were entered into the multivariate analysis model, and Cox regression (Forward LR) was then fitted to assess their relationship. All *p*-values were 2-sided, and values <0.05 were considered to be statistically significant. All statistical analyses were performed using the Statistical Package for Social Sciences version 17 (SPSS Inc., Chicago, IL, USA) for Windows (Microsoft Corporation, Redmond, WA, USA).

Results. The detailed demographics of patients included in the study are listed in **Table 1**. Among the 67 female patients, the distribution of patients with luminal A was 7 (10.4%), luminal B was 23 (34.3%), HER-2 positive was 16 (23.9%), and triple negative subtypes was 21 (31.4%). The median age at diagnosis was 45 years (range: 25-78 years), and the median BMI was 24 kg/m^2 (range: 17.3-34.2 kg/m^2). In 12% of cases, the disease occurred during pregnancy or lactation. The most common clinical presentation of the disease included the flattening, retraction, blistering, or crusting of the nipple (89%), palpable draining of the lymph

Table 1 - Clinical, pathological, and therapeutic characteristics of patients with inflammatory breast cancer.

Variables	All cases (n=67)	Luminal A (n=7)	Luminal B (n=23)	HER-2 positive (n=16)	Triple negative (n=21)	*P*-value
Clinical characteristics						
Median age, years	45	45	49	39	45	0.147
Median BMI, kg/m^2	24.0	23.2	24.9	23.4	24.1	0.688
Premenopausal, %	67	71	57	88	62	0.212
Presentation, %						
Diffuse erythema	84	71	83	81	91	0.668
Edema (Peau d'orange)	66	86	61	63	67	0.668
Nipple involvement	89	100	91	93	81	0.433
Underlying mass	88	86	91	87	86	0.941
Palpable LN	89	86	83	100	91	0.388
Tumor stage, %						0.812
IIIB	67	71	74	63	62	
IIIC	33	29	26	37	38	
Pathological characteristics, %						
Grade III	34	29	44	19	38	0.422
HR positive	45	100	100	0	0	<0.001
HER-2 positive	33	0	26	100	0	<0.001
Ki-67 LI						<0.001
≤14%	22	100	4	6	29	
14-40%	45	0	74	38	33	
≥40%	33	0	22	56	38	
Treatment characteristics, %				50		
ORR	71	100	70	75	80	0.083
Surgery	79	100	74	50	81	0.488
≥4 LN positive	47	57	41	31	47	0.905
Hormone therapy	51	86	91	75	10	<0.001
Radiation	70	71	65	56	71	0.926
Trastuzumab therapy	18	14	9	50	0	<0.001

BMI - body mass index, LN - lymph node, HR - hormonal receptor, HER - human epidermal growth factor receptor, LI - labeling index, ORR - objective response rate

nodes (89%), detection of an underlying mass (88%), diffuse erythema (84%), and edema (66%). Elevated Ki-67 LI (>14%) was detected most frequently in luminal B (96%) and HER-2 positive (94%) subtypes, and was less abundant (71%) in triple negative IBC. The ORR to neoadjuvant therapy in luminal A was 100%, luminal B was 70%, HER-2 positive was 50%, and triple negative subtypes was 80%. Fifty-four patients underwent modified radical mastectomy. Three patients with luminal A and luminal B subtypes did not receive hormone therapy due to disease progression before the completion of adjuvant treatment. Among those patients who received hormone therapy, 31% of HER-2 positive and 10% of triple negative patients transitioned from HR-negative to HR-positive as demonstrated by the analysis of core needle biopsies and resection specimens. Furthermore, the subgroups also showed differences in HR, and HER-2 status, Ki-67 LI, and response to hormone and trastuzumab therapies. The follow-up period ranged from 8-55 months with a median follow-up time of 24 months. Overall, locoregional recurrences were observed in 25 (37.3%) patients. Contralateral breast metastases was observed in 8 (11.9%) and distant metastases in 55 (82.1%) patients. During follow-up, 54 (80.6%) patients with IBC died due to the disease. The 2-year OS rate was 55% (95% CI; 43-67%). As shown in **Figure 1**, the median OS time among patients with luminal A was 35 months (95% CI; 27-42), luminal B was 30 months (95% CI; 22-37), HER-2 positive was 24 months

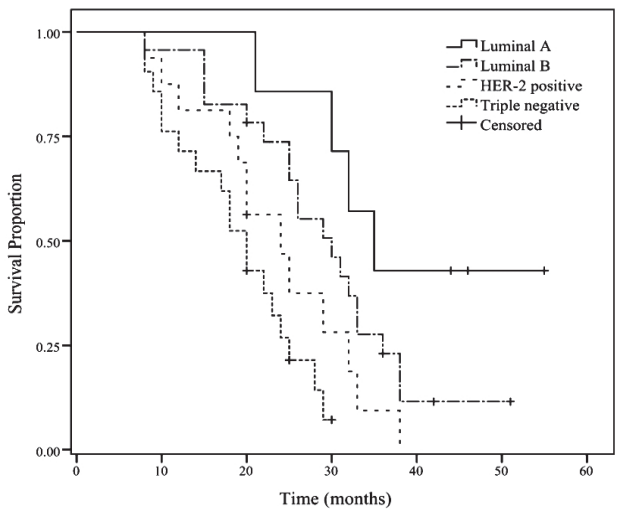

Figure 1 - The inflammatory breast cancer (IBC) overall survival curves for luminal A, luminal B, human epidermal growth factor receptor (HER)-2 positive and triple negative IBC subtypes. Patients were censored if the follow-up information was unavailable due to fatality, or loss of contact.

Table 2 - Identification of survival-associated factors in patients with inflammatory breast cancer (IBC) using a univariate analysis.

Variables	OS (95% CI)*	*P*-value
Age, years		0.918
<45	25 (18-32)	
≥45	28 (23-33)	
BMI, kg/m²		0.279
<24	21 (17-24)	
≥24	30 (26-33)	
Menopausal status		0.230
Premenopausal	26 (19-32)	
Postmenopausal	24 (15-32)	
LN palpable		0.200
Yes	25 (19-30)	
No	35 (25-45)	
Stage		0.242
IIIB	26 (22-29)	
IIIC	20 (14-26)	
HR		0.001
Positive	31 (25-37)	
Negative	20 (15-24)	
HER-2		0.170
Positive	25 (20-30)	
Negative	28 (23-33)	
Ki-67 LI		0.008
≤14%	30 (18-42)	
14-40%	28 (23-32)	
≥40%	20 (18-22)	
Subtype		0.002
Luminal A	49 (29-68)	
Luminal B	30 (25-34)	
HER-2 positive	25 (17-32)	
Triple negative	20 (13-26)	
ORR		<0.001
Yes	30 (26-34)	
No	15 (9-21)	
Surgery		<0.001
Yes	29 (25-32)	
No	12 (10-14)	
LN metastasis		0.051
<4	31 (26-35)	
≥4	25 (17-33)	
Endocrine therapy		0.012
Yes	30 (26-34)	
No	20 (17-22)	
Radiation		0.002
Yes	29 (26-32)	
No	18 (12-24)	
Trastuzumab		0.413
Yes	25 (13-36)	
No	26 (22-30)	

CI - confidence interval, OS - overall survival, BMI - body mass index, LN - lymph node, HR - hormonal receptor, ORR - objective response rate, *range in months

(95% CI; 17-31), and triple negative subtypes was 20 months (95% CI; 17-23), and these differences were significantly different (p=0.001). As the data indicates, the OS for triple negative IBC disease was worse than any of the other 3 subtypes of IBC. Pair-wise comparisons determined significant differences in survival between luminal A and HER-2 positive subtypes (p=0.014), luminal A and triple negative subtypes (p=0.002), and luminal B and triple negative subtypes (p=0.001). To identify the potential survival-associated factors, univariate analysis was performed and the results are summarized in **Table 2**. Several parameters were found to be associated with a significantly improved survival outcome. These included low Ki-67 LI, positive hormonal status, objective response to neoadjuvant chemotherapy, surgery, endocrine therapy, and radiation therapy. Using a multivariate Cox regression test (**Table 3**), a strong association between subtypes and OS was found. Compared with the triple negative subtype, luminal A (hazard ratio: 0.245; 95% CI: 0.065-0.920; p=0.037), luminal B (hazard ratio: 0.462; 95% CI: 0.212-0.997; p=0.048), and HER-2 positive subtypes (hazard ratio: 0.532; 95% CI: 0.175-0.926; p=0.032) were independent prognostic factors for a better overall survival. Compared with patients whose tumors displayed Ki-67 LI ≥40%, patients' risk of death from IBC decreased by 62% and 55% when their tumors had a Ki-67 LI of ≤14% (hazard ratio: 0.382; 95% CI: 0.139-1.048; p=0.062), or between 14-40% (hazard ratio: 0.452; 95% CI: 0.226-0.907; p=0.025) (**Figure 2A**). Additionally, the use of surgery as a treatment strategy significantly prolonged OS (**Figure 2B**).

Table 3 - Multivariate model for overall survival in women with IBC.

Variables	Hazard ratio	95% CI*	*P*-value
Subtype			
Triple negative	1.000		
Luminal A	0.245	0.065-0.920	0.037
Luminal B	0.462	0.212-0.997	0.048
HER-2 positive	0.532	0.175-0.926	0.032
Ki-67 LI			
≥40%	1.000		
≤14%	0.382	0.139-1.048	0.062
14-40%	0.452	0.226-0.907	0.025
Surgery			
No	1.000		
Yes	0.091	0.037-0.225	<0.001

IBC - inflammatory breast cancer, CI - confidence interval, HER - human epidermal growth factor receptor

Discussion. Breast cancer classification using the standards proposed in the 2011 St. Gallen Conference[3] have been widely accepted, and used in clinical practice. The value of the proposed classification to guide treatment and provide more accurate prognoses has been confirmed in the early and advanced stages of breast cancers.[5,6] However, the significance of the clinical classifications based on ER, PR, HER-2, and Ki-67 status has not been reported for IBC patients. Therefore, it is critical that a systematic study of clinical outcomes is performed for those with IBC.

A microarray analysis of IBC and non-IBC patients by Van Laere et al,[2] found that all molecular subtypes expressed in non-IBC patients were also detectable in IBC patients, but that IBC tumors had lower prevalence of the luminal A subtype (19% versus 42%), and higher incidence of the HER2-enriched subtype (22% versus 9%). These results are consistent with the distribution of the 4 subtypes in this study using surrogate markers.

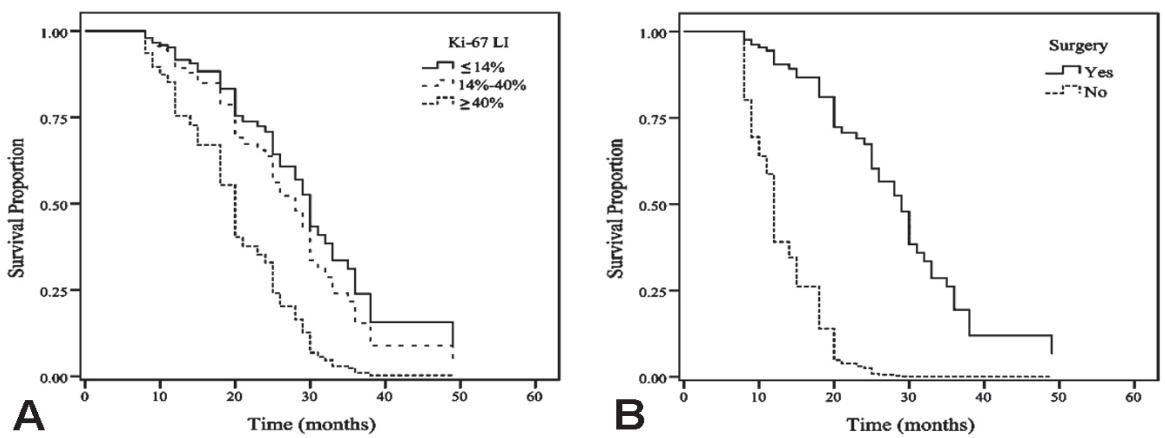

Figure 2 - The inflammatory breast cancer overall survival analysis using a multivariate model. Results are stratified by Ki-67 LI (**A**) and (**B**) surgical status.

A previous retrospective study from our group examined the percentage of each subtype in breast cancer patients in a Chinese cohort, and found that the proportion of these 4 subtypes was 57% (luminal A), 11% (luminal B), 6.1% (HER-2 positive), and 24% (triple negative)in non-IBC patients.[7] This further confirms that IBC has subtypes related to poor prognosis. Due to the limitations of gene profiling, Li et al[8] used ER, PR, and HER-2 status to define the 4 subtypes of IBC. They found that the triple negative subtype was associated with poor OS, and high locoregional relapse. However, they did not investigate the effect of Ki-67 on the prognostic outcome. In our retrospective findings, the triple negative subtype had a worse OS outcome than the other 3 subgroups (p=0.025), and Ki-67 LI did influence the outcome of IBC.

In this retrospective study, elevated Ki-67 LI was associated with shorter OS. Additional statistical analysis showed that Ki-67 was also an independent prognostic factor. This is in accordance with several other reports that have shown that Ki-67 expression correlated with a higher risk of relapse and worse survival for breast cancer patients.[9-12] Multivariate analysis of Ki-67 index uncovered that there was no significant prognostic difference between patients with more than 14% Ki-67 labeling, and patients with less than 14% Ki-67 labeling. However, this cutoff point for Ki-67 index is not well accepted, and was increased to 20% at the Thirteenth St. Gallen Conference.[13] Using a cut-off point of 40%, an obvious declining survival curve among patients with higher Ki-67 scores was found (p=0.025). This suggests that the cutoff value for classifying the expression of Ki-67 might need to be adjusted for this rapidly aggressive type of breast cancer. Due to its invasive biological behavior, IBC might have higher basal levels of Ki-67 relative to conventional breast cancer. Indeed, we observed that low Ki-67 LI (<14%) existed in only one-fifth of patients. Further studies using larger sample sizes, and longer follow-up times will help to ease out the differences between IBC and conventional breast cancer.

Surgery also contributed to greater levels of OS. In a study of IBC patients who had received chemotherapy, Panades et al[14] reported that the 10-year, local-recurrence-free survival rate was higher in patients who underwent mastectomy than in those who did not. In a chemotherapy-based modality treatment, surgery still contributed to improved survival for IBC. Taking into account dermal lymphatic tumor emboli,[15] and high recurrence rates, surgical tumor removal definitely reduces recurrence rates.

In addition to the identified differences between subtypes of IBC, we also observed that many other features including age, BMI, menopausal status, presentation, stage, tumor grade, ORR, and palpable lymph nodes were associated with OS but were not statistically different between the 4 subgroups. The lack of significance suggests that these features are more related to the aggressive nature of IBC. Other epidemiological studies of IBC have indicated that the greatest risk factors include high BMI and young age at disease onset,[1] which is consistent with our findings. In this study, the mean age of onset was 45 years, slightly younger than 47.3 years in our former report.[7] The median BMI was 24.0 kg/m^2, which is the cut-off point for overweight status in the Chinese population.[16] A previous report also showed that high BMI was associated with an increased the risk of IBC,[17] but the exact of role of BMI in IBC remains to be elucidated.

There were some limitations to this study. First, an international consensus is still lacking on a true IBC definition and criteria. The cases in this report were included based on the most widely used definition and criteria proposed by the American Joint Committee on Cancer (AJCC) and the Expert Panel of the First International IBC Conference.[18,19] Second, the diagnosis of IBC in this work relied on clinical presentation and pathological results obtained by core needle biopsy before treatment. This strategy was utilized to avoid any indirect effects of adjuvant chemotherapy on biomarker status.[20-22] However, as a biopsy contains limited tissue to perform IHC, the results may have been skewed because of tumor heterogeneity. Third, because the incidence of IBC is quite low, data from different research centers were hard to be directly compared due to its rarity and non-uniform diagnostic criteria. Although to date, this study included the largest number of Chinese IBC patients, more cases are needed to further explore the differences between IBC subtypes and their effect on therapeutic response and prognosis.

In conclusion, we have demonstrated that different breast cancer subtypes, classified by the pathological markers, ER, PR, HER-2 and Ki-67 were associated with OS in IBC patients. Furthermore, elevated Ki-67 LI was associated with increased risk of death, while surgery was found to prolong OS. Taken together, this study indicates that IBC is a heterogeneous disease and distinct outcomes are associated with different subtypes.

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