Am J Transl Res 2025;17(9):7158-7169
www.ajtr.org /ISSN:1943-8141/AJTR0166588

Original Article

Clinical and pathological characteristics and prognosis analysis of breast cancer patients stratified by age

Junjie Fan[1], Huajuan Ruan[1], Danqin Zheng[1], Jinjing Lv[1], Guojun Jiang[1], Yanfen Chen[2]

[1]*Department of Pathology, The First People's Hospital of Lin'an District, Hangzhou 311300, Zhejiang, China;* [2]*Department of General Surgery, The First People's Hospital of Lin'an District, Hangzhou 311300, Zhejiang, China*

Received June 4, 2025; Accepted August 30, 2025; Epub September 15, 2025; Published September 30, 2025

Abstract: Objective: To analyze the clinical characteristics of breast cancer patients across different age groups and their impact on prognosis. Methods: A retrospective study was conducted from January 2022 to December 2023, including 105 breast cancer patients. These patients were stratified into three groups: young (<40 years), middle-aged (40-59 years), and elderly (≥60 years). Results: The mean age at diagnosis was 52.74 years, with the highest incidence observed in the middle-aged group. Significant differences were found across age groups in histological grade, tumor size, molecular subtype, Ki67, carcinoembryonic antigen (CEA), and carbohydrate antigen 15-3 (CA15-3) (all P<0.05). Disease-free survival (DFS) rates varied significantly across age groups, with differences in histological grade, tumor size, molecular subtype, Ki67, CEA, and CA15-3 levels (*P*<0.05). Multivariate analysis revealed that age (both young and elderly), pathological stage (stage III), and molecular subtype (triple-negative) are independent risk factors for adverse prognostic events in breast cancer patients (*P*<0.05). Additionally, there was an interaction between age and molecular subtype, with significantly increased prognostic risks for the triple-negative type in the young (HR=21.418, *P*<0.05), human epidermal growth factor receptor 2 overexpression in the young (HR=11.216, *P*<0.05), and luminal B in the elderly (HR=8.190, *P*<0.05). Conclusion: The clinical characteristics and prognosis of breast cancer patients vary significantly by age group. Combining age with molecular subtype can optimize risk stratification and provide a valuable reference for individualized treatment and prognosis management.

Keywords: Breast cancer, age stratification, pathological characteristics, tumor marker, poor prognosis, risk management

Introduction

Breast cancer remains the most prevalent and lethal malignancy among women worldwide, with the highest standardized incidence and mortality rates globally. In 2022, China reported 357,000 new breast cancer cases and 75,000 deaths, accounting for 15.5% and 11.3% of the global totals for breast cancer cases and deaths in women, respectively [1]. As lifestyle changes, reproductive patterns evolve, and economic development accelerates, the incidence of breast cancer has shown a significant upward trend. Projections indicate that by 2030, the number of newly diagnosed cases in China will exceed 400,000, with deaths surpassing 100,000 [2].

From an age distribution perspective, breast cancer incidence peaks in the 45-65 year age group [1, 3], while the incidence among individuals under 40 is relatively low [4]. Age is a critical factor influencing breast cancer prognosis. Studies indicate that young women with breast cancer often face a more aggressive disease with poorer outcomes [5-7], possibly due to unfavorable biomarker status or pathological features [8]. Additionally, elderly patients may experience treatment limitations and reduced tolerance due to age-related functional decline and comorbidities. Hence, the impact of age differences on breast cancer prognosis deserves significant attention.

Moreover, breast cancer exhibits notable clinical heterogeneity, including at the molecular and genetic levels. Even with similar pathological types and stages, genetic variations can lead to divergent responses to treatment and outcomes. However, most current studies on

https://doi.org/10.62347/SYRZ6952

age stratification in breast cancer focus solely on the effect of age, with relatively few exploring the combined influence of age and other clinical characteristics. Therefore, this study aims to systematically analyze the clinical characteristics of breast cancer patients across different age groups and investigate how the interaction between age and other clinical features affects prognosis. The goal is to provide more accurate risk assessments and a foundation for personalized treatment decisions in clinical practice.

Materials and methods

Research subjects

This study is a retrospective cohort analysis, including 105 breast cancer patients who received comprehensive treatment at The First People's Hospital of Lin'an District, Hangzhou, from January 2022 to December 2023. Patients were continuously enrolled through the hospital's electronic medical record system. Based on the "Chinese Consensus Guidelines for Breast Cancer in Young Women: Clinical Practice and Fertility Preservation" [9] and the World Health Organization's age classification [10], patients were stratified into three groups: youth (<40 years), middle-aged (40-59 years), and elderly (≥60 years). This study was approved by the Ethics Committee of The First People's Hospital of Lin'an District, Hangzhou.

Inclusion criteria: (1) Female patients with primary breast cancer diagnosed by pathology; (2) Age >18 years; (3) Complete research data available.

Exclusion criteria: (1) History of other malignant tumors or coexistence with other malignancies; (2) Non-primary tumors; (3) Bilateral primary breast cancer; (4) Prior anti-tumor treatment; (5) Rare pathological tissue types; (6) Severe organ dysfunction (e.g., end-stage cardiovascular or cerebrovascular diseases, liver and kidney failure); (7) Pregnant or lactating breast cancer patients; (8) Loss to follow-up.

Sample size calculation

Based on pre-test data and literature, the estimated disease-free survival (DFS) rates for the youth, middle-aged, and elderly groups were 65%, 85%, and 70%, respectively (p_1, p_2, p_3). With a significance level of α=0.05, a power of 80% (β=0.20), the required sample size was 68 cases. Considering a 20% attrition rate, at least 82 cases were needed. The formula used is as follows:

$$n = \frac{(Z_{1-\alpha/2} + Z_{1-\beta})^2 \times [p_1(1-p_1) + p_2(1-p_2) + p_3(1-p_3)]}{(p_1-p_2)^2 + (p_1-p_3)^2 + (p_2-p_3)^2}$$

Data collection

Basic and treatment information: Data on age at diagnosis, body mass index (BMI), menstrual history (age of menarche, age of menopause), reproductive history (number of deliveries, age at first childbirth), and treatment modalities (surgery, radiotherapy, chemotherapy, endocrine therapy, and targeted therapy) were collected.

Pathological characteristics

Pathological characteristics included tissue type, pathological stage, histological grade, tumor size, molecular subtype, and immunohistochemical markers (estrogen receptor [ER], progesterone receptor [PR], human epidermal growth factor receptor 2 [HER-2], Ki67, and CD8+ T lymphocytes). Pathological diagnoses were based on the 5th Edition of the Classification Criteria for Breast Tumors (2019) [11] by the World Health Organization. Histological grading followed the Nottingham Histological Grading System, and molecular typing adhered to the 2019 St. Gallen International Expert Consensus. Pathological staging was based on the 7th Edition of the American Cancer Society Handbook of Cancer Staging. Tumor tissue specimens were analyzed using the immunohistochemical SP method. Two pathologists independently reviewed all specimens using a double-blind approach, assessing staining features and receptor expression in tumor cells.

ER/PR criteria: Negative if nuclear staining is <1%, positive if ≥1%.

HER-2 criteria: Negative if membrane staining score is "-" or "+", positive if "+++"; for "++", fluorescence in situ hybridization is performed: gene amplification is considered positive, no amplification is negative.

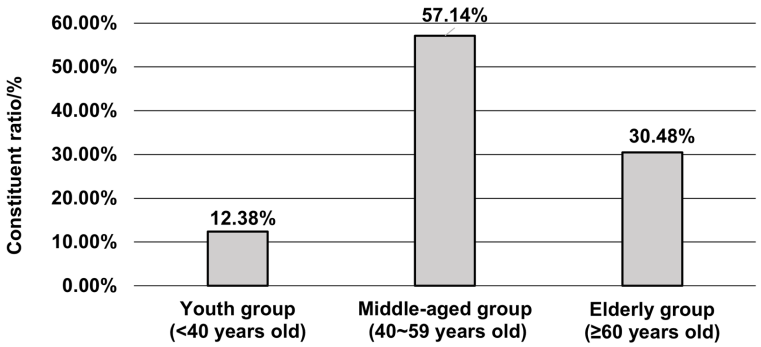

Figure 1. Age distribution characteristics.

Ki-67 criteria: Expression is determined by the percentage of positive staining in tumor cell nuclei; Ki-67 ≥14% is considered high expression, and Ki-67 <14% is low expression [12, 13].

Tumor markers

Approximately 5-10 mL of venous blood was collected in the morning after an overnight fast, and serum was isolated by centrifugation. The levels of alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), carbohydrate antigens CA199, CA125carbohydrate antigen 15-3 (CA15-3), carbohydrate antigen 724 (CA724), tissue polypeptide antigen (TPA), and human epididymal protein 4 (HE4) were measured using chemiluminescence.

Follow-up and prognosis analysis

The follow-up continued until December 2024, with a median follow-up time of 24 months (range 19-28 months). During this period, adverse prognostic events (local/regional recurrence, distant metastasis, contralateral breast cancer, secondary primary tumors, and mortality) were recorded. DFS was defined as the time from pathological diagnosis to the first occurrence of any of these events. If no event occurred, patients were followed until the last visit.

Statistical methods

Statistical analysis was performed using SPSS 26.0. For quantitative data with a normal distribution, results were presented as mean ± standard deviation ($\bar{x} \pm s$). One-way ANOVA was used for comparisons when the data met the homogeneity of variance assumption, with post hoc tests conducted using the Bonferroni or Tamhane methods. Categorical data were expressed as counts and percentages [n (%)], and comparisons were made using χ^2 tests. Ordinal data were analyzed using the Kruskal-Wallis test. Survival analysis was conducted using the Kaplan-Meier method, with DFS rates assessed using the Log-rank test. Cox regression was employed to identify factors influencing DFS in breast cancer patients. Statistical significance was set at $P<0.05$.

Results

Age distribution

The average age at diagnosis for the 105 patients was (52.74±10.79) years. The youth group represented 12.38% (13/105), the middle-aged group 57.14% (60/105), and the elderly group 30.48% (32/105), as shown in **Figure 1**. The middle-aged group had the highest incidence rate.

Basic information and treatment characteristics

Among the 105 patients, the distribution of BMI was relatively balanced. Most patients had a menarche age of ≥12 years. The proportion of premenopausal patients was 49.52%, while 76.19% of postmenopausal patients were aged 51 or older. Most patients delivered 2-3 babies, and the majority had their first childbirth at ≥23 years. The predominant surgical method was modified radical surgery, with high acceptance rates for chemotherapy and radiotherapy. **Table 1** summarizes the treatment data.

Pathological characteristics by age stratification

Significant statistical differences (all $P<0.05$) were found in histological grade, tumor size, molecular typing, and Ki67 expression across age groups. The young group had the highest proportion of poorly differentiated tumors, while the elderly group had the highest proportion of well-differentiated tumors. In terms of tumor size, the young group had the highest

Table 1. Characteristics of basic data and treatment data

Data	Case (n)	Composition ratio (%)
Body mass index		
<22 kg/m^2	54	51.43
≥22 kg/m^2	51	48.57
Age of menarche		
<12 years	29	27.62
≥12 years	76	72.38
Age of menopause		
Premenopausal	52	49.52
<51 years	25	23.81
≥51 years	80	76.19
Number of deliveries		
<2	11	10.48
2-3	77	73.33
≥4	17	16.19
Age of first childbearing		
<23 years	40	38.10
≥23 years	65	61.90
Surgical method		
Modified eradication technique	89	84.76
Non-modified eradication surgery	16	15.24
Chemotherapy		
No	25	23.81
Yes	80	76.19
Radiotherapy		
No	33	31.43
Yes	72	68.57
Endocrine therapy		
No	47	44.76
Yes	58	55.24
Targeted therapy		
No	79	75.24
Yes	26	24.76

percentage of Tis-T2 tumors, while the middle-aged group had the highest percentage of T3-T4 tumors. The middle-aged group had the highest proportion of luminal A tumors. The proportions of luminal B tumors were similar between the young and elderly groups. The middle-aged and elderly groups had similar proportions of HER-2 overexpression, while the young group had a significantly higher proportion of triple-negative tumors. The youth group had 100% of tumors expressing Ki67 ≥14%, while there was no marked difference between the middle-aged and elderly groups. **Table 2** provides detailed data.

Tumor markers by age stratification

Significant differences in CEA and CA15-3 levels were observed between the three groups (both P<0.05). Pairwise comparisons revealed no significant differences in CEA between the youth and middle-aged groups, or between the youth and elderly groups (both P>0.05). However, the middle-aged group had significantly lower CEA levels than the elderly group (P<0.05). No significant differences in CA15-3 were found between the middle-aged and young groups, or between the middle-aged and elderly groups (both P>0.05). However, the young group had significantly lower CA15-3 levels compared to the elderly group (P<0.05). **Table 3** summarizes the findings.

Prognostic analysis by age stratification

Among the 105 patients, 23 experienced adverse prognostic events, including 11 cases of local/regional recurrence, 14 cases of distant metastasis, and 2 cases of second primary tumors. The DFS rate for the youth group was 61.54% (8/13), with an average survival time of 25.18 months and a median survival time of 24 months. The DFS rate for the middle-aged group was 86.67% (52/60), with an average survival time of 30.69 months. The DFS rate for the elderly group was 68.75% (22/32), with an average survival time of 27.01 months and a median survival time of 30 months, as shown in **Figure 2**. The cumulative DFS rates showed that the youth group had the lowest rate (Log-rank χ^2=8.316, P=0.016). Pairwise comparisons indicated that the DFS rate in the youth group was significantly lower than in the middle-aged group (Log-rank χ^2=6.508, P=0.011), and the DFS rate in

Table 2. Pathological characteristics under different age stratification [n (%)]

Data	Young group (n=13)	Middle-aged group (n=60)	Elderly group (n=32)	χ^2/Z	*P*
Pathological tissue type				4.797	0.538
Invasive ductal carcinoma	11 (84.62)	44 (73.33)	21 (65.63)		
Invasive lobular carcinoma	1 (7.69)	4 (6.67)	2 (6.25)		
Carcinoma in situ	1 (7.69)	2 (3.33)	2 (6.25)		
Hybrid type	0	10 (16.67)	7 (21.88)		
Pathological staging				2.161	0.732
I	4 (30.77)	12 (20.00)	5 (15.63)		
II	7 (53.85)	34 (56.67)	17 (53.13)		
III	2 (15.38)	14 (23.33)	10 (31.25)		
Histological grading				7.344	0.025
Highly/moderately differentiated	3 (23.08)	27 (45.00)	21 (65.63)		
Low differentiation	10 (76.92)	33 (55.00)	11 (34.38)		
Tumor size				6.866	0.032
Tis-T_2	9 (69.23)	20 (33.33)	14 (43.75)		
T_3	4 (30.77)	26 (43.33)	12 (37.50)		
T_4	0	14 (23.33)	6 (18.75)		
Molecular typing				12.447	0.038
luminal A type	0	16 (26.67)	5 (15.63)		
luminal B type	7 (53.85)	23 (38.33)	17 (53.13)		
HER-2 overexpression type	2 (15.38)	17 (28.33)	9 (28.13)		
Triple-negative type	4 (30.77)	4 (6.67)	1 (3.13)		
ER/PR				0.903	0.637
(-)	6 (46.15)	21 (35.00)	10 (31.25)		
(+)	7 (53.85)	39 (65.00)	22 (68.75)		
HER-2				1.067	0.587
(-)	11 (84.62)	43 (71.67)	23 (71.87)		
(+)	2 (15.38)	17 (28.33)	9 (28.13)		
Ki67				9.858	0.007
<14%	0	20 (33.33)	11 (34.38)		
≥14%	13 (100.00)	40 (66.67)	21 (65.63)		
HER-2				3.706	0.157
(-)	5 (38.46)	31 (51.67)	10 (31.25)		
(+)	8 (61.54)	29 (48.33)	22 (68.75)		
CD8+				2.980	0.225
(-)	7 (53.85)	39 (65.00)	25 (78.13)		
(+)	6 (46.15)	21 (35.00)	7 (21.88)		

ER: estrogen receptor; PR: progesterone receptor; HER-2: human epidermal growth factor receptor 2; CD8+: CD8 positive T lymphocytes.

the elderly group was significantly lower than in the middle-aged group (Log-rank χ^2= 5.178, P=0.023). No significant difference in DFS rate was observed between the youth and elderly groups (Log-rank χ^2=0.439, P=0.507).

Prognostic analysis stratified by age and clinical characteristics

Patients were classified into low- and high-value groups based on median CEA and CA15-3 levels. The low-value group included patients

Table 3. Tumor marker levels in different age stratifications ($\bar{x} \pm s$)

Data	Young group (n=13)	Middle-aged group (n=60)	Elderly group (n=32)	*F*	*P*
AFP (ng/mL)	28.01±10.32	27.39±9.87	31.03±9.80	1.480	0.232
CEA (ng/mL)	5.59±1.55	5.27±1.27*	6.64±1.60	9.849	<0.001
CA199 (U/mL)	37.50±6.47	40.50±4.84	39.08±4.20	2.373	0.098
CA125 (U/mL)	48.18±8.72	46.37±8.40	45.24±9.62	0.524	0.594
CA15-3 (kU/L)	37.35±5.19*	40.08±6.03	42.67±6.97	3.728	0.027
CA724 (U/mL)	32.47±8.68	29.92±7.28	27.44±7.33	2.337	0.102
TPA (U/L)	149.41±24.17	151.53±21.54	148.76±24.41	0.164	0.849
HE49 (pmol/L)	69.52±11.47	65.88±8.19	68.53±9.77	1.392	0.253

AFP: alpha-fetoprotein; CEA: carcinoembryonic antigen; CA199: carbohydrate antigen; CA125: carbohydrate antigen 125; CA15-3: carbohydrate antigen 15-3; CA724: carbohydrate antigen 724; TPA: tissue polypeptide antigen; HE4: human epididymal protein 4 (HE4); *: Compared with the elderly group, *P*<0.05.

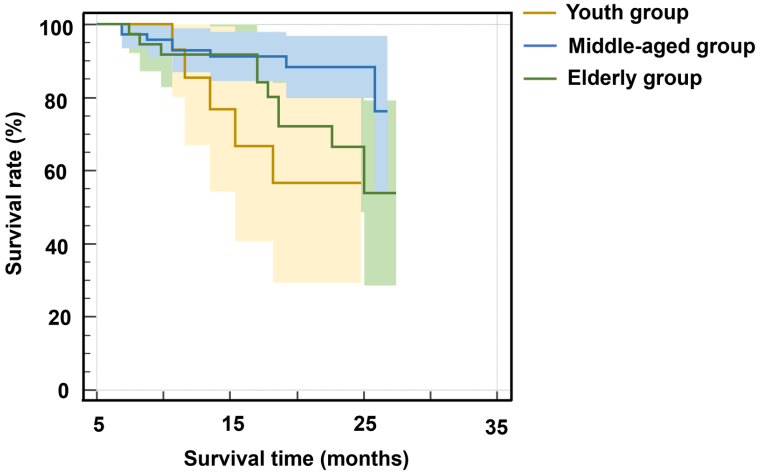

Figure 2. Kaplan-Meier survival analysis under different age stratifications. The shaded part was 95% CI.

with CEA <5.8 ng/mL and CA15-3 <40 kU/L. No significant differences in the cumulative DFS rate were observed across histological grades, tumor sizes, molecular subtypes, Ki67, CEA, or CA15-3 (all P>0.05). See **Figure 3**. However, in the comparison of 9 subgroups, significant differences in the cumulative DFS rate were observed (P<0.05). The elderly group had the lowest DFS rate and survival time in subgroups with poorly differentiated tumors, luminal B subtype, and low/high CA15-3 values. In subgroups with T3 stage, HER-2 overexpression, Ki67 ≥14%, and low CEA values, the DFS rate and survival time were lowest in the youth group. **Table 4** provides detailed comparisons.

Analysis of prognostic influencing factors

Univariate Cox regression analysis revealed that age, pathological stage, and molecular subtype were significant factors for unfavorable prognostic events in breast cancer patients (P<0.05). Multivariate Cox regression analysis identified age (both young and elderly), pathological stage (stage III), and molecular subtype (triple-negative) as independent risk factors for adverse prognostic events (all P<0.05), as shown in **Figure 4**.

Impact of age and molecular typing interaction on prognosis

The interaction between age and molecular subtype significantly influenced breast cancer prognosis (P<0.05). The risk of poor prognosis was significantly higher for young patients with triple-negative type (HR=21.418, 95% CI: 4.762-36.428), young patients with HER-2 overexpression (HR=11.216, 95% CI: 3.642-20.530), and elderly patients with luminal B type (HR=8.190, 95% CI: 1.526-27.436), as shown in **Figure 5**.

Discussion

The ongoing increase in breast cancer incidence can be attributed to the combined effect of multiple factors. In regions with higher economic levels, breast cancer incidence tends to be higher, which is closely linked to lifestyle and behavioral patterns. Delayed childbearing, reduced fertility rates, and lower breastfeeding rates are well-established risk factors for breast cancer [14]. Additionally, improvements

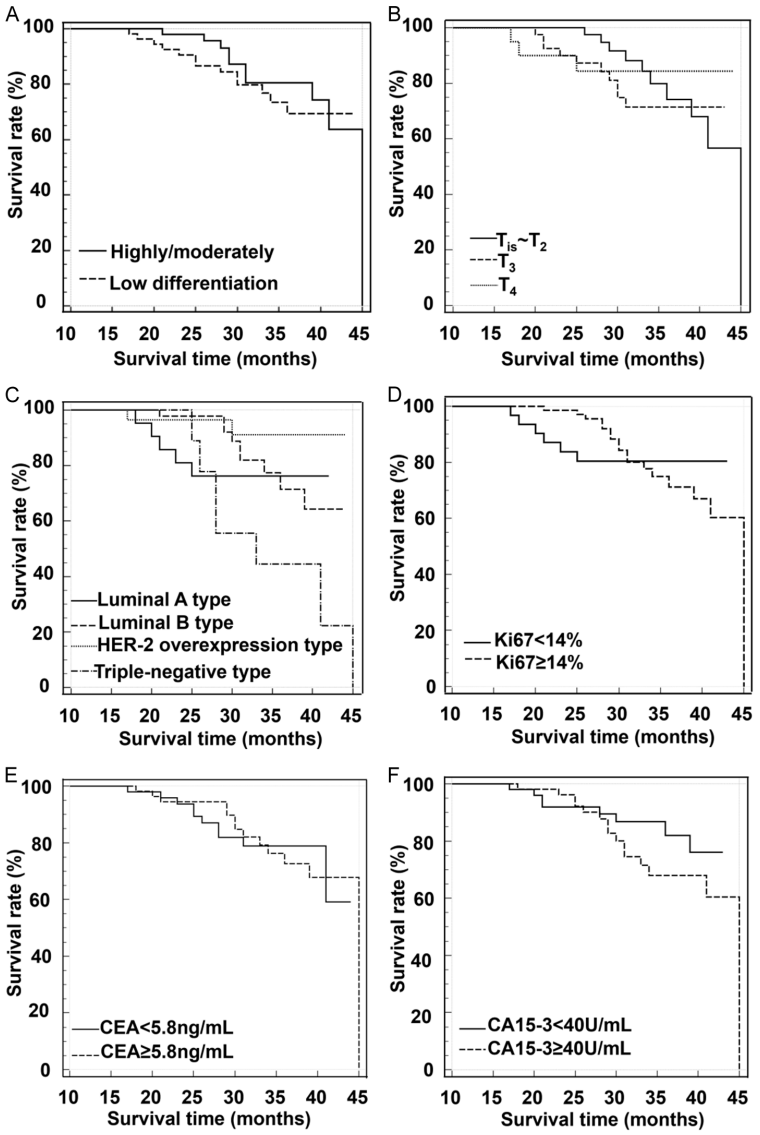

Figure 3. Kaplan-Meier survival analysis under different clinical feature stratification. A: Analysis of different histological grades; B: Analysis of different tumor sizes; C: Analysis of different molecular typing; D: Analysis of different Ki67; E: Analysis of Different CEA; F: Analysis of different CA15-3; HER-2: human epidermal growth factor receptor 2; CEA: carcinoembryonic antigen; CA15-3: carbohydrate antigen 15-3.

in living standards, often associated with longer life expectancies, are accompanied by a rise in the incidence of breast cancer and other malignancies, particularly with age. With China's rapid economic growth, the Westernization of lifestyles, and an aging population, the incidence of breast cancer among Chinese women has significantly increased, with a trend toward younger ages at onset [15]. Given these factors, it is crucial to recognize the distinct age distribution of breast cancer onset and develop tailored screening and prevention strategies for different age groups to effectively reduce the disease burden.

In this study, the age of diagnosis was primarily between 40 and 59 years, with a mean age of 52.74 years, consistent with the findings from the Cancer Registration Center of China's annual report [16]. Among the patients, the youth group accounted for 12.38%, and the elderly group for 30.48%. This age distribution aligns closely with reports from domestic scholars [17, 18].

In the prognostic analysis, the DFS rate in both the youth and elderly groups was significantly lower than that in the middle-aged group, which is consistent with previous studies [19, 20]. This may be due to the more aggressive tumor biology in the younger group, characterized by poorly differentiated tumors, triple-negative subtypes, and high Ki-67 expression. In the subgroup with T3 stage, HER-2 overexpression, ER positivity, and high Ki-67 expression, the prognosis of young patients was also relatively poor. The "dormant" nature of ER-positive breast cancer cells contributes to a longer recurrence risk, and studies have shown that 7% of ER-positive breast cancer patients experience distant metastasis at the time of first diagnosis [21]. A large international study identified disseminated tumor cells (DTCs) as an independent risk factor for bone metastasis in early-stage breast cancer. DTC detection was significantly associated with high tumor grade, large tumor size, and HER-2 overexpression [22]. Previous studies indicate that luminal A and luminal B subtypes have the best prognosis, and HER-2 overexpression patients benefit from anti-HER-2 therapy [23]. However,

Table 4. Prognostic analysis stratified by age combined with clinical characteristics

Factor 1	Factor 2	Survival time (months)		DFS rate (%)	Log-rank χ^2	*P*
		Average value	Median value			
Histological grading (Highly/moderately differentiated)	Youth	19.00	-	66.67	2.564	0.277
	Middle-aged	30.65	-	85.19		
	Elderly	28.79	-	76.19		
Histological grading (Low differentiation)	Youth	25.65	-	60.00	7.477	0.024
	Middle-aged	30.75	-	87.88		
	Elderly	21.86	27.00	54.55		
Tumor size (Tis~T_2)	Youth	26.85	-	66.67	1.696	0.428
	Middle-aged	30.37	32.00	85.00		
	Elderly	29.30	30.00	71.43		
Tumor size (T_3)	Youth	19.33	21.00	50.00	6.090	0.048
	Middle-aged	30.004	-	84.62		
	Elderly	24.25	-	66.67		
Tumor size (T_4)	Middle-aged	29.85	-	92.86	2.806	0.094
	Elderly	21.50	-	66.67		
Molecular typing (luminal A type)	Middle-aged	29.44	-	81.25	1.484	0.223
	Elderly	22.60	-	60.00		
Molecular typing (luminal B type)	Youth	31.00	-	100.00	8.874	0.012
	Middle-aged	31.32	-	91.30		
	Elderly	26.24	27.00	58.82		
Molecular typing (HER-2 overexpression type)	Youth	21.00	21.00	50.00	7.564	0.023
	Middle-aged	32.00	-	100.00		
	Elderly	29.33	-	88.89		
Molecular typing (Triple-negative type)	Youth	19.00	17.00	0	2.519	0.284
	Middle-aged	24.75	19.00	25.00		
	Elderly	25.00	-	100.00		
Ki67<14%	Middle-aged	30.05	-	85.00	0.911	0.340
	Elderly	25.09	-	72.73		
Ki67≥14%	Youth	25.18	24.00	61.54	7.830	0.020
	Middle-aged	30.96	-	87.50		
	Elderly	27.76	30.00	66.67		
CEA (Low value)	Youth	20.00	19.00	40.00	7.782	0.020
	Middle-aged	30.50	32.00	86.49		
	Elderly	23.43	-	71.43		
CEA (High value)	Youth	27.60	-	75.00	2.723	0.256
	Middle-aged	30.68	-	86.96		
	Elderly	27.43	30.00	68.00		
CA15-3 (Low value)	Youth	27.92	-	77.78	6.758	0.034
	Middle-aged	31.69	-	93.75		
	Elderly	26.45	30.00	63.64		
CA15-3 (High value)	Youth	20.25	17.00	70.00	5.682	0.058
	Middle-aged	29.69	-	93.75		
	Elderly	26.88	-	58.33		

HER-2: human epidermal growth factor receptor 2; CEA: carcinoembryonic antigen; CA15-3: carbohydrate antigen 15-3.

elderly patients often exhibit elevated tumor marker levels, such as CEA and CA15-3, suggesting a higher tumor burden or more advanced disease, which may contribute to a poorer prognosis [24].

Multivariate Cox regression analysis demonstrated that age (both young and elderly), pathological stage (stage III), and molecular subtype (triple-negative) were independent risk factors influencing the unfavorable prognosis of breast cancer, consistent with previous studies [25-27]. Additionally, the interaction between age and molecular subtype significantly impacted prognosis. The risk of adverse prognosis was notably higher in young patients with triple-neg-

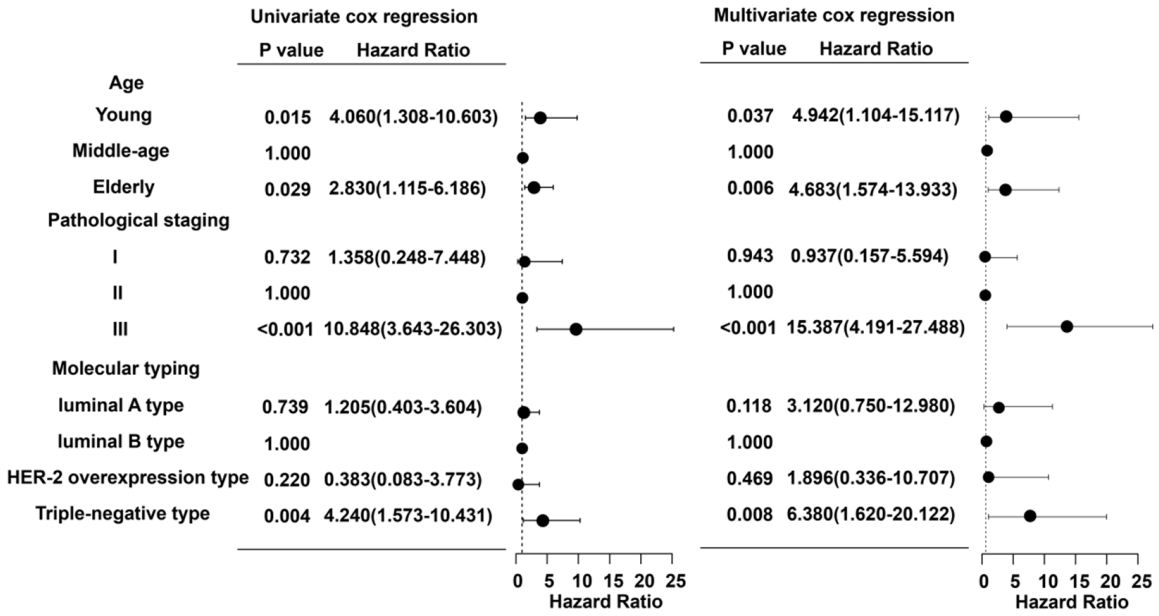

Figure 4. Cox regression analyses. HER-2: human epidermal growth factor receptor 2.

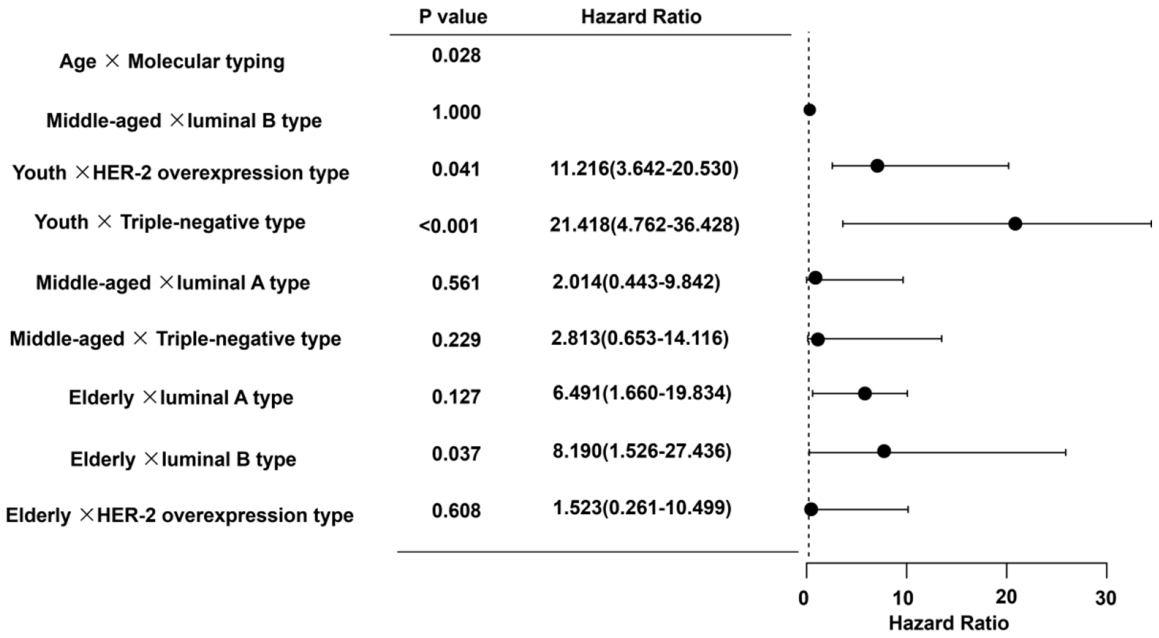

Figure 5. The influence of the interaction between age and molecular typing on prognosis. HER-2: human epidermal growth factor receptor 2.

ative breast cancer, young patients with HER-2 overexpression, and elderly patients with luminal B type. This can be explained by several factors: young patients often lack typical clinical manifestations, have unclear imaging features, and possess high breast gland density, making early tumor detection more challenging. Furthermore, the sensitivity of imaging techniques, such as molybdenum target imaging, is relatively low in young patients [28, 29]. Additionally, young patients face age-related challenges, including fertility concerns, psychological stress, and adjusting to social roles, which can delay diagnosis and contribute to an

increased psychological burden, ultimately affecting prognosis. Notably, triple-negative breast cancer is closely linked to hereditary breast cancer susceptibility genes, such as BRCA1, making it a key subtype for identifying hereditary breast cancer [30]. Hereditary breast cancer susceptibility is more common in younger women, further exacerbating the poor prognosis in young patients with triple-negative breast cancer [31]. Studies have shown that breast gland density decreases with age, and in patients under 45 years, HER-2 overexpressing tumors exhibit relatively higher density, suggesting that young HER-2 overexpression patients are more prone to developing more aggressive tumors [32]. Luminal B breast cancer, more common in elderly patients, has significantly higher cell proliferation activity than Luminal A and is less responsive to endocrine therapy. The options for subsequent treatments after therapy failure are limited [33]. However, recent developments in antibody-drug conjugates, such as T-DXd, have opened new treatment possibilities for this subtype. Hormonal imbalances play a key role in breast cancer, and elderly patients, who are in a state of estrogen imbalance, may have tumors that grow more readily [34, 35]. While these two subtypes generally have poor prognosis, the effect of age on prognosis was more prominent in young patients with triple-negative and HER-2 overexpression, with no significant interaction between age and these subtypes in this study.

In this study, a straightforward method for analyzing the interaction between age and molecular subtype was employed, revealing that this interaction provides stronger risk stratification than traditional single-factor analysis. Previous studies have suggested that age independently affects the prognosis of triple-negative breast cancer (HR=1.48/HR=1.55) [36, 37]. However, the HR for young triple-negative patients in this study was as high as 21.418, indicating that the interaction model can identify extremely high-risk groups not captured by traditional analyses. This nonlinear amplification effect suggests a biological synergy between age and molecular subtype. Unlike previous studies that consider age as an independent factor, our interaction model precisely targeted high-risk subgroups and found no significant increase in risk for other combinations.

This study has several limitations. The sample size of 105 cases may not fully represent the characteristics of patients across different age groups, and the results should be interpreted with caution. The retrospective design introduces information bias and makes it difficult to control for confounding factors. The relatively short follow-up period is not ideal for evaluating long-term prognosis. Future research should involve larger sample sizes, multi-center prospective studies, longer follow-up periods, and a deeper exploration of the biological mechanisms behind the synergistic effect of age and molecular typing, including gene expression and the immune microenvironment. The clinical value of this approach should be verified through prospective cohorts, ultimately guiding the optimization of treatment strategies tailored to specific age and molecular subtypes of breast cancer.

Conclusion

This study retrospectively analyzed 105 breast cancer patients across different age groups, highlighting the significant role of age in the clinical characteristics and prognosis of breast cancer. Multivariate analysis confirmed that age (both young and elderly), pathological stage (stage III), and molecular subtype (triple-negative) were independent risk factors for prognosis. Additionally, the interaction between age and molecular subtype was significant, with particularly poor prognosis in young patients with triple-negative type, young patients with HER-2 overexpression, and elderly patients with luminal B type. The age-molecular typing stratification model developed in this study can help identify high-risk subsets and support more individualized management strategies for different age groups. Prospective studies are needed to verify whether this model can optimize treatment decisions in the future.

Disclosure of conflict of interest

None.

Address correspondence to: Yanfen Chen, Department of General Surgery, The First People's Hospital of Lin'an District, No. 360, Yikang Street, Jinnan Street, Lin'an District, Hangzhou 311300, Zhejiang, China. Tel: +86-0571-61112631; E-mail: cyfbbk@163.com

References

[1] Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I and Jemal A. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2024; 74: 229-263.

[2] Lei S, Zheng R, Zhang S, Chen R, Wang S, Sun K, Zeng H, Wei W and He J. Breast cancer incidence and mortality in women in China: temporal trends and projections to 2030. Cancer Biol Med 2021; 18: 900-909.

[3] United Nations, Department of Economic and Social Affairs, Population Division. World population prospects 2024. [2024-08-01]. https://population.un.org/wpp/.

[4] Suter MB and Pagani O. Should age impact breast cancer management in young women? Fine tuning of treatment guidelines. Ther Adv Med Oncol 2018; 10: 1758835918776923.

[5] Verdial FC, Mamtani A, Pawloski KR, Sevilimedu V, D'Alfonso TM, Zhang H, Gemignani ML, Barrio AV, Morrow M and Tadros AB. The effect of age on outcomes after neoadjuvant chemotherapy for breast cancer. Ann Surg Oncol 2022; 29: 3810-3819.

[6] Ingebriktsen LM, Humlevik ROC, Svanøe AA, Sæle AKM, Winge I, Toska K, Kalvenes MB, Davidsen B, Heie A, Knutsvik G, Askeland C, Stefansson IM, Hoivik EA, Akslen LA and Wik E. Elevated expression of Aurora-A/AURKA in breast cancer associates with younger age and aggressive features. Breast Cancer Res 2024; 26: 126.

[7] Humlevik ROC, Svanøe AA, Aas T, Heie A, Sæle AKM, Akslen LA, Wik E and Hoivik EA. Distinct clinicopathological features and treatment differences in breast cancer patients of young age. Sci Rep 2025; 15: 5655.

[8] B Jackson E, Gondara L, Speers C, Diocee R, M Nichol A, Lohrisch C and A Gelmon K. Does age affect outcome with breast cancer? Breast 2023; 70: 25-31.

[9] China Guideline Committee of Clinical Practice and Fertility Preservation for Breast Cancer in Young Women. Chinese consensus guidelines for breast cancer in young women: clinical practice and fertility preservation. Zhonghua Zhong Liu Za Zhi 2019; 41: 486-495.

[10] Organization WH. World Health Day 2012: ageing and health: toolkit for event organizers. World Health Organization 2012.

[11] Tan PH, Ellis I, Allison K, Brogi E, Fox SB, Lakhani S, Lazar AJ, Morris EA, Sahin A, Salgado R, Sapino A, Sasano H, Schnitt S, Sotiriou C, van Diest P, White VA, Lokuhetty D and Cree IA; WHO Classification of Tumours Editorial Board. The 2019 World Health Organization classification of tumours of the breast. Histopathology 2020; 77: 181-185.

[12] Li F, Wang Y, Dou H, Chen X, Wang J and Xiao M. Association of immune inflammatory biomarkers with pathological complete response and clinical prognosis in young breast cancer patients undergoing neoadjuvant chemotherapy. Front Oncol 2024; 14: 1349021.

[13] Zhang X, Cui H, Hu N, Han P, Fan W, Wang P, Zuo X, Zhao D, Huang H, Li S, Kong H, Peng F, Tian J and Zhang L. Correlation of androgen receptor with ultrasound, clinicopathological features and clinical outcomes in breast cancer. Insights Imaging 2023; 14: 46.

[14] Wilkinson L and Gathani T. Understanding breast cancer as a global health concern. Br J Radiol 2022; 95: 20211033.

[15] Coughlin SS. Social determinants of breast cancer risk, stage, and survival. Breast Cancer Res Treat 2019; 177: 537-548.

[16] Chen W, Zheng R, Zuo T, Zeng H, Zhang S and He J. National cancer incidence and mortality in China, 2012. Chin J Cancer Res 2016; 28: 1-11.

[17] Sun K, Zhang B, Lei S, Zheng R, Liang X, Li L, Feng X, Zhang S, Zeng H, Yao Y, Ma P, Wang S, Chen R, Han B, Wei W and He J. Incidence, mortality, and disability-adjusted life years of female breast cancer in China, 2022. Chin Med J (Engl) 2024; 137: 2429-2436.

[18] Li N, Deng Y, Zhou L, Tian T, Yang S, Wu Y, Zheng Y, Zhai Z, Hao Q, Song D, Zhang D, Kang H and Dai Z. Global burden of breast cancer and attributable risk factors in 195 countries and territories, from 1990 to 2017: results from the Global Burden of Disease Study 2017. J Hematol Oncol 2019; 12: 140.

[19] Li H, Zuo TT, Zeng HM, Zheng RS, Yang L, Li HC, Liu S, Yuan YN, Wang N and Chen WQ. Clinical features and prognostic analysis of female breast cancer in different diagnosed ages. Zhonghua Zhong Liu Za Zhi 2021; 43: 126-131.

[20] Chung WP, Lee KT, Chen YP, Hsu YT, Loh ZJ, Huang CC and Hsu HP. The prognosis of early-stage breast cancer in extremely young female patients. Medicine (Baltimore) 2021; 100: e24076.

[21] Rueda OM, Sammut SJ, Seoane JA, Chin SF, Caswell-Jin JL, Callari M, Batra R, Pereira B, Bruna A, Ali HR, Provenzano E, Liu B, Parisien M, Gillett C, McKinney S, Green AR, Murphy L, Purushotham A, Ellis IO, Pharoah PD, Rueda C, Aparicio S, Caldas C and Curtis C. Dynamics of breast-cancer relapse reveal late-recurring ER-positive genomic subgroups. Nature 2019; 567: 399-404.

[22] Hartkopf AD, Brucker SY, Taran FA, Harbeck N, von Au A, Naume B, Pierga JY, Hoffmann O,

Beckmann MW, Rydén L, Fehm T, Aft R, Solà M, Walter V, Rack B, Schuetz F, Borgen E, Ta MH, Bittner AK, Fasching PA, Fernö M, Krawczyk N, Weilbaecher K, Margelí M, Hahn M, Jueckstock J, Domschke C, Bidard FC, Kasimir-Bauer S, Schoenfisch B, Kurt AG, Wallwiener M, Gebauer G, Klein CA, Wallwiener D, Janni W and Pantel K. Disseminated tumour cells from the bone marrow of early breast cancer patients: results from an international pooled analysis. Eur J Cancer 2021; 154: 128-137.

[23] Derakhshan F and Reis-Filho JS. Pathogenesis of triple-negative breast cancer. Annu Rev Pathol 2022; 17: 181-204.

[24] Li Y, Zhang H, Merkher Y, Chen L, Liu N, Leonov S and Chen Y. Recent advances in therapeutic strategies for triple-negative breast cancer. J Hematol Oncol 2022; 15: 121.

[25] Wang W, Tian B, Xu X, Zhang X, Wang Y, Du L and Jing J. Clinical features and prognostic factors of breast cancer in young women: a retrospective single-center study. Arch Gynecol Obstet 2023; 307: 957-968.

[26] Abubakar M, Guo C, Koka H, Zhu B, Deng J, Hu N, Zhou B, Garcia-Closas M, Lu N and Yang XR. Impact of breast cancer risk factors on clinically relevant prognostic biomarkers for primary breast cancer. Breast Cancer Res Treat 2021; 189: 483-495.

[27] Yoon TI, Kwak BS, Yi OV, Kim S, Um E, Yun KW, Shin HN, Lee S, Sohn G, Chung IY, Kim J, Ko BS, Lee JW, Son BH, Ahn SH and Kim HJ. Age-related risk factors associated with primary contralateral breast cancer among younger women versus older women. Breast Cancer Res Treat 2019; 173: 657-665.

[28] Hu X, Myers KS, Oluyemi ET, Philip M, Azizi A and Ambinder EB. Presentation and characteristics of breast cancer in young women under age 40. Breast Cancer Res Treat 2021; 186: 209-217.

[29] Lee J, Kim SH, Kang BJ, Lee A, Park WC and Hwang J. Imaging characteristics of young age breast cancer (YABC) focusing on pathologic correlation and disease recurrence. Sci Rep 2021; 11: 20205.

[30] Won KA and Spruck C. Triple-negative breast cancer therapy: current and future perspectives (review). Int J Oncol 2020; 57: 1245-1261.

[31] Tung N, Lin NU, Kidd J, Allen BA, Singh N, Wenstrup RJ, Hartman AR, Winer EP and Garber JE. Frequency of germline mutations in 25 cancer susceptibility genes in a sequential series of patients with breast cancer. J Clin Oncol 2016; 34: 1460-8.

[32] Hu CY, Ma WJ, Liu J and Liu PF. Correlation between breast density and age, breast cancer molecular subtype. Zhonghua Yi Xue Za Zhi 2019; 99: 49-52.

[33] Modi S, Park H, Murthy RK, Iwata H, Tamura K, Tsurutani J, Moreno-Aspitia A, Doi T, Sagara Y, Redfern C, Krop IE, Lee C, Fujisaki Y, Sugihara M, Zhang L, Shahidi J and Takahashi S. Antitumor activity and safety of trastuzumab deruxtecan in patients with HER2-low-expressing advanced breast cancer: results from a phase Ib study. J Clin Oncol 2020; 38: 1887-1896.

[34] Kim J and Munster PN. Estrogens and breast cancer. Ann Oncol 2025; 36: 134-148.

[35] Huber-Keener KJ. Cancer genetics and breast cancer. Best Pract Res Clin Obstet Gynaecol 2022; 82: 3-11.

[36] Zhou HL and Chen DD. Prognosis of patients with triple-negative breast cancer: a population-based study from SEER database. Clin Breast Cancer 2023; 23: e85-e94.

[37] Tan H and Fu D. Influence of advanced age on the prognosis of triple-negative breast cancer patients: a surveillance, epidemiology, and end results-based study. J Cancer Res Ther 2023; 19: S0.