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Evaluation of Age-related Clinical and Molecular Characteristics in a Single-center Real-world Breast Cancer Cohort

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ABSTRACT

Objective: Breast cancer exhibits biological heterogeneity that varies across age groups and influences treatment decisions. This study aimed to evaluate age-related differences in biomarker profiles, surrogate molecular subtypes, and treatment patterns in a single-center real-world breast cancer cohort.

Material and Methods: This retrospective cohort study included 1,124 patients with invasive breast cancer diagnosed or followed between January 2020 and June 2025. Estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2) status, and Ki-67 proliferation index were analyzed. Tumors were classified into surrogate molecular subtypes according to the St. Gallen and European Society for Medical Oncology recommendations. Biomarker distributions, molecular subtypes, and treatment modalities were compared across age groups. Multivariable logistic regression analyses were performed to identify independent predictors of HER2 positivity and triple-negative breast cancer (TNBC).

Results: Significant age-related differences were observed in ER status, HER2 status, Ki-67 index, and surrogate molecular subtype distribution. Younger patients more frequently exhibited ER negativity, HER2 positivity, high proliferative activity, and aggressive molecular subtypes, whereas older patients predominantly presented with hormone receptor-positive, lower-proliferation tumors. Neoadjuvant therapy was more frequently used in younger patients, while treatment de-escalation was observed in older age groups. The HER2-low phenotype was identified in 18.4% of the cohort. Age, PR status, Ki-67 level, and histological grade were independent predictors of HER2 positivity and TNBC.

Conclusion: Age-related biological differences in breast cancer are closely aligned with real-world treatment decisions. Treatment strategies are primarily guided by tumor biology rather than chronological age alone.

Keywords: Breast cancer; age groups; biomarkers; molecular subtypes; real-world data

INTRODUCTION

Breast cancer remains the most frequently diagnosed malignancy among women worldwide and is one of the leading causes of cancer-related mortality.[1] The disease exhibits marked biological heterogeneity, ranging from indolent hormone receptor-positive tumors to biologically aggressive subtypes. This diversity underscores the importance of biomarker-based risk assessment in diagnostic and therapeutic decision-making.

In routine clinical practice, estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2) status, and the Ki-67 proliferation index are widely used to assess prognosis and guide neoadjuvant and adjuvant treatment strategies.[2,3] Because genomic profiling is not universally available, surrogate molecular subtyping based on the St. Gallen Consensus and European Society for Medical Oncology (ESMO) recommendations—namely luminal A, luminal B, HER2-positive non-luminal, and triple-negative breast cancer (TNBC)—is commonly applied in clinical settings.[4,5]

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Within this framework, the Ki-67 proliferation index contributes to distinguishing biological behavior, particularly in luminal tumors. However, due to variability in assessment and interpretation, Ki-67 is generally considered a complementary marker rather than a standalone determinant of treatment decisions.[6]

In recent years, the HER2-low phenotype, defined by low levels of HER2 expression, has gained attention, particularly in the context of metastatic disease and targeted therapies. Current American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines emphasize that HER2-low should not be regarded as a distinct biological subtype but rather as a treatment-related classification.[2,7]

Age is an important clinical factor associated with tumor biology and treatment patterns in breast cancer. Population-based studies have reported higher frequencies of HER2-positive and triple-negative tumors in younger patients, whereas hormone receptor-positive and lower-proliferation tumors are more common in older age groups.[8,9] Although these biological features have been evaluated in various settings, data integrating age-related biomarker distribution, surrogate molecular subtypes, and real-world treatment approaches remain limited. Therefore, this study aimed to evaluate age-related biomarker profiles, surrogate molecular subtypes, and treatment patterns in a large, single-center real-world breast cancer cohort.

MATERIAL AND METHODS

Study Design and Patient Selection

This study was designed as a single-center retrospective cohort study. Data were obtained retrospectively from the electronic medical records of patients who were diagnosed with or were followed for breast cancer between January 2020 and June 2025. A total of 1,124 patients with invasive breast carcinoma were included. Eligible patients had complete immunohistochemical data on ER, PR, and HER2 status, and the Ki-67 proliferation index, as well as available systemic treatment information. Patients with ductal carcinoma in situ and those with missing clinical, pathological, or treatment-related data were excluded.

Clinical and Pathological Variables

Recorded clinical variables included age at diagnosis, age groups, menopausal status when available, presence of metastatic disease at diagnosis, and surgical treatment information. Pathological evaluation included histological subtype (invasive ductal, invasive lobular, or other), histological grade, lymph node status, and metastatic disease at diagnosis. Histological grade was classified according to the Nottingham grading system as Grade 1-3.[10]

Immunohistochemical Assessment

ER and PR expressions were reported as percentages of tumor cells with nuclear staining. Tumors with >10% staining were considered positive, while cases with 1-10% staining were classified as low-positive. HER2 status was evaluated according to ASCO/CAP guidelines.[11] Tumors with immunohistochemical scores of 0-1+ were considered negative, and those with 3+ were considered positive. For cases scored as 2+, fluorescence or silver *in situ* hybridization results were used for final classification.[12] HER2-low tumors were defined as cases showing HER2 1+ or 2+ expression without gene amplification. The HER2-low phenotype was assessed for descriptive purposes and was not considered a separate molecular subtype. The Ki-67 proliferation index was categorized as ≤20%, 20-50%, and >50% based on pathology reports.

Surrogate Molecular Subtypes

Based on immunohistochemical findings, tumors were classified into surrogate molecular subtypes.[13] ER and/or PR-positive, HER2-negative tumors with low proliferation were classified as luminal A. Hormone receptor-positive tumors with high proliferation and/or HER2 positivity were classified as luminal B. Hormone receptor-negative and HER2-positive tumors were classified as HER2-positive (non-luminal), whereas tumors negative for ER, PR, and HER2 were classified as TNBC. Molecular subtype definitions followed the St. Gallen Consensus and ESMO recommendations.

Treatment Modalities

Treatment approaches were recorded as neoadjuvant, adjuvant, or palliative. Neoadjuvant therapy included systemic chemotherapy and/or targeted agents administered before surgery. Adjuvant therapy, administered after surgery, included chemotherapy, endocrine therapy, and targeted agents. Radiotherapy was evaluated separately.

Ethical Approval

This study was approved by the Çanakkale Onsekiz Mart University Rectorate Non-Interventional Clinical Research Ethics Committee (approval number: 2025-387, date: 10.12.2025). The study was conducted in accordance with the Declaration of Helsinki, and patient data were anonymized prior to analysis.

Statistical Analysis

Statistical analyses were performed using IBM SPSS, version 26 (SPSS Inc., Chicago, IL, USA). Continuous variables were presented as mean ± standard deviation or median (minimum-maximum), and categorical variables were presented as frequencies and percentages. Biomarker

distributions and molecular subtypes across age groups were summarized in tables. Group comparisons were performed using the chi-square test or Fisher's exact test when appropriate. For continuous variables that were not normally distributed, the Mann-Whitney U or Kruskal-Wallis tests were applied. Separate multivariable logistic regression models were constructed to identify independent predictors of HER2 positivity and TNBC. Variables with p<0.10 in univariable analyses and variables considered clinically relevant were included in multivariable models. Results were reported as odds ratios with 95% confidence intervals. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 1,124 patients were included in the analysis. The mean age at diagnosis was 55.44±12.20 years, with a median age of 55 years (range, 20-92) (Table 1). The largest proportion of patients was in the 50-59 age group (n=315), followed by the 60-69 (n=293) and 40-49 (n=267) age groups. There were 106 patients aged 18-39 years and 143 patients aged ≥70 years (Figure 1).

Distribution of Biomarkers by Age Group

ER status differed significantly across age groups (p=0.009) (Table 2). ER negativity was most frequent in the 18-39 years age group (33.0%) and decreased with advancing age. Overall, ER expression >10% was observed in 77.6% of the cohort (872/1,124). PR status did not differ significantly across age groups (p=0.086) (Table 2).

HER2 status was significantly associated with age (p<0.001) (Table 2). HER2 positivity was highest in patients aged 18-39 years (43.4%), whereas rates ranged between 19.5% and 24.1% in patients aged 40-69 years and were 21.0% in those aged ≥70 years. The HER2-low phenotype was identified in 18.4% of the overall cohort, while 57.7% of tumors were HER2-negative.

The Ki-67 proliferation index differed significantly across age groups (p=0.008) (Table 2). High proliferation (>50%) was more common in younger patients, observed in 23.6% of the 18-39 age group compared with 11.2% in patients aged ≥70 years. Histological grade distribution did not differ significantly among age groups (p=0.702) (Table 2).

Distribution of Surrogate Molecular Subtypes

The distribution of surrogate molecular subtypes varied significantly by age group (p<0.001) (Table 3). In the overall cohort, luminal A accounted for 35.7%, luminal B (HER2-negative) for 29.4%, luminal B (HER2-positive) for 16.3%, HER2-positive non-luminal for 7.6%, and TNBC for 11.0%. The proportion of luminal A tumors was lowest in patients aged 18-39 years (19.8%) and highest in those aged 60-69 years (41.3%) and ≥70 years (40.6%).

TABLE 1: Descriptive statistics of age at diagnosis across age groups.

Age group (years)	Mean ± SD	Median (min-max)
18-39	34.74±3.88	36 (20-39)
40-49	44.78±2.77	45 (40-49)
50-59	54.49±2.88	55 (50-59)
60-69	63.82±2.84	63 (60-69)
≥70	75.64±4.94	74 (70-92)
Total cohort	**55.44±12.20**	**55 (20-92)**

SD: Standard deviation; min-max: Minimum-maximum.

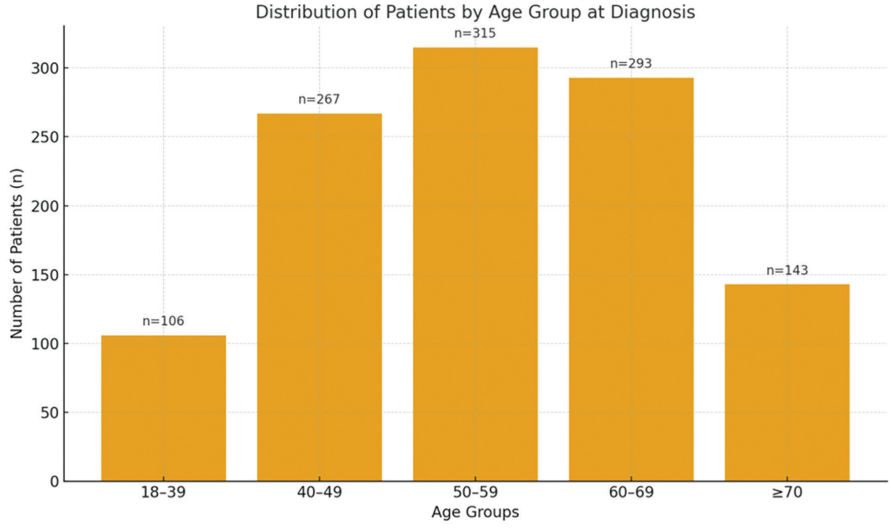

FIGURE 1: Distribution of patients by age group at diagnosis (n=1,124).

Tumor Characteristics and Treatment Patterns

Metastatic disease at diagnosis was present in 24.7% of the cohort (Table 4). The highest rate was observed in the 18-39 age group (33.0%), followed by patients aged ≥70 years (29.4%), whereas rates ranged from 21.0% to 23.5% in patients aged 40-69 years (p=0.060).

The use of neoadjuvant therapy differed significantly across age groups (p<0.001) (Table 4), with the highest rate in patients aged 18-39 years (43.4%) and the lowest in those aged ≥70 years (19.6%). No significant differences were observed among age groups regarding adjuvant therapy, surgical intervention, axillary lymph node dissection, or type of surgery (Table 4). The use of radiotherapy (p<0.001) and endocrine therapy (p=0.018) varied significantly by age group.

Multivariable Analyses

In the multivariable logistic regression model evaluating predictors of HER2 positivity (Table 5), PR negativity, younger age, higher Ki-67 levels, and higher histological grade were identified as independent predictors.

In the multivariable model for TNBC (Table 6), higher Ki-67 proliferation categories and grade 3 histology were independently associated with TNBC. Age group was not independently associated with TNBC. Comparative distributions of independent predictors across treatment models are presented in Figure 2.

TABLE 2: Distribution of ER, PR, HER2, Ki-67 and histological grade across age groups.

Biomarker/feature	18-39	40-49	50-59	60-69	≥70	Total cohort	p-value
ER status							
ER-	35 (33.0%)	50 (18.7%)	65 (20.6%)	44 (15.0%)	25 (17.5%)	219 (19.5%)	
ER, 1-10%	2 (1.9%)	10 (3.7%)	9 (2.9%)	11 (3.8%)	1 (0.7%)	33 (2.9%)	**0.009**
ER, >10%	69 (65.1%)	207 (77.5%)	241 (76.5%)	238 (81.2%)	117 (81.8%)	872 (77.6%)	
PR status							
PR-	40 (37.7%)	63 (23.6%)	90 (28.6%)	84 (28.7%)	43 (30.1%)	320 (28.5%)	
PR, 1-10%	10 (9.4%)	17 (6.4%)	30 (9.5%)	19 (6.5%)	7 (4.9%)	83 (7.4%)	**0.086**
PR, >10%	56 (52.8%)	187 (70.0%)	195 (61.9%)	190 (64.8%)	93 (65.0%)	721 (64.1%)	
HER2 status							
HER2-	46 (43.4%)	159 (59.6%)	178 (56.5%)	176 (60.1%)	90 (62.9%)	649 (57.7%)	
HER2-low	14 (13.2%)	49 (18.4%)	61 (19.4%)	60 (20.5%)	23 (16.1%)	207 (18.4%)	**<0.001**
HER2+	46 (43.4%)	59 (22.1%)	76 (24.1%)	57 (19.5%)	30 (21.0%)	268 (23.8%)	
Ki-67 index							
≤20%	28 (26.4%)	105 (39.3%)	124 (39.4%)	135 (46.1%)	67 (46.9%)	459 (40.8%)	
20-50%	53 (50.0%)	125 (46.8%)	133 (42.2%)	113 (38.6%)	60 (42.0%)	484 (43.1%)	**0.008**
>50%	25 (23.6%)	37 (13.9%)	58 (18.4%)	45 (15.4%)	16 (11.2%)	181 (16.1%)	
Histological grade							
Grade 1	7 (6.6%)	26 (9.7%)	27 (8.6%)	37 (12.6%)	11 (7.7%)	108 (9.6%)	
Grade 2	71 (67.0%)	167 (62.5%)	203 (64.4%)	177 (60.4%)	93 (65.0%)	711 (63.3%)	**0.702**
Grade 3	28 (26.4%)	74 (27.7%)	85 (27.0%)	79 (27.0%)	39 (27.3%)	305 (27.1%)	

ER: Estrogen receptor; PR: Progesterone receptor; HER2: Human epidermal growth factor receptor 2; Ki-67: Proliferative index.

TABLE 3: Distribution of molecular subtypes across age groups.

Molecular subtype	18-39	40-49	50-59	60-69	≥70	Total cohort	p-value
Luminal A	21 (19.8%)	98 (36.7%)	103 (32.7%)	121 (41.3%)	58 (40.6%)	**401 (35.7%)**	
Luminal B (HER2-)	25 (23.6%)	82 (30.7%)	98 (31.1%)	86 (29.4%)	40 (28.0%)	**331 (29.4%)**	
Luminal B (HER2+)	26 (24.5%)	40 (15.0%)	52 (16.5%)	44 (15.0%)	21 (14.7%)	**183 (16.3%)**	**<0.001**
HER2-positive (non-luminal)	20 (18.9%)	19 (7.1%)	24 (7.6%)	13 (4.4%)	9 (6.3%)	**85 (7.6%)**	
Triple-negative	14 (13.2%)	28 (10.5%)	38 (12.1%)	29 (9.9%)	15 (10.5%)	**124 (11.0%)**	

HER2: Human epidermal growth factor receptor 2.

TABLE 4: Distribution of tumor morphology and treatment modalities across age groups.							
Variable	**18-39**	**40-49**	**50-59**	**60-69**	**≥70**	**Total cohort**	**p-value**
Tumor morphology							
IDC	93 (87.7%)	216 (80.9%)	271 (86.0%)	239 (81.6%)	108 (75.5%)	927 (82.4%)	**0.115**
ILC	5 (4.7%)	21 (7.9%)	20 (6.3%)	29 (9.9%)	14 (9.8%)	89 (7.9%)	
Other	8 (7.5%)	30 (11.2%)	24 (7.6%)	25 (8.5%)	21 (14.7%)	108 (9.6%)	
Metastatic disease							
Absent	71 (67.0%)	210 (78.7%)	240 (76.2%)	226 (77.1%)	99 (69.2%)	846 (75.3%)	**0.060**
Present	35 (33.0%)	56 (21.0%)	74 (23.5%)	65 (22.2%)	42 (29.4%)	272 (24.7%)	
Neoadjuvant therapy							
No	60 (56.6%)	193 (72.3%)	225 (71.4%)	240 (81.9%)	115 (80.4%)	833 (74.1%)	**<0.001**
Yes	46 (43.4%)	74 (27.7%)	90 (28.6%)	53 (18.1%)	28 (19.6%)	291 (25.9%)	
Adjuvant therapy							
No	29 (27.4%)	52 (19.5%)	77 (24.4%)	68 (23.2%)	36 (25.2%)	262 (23.3%)	**0.452**
Yes	76 (71.7%)	213 (79.8%)	234 (74.3%)	223 (76.1%)	103 (72.0%)	849 (75.5%)	
Surgery performed							
No	10 (9.4%)	15 (5.6%)	24 (7.6%)	28 (9.6%)	17 (11.9%)	94 (8.4%)	**0.209**
Yes	96 (90.6%)	252 (94.4%)	291 (92.4%)	265 (90.4%)	126 (88.1%)	1030 (91.6%)	
ALND							
No	45 (42.5%)	126 (47.2%)	154 (48.9%)	153 (52.2%)	66 (46.2%)	544 (48.4%)	**0.450**
Yes	61 (57.5%)	141 (52.8%)	161 (51.1%)	140 (47.8%)	77 (53.8%)	580 (51.6%)	
Type of surgery							
None	9 (8.5%)	14 (5.2%)	24 (7.6%)	29 (9.9%)	14 (9.8%)	90 (8.0%)	**0.508**
Breast-conserving surgery	43 (40.6%)	124 (46.4%)	134 (42.5%)	119 (40.6%)	53 (37.1%)	473 (42.1%)	
Total mastectomy	54 (50.9%)	129 (48.3%)	157 (49.8%)	145 (49.5%)	76 (53.1%)	561 (49.9%)	
Radiotherapy							
No	18 (17.0%)	42 (15.7%)	64 (20.3%)	70 (23.9%)	48 (33.6%)	242 (21.5%)	**<0.001**
Yes	88 (83.0%)	225 (84.3%)	251 (79.7%)	223 (76.1%)	95 (66.4%)	882 (78.5%)	
Endocrine therapy							
No	34 (32.1%)	47 (17.6%)	63 (20.0%)	51 (17.4%)	29 (20.3%)	224 (19.9%)	**0.018**
Yes	72 (67.9%)	220 (82.4%)	252 (80.0%)	242 (82.6%)	114 (79.7%)	900 (80.1%)	

IDC: Invasive ductal carcinoma; ILC: Invasive lobular carcinoma; ALND: Axillary lymph node dissection.

DISCUSSION

Breast cancer is characterized by substantial biological heterogeneity, which directly influences clinical behavior and treatment strategies. Although biomarker-based risk stratification is well established in routine practice, data describing how age-related biological differences translate into real-world treatment patterns remain limited. In this large single-center cohort, we evaluated age-associated distributions of biomarkers and surrogate molecular subtypes to assess how guideline-defined biological risk profiles are reflected in daily clinical practice.[14]

The median age at diagnosis in our cohort was 55 years, with most patients clustered between 50 and 69 years, consistent with national data from Türkiye and global epidemiological reports.[15] The distinctive strength of this study lies in the integrated evaluation of biological features and treatment patterns across age groups. The higher frequency of ER negativity, HER2 positivity, and elevated proliferative activity in younger patients, contrasted with the predominance of hormone receptor-positive and lower-proliferation tumors in older patients, aligns with previously reported population-based trends.[16,17] Importantly, our findings demonstrate that these biological differences are accompanied by parallel differences in treatment intensity, particularly with respect to neoadjuvant systemic therapy.

TABLE 5: Independent predictors of HER2 positivity (multivariable logistic regression Model 1).

Predictor	Category	OR (95% CI)	p-value
ER status	≥10% (ref)	—	0.249
	1-9%	1.74 (0.79-3.83)	0.171
	Negative	0.90 (0.55-1.48)	0.684
PR status	≥10% (ref)	—	<0.001
	1-9%	0.86 (0.46-1.60)	0.634
	Negative	0.43 (0.27-0.68)	<0.001
Age group	18-39 (ref)	—	0.002
	40-49	0.41 (0.24-0.68)	0.001
	50-59	0.44 (0.27-0.72)	0.001
	60-69	0.35 (0.21-0.59)	<0.001
	≥70	0.38 (0.21-0.70)	0.002
Ki-67 group	<20% (ref)	—	<0.001
	20-49%	2.69 (1.85-3.91)	<0.001
	≥50%	1.38 (0.84-2.26)	0.205
Histological grade	Grade 1 (ref)	—	0.001
	Grade 2	6.01 (1.84-19.69)	0.003
	Grade 3	8.95 (2.66-30.16)	<0.001
Tumor type	IDC (ref)	—	0.125
	ILC	0.74 (0.40-1.35)	0.324
	Other	0.58 (0.33-1.03)	0.064

ER: Estrogen receptor; PR: Progesterone receptor; IDC: Invasive ductal carcinoma; ILC: Invasive lobular carcinoma; CI: Confidence interval; OR: Odds ratio; Ki-67: Proliferative index.

TABLE 6: Independent predictors of triple-negative phenotype (multivariable logistic regression Model 2).

Predictor	Category	OR (95% CI)	p-value
Age group	18-39 (ref)	—	—
	40-49	0.86 (0.39-1.87)	0.699
	50-59	1.10 (0.52-2.29)	0.809
	60-69	0.94 (0.44-2.02)	0.876
	≥70	1.20 (0.51-2.85)	0.677
Ki-67 index	≤20% (ref)	—	—
	20-50%	2.87 (1.47-5.61)	0.002
	>50%	12.10 (6.06-24.17)	<0.001
Histological grade	Grade 2 (ref)	—	—
	Grade 3	2.79 (1.79-4.33)	<0.001
Tumor type	IDC (ref)	—	—
	ILC	0.67 (0.23-1.94)	0.457
	Other	1.81 (0.94-3.46)	0.074

Due to the absence of TNBC cases in the grade 1 category, grade 1 and grade 2 tumors were combined in the multivariable regression model. IDC: Invasive ductal carcinoma; ILC: Invasive lobular carcinoma; OR: Odds ratio; CI: Confidence interval; TNBC: Triple-negative breast cancer; Ki-67: Proliferative index.

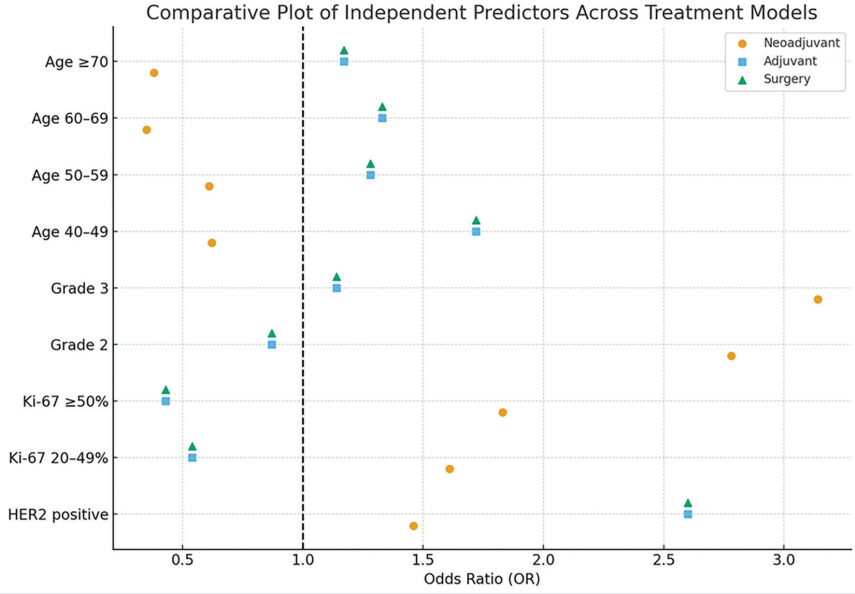

FIGURE 2: Comparative plot of independent predictors across neoadjuvant, adjuvant, and surgical treatment models. Comparative plot illustrating adjusted odds ratios (ORs) for key independent predictors across three multivariable logistic regression models: neoadjuvant therapy (orange circles), adjuvant therapy (blue squares), and surgical treatment (green triangles). The vertical dashed line at OR=1.0 represents the null effect. Each point reflects the estimated OR for the corresponding predictor relative to its reference category.

HER2: Human epidermal growth factor receptor 2; Ki-67: Proliferative index

In older age groups, the predominance of biologically indolent tumor phenotypes and the lower use of intensive systemic treatments are consistent with real-world series that include very elderly patients. Prior studies have shown that patients aged 80 years and older are more likely to harbor luminal tumors, to undergo de-escalated axillary surgery, and are less likely to receive chemotherapy. Moreover, non-breast cancer-related mortality represents a substantial proportion of deaths in this population, underscoring the importance of competing risks in prognostic assessment. Together, these observations support the notion that treatment decisions in older patients are guided not only by tumor biology but also by overall health status and comorbidity burden.[18,19]

ER positivity increased with advancing age, consistent with national and international data. In contrast, PR expression did not differ significantly across age groups. This finding is notable, as PR is more sensitive than ER to pre-analytical variability and biological heterogeneity. The prognostic and predictive value of PR remains debated and is often context-dependent, emerging in conjunction with proliferation, HER2 status, and molecular subtype. Our results suggest that aggressive tumor biology in younger patients does not uniformly affect all biomarkers and that PR should be interpreted within a multidimensional biological framework rather than as an age-specific marker.[20,21]

Marked age-related differences were observed in HER2 status and surrogate molecular subtype distribution. HER2-positive tumors were more frequent in younger patients, in line with population-based studies reporting higher rates of HER2-positive and triple-negative disease at younger ages. Similar to the findings of Turhan and Özyurt[8], HER2-enriched and triple-negative subtypes were more common in patients under 40 years of age. In our cohort, the higher prevalence of HER2 positivity among patients receiving neoadjuvant therapy indicates that HER2 amplification is a key driver of treatment intensification in real-world practice, supporting biology-driven rather than age-driven treatment selection.[17,22]

The Ki-67 proliferation index was a prominent indicator of age-related biological variation. Higher Ki-67 levels were more common among younger patients, reflecting a predominance of highly proliferative tumors and aligning with previous reports. Elevated Ki-67 was also associated with neoadjuvant treatment use, indicating concordance between proliferative activity and treatment intensity. However, Ki-67 was not used as a standalone determinant; instead, it contributed to integrated biological risk assessment. These findings support the use of Ki-67 as a complementary marker interpreted within the broader context of tumor biology rather than by fixed thresholds.[23-25]

In our cohort, the HER2-low phenotype (immunohistochemistry 1+ or 2+ with negative fluorescence *in situ* hybridization) was observed in 18.4% of patients, a rate consistent with those reported in real-world series. This finding indicates that HER2-low tumors constitute a clinically relevant proportion of breast cancer cases in routine practice. However, in line with current ASCO/CAP recommendations, HER2-low should be regarded as a treatment-oriented classification rather than an independent biological subtype, particularly in the metastatic setting.[2,26] Accordingly, HER2-low status in this study was evaluated descriptively to reflect its real-world prevalence rather than for prognostic stratification. Given the known interobserver variability and technical limitations in assessing low-level HER2 expression, these findings should be interpreted with caution. Overall, our results align with contemporary literature emphasizing the need for diagnostic standardization rather than a biological redefinition of the HER2-low category.

Histological grade is a key pathological marker reflecting tumor aggressiveness in invasive breast cancer. Rakha et al.[27] demonstrated a strong association between Nottingham histological grade and both disease-free and breast cancer-specific survival. In our cohort, high-grade tumors clustered predominantly within biologically aggressive molecular subtypes, reinforcing the role of histological grade in integrated clinical and biological risk assessment. In contrast, the lack of age-related differences in PR expression suggests that risk stratification in breast cancer is driven primarily by ER status, HER2 expression, and proliferative activity rather than by PR alone.

Luminal B breast cancer warrants particular attention due to its heterogeneous biological behavior. Kang et al.[28] reported significantly different clinical outcomes when luminal B tumors were stratified by HER2 status. Similarly, Chen et al.[29] showed that HER2-negative luminal B1 tumors exhibit more aggressive pathological features and higher recurrence risk compared with luminal A tumors. The heterogeneity observed among luminal subtypes in our cohort is consistent with contemporary genomic and clinical data, indicating that high-proliferation luminal B tumors carry increased biological risk and may derive greater benefit from adjuvant chemotherapy.[30]

Study Limitations

One of the major strengths of this study is the large, single-center real-world cohort. With 1,124 patients, it represents one of the most comprehensive datasets reported from Türkiye in this field. Nevertheless, the retrospective design and single-center nature of the study limit the ability to draw causal inferences. In addition, the lack of detailed data on

comorbidities and performance status restricts the scope of clinical interpretation.

Despite these limitations, the findings provide a solid basis for hypothesis generation and support the need for future prospective studies.

This large real-world cohort demonstrates the dynamic interplay between tumor biological risk profiles and treatment decisions in breast cancer. The alignment of aggressive tumor biology with more intensive treatment approaches in younger patients and the de-escalation of treatment parallel to indolent biology in older patients reflect the practical implementation of biology-driven individualized care. These findings underscore that treatment strategies in breast cancer are shaped primarily by tumor biology rather than chronological age alone.

CONCLUSION

This study demonstrates that age-related differences in breast cancer biology are not merely descriptive; they actively influence clinical decision-making in real-world practice. In this large cohort, biomarker profiles and surrogate molecular subtypes varied systematically across age groups and were closely aligned with the type and intensity of treatment strategies. These findings indicate that treatment selection in routine practice is guided primarily by tumor biological characteristics rather than chronological age alone.

The HER2-low phenotype was observed at a clinically meaningful frequency; however, our results support its interpretation as a treatment-oriented classification rather than an independent biological subtype. Overall, this study confirms that biology-driven individualized treatment approaches are effectively implemented in real-world breast cancer care and that age-related biological heterogeneity has tangible clinical implications. These findings provide a strong framework for future prospective and multicenter studies.

Ethics

Ethics Committee Approval: This study was approved by the Çanakkale Onsekiz Mart University Rectorate Non-Interventional Clinical Research Ethics Committee (approval number: 2025-387, date: 10.12.2025).

Informed Consent: Retrospective study.

Footnotes

Author Contributions

Surgical and Medical Practices: V.Ç., İ.G., S.C., E.Ö., Y.G.T., Ş.S.E., Y.Ç., Concept: V.Ç., İ.G., Y.Ç., Design: V.Ç., İ.G., Y.Ç., Data Collection or Processing: V.Ç., S.C., E.Ö., Y.G.T., Ş.S.E., Analysis or Interpretation: V.Ç., İ.G., S.C., Y.Ç., Literature Search: V.Ç., İ.G., S.C., Ş.S.E., Writing: V.Ç., İ.G., Y.Ç.

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