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Middle-aged, not the youngest, patients have the worst independent survival in ER-negative metastatic breast cancer: a retrospective cohort study

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Abstract

Background

The prognostic role of age in metastatic breast cancer (MBC) remains unclear and may vary according to tumor biology. We investigated whether the impact of age on survival differs by estrogen receptor (ER) status in metastatic breast cancer.

Methods

We conducted a retrospective cohort study of 657 patients with MBC treated at a single tertiary center between 2000 and 2022. Patients were stratified by ER status (ER-positive, n = 419; ER-negative, n = 238) and categorized into three age groups: young (< 35 years), middle-aged (35–50 years), and older (> 50 years). Overall survival (OS) was analyzed using Kaplan–Meier estimates and multivariable Cox proportional hazards models, with a sensitivity analysis using multiple imputation to evaluate the impact of Ki-67 adjustment.

Results

In ER-positive MBC, age was not associated with OS (log-rank p = 0.91); bone metastasis differed across age groups (46.2%, 51.8%, 36.0% for young, middle-aged, older; p = 0.007) without affecting survival. In ER-negative MBC, age was significantly associated with OS (log-rank p = 0.02), with young and middle-aged patients showing aggressive features including high Ki-67 and early relapse (6–24 months: 77.8%, 55.1%, 36.1%, respectively; p = 0.003). In multivariable analysis, middle-aged patients had higher risk of death than older patients (hazard ratio 1.77, 95% CI 1.12–2.81; p = 0.015), which persisted after Ki-67 adjustment (1.76, 95% CI 1.11–2.81; p = 0.017), whereas Ki-67 itself was not independently prognostic.

Conclusions

The prognostic impact of age in MBC strongly depends on ER status. While age lacks prognostic significance in ER-positive disease, it independently predicts survival in ER-negative MBC, with the highest risk among middle-aged patients. Robust to Ki-67 adjustment, age may be an integrative marker reflecting tumor biology beyond proliferation indices.

Background

Metastatic breast cancer (MBC) remains an incurable disease despite substantial therapeutic advances, with reported median overall survival ranging from approximately 2 to 4 years depending on tumor subtype and treatment era (1, 2). Over the past two decades, the incorporation of targeted therapies, including CDK4/6 inhibitors, HER2-directed agents, and improved chemotherapy regimens, has led to

incremental improvements in survival outcomes (2–6). Nevertheless, MBC is characterized by pronounced clinical and biological heterogeneity, with substantial variability in disease progression, treatment response, and survival across patients (7, 8). This heterogeneity highlights the importance of identifying robust prognostic factors to better stratify patients and guide treatment strategies.

Tumor subtype, defined by hormone receptor and HER2 status, is among the strongest determinants of prognosis in breast cancer, influencing both metastatic patterns and survival (8–10). Hormone receptor–positive tumors tend to metastasize to bone and follow a relatively indolent course, whereas triple-negative breast cancer is associated with early visceral relapse and poorer outcomes (9, 11).

Among patient-related factors, age at diagnosis has been increasingly recognized as a biologically meaningful prognostic variable. Younger patients more frequently present with high-grade tumors, elevated Ki-67 proliferation index, and aggressive molecular subtypes, including triple-negative and HER2-positive disease (12–14). In early-stage disease, young age has been associated with inferior outcomes, particularly in hormone receptor–positive tumors, where distinct molecular features and differential response to endocrine therapy may contribute to worse prognosis (13, 15, 16). However, the extent to which age independently influences prognosis—beyond its association with adverse tumor features—remains an area of ongoing investigation.

In the metastatic setting, the prognostic significance of age is less well established and may differ fundamentally from that observed in early-stage disease. Several studies have suggested that younger patients with MBC, particularly those with hormone receptor–negative tumors, experience accelerated disease progression and poorer survival outcomes (17, 18). These findings have been attributed not only to higher proliferative activity but also to distinct biological characteristics, including rapid disease progression and early metastatic dissemination (1, 14). Conversely, in hormone receptor–positive MBC, the prognostic impact of age appears attenuated, potentially because widespread use of endocrine therapy and ovarian function suppression may mitigate age-related biological differences (18, 19). Moreover, commonly used biomarkers such as Ki-67, while informative for tumor proliferation, may not fully capture the complexity of metastatic disease behavior, including relapse timing and patterns of progression (14, 19). These observations suggest that age may serve as an integrative clinical surrogate reflecting aspects of disease behavior beyond those captured by conventional prognostic markers, particularly in specific subtype-defined populations.

Despite these insights, the differential impact of age across tumor subtypes in metastatic breast cancer has not been fully elucidated, and it remains unclear whether the prognostic relevance of age varies between ER-positive and ER-negative disease. To address this gap, we conducted a retrospective cohort study to evaluate the prognostic impact of age according to ER status in patients with metastatic breast cancer. Our specific objectives were to determine whether age is differentially associated with overall survival in ER-positive and ER-negative disease, to characterize the clinicopathologic features associated with age in each subgroup, and to assess whether any age–survival association is robust to adjustment for the Ki-67 proliferation index.

Methods

Study design and ethics

This was a retrospective cohort study based on data from an existing institutional cohort of patients with metastatic breast cancer (MBC) treated at Ewha Womans University Mokdong Hospital between January 2000 and December 2022, and was reported per STROBE guidelines (20). The study protocol was approved by the Institutional Review Board of the Ewha Womans University Medical Center (approval number EUMC 2023-07-056), and the requirement for written informed consent was waived due to the retrospective design and the use of de-identified data. All procedures were conducted in accordance with the Declaration of Helsinki.

Patient population

We identified consecutive female patients diagnosed with metastatic breast cancer at Ewha Womans University Mokdong Hospital between January 2000 and December 2022. Metastatic disease was defined as histologically confirmed invasive breast carcinoma with radiologic or pathologic evidence of distant metastasis (American Joint Committee on Cancer [AJCC] stage IV), including both de novo stage IV disease and disease that recurred at a distant site after initial curative-intent treatment. Patients diagnosed before January 2000 were not included because routine human epidermal growth factor receptor 2 (HER2) testing had not yet been implemented at our institution.

Of 679 patients initially identified, 22 were excluded (16 with unknown estrogen receptor status, 6 with incomplete survival data). The final analytic cohort comprised 657 patients: 419 with ER-positive disease and 238 with ER-negative disease. The patient selection process is summarized in Figure 1.

Clinical variables and pathologic assessment

Clinicopathologic data were extracted from institutional electronic medical records. Hormone receptor status — estrogen receptor (ER) and progesterone receptor (PR) — was determined by immunohistochemistry (IHC); positivity was defined as ≥1% of tumor cell nuclei staining, in accordance with the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines (21). HER2 status was assessed by IHC, with IHC 1+ considered negative and IHC 2+ (equivocal) confirmed by silver in situ hybridization (SISH); HER2 positivity was defined as IHC 3+ or SISH amplification (22). Ki-67 proliferation index was assessed by IHC using the MIB-1 antibody and was dichotomized as low (<20%) versus high (≥20%), corresponding to the St. Gallen consensus cutoff (23). Histologic grade was determined using the modified Bloom–Richardson (Nottingham) grading system.

Tumor stage (T), nodal stage (N), and metastatic stage (M) were assigned according to the AJCC staging manual applicable at the time of diagnosis. **Sites of distant metastasis were recorded at the time of first metastatic presentation. For the multivariable analysis, each patient was assigned to a single mutually exclusive site-of-first-metastasis category using the following clinically based hierarchy: brain > visceral (non-brain visceral organs including liver and lung) > bone > other. Patients**

with concurrent involvement of multiple organs were classified by the highest-priority site. The individual site-specific metastases (bone, visceral, brain, liver, lung) shown in Table 1 are non-mutually exclusive and may overlap within a patient. Time from primary diagnosis to first metastasis was categorized as de novo (<6 months), early (6–24 months), or late (≥24 months) recurrence.

Patients were stratified into ER-positive and ER-negative groups based on ER status at the time of initial breast cancer diagnosis. For all subtype-related analyses, tumor subtype was defined according to receptor status at the time of first metastatic diagnosis, using the most recent available biopsy of metastatic tissue whenever a re-biopsy was performed; when metastatic tissue was not available, the primary tumor subtype was carried forward.

Patients were further categorized into three age groups based on age at initial diagnosis: young (<35 years), middle-aged (35–50 years), and older (>50 years). These cutoffs were chosen a priori because age <35 years is a widely recognized threshold for very-young breast cancer associated with distinct tumor biology (13), and age 50 approximates the median age at menopause in Korean women, thereby reasonably separating predominantly premenopausal and postmenopausal populations..

Outcomes

The primary endpoint was overall survival (OS), defined from initial breast cancer diagnosis to death from any cause; survivors were censored at last follow-up or December 31, 2022. **Because OS was timed from initial diagnosis rather than from metastasis, follow-up could extend beyond the 2000–2022 study window: 18 patients (2.7%) had OS exceeding 20 years (maximum 31.6 years), reflecting pre-2000 diagnoses followed through to a later metastatic event.** Dates and causes of death were ascertained from the institutional medical record and cross-checked with the Korean national death registry (Statistics Korea) to ensure completeness of mortality ascertainment. Secondary descriptive outcomes included site-specific metastatic patterns and time from primary diagnosis to first metastasis.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics version 25 (IBM Corp., Armonk, NY, USA); the sensitivity analysis with multiple imputation was conducted in R version 4.4 (R Foundation for Statistical Computing, Vienna, Austria) using the mice and survival packages.

Continuous variables are reported as median (range) and categorical variables as counts (percentages). The median age between the ER-positive and ER-negative cohorts was compared using the Mann–Whitney U test. Baseline characteristics were compared across the three age groups within each ER-defined cohort using the chi-square test or Fisher's exact test, as appropriate. Overall survival was estimated using the Kaplan–Meier method and compared across age groups with the log-rank test within each ER cohort.

Multivariable Cox proportional hazards regression identified independent predictors of overall survival, adjusting for age group (reference: >50 years), time to first metastasis (reference: ≥24 months), site of first metastasis (reference: bone), and tumor subtype at diagnosis (reference: HR+HER2−). Covariates were selected a priori based on established prognostic relevance to reduce variable-selection bias. The proportional hazards assumption was evaluated with scaled Schoenfeld residuals; no material violations were observed.

To address missing Ki-67 values (n = 115; 17.4%), a sensitivity analysis was conducted using multiple imputation by chained equations (MICE) with 20 imputed datasets. The imputation model included age, tumor stage, nodal stage, histologic grade, HER2 status, tumor subtype, time to first metastasis, site of metastasis, the Nelson–Aalen estimate of the cumulative baseline hazard, and the event indicator, following the approach of White and Royston (24). Binary logistic regression was used to impute dichotomized Ki-67 status (<20% vs. ≥20%). Multivariable Cox regression was performed on each imputed dataset and the estimates were pooled using Rubin's rules.

All statistical tests were two-sided, and a P value < 0.05 was considered statistically significant. Kaplan–Meier curves were displayed up to 240 months for readability, given the few patients with longer observation.

Results

Patient characteristics

Among the 657 patients included in the analysis, 419 (63.8%) had ER-positive and 238 (36.2%) had ER-negative disease. The median age at initial diagnosis was 47 years (range, 23–87; interquartile range, 41–55) overall, and was similar between the ER-positive (median 47 years; range, 25–87; IQR, 41–55) and ER-negative (median 48 years; range, 23–87; IQR, 40–55) cohorts (p= 0.93). Baseline characteristics stratified by ER status and age group are summarized in Table 1.

Table 1.

Clinicopathologic characteristics of patients with metastatic breast cancer stratified by estrogen receptor status and age at diagnosis.

Variables	ER-positive (N = 419)				ER-negative (N = 238)			
	<35 (N=13)	35-50 (N=195)	>50 (N=211)	P-value	<35 (N=18)	35-50 (N=98)	>50 (N=122)	P-value
T stage				**0.918**				**0.340**
T0	0 (0.0)	4 (2.1)	5 (2.4)		0 (0.0)	6 (6.1)	5 (4.1)	
T1	3 (23.1)	43 (22.1)	42 (19.9)		5 (27.8)	23 (23.5)	28 (23.0)	
T2	6 (46.2)	89 (45.6)	88 (41.7)		9 (50.0)	33 (33.7)	56 (45.9)	
T3	0 (0.0)	23 (11.8)	21 (10.0)		4 (22.2)	17 (17.3)	13 (10.7)	
T4	0 (0.0)	15 (7.7)	17 (8.1)		0 (0.0)	2 (2.0)	8 (6.6)	
Unknown	4 (30.8)	21 (10.8)	38 (18.0)		0 (0.0)	17 (17.3)	12 (9.8)	
N stage				**0.642**				**0.276**
N0	3 (23.1)	43 (22.1)	54 (25.6)		8 (44.4)	23 (23.5)	44 (36.1)	
N1	2 (15.4)	52 (26.7)	45 (21.3)		3 (16.7)	25 (25.5)	19 (15.6)	
N2	3 (23.1)	38 (19.5)	31 (14.7)		2 (11.1)	16 (16.3)	18 (14.8)	
N3	1 (7.7)	39 (20.0)	42 (19.9)		5 (27.8)	17 (17.3)	28 (23.0)	
Unknown	4 (30.8)	23 (11.8)	39 (18.5)		0 (0.0)	17 (17.3)	13 (10.7)	
Histologic type				**0.071**				**0.227**
Ductal	11 (84.6)	180 (92.3)	174 (82.5)		15 (83.3)	92 (93.9)	109 (89.3)	
Lobular	0 (0.0)	3 (1.5)	12 (5.7)		1 (5.6)	1 (1.0)	1 (0.8)	
Others	0 (0.0)	3 (1.5)	8 (3.8)		2 (11.1)	3 (3.1)	9 (7.4)	
Unknown	2 (15.4)	9 (4.6)	15 (7.1)		0 (0.0)	2 (2.0)	3 (2.5)	
Histologic grade				**0.072**				**0.617**

Grade 1	2 (15.4)	12 (6.2)	11 (5.2)		0 (0.0)	0 (0.0)	1 (0.8)	
Grade 2	0 (0.0)	64 (32.8)	71 (33.6)		2 (11.1)	16 (16.3)	23 (18.9)	
Grade 3	5 (38.5)	46 (23.6)	51 (24.2)		14 (77.8)	46 (46.9)	59 (48.4)	
Unknown	6 (46.2)	73 (37.4)	78 (37.0)		2 (11.1)	36 (36.7)	39 (32.0)	
Ki-67				**0.359**				**0.055**
Low (<20%)	6 (46.2)	70 (35.9)	89 (42.2)		0 (0.0)	13 (13.3)	25 (20.5)	
High (≥20%)	5 (38.5)	92 (47.2)	83 (39.3)		18 (100.0)	76 (77.6)	81 (66.4)	
Unknown	2 (15.4)	33 (16.9)	39 (18.5)		0 (0.0)	9 (9.2)	16 (13.1)	
Progesterone receptor				**0.168**				**0.575**
Positive	12 (92.3)	169 (86.7)	169 (80.1)		1 (5.6)	10 (10.2)	16 (13.1)	
Negative	1 (7.7)	26 (13.3)	41 (19.4)		17 (94.4)	88 (89.8)	106 (86.9)	
Unknown	0 (0.0)	0 (0.0)	1 (0.5)		0 (0.0)	0 (0.0)	0 (0.0)	
Tumor subtype				**0.157**				**0.078**
HR+HER2−	7 (53.8)	151 (77.4)	160 (75.8)		0 (0.0)	7 (7.1)	9 (7.4)	
HER2+	6 (46.2)	44 (22.6)	51 (24.2)		2 (11.1)	37 (37.8)	48 (39.3)	
TNBC	—	—	—		16 (88.9)	54 (55.1)	65 (53.3)	
Visceral metastasis				**0.649**				**0.546**
Yes	5 (38.5)	64 (32.8)	79 (37.4)		7 (38.9)	31 (31.6)	47 (38.5)	
No	8 (61.5)	131 (67.2)	132 (62.6)		11 (61.1)	67 (68.4)	75 (61.5)	
Bone metastasis				**0.007**				**0.365**

Yes	6 (46.2)	101 (51.8)	76 (36.0)		5 (27.8)	18 (18.4)	18 (14.8)	
No	7 (53.8)	94 (48.2)	135 (64.0)		13 (72.2)	80 (81.6)	104 (85.2)	
Brain metastasis				**0.296**				**1.000**
Yes	3 (23.1)	41 (21.0)	33 (15.6)		6 (33.3)	33 (33.7)	41 (33.6)	
No	10 (76.9)	154 (79.0)	178 (84.4)		12 (66.7)	65 (66.3)	81 (66.4)	
Liver metastasis				**0.251**				**0.966**
Yes	1 (7.7)	25 (12.8)	38 (18.0)		3 (16.7)	14 (14.3)	18 (14.8)	
No	12 (92.3)	170 (87.2)	173 (82.0)		15 (83.3)	84 (85.7)	104 (85.2)	
Lung metastasis				**0.800**				**0.546**
Yes	4 (30.8)	44 (22.6)	48 (22.7)		6 (33.3)	22 (22.4)	33 (27.0)	
No	9 (69.2)	151 (77.4)	163 (77.3)		12 (66.7)	76 (77.6)	89 (73.0)	
Time to first metastasis				**0.634**				**0.003**
De novo (<6 mo)	4 (30.8)	49 (25.1)	43 (20.4)		0 (0.0)	15 (15.3)	23 (18.9)	
6-24 months	3 (23.1)	37 (19.0)	37 (17.5)		14 (77.8)	54 (55.1)	44 (36.1)	
≥24 months	6 (46.2)	109 (55.9)	131 (62.1)		4 (22.2)	29 (29.6)	55 (45.1)	
Breast surgery				**0.870**				**0.779**
Mastectomy	4 (30.8)	77 (39.5)	80 (37.9)		7 (38.9)	31 (31.6)	45 (36.9)	
Breast-conserving	5 (38.5)	79 (40.5)	90 (42.7)		11 (61.1)	49 (50.0)	58 (47.5)	
Unknown	4 (30.8)	39 (20.0)	41 (19.4)		0 (0.0)	18 (18.4)	19 (15.6)	
Axillary surgery				**0.549**				**0.083**

SLNB only	3 (23.1)	35 (17.9)	46 (21.8)		0 (0.0)	21 (21.4)	20 (16.4)	
ALND	8 (61.5)	155 (79.5)	162 (76.8)		18 (100.0)	77 (78.6)	101 (82.8)	
Unknown	2 (15.4)	5 (2.6)	3 (1.4)		0 (0.0)	0 (0.0)	1 (0.8)	
Neoadjuvant chemotherapy				**0.799**				**0.066**
Yes	1 (7.7)	27 (13.8)	30 (14.2)		9 (50.0)	34 (34.7)	31 (25.4)	
No	12 (92.3)	168 (86.2)	181 (85.8)		9 (50.0)	64 (65.3)	91 (74.6)	
Adjuvant chemotherapy				**0.896**				**0.293**
Yes	7 (53.8)	116 (59.5)	123 (58.3)		15 (83.3)	65 (66.3)	79 (64.8)	
No	6 (46.2)	79 (40.5)	88 (41.7)		3 (16.7)	33 (33.7)	43 (35.2)	
Adjuvant radiotherapy				**0.903**				**0.090**
Yes	6 (46.2)	92 (47.2)	104 (49.3)		14 (77.8)	56 (57.1)	62 (50.8)	
No	7 (53.8)	103 (52.8)	106 (50.2)		4 (22.2)	42 (42.9)	60 (49.2)	
Unknown	0 (0.0)	0 (0.0)	1 (0.5)		0 (0.0)	0 (0.0)	0 (0.0)	

Data presented as n (%).

Abbreviations: ER, estrogen receptor; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; TNBC, triple-negative breast cancer; SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection.

Statistical tests: P-values were calculated using the chi-square test or Fisher's exact test, comparing age groups (<35, 35–50, >50 years) within each ER-defined cohort. P-values for variables with unknown categories were computed excluding unknown cases.

In the ER-positive cohort, 13 (3.1%), 195 (46.5%), and 211 (50.4%) patients were young (<35 years), middle-aged (35–50 years), and older (>50 years), respectively. Most variables did not differ across age groups, but **the proportion with bone metastasis differed significantly among age groups (46.2% in young, 51.8% in middle-aged, and 36.0% in older patients; p = 0.007).**

In the ER-negative cohort, 18 (7.6%), 98 (41.2%), and 122 (51.3%) patients were young, middle-aged, and older, respectively. Younger patients demonstrated features consistent with more aggressive tumor biology. All young patients exhibited high Ki-67 expression (100%), compared with 86.7% and 79.5% in the middle-aged and older groups, respectively (p = 0.055). In addition, time to first metastasis differed significantly across age groups, with younger patients more likely to develop metastasis within 6–24 months **(77.8% in young, 55.1% in middle-aged, and 36.1% in older patients; p = 0.003).**

Subtype distribution did not differ significantly across age groups in the ER-positive cohort, with HR+HER2− disease being the most common subtype. In contrast, triple-negative breast cancer was more prevalent in the ER-negative cohort, particularly among young patients. Surgical treatment patterns and the use of neoadjuvant and adjuvant therapies were comparable across age groups in both cohorts.

Re-biopsy of metastatic tissue was performed in 384 of 657 patients (58.4%), allowing paired comparison of primary and metastatic tumor subtypes. A discordance in tumor subtype between the primary and first metastatic site was observed in 106 patients (27.6%): 24.2% (59/244) in the ER-positive cohort and 33.6% (47/140) in the ER-negative cohort. The most common transitions were loss of hormone receptor expression (HR+HER2− to triple-negative breast cancer [TNBC], n = 32) and loss of HER2 positivity (HER2+ to HR+HER2−, n = 19).

Overall survival according to age and ER status

With a median follow-up of 65 months, a total of 229 deaths (34.9%) were observed. In the overall population, there was no significant difference in overall survival (OS) among age groups (log-rank p = 0.24) (Figure 2A).

In the ER-positive cohort, 143 patients (34.1%) died. OS did not differ significantly across age groups (log-rank p = 0.91) (Figure 2B), with comparable survival distributions among young, middle-aged, and older patients. The median OS was 130 months in young patients, 187 months in middle-aged patients, and 117 months in older patients; the median OS estimate for the young group should be interpreted with caution given the small sample size (n = 13).

In contrast, in the ER-negative cohort, 86 patients (36.1%) died, and OS differed significantly according to age (log-rank p = 0.02) (Figure 2C). Young patients had inferior survival compared with middle-aged and older patients. The median OS was 95 months in young patients and 125 months in middle-aged patients, whereas the median OS was not reached in older patients.

Multivariable analysis of overall survival

In the ER-positive cohort, age was not independently associated with OS (overall p = 0.38) (Table 2). Longer time to first metastasis was strongly favorable (de novo vs. ≥24 months: HR 4.24, 95% CI 2.68–6.72, p < 0.001), and brain metastasis conferred the worst site-specific outcome (HR 1.93, p = 0.011); tumor subtype was not prognostic.

Table 2.

Multivariable Cox regression analysis of factors associated with overall survival in metastatic breast cancer, stratified by estrogen receptor status.

Variables	ER-positive (N=419)		ER-negative (N=238)	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age group		**0.38**		**0.04**
>50 years (older)	1.00 (Reference)	-	1.00 (Reference)	-
35-50 years (middle-aged)	0.85 (0.60-1.20)	0.352	1.77 (1.12-2.81)	0.015
<35 years (young)	0.50 (0.16-1.62)	0.251	1.15 (0.47-2.81)	0.761
Time to first metastasis		**<0.001**		**<0.001**
≥24 months	1.00 (Reference)	-	1.00 (Reference)	-
6-24 months	3.60 (2.32-5.59)	<0.001	3.40 (2.00-5.76)	<0.001
De novo (<6 months)	4.24 (2.68-6.72)	<0.001	6.26 (2.93-13.39)	<0.001
Site of first metastasis		**<0.001**		**<0.001**
Bone	1.00 (Reference)	-	1.00 (Reference)	-
Visceral	1.60 (0.97-2.65)	0.067	1.45 (0.54-3.93)	0.461
Brain	1.93 (1.17-3.19)	0.011	1.59 (0.64-3.99)	0.320
Others	0.70 (0.41-1.21)	0.203	0.41 (0.15-1.10)	0.076
Tumor subtype		**0.60**		**0.008**
HR+HER2-	1.00 (Reference)	-	0.62 (0.24-1.65)	0.341
HER2+	0.90 (0.61-1.34)	0.603	0.45 (0.27-0.75)	0.002
TNBC	—	—	1.00 (Reference)	-

Abbreviations: HR, hazard ratio; CI, confidence interval; ER, estrogen receptor; HR+, hormone receptor–positive (either estrogen receptor–positive or progesterone receptor–positive); HER2+, human epidermal growth factor receptor 2; TNBC, triple-negative breast cancer.

Note: Bold p-values indicate overall p-values for each categorical variable from joint Wald tests. Hazard ratios estimated from multivariable Cox proportional hazards models separately fitted within the ER-positive and ER-negative cohorts, adjusting simultaneously for age group, time to first metastasis, site of first metastasis, and tumor subtype. Tumor subtype was classified into three categories (HR+HER2−, HER2+, TNBC). Site of first metastasis is a mutually exclusive single-category variable assigned using a

clinically based hierarchy (brain > visceral > bone > other); individual site-specific metastases shown in Table 1 are non-mutually exclusive.

In the ER-negative cohort, age was independently associated with OS (overall p = 0.04). Compared with older patients (>50 years), middle-aged patients (35–50 years) had a significantly higher risk of death (HR 1.77, 95% CI 1.12–2.81, p = 0.015). Young patients (<35 years) did not show a statistically significant difference in risk compared with older patients (HR 1.15, 95% CI 0.47–2.81, p = 0.761); however, the wide confidence interval indicates that this subgroup (n = 18) was underpowered to detect smaller effect sizes, and the point estimate should not be interpreted as evidence of similar outcomes.

Time to first metastasis was the strongest prognostic factor in the ER-negative cohort (de novo vs. ≥24 months: HR 6.26, 95% CI 2.93–13.39, p < 0.001; 6–24 months vs. ≥24 months: HR 3.40, 95% CI 2.00–5.76, p < 0.001). Tumor subtype was also significantly associated with survival (overall p = 0.008), compared with triple-negative breast cancer as the reference, HER2+ disease was associated with significantly better survival (HR 0.45, 95% CI 0.27–0.75, p = 0.002), whereas HR+HER2− disease showed no significant difference (HR 0.62, 95% CI 0.24–1.65, p = 0.341). Metastatic site showed an overall significant association with survival (overall p < 0.001); however, no individual metastatic site reached statistical significance compared with bone after adjustment.

Sensitivity analysis with Ki-67 adjustment

To evaluate potential confounding by tumor proliferation index, a sensitivity analysis was conducted using multiple imputation to address missing Ki-67 values (17.4%). After imputation and inclusion of Ki-67 (low [<20%] vs. high [≥20%]) in the multivariable Cox model, the findings remained consistent with the primary analysis (Supplementary Table S1). In the ER-positive cohort, age showed no association with OS (middle-aged vs. older: HR 0.84, 95% CI 0.59–1.19, p = 0.32). In the ER-negative cohort, middle-aged patients retained a significantly elevated risk of death compared with older patients (HR 1.76, 95% CI 1.11–2.81, p = 0.017), whereas Ki-67 status was not independently prognostic in either cohort (ER-positive: HR 1.17, 95% CI 0.79–1.74, p = 0.44; ER-negative: HR 1.45, 95% CI 0.70–3.01, p = 0.31). These findings indicate that the prognostic impact of age in ER-negative metastatic breast cancer is robust to adjustment for Ki-67.

Discussion

In this retrospective cohort of 657 patients with metastatic breast cancer, we evaluated the prognostic impact of age at diagnosis stratified by estrogen receptor (ER) status, and demonstrated three principal findings. First, the prognostic impact of age on overall survival differed fundamentally between ER-positive and ER-negative disease: age had no prognostic influence in ER-positive metastatic breast cancer, whereas in ER-negative disease, age was independently associated with survival. Second, within the ER-negative cohort, although Kaplan–Meier curves showed numerically worse overall survival in young patients (<35 years), multivariable analysis identified middle-aged patients (35–50 years) as the group with a significantly elevated, independent risk of death compared with older (>50 years) patients

(HR 1.77, 95% CI 1.12–2.81, p=0.015). Third, and most importantly, this age effect was robust to adjustment for the Ki-67 proliferation index using multiple imputation, whereas Ki-67 itself was not independently prognostic in either ER-defined cohort. These findings suggest that age captures biological information about metastatic breast cancer that is not fully explained by conventional proliferation markers.

In the ER-positive cohort, overall survival did not differ significantly across age groups (log-rank p=0.91), consistent with recent evidence that the prognostic value of age is attenuated once metastatic breast cancer is established and effective endocrine-based systemic therapy is widely used (25, 26). In a French ESME cohort of 16,703 patients with MBC, hormone receptor–positive disease showed relatively preserved outcomes across age strata, supporting the view that the biological relevance of young age in hormone-driven disease diminishes once widespread metastasis has occurred (26). A similar pattern was described in the prospective EMBRACE study, in which the excess mortality associated with young age at MBC diagnosis was driven primarily by luminal-B–like and HER2-positive disease rather than by ER-positive disease as a whole (27). Our ER-positive cohort also demonstrated that the prevalence of bone metastasis differed significantly across age groups (46.2% in young, 51.8% in middle-aged, and 36.0% in older patients; p = 0.007), consistent with the known osteotropism of hormone receptor–positive disease (28, 29). Importantly, this age-related difference in metastatic pattern did not translate into survival differences, likely reflecting the relatively indolent biology and effective therapeutic options for bone-predominant hormone receptor–positive MBC (1, 30).

In contrast, in the ER-negative cohort, overall survival differed significantly by age (log-rank p = 0.02), and clinicopathologic features were consistent with aggressive disease, including universally high Ki-67 (100%) in young patients and a graded distribution of early metastatic relapse across age groups (6–24 months: 77.8% in young, 55.1% in middle-aged, and 36.1% in older patients; p = 0.003). On the Kaplan–Meier curves, young patients displayed the lowest survival probabilities overall, reinforcing the long-held clinical perception that young age at MBC diagnosis portends an aggressive course (16, 31, 32). However, after multivariable adjustment, it was middle-aged patients—not the youngest subgroup—who retained a significantly elevated, independent risk of death compared with older patients (HR 1.77, 95% CI 1.12–2.81, p=0.015), while the point estimate for the <35-year group was centered near 1 with a wide confidence interval (HR 1.15, 95% CI 0.47–2.81, p=0.761). This apparent paradox reflects, in part, the small sample size of the <35 ER-negative subgroup (n=18), which is underpowered to detect moderate effect sizes; nevertheless, it also suggests that the univariable survival disadvantage of very young patients with ER-negative MBC is largely mediated through their concurrent adverse tumor features (high proliferation, early metastasis, triple-negative biology), which the multivariable model explicitly adjusts for. In other words, being young itself is a marker of aggressive disease biology in ER-negative MBC, and once that biology is statistically controlled for, the remaining independent risk appears concentrated in the 35–50 year window. A similar, nuanced pattern has been reported in large population-based analyses. In the recent SEER-based analysis by Xiao et al., younger women with HR-negative de novo MBC did not demonstrate a consistent survival advantage over middle-aged patients once tumor characteristics were adjusted for (33), and a separate large SEER study by Chen et al. similarly found that

middle-aged patients with HR-negative metastatic disease can have a comparable or worse prognosis than their younger counterparts after adjustment (34, 35). Our findings extend these observations by providing subtype-stratified evidence from a Korean cohort, supporting the view that chronological age alone is an insufficient risk descriptor and must be interpreted together with ER status and the underlying tumor biology (36).

The central novel contribution of the present study is the demonstration that the age effect in ER-negative MBC is robust to adjustment for Ki-67. In a sensitivity analysis using multiple imputation to handle missing Ki-67 values (17.4%), the hazard ratio for middle-aged compared with older patients was essentially unchanged (HR 1.76, 95% CI 1.11–2.81, p=0.017), whereas Ki-67 dichotomized at 20% was not independently associated with overall survival in either cohort (ER-positive HR 1.17, p=0.44; ER-negative HR 1.45, p=0.31). This finding has two important implications. First, it argues against the simplistic view that the prognostic signal of age merely reflects tumor proliferation captured by Ki-67. Although Ki-67 has well-established prognostic value in early-stage breast cancer (37, 38), its utility in the metastatic setting has always been less clear, with meta-analyses showing modest effect sizes and substantial interlaboratory variability (37). Even under the updated IKWG consensus framework, which recommends using only extreme Ki-67 values (<5% or ≥30%) for clinical decision making, the marker captures only one dimension of tumor biology—proliferative activity at a single snapshot in time (37). In contrast to early-stage ER-positive breast cancer, where the adverse prognostic impact of very young age is often attributed to endocrine resistance (39), the persistence of an age effect in ER-negative metastatic disease after adjustment for Ki-67 suggests that age reflects biological dimensions beyond proliferation. These may include metastatic competence, immune–stromal interactions, clonal heterogeneity, and treatment resistance, which are not captured by Ki-67 alone (40, 41). The present data suggest that age encodes additional biological information beyond proliferation, potentially including features of the tumor microenvironment, immune contexture, and host-intrinsic factors that Ki-67 does not measure. Consistent with this, recent transcriptomic and single-cell analyses have shown that breast tumors arising in younger hosts exhibit distinct microenvironmental features, including altered stromal inflammatory responses and reduced immune cell metabolism, relative to tumors arising in older hosts, independent of proliferation status (42). Second, this robustness strengthens the clinical utility of age as an integrative prognostic marker in ER-negative MBC: even when proliferation data are incomplete or non-informative, age at diagnosis continues to stratify risk. This is particularly relevant for real-world retrospective cohorts and resource-limited settings, where Ki-67 results are variably available and not always standardized (38).

The most powerful prognostic factor in both ER-defined cohorts was time from primary diagnosis to first metastasis (de novo vs. ≥24 months HR 4.24 in ER-positive and 6.26 in ER-negative; both p<0.001), consistent with long-standing evidence that the interval from initial diagnosis to metastatic relapse reflects underlying tumor aggressiveness and that de novo stage IV disease carries a distinct biological and clinical profile (43). In our ER-negative cohort, this factor was closely intertwined with age: young and middle-aged patients were substantially more likely to experience early (6–24 month) metastatic relapse than older patients, reinforcing the conclusion that accelerated disease trajectory is a defining

feature of non-hormone-driven MBC in younger hosts. A complementary finding was that 27.6% (106/384) of patients who underwent metastatic re-biopsy demonstrated a change in tumor subtype compared with the primary, with discordance higher in the ER-negative cohort (33.6%) than in the ER-positive cohort (24.2%). This discordance rate is consistent with several recent large series (18–32% globally) (44, 45) and with the large French ESME cohort, in which loss of hormone receptor expression at metastasis was independently associated with an approximately 50% higher risk of death (26). A 2023 analysis by Lin et al. of 93 paired primary–bone metastases further showed that loss of hormone receptor expression carries a markedly worse prognosis (adjusted HR for OS = 6.09) (46). Our observation that ER-negative disease more frequently exhibits subtype drift—combined with its worse outcomes in middle-aged patients—suggests that tumor heterogeneity and phenotypic plasticity may be especially pronounced in non-hormone-driven MBC and supports routine metastatic re-biopsy whenever technically feasible (44, 47). As expected, within the ER-negative cohort HER2-positive disease showed significantly better survival than triple-negative breast cancer (HR 0.45, 95% CI 0.27–0.75, p=0.002), consistent with the established survival benefit of HER2-targeted therapy (48).

Clinically, these findings argue for a more nuanced, ER-stratified interpretation of age in the management of MBC. In ER-positive disease, chronological age alone should not drive prognostic discussions or treatment intensity. In ER-negative disease, age is a meaningful independent variable, but the excess risk is concentrated in middle-aged rather than the youngest patients. Middle-aged women with ER-negative disease may warrant heightened surveillance, intensified therapy, and prioritized trial enrollment, while very young patients' poor survival reflects aggressive tumor biology rather than age as an independent factor.

This study has several strengths. We analyzed a sizeable, well-characterized single-institution cohort spanning over two decades, with detailed clinicopathologic annotation including tumor subtype at both primary and metastatic biopsy, allowing us to use the most recent metastatic subtype for analyses when available. Mortality ascertainment was strengthened by cross-linkage with the Korean national death registry, reducing the risk of informative censoring. Most importantly, we addressed the common problem of missing Ki-67 values with multiple imputation rather than complete-case analysis, which enabled a robust sensitivity analysis that preserved statistical power and supported the robustness of the main findings. Several limitations should, however, be acknowledged. First, this was a retrospective single-center study in a Korean population, and the findings may not fully generalize to other ethnic groups, although comparable subtype-specific age-prognosis patterns have been reported in East Asian, European, and North American cohorts (31, 33, 35). Second, the <35-year ER-negative subgroup was small (n=18), limiting statistical power to detect moderate age effects in this subgroup and contributing to the wide confidence interval observed. Third, the study period (2000–2022) spans substantial evolution in systemic therapy, including the introduction of dual HER2 blockade, CDK4/6 inhibitors, and immunotherapy for triple-negative disease; although treatment era was not explicitly modeled, the stratification by ER status and adjustment for time to metastasis partially mitigate this concern (30). Fourth, HER2 assessment during the earliest years used evolving guideline criteria, although the IHC/SISH framework used at our institution is consistent with current ASCO/CAP recommendations

(47). Fifth, metastatic re-biopsy was performed in 59.1% of patients; results from the 40.9% of patients without re-biopsy should be interpreted with the understanding that some subtype discordance may have been missed. Finally, although multiple imputation handled Ki-67 missingness rigorously, residual confounding from unmeasured variables such as BRCA mutation status, germline genetic background, or socioeconomic factors cannot be excluded.

Conclusion

In summary, in ER-negative metastatic breast cancer the prognostic effect of age is driven not by the youngest patients but by the middle-aged group (35–50 years), independent of Ki-67. These findings support an ER-stratified interpretation of age and identify middle-aged women with ER-negative disease as a clinically meaningful subgroup warranting closer surveillance and prioritized trial enrollment.

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of the Ewha Womans University Medical Center (approval number EUMC 2023-07-056). The requirement for written informed consent was waived owing to the retrospective design and the use of de-identified data. All procedures were conducted in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable. The manuscript does not contain any individual person’s identifying data or images.

Availability of data and materials

The datasets generated and analyzed during the current study are not publicly available because they contain potentially identifying clinical information from a single institution and the IRB approval was granted under conditions of restricted data access. De-identified data are available from the corresponding author upon reasonable request and with permission of the Institutional Review Board of Ewha Womans University Medical Center.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

SJH and JW conceived and designed the study. SJH performed the data collection, statistical analyses, and drafted the manuscript. HAL provided statistical guidance and reviewed the statistical methodology. KEL contributed to clinical data interpretation and reviewed the manuscript. AH, JL, HGK, JWL, WL, BIM, and SHA contributed to data collection. JW supervised the study and revised the manuscript. All authors read and approved the final manuscript.

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Authors' information (optional)

Not applicable.

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Figures

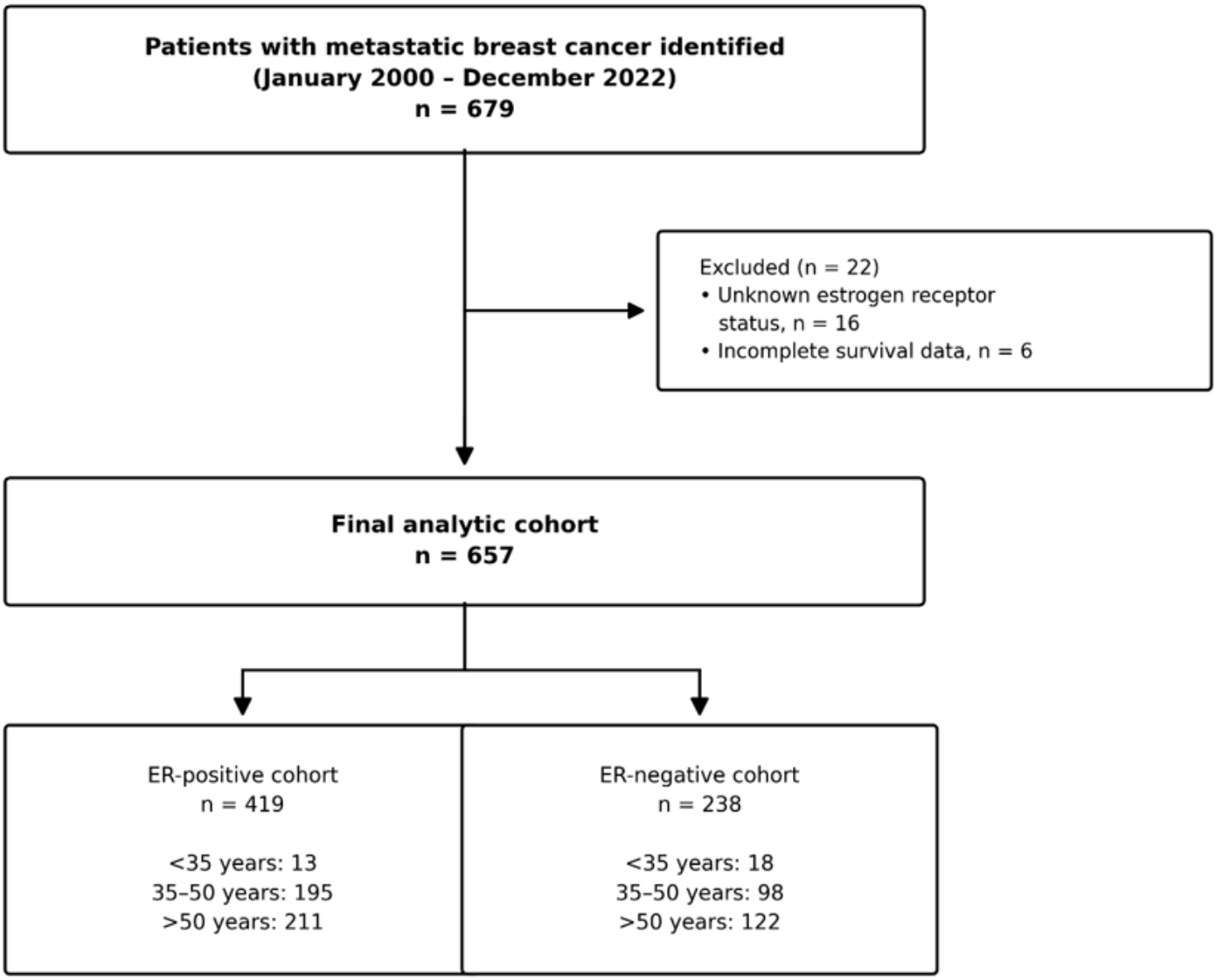


Figure 1

Flow diagram of patient selection. Of 679 patients initially identified, 22 were excluded (16 with unknown estrogen receptor status, 6 with incomplete survival data), yielding a final analytic cohort of 657 patients (419 ER-positive, 238 ER-negative).

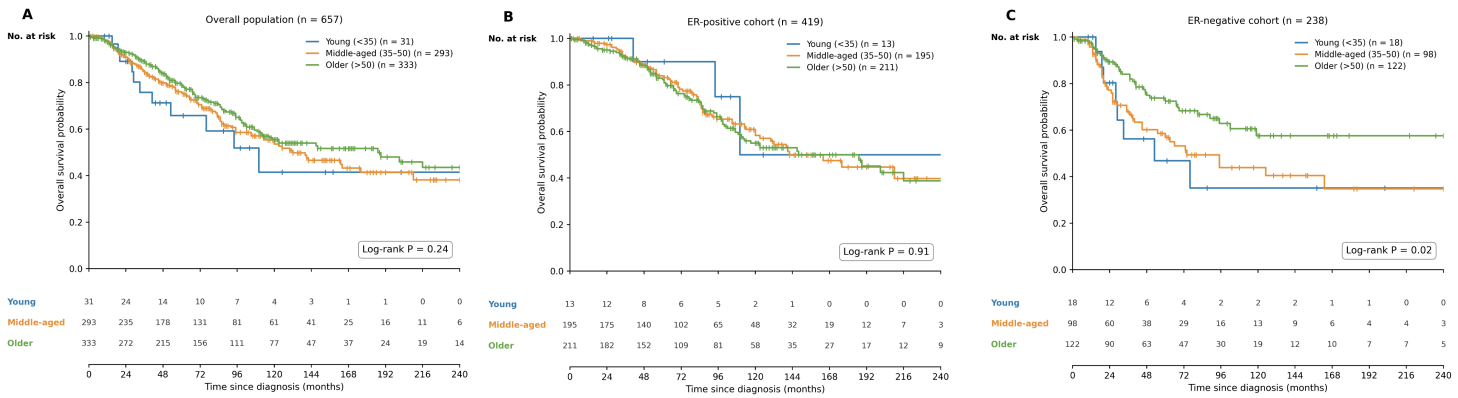


Figure 2

Kaplan–Meier curves of overall survival by age group. (A) Overall population (n = 657); log-rank p = 0.24. (B) ER-positive cohort (n = 419); log-rank p = 0.91. (C) ER-negative cohort (n = 238); log-rank p = 0.02. Patients were stratified into three age groups: young (<35 years), middle-aged (35–50 years), and older (>50 years). Tick marks indicate censored observations. Numbers of patients at risk at 24-month intervals are shown below each panel. ER, estrogen receptor.

Supplementary Files

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- SupplementaryTableS1.docx