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Socioeconomic disparities and osteoarthritis impact hormone therapy adherence in breast cancer

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ABSTRACT

Purpose: Adherence to adjuvant hormone therapy (AHT) is critical for improving survival in breast cancer patients. This study examines how socioeconomic disparities, osteoarthritis (OA), and OA symptom onset timing influence AHT adherence and survival outcomes.

Patients and methods: This retrospective cohort study included 33,142 women with invasive breast cancer (2011–2015) from the Korean National Health Insurance Service. Group-based trajectory modeling (GBTM) identified AHT adherence patterns based on the proportion of days covered (PDC) over five years. Competing risk regression and Cox models assessed the impact of socioeconomic factors, pre-treatment OA, NSAID use, and other variables on AHT discontinuation and survival.

Results: GBTM revealed two adherence patterns: high adherence (83.4 %) and low adherence (16.6 %), with the latter showing a rapid decline in PDC. The low adherence group had a significantly higher risk of treatment discontinuation (SHR: 14.06; 95 % CI: 12.50–14.96; $p < 0.001$) and mortality (HR: 3.56; 95 % CI: 3.09–4.09; $p < 0.001$). A longer OA history before AHT ($p = 0.001$) and pre-AHT NSAID use ($p < 0.001$) were linked to higher discontinuation risk. Patients with Medical Aid/Veteran insurance (OR: 0.60; 95 % CI: 0.53–0.67; $p < 0.001$) and those in non-capital regions (OR: 0.74; 95 % CI: 0.69–0.79; $p < 0.001$) were less likely to show high adherence.

Conclusion: AHT adherence is influenced by socioeconomic factors, pre-existing OA, and OA symptom timing, affecting survival outcomes. Tailored interventions are needed to improve AHT adherence and survival.

1. Introduction

Adherence to adjuvant hormone therapy (AHT) is essential for maximizing survival benefits in women with hormone receptor–positive breast cancer [1,2]. Despite the proven efficacy of AHT in reducing recurrence and mortality rates [3,4], nonadherence and early discontinuation remain significant challenges, compromising treatment outcomes [5,6].

Several factors influence AHT adherence, including socioeconomic disparities, side effects, and comorbid conditions [7,8]. Socioeconomic status (SES) affects both access to care and adherence behaviors. Patients with lower SES, inadequate insurance coverage, or residing in rural areas often face barriers such as financial constraints, limited access to healthcare facilities, and lack of social support, leading to decreased adherence to AHT [9,10]. For instance, Ward et al. [9] demonstrated that patients with inadequate insurance were less likely to initiate and adhere to AHT due to higher out-of-pocket costs and financial hardship. Similarly, Nattinger et al. [10] reported that rural breast cancer patients had lower rates of AHT adherence compared to urban counterparts, potentially due to limited access to specialized oncology services and longer travel distances to treatment centers.

Comorbid conditions, particularly osteoarthritis (OA), have also been implicated in affecting AHT adherence [11,12]. OA is prevalent among older adults and can exacerbate musculoskeletal symptoms associated with AHT, such as arthralgia and joint stiffness, potentially leading to increased discontinuation rates [13,14]. Partridge et al. [13] found that patients experiencing musculoskeletal side effects were significantly more likely to discontinue therapy prematurely. Moreover, the duration of OA prior to cancer diagnosis may influence adherence patterns. Patients with a longer history of OA may have entrenched pain and disability, interfering with their ability to adhere consistently to AHT [11,15]. The timing of OA symptom onset relative to AHT initiation

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may also play a critical role in adherence. Patients who develop OA symptoms after starting AHT may be better equipped to manage side effects and maintain adherence due to established coping mechanisms and adherence behaviors [16,17]. Conversely, those with pre-existing OA may face compounded symptom burdens, increasing the likelihood of discontinuation [11].

Despite these insights, limited research has explored the combined impact of socioeconomic disparities and OA burden, including the timing of OA symptoms, on AHT adherence and survival outcomes in breast cancer patients. Understanding these complex interactions is crucial for developing targeted interventions to improve adherence and optimize treatment efficacy. Therefore, this study investigates the interplay of socioeconomic factors, pre-existing OA, and the timing of OA symptom onset in influencing AHT adherence and survival in a nationwide cohort of breast cancer patients. By utilizing comprehensive national health insurance data and advanced statistical modeling, we aim to identify high-risk groups and inform strategies to enhance adherence and ultimately improve survival outcomes.

2. Methods

2.1. Data sources and study population

This nationwide retrospective cohort study utilized data from the Korean National Health Insurance Service (NHIS) database between 2011 and 2015. The NHIS database, covering nearly the entire Korean population with mandatory universal health coverage, provided data on medical claims, prescriptions, demographics, and socioeconomic status. To supplement the NHIS data, we linked data from the National Cancer Center (NCC) cancer registry, and Korean National Statistical Office death registry between 2011 and 2020 to obtain data on cancer diagnosis, osteoarthritis diagnosis, and death, respectively. Patients were included if they were (1) women aged 19 years or older, (2) diagnosed with primary invasive breast cancer (ICD-10 code: C50) between 2011 and 2015 based on the NCC cancer registry data, (3) initiated AHT within one year of diagnosis with available prescription records in the NHIS database, and (4) had at least 5 years of follow-up data available for calculating PDC, or died within the 5-year follow-up period. We excluded patients who received radiotherapy (RT) alone without AHT or neither AHT nor RT.

We further categorized patients based on their surgery type, distinguishing between breast-conserving surgery (BCS) and mastectomy. Also, we inferred the surgical approach based on the absence or presence of axillary lymph node dissection (ALND) procedure codes. To capture AHT use, we identified patients with prescription records for tamoxifen or aromatase inhibitors (AIs) within one year of their breast cancer diagnosis. For chemotherapy, we considered patients with records of specific procedure codes and/or drug codes for commonly used chemotherapeutic agents. To evaluate osteoarthritis-related healthcare utilization, we considered the presence of OA-related ICD-10 codes (M15-M19). Under this diagnosis timeframe, we identified the use of rehabilitation therapy, such as physical therapy or occupational therapy, and the prescription of NSAIDs for pain management as indicators of OA-related treatments, by using corresponding claim codes.

2.2. Assessment of adherence: the proportion of days covered and trajectory analysis

AHT included the use of tamoxifen or aromatase inhibitors (AIs) based on their prescription records. Adherence to AHT was measured using the proportion of days covered (PDC), a widely accepted metric in medication adherence research [18,19]. Adherence to AHT was quantified using the proportion of days covered (PDC), calculated for each 6-month interval as:

PDC = (Number of days with medication supply)÷(Total number of days in the 6-month interval).

The denominator was adjusted to account for censoring due to death. Individual PDC values were aggregated over time to derive personalized trajectories of AHT adherence over five years.

Group-based trajectory modeling (GBTM) [20,21] was employed to identify distinct adherence trajectories based on longitudinal PDC values. We tested various group numbers (2–4) and polynomial orders (1–3), selecting the model with the lowest Akaike Information Criterion (AIC) and clinically interpretable trajectories. This modelling and selection were performed by using the 'traj' package within the STATA program.

2.3. Statistical analysis

Demographic, socioeconomic, and clinical characteristics were described using means, standard deviations, medians, interquartile ranges (IQR), counts, and percentages, as appropriate. Wilcoxon rank-sum tests and Chi-square tests were used to compare baseline characteristics between adherence trajectory groups. Recognizing that death could preclude the event of treatment discontinuation, we employed competing-risks regression analysis [22] using the 'stcrreg' command in STATA. This approach allowed us to evaluate the association of various factors with treatment discontinuation, considering death as a competing event. Subdistribution hazard ratios (SHR) and 95 % CI were reported, and cumulative incidence curves were generated to visualize the probabilities of treatment discontinuation over time. We also performed logistic regression analysis to further explore factors associated with high adherence group membership. We conducted separate analyses to investigate the role of both pre- and post-treatment osteoarthritis, including OA diagnosis, NSAID use, timing, and costs, and their potential association with AHT adherence. Additionally, we explored the relationship between sociodemographic factors and adherence patterns. To assess the association between adherence trajectories and overall survival, we used a Cox proportional hazards model, adjusting for potential confounders. We calculated Hazard ratios (HR) and 95 % confidence intervals (CI) and generated Kaplan-Meier survival curves for each trajectory group to visualize the survival differences. All statistical analyses were performed using SAS (version 9.4 or higher) and STATA (version 18).

2.4. Ethical considerations

The study was approved by the Institutional Review Board (IRB) of Seoul National University Hospital (IRB No. E−2212-080-1385), and informed consent was waived due to the retrospective nature of the study and the use of deidentified administrative data.

3. Results

This nationwide retrospective cohort study included 33,142 women diagnosed with primary invasive breast cancer between 2011 and 2015, utilizing data from the Korean National Health Insurance Service database. The inclusion criteria were women aged 20 years or older who initiated AHT within one year of diagnosis and had at least five years of follow-up data. Patients with missing essential data were excluded. Detail flowchart was provided in Fig. 1A.

3.1. Trajectory analysis of adjuvant hormone therapy adherence

To identify distinct adherence trajectories, we employed GBTM, analyzing longitudinal PDC values calculated at 6-month intervals over five years. We evaluated models with varying group numbers (2–4) and polynomial orders (1–3) using AIC as a model selection criterion. This process identified a two-group model with linear trajectories as the best fit for the data (see Supplementary Table 1 for detailed model comparison results).

Fig. 1B depicts the distinct adherence trajectories for the low and

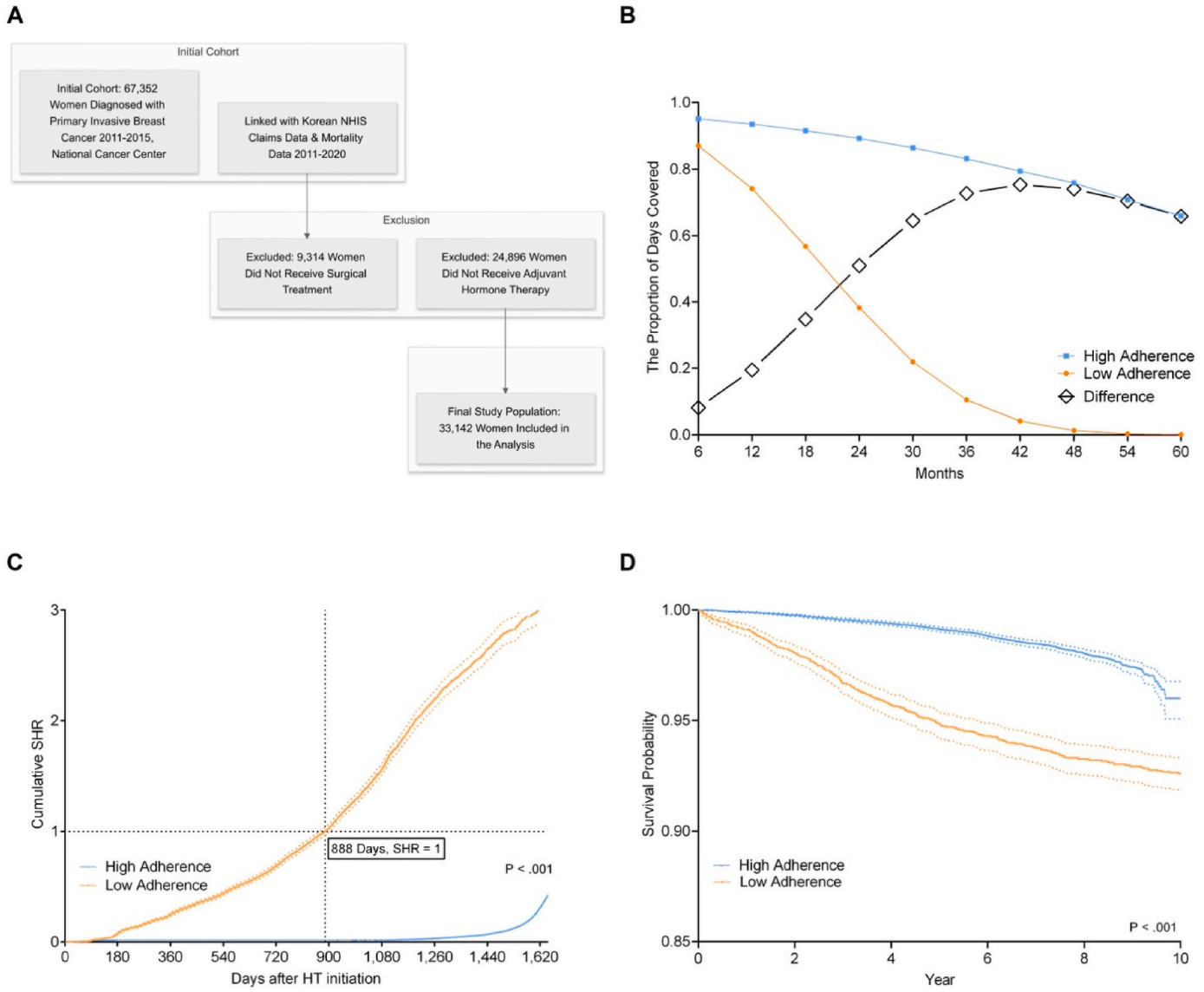

Fig. 1. Cohort Selection, Adherence Trajectories, Discontinuation Risk, and Survival Outcomes. (A) Flowchart depicting the study cohort selection process. Beginning with a nationwide cohort of women diagnosed with primary invasive breast cancer between 2011 and 2015, we applied exclusion criteria to arrive at the final study population of 33,142 women who initiated adjuvant hormone therapy (AHT). (B) Distinct AHT adherence trajectories over 60 months for the high adherence (blue) and low adherence (orange) groups, as identified by group-based trajectory modeling (GBTM). The gray diamonds represent the difference in Proportion of Days Covered (PDC) between the two groups at each time point. **(C)** Cumulative incidence curves of AHT discontinuation, accounting for death as a competing risk. The low adherence group (orange) demonstrates a significantly higher risk of discontinuation compared to the high adherence group (blue). **(D)** Kaplan-Meier survival curves depicting overall survival probability for the high adherence (blue) and low adherence (orange) groups. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

high adherence groups over 60 months. As illustrated, patients in the high adherence group consistently maintained a high PDC, remaining above 80 % for the first three years of follow-up and subsequently demonstrating a gradual decline to 65.3 % (95 % CI, 65.3 %–66.5 %) by 60 months. Conversely, the low adherence group experienced a sharp and consistent reduction in adherence over time. PDC in this group dropped below 60 % within 18 months, plummeting to near-zero levels by 54 months. The most pronounced difference in adherence between the two groups (75.3 %) was observed at 42 months, with the high adherence group maintaining a PDC of 79.4 % (95 % CI, 79.2 %–79.6 %), whereas the low adherence group exhibited a PDC of merely 4.1 % (95 % CI, 3.6 %–4.5 %). This contrast highlights the significant divergence in long-term AHT use between these two groups, emphasizing the crucial need for timely and effective interventions to support adherence, particularly within the first three years of therapy.

Fig. 1C presents the cumulative SHR for treatment discontinuation or mortality over a five-year period, stratified by adherence trajectory groups. The low adherence group (orange line) demonstrates a markedly elevated and progressive increase in cumulative SHR, reflecting a significant and continuous risk of adverse outcomes related to non-adherence to AHT. Notably, a critical juncture is observed at 888 days post–AHT initiation, where the cumulative SHR for the low adherence group crosses the threshold of 1.0, indicating an equal or greater risk of treatment discontinuation compared to the baseline. Beyond this point, the risk in the low adherence group escalates sharply, underscoring the compounded negative impact of sustained nonadherence. In contrast, the high adherence group (blue line) maintains a stable and substantially lower cumulative SHR throughout the study period, with only a minimal increase observed after approximately 1,440 days. These findings highlight the importance of early and sustained adherence,

particularly within the first 888 days.

3.2. Baseline characteristics

Table 1 presents the baseline characteristics of the 33,142 breast cancer patients included in the study, stratified by adherence trajectory group. The low adherence group (n = 5,488; 16.6 %) exhibited significant disparities in socioeconomic factors compared to the high adherence group (n = 27,654; 83.4 %). A larger proportion of patients in the low adherence group were covered by Medical Aid/Veteran insurance (8.7 % vs. 4.8 %; $P < .001$) and resided in non-metropolitan areas (36.1 % vs. 29.4 %; $P < .001$).

These socioeconomic disparities were accompanied by differences in clinical characteristics suggestive of potentially greater disease burden and healthcare access barriers in the low adherence group. The median time from the initial diagnosis of OA to AHT initiation was notably longer in the low adherence group (394.0 days vs. 133.0 days; $P < .001$), suggesting a long history of OA before cancer treatment. Similarly, the low adherence group had longer pre-AHT durations of NSAID use (312.5 days vs. 181 days; $P = .005$). Notably, a greater proportion of patients in the low adherence group received chemotherapy (73.8 % vs. 59.6 %; $P < .001$), potentially reflecting more advanced disease or treatment decisions driven by clinical urgency.

Beyond socioeconomic and treatment-related factors, pre-existing comorbidities, particularly OA, demonstrated an association with adherence group membership. The low adherence group had a significantly higher proportion of patients with an OA diagnosis before starting AHT (1.9 % vs. 0.7 %; $P < .001$). These findings highlight a potential interaction between managing pre-existing comorbidities and adherence to adjuvant therapy in this population.

3.3. Factors associated with treatment discontinuation

Table 2 summarizes the results of competing risk regression analyses for factors associated with AHT discontinuation, with death considered a competing event. Notably, belonging to the low adherence trajectory group demonstrated a profound hazardous effect, showing a dramatically higher risk for treatment discontinuation (SHR, 14.17; 95 % CI, 13.31 to 15.07; $P < .001$). This finding highlights the significant impact of consistent adherence on reducing the risk of premature treatment cessation.

Focusing on pre-treatment variables significantly associated with treatment discontinuation, the presence of OA diagnosis before initiating AHT emerged as a significant risk factor (SHR, very large; $P = .001$). Similarly, pre-AHT use of NSAIDs, a potential marker for managing pain and inflammation related to OA, demonstrated a strong association with a higher risk of treatment discontinuation (SHR, very small; $P = .039$).

The impact of OA on treatment discontinuation is further evidenced by the strong negative association observed for the time elapsed between the first OA diagnosis and AHT initiation (SHR, 1.00; 95 % CI, 1.00 to 1.00; $P = .001$). This indicates that patients with a longer history of OA diagnosis were likely to discontinue treatment prematurely. In contrast, the longer time elapsed between AHT initiation and the first NSAID prescription due to OA was associated with lower risk of AHT discontinuation (SHR, 0.99; 95 % CI, 0.99 to 0.99; $P < .001$). This may suggest that patients who have a longer interval between AHT and subsequent OA symptoms are better equipped to maintain adherence to their treatment regimen.

3.4. Factors associated with membership of high adherence group

Table 3 presents the results of logistic regression analyses identifying factors associated with belonging to the high adherence trajectory group. Older age was significantly associated with decreased odds of high adherence (multivariate OR, 0.99; 95 % CI, 0.98 to 1.00; $P < .001$).

Table 1
Baseline Characteristics of Breast Cancer Patients by Adherence to Adjuvant Hormone Therapy (Low Adherence vs. High Adherence Groups).

Variable	Low Adherence (N = 5,488, 16.6 %)	High Adherence (N = 27,654, 83.4 %)	P-value
Age at Diagnosis, Median (IQR)	50.0 (45.0–60.0)	50.0 (45.0–60.0)	0.001
Residential Area, n (%):			<0.001
- Metro Cities/ Provinces	3,506 (63.9 %)	19,517 (70.6 %)	
- Capital Area/Others	1,982 (36.1 %)	8,137 (29.4 %)	
Insurance Type			<0.001
- National Health Insurance	5,008 (91.3 %)	26,330 (95.2 %)	
- Medical Aid/Veteran	480 (8.7 %)	1,324 (4.8 %)	
Treatment Group			<0.001
- HT Alone	1,573 (28.7 %)	6,955 (25.2 %)	
- RT/HT	3,915 (71.3 %)	20,699 (74.8 %)	
Surgery Type			<0.001
- BCS	1,137 (20.7 %)	5,506 (19.9 %)	
- Mastectomy	4,351 (79.3 %)	22,148 (80.1 %)	
Axillary Lymph Node Dissection			<0.001
- No ALND	5,412 (98.6 %)	27,597 (99.8 %)	
- ALND	76 (1.4 %)	57 (0.2 %)	
Chemotherapy/Target Therapy			<0.001
- No	1,438 (26.2 %)	11,161 (40.4 %)	
- Yes	4,050 (73.8 %)	16,493 (59.6 %)	
Radiotherapy ≥16 Fractions			<0.001
- No	2,131 (38.8 %)	9,786 (35.4 %)	
- Yes	3,357 (61.2 %)	17,868 (64.6 %)	
AI Ratio			<0.001
- ≤50 %	4,691 (85.5 %)	22,466 (81.2 %)	
- >50 %	797 (14.5 %)	5,188 (18.8 %)	
Therapy Discontinuation within 5 years			<0.001
- No	357 (6.5 %)	17,600 (63.6 %)	
- Yes	5,131 (93.5 %)	10,054 (36.4 %)	
Pre-Therapy Variables			
OA Diagnosis Before HT Start, n (%):			<0.001
- No	5,381 (98.1 %)	27,451 (99.3 %)	
- Yes	107 (1.9 %)	203 (0.7 %)	
The Use of NSAID Before HT Start			
- No	5,446 (99.2 %)	27,583 (99.7 %)	<0.001
- Yes	42 (0.8 %)	71 (0.3 %)	
Days from First OA Diagnosis to HT Start, Median (IQR)	394.0 (114.0–1,117.0)	133.0 (50.0–232.0)	<0.001
Days from First NSAID Prescription to HT Start	312.5 (167.0–1,117.0)	181.0 (79.0–292.0)	0.005
Duration of OA Treatment Before HT Start, Days	0 (0–80)	0 (0–96)	0.001
Duration of NSAID Treatment Before HT Start, Days	0 (0–105)	0 (0–35)	<0.001
Cost of Pre-HT OA Treatment, Won	0 (0–196,740)	0 (0–903,000)	0.007
Cost of Pre-HT NSAID Use, Won	0 (0–91,260)	0 (0–23,880)	<0.001
Post-Therapy Variables			
OA diagnosis After HT Start, n (%):			0.130
- No	152 (2.8 %)	670 (2.4 %)	
- Yes	5,336 (97.2 %)	26,984 (97.6 %)	
The Use of NSAID After HT Start			0.122
- No	5,437 (99.1 %)	27,452 (99.3 %)	
- Yes	51 (0.9 %)	202 (0.7 %)	

(continued on next page)

Table 1 (*continued*)

Variable	Low Adherence (N = 5,488, 16.6 %)	High Adherence (N = 27,654, 83.4 %)	P-value
Days from HT Start to First OA Diagnosis, Median (IQR)	337.5 (47.0–781.0)	470.0 (122.0–1,072.0)	0.002
Days from HT Start to First NSAID Prescription	364.0 (85.0–1,059.0)	608.0 (208.0–1,421.0)	0.055
Duration of OA Treatment After HT Start, Days	0 (0–147)	0 (0–290)	0.504
Duration of NSAID Treatment After HT Start, Days	0 (0–210)	0 (0–480)	0.123
Cost of Post-HT OA Treatment, Won	0 (0–221,440)	0 (0–583,450)	0.859
Cost of Post-HT NSAID Use, Won	0 (0–156,300)	0 (0–332,514)	0.123

Abbreviations: **ALND**: Axillary Lymph Node Dissection; **AI**: Aromatase Inhibitor; **BCS**: Breast-Conserving Surgery; **HT**: Hormone Therapy; **IQR**: Interquartile Range; **NSAID**: Nonsteroidal Anti-Inflammatory Drug; **OA**: Osteoarthritis; PDC: Proportion of Days Covered; **RT/HT**: Radiotherapy and Hormone Therapy.

Similarly, being covered by Medical Aid/Veteran insurance compared to National Health Insurance was significantly associated with lower adherence (multivariate OR, 0.60; 95 % CI, 0.53 to 0.67; $P < .001$), emphasizing the potential impact of financial and resource disparities on adherence patterns. Living in non-capital areas compared to the capital area was also associated with lesser odds of belonging to the high adherence group (multivariate OR, 0.74; 95 % CI, 0.69 to 0.79; $P < .001$), further highlighting geographical disparities in access to healthcare and support services.

The analysis revealed several factors related to pre-treatment comorbidity and healthcare utilization that significantly influenced adherence. Notably, pre-existing OA diagnosis demonstrated a strikingly strong negative association with high adherence (OR, very small; $P < .001$). Similarly, longer history of pre-AHT OA diagnosis was significantly associated with lower adherence (OR, 0.99; 95 % CI, 0.99 to 0.99; $P < .001$).

In terms of treatment-related factors influencing adherence, receiving chemotherapy or targeted therapy was significantly associated with lower odds of belonging to the high adherence group (OR, 0.44; 95 % CI, 0.41 to 0.48; $P < .001$). This finding suggests that the cumulative burden of complex treatment regimens and potential side effects could negatively impact patients' adherence to long-term hormonal therapy. Conversely, a greater proportion of aromatase inhibitor (AI) use within the AHT regimen was positively associated with high adherence (OR, 2.41; 95 % CI, 2.19 to 2.65; $P < .001$). This finding might indicate that patients who are better able to tolerate the potential side effects of AIs, particularly those related to OA, were more likely to continue their prescribed regimen and, consequently, be classified within the high adherence trajectory group.

3.5. Overall survival analysis

Fig. 1D illustrates the Kaplan-Meier survival curves for the high and low adherence groups. Patients in the low adherence group experienced significantly lower overall survival probabilities compared to the high adherence group (log-rank test, $P < .001$), emphasizing the substantial impact of sustained AHT adherence on long-term survival outcomes. Table 4 presents the findings from the Cox proportional hazards models assessing the impact of various factors on overall survival at last follow-up (December 31, 2023). The low adherence trajectory group showed a negative effect with significantly increased risk of death compared to the high adherence group (multivariate HR, 3.56; 95 % CI, 3.09 to 4.09; $P < .001$), reinforcing the critical link between consistent adherence and long-term survival in this population.

Table 2
Competing risk analysis for treatment discontinuation.

Variable	Univariate SHR (95 % CI)	P	Multivariate SHR (95 % CI)	P
Trajectory Group (Low Adherence)	14.17 (13.31–15.07)	<0.001	14.06 (12.50–14.96)	<0.001
Age at Diagnosis (Incremental)	1.01 (1.00–1.01)	<0.001	0.99 (0.99–1.00)	0.013
Insurance Type (Medical Aid/ Veteran vs. NHI)	1.28 (1.19–1.38)	<0.001	0.93 (0.84–1.03)	0.188
Residential Area (Other vs. Capital)	1.09 (1.05–1.12)	<0.001	0.99 (0.95–1.04)	0.684
Surgery Type (Mastectomy vs. BCS)	0.94 (0.90–0.98)	0.002	0.94 (0.89–0.98)	0.010
ALND (Yes vs. No)	2.10 (1.60–2.75)	<0.001	0.70 (0.48–1.00)	0.053
Treatment (RT/HT vs. HT alone)	0.98 (0.94–1.01)	0.208	Not Included	–
Chemotherapy/ Target Therapy (Yes vs. No)	1.40 (1.35–1.44)	<0.001	1.14 (1.10–1.19)	<0.001
Ratio of AI (Incremental)	1.01 (0.97–1.05)	0.652	Not Included	–
Radiotherapy ≥16 Fractions	1.01 (0.97–1.04)	0.638	Not Included	–
Pre-Therapy Variables				
OA Diagnosis Before HT Start (Yes vs. No)	2.02 (1.74–2.36)	<0.001	∞ (Not estimable*)	0.001
The Use of NSAID Before HT Start (Yes vs. No)	2.57 (2.03–3.27)	<0.001	0 (Not estimable*)	0.039
Days from First OA Diagnosis to HT Start	0.99 (0.99–1.00)	<0.001	1.00 (1.00–1.00)	0.001
Days from First NSAID Prescription to HT Start	0.99 (0.99–1.00)	<0.001	0.99 (0.99–1.00)	
Duration of OA Treatment Before HT Start	1.01 (1.00–1.01)	0.003	1.00 (0.99–1.00)	0.448
Duration of NSAID Treatment Before HT Start	1.00 (1.00–1.00)	<0.001	0.99 (0.98–1.00)	0.279
Cost of Pre-HT OA Treatment	1.00 (0.99–1.00)	0.150	Not Included	–
Cost of Pre-HT NSAID Use	1.00 (1.00–1.00)	<0.001	1.00 (0.99–1.00)	0.226
Post-Therapy Variables				
OA diagnosis After HT Start (Yes vs. No)	1.10 (1.00–1.22)	0.059	Not Included	–
The Use of NSAID After HT Start	1.23 (1.03–1.47)	0.021	0 (Not estimable*)	<0.001
Days from HT Start to First OA Diagnosis	0.99 (0.99–1.00)	0.055	Not Included	–
Days from HT Start to First NSAID Prescription	0.99 (0.99–1.00)	0.019	0.99 (0.99–0.99)	<0.001
Duration of OA Treatment After HT Start	1.00 (1.00–1.00)	<0.001	1.00 (0.99–1.00)	0.263
Duration of NSAID Treatment After HT Start	1.00 (0.99–1.00)	0.754	Not Included	–
Cost of Post-HT OA Treatment	1.00 (0.99–1.00)	0.823	Not Included	–
Cost of Post-HT NSAID Use	1.00 (0.99–1.00)	0.790	Not Included	–

Abbreviations: ALND, Axillary Lymph Node Dissection; **AI**, Aromatase Inhibitor; **BCS**, Breast-Conserving Surgery; **CI**, Confidence Interval; **NHI**, National Health Insurance; **OA**, Osteoarthritis; **RT/HT**, Radiotherapy and Hormone Therapy; **SHR**, Sub-Hazard Ratio. ***Note:*** *Odds ratios could not be reliably estimated due to low event counts in the data.*

Table 3
Logistic regression analysis for high adherence group.

Variable	Univariate OR (95 % CI)	P	Multivariate OR (95 % CI)	P
Age at Diagnosis (Incremental)	0.98 (0.98–0.99)	<0.001	0.99 (0.98–1.00)	<0.001
Insurance Type (Medical Aid/ Veteran vs. NHI)	0.52 (0.47–0.58)	<0.001	0.60 (0.53–0.67)	<0.001
Residential Area (Other vs. Capital)	0.74 (0.69–0.78)	<0.001	0.74 (0.69–0.79)	<0.001
Surgery Type (Mastectomy vs. BCS)	1.05 (0.98–1.13)	0.172	Not Included	–
Axillary Lymph Node Dissection (Yes vs. No)	0.15 (0.10–0.21)	<0.001	0.15 (0.11–0.22)	<0.001
Treatment (RT/HT vs. HT Alone)	1.20 (1.12–1.28)	<0.001	1.10 (0.99–1.23)	0.069
Chemo/Target Therapy (Yes vs. No)	0.53 (0.49–0.56)	<0.001	0.44 (0.41–0.48)	<0.001
AI Ratio (Incremental)	1.44 (1.32–1.56)	<0.001	2.39 (2.17–2.64)	<0.001
Radiotherapy ≥16 Fractions	1.16 (1.09–1.23)	<0.001	1.08 (0.98–1.20)	0.115
Pre-Therapy Variables				
OA Diagnosis Before HT Start (Yes vs. No)	0.37 (0.29–0.47)	<0.001	0 (Not estimable*)	<0.001
The Use of NSAID Before HT Start (Yes vs. No)	0.33 (0.23–0.49)	<0.001	∞ (Not estimable*)	0.080
Days from First OA Diagnosis to HT Start	1.00 (1.00–1.00)	<0.001	0.99 (0.99–0.99)	<0.001
Days from First NSAID Prescription to HT Start	0.99 (0.99–0.99)	0.029	1.00 (0.99–1.00)	0.081
Duration of OA Treatment Before HT Start	0.99 (0.98–1.00)	0.065	Not Included	–
Duration of NSAID Treatment Before HT Start	0.99 (0.98–1.00)	0.003	0.97 (0.93–1.01)	0.170
Cost of Pre-HT OA Treatment	0.99 (0.99–1.00)	0.884	Not Included	–
Cost of Pre-HT NSAID Use	0.99 (0.99–0.99)	0.016	1.00 (0.99–1.00)	0.154
Post-Therapy Variables				
OA diagnosis After HT Start (Yes vs. No)	0.87 (0.73–1.04)	0.132	Not Included	–
The Use of NSAID After HT Start	0.78 (0.58–1.07)	0.123	Not Included	–
Days from HT Start to First OA Diagnosis	1.00 (0.99–1.00)	0.127	Not Included	–
Days from HT Start to First NSAID Prescription	1.00 (0.99–1.00)	0.120	Not Included	–
Duration of OA Treatment After HT Start	0.99 (0.99–1.00)	0.113	Not Included	–
Duration of NSAID Treatment After HT Start	1.00 (0.99–1.00)	0.875	Not Included	–
Cost of Post-HT OA Treatment	0.99 (0.99–1.00)	0.581	Not Included	–
Cost of Post-HT NSAID Use	1.00 (0.99–1.00)	0.882	Not Included	–

Abbreviations: ALND: Axillary Lymph Node Dissection; **AI**: Aromatase Inhibitor; **BCS**: Breast-Conserving Surgery; **CI,** Confidence Interval; **HT**: Hormone Therapy; **NHI**: National Health Insurance; **OA**: Osteoarthritis; **OR**: Odds Ratio; **RT/HT**: Radiotherapy and Hormone Therapy. ***Note:*** *Odds ratios could not be reliably estimated due to low event counts in the data.*

Table 4
Cox regression analysis of factors associated with survival.

Variable	Univariate HR (95 % CI)	P	Multivariate HR (95 % CI)	P
Trajectory Group (Low Adherence)	4.93 (4.31–5.64)	<0.001	3.56 (3.09–4.09)	<0.001
Age at Diagnosis	1.24 (1.23–1.25)	<0.001	1.23 (1.22–1.25)	<0.001
Insurance Type (Medical Aid/ Veteran vs. NHI)	3.10 (2.57–3.75)	<0.001	1.35 (1.11–1.63)	0.002
Residential Area (Non-Capital vs. Capital)	1.84 (1.61–2.10)	<0.001	1.26 (1.01–1.45)	0.001
Surgery Type (Mastectomy vs. BCS)	1.22 (1.02–1.45)	0.029	1.23 (1.03–1.47)	0.022
ALND (Yes vs. No)	2.73 (1.30–5.75)	0.008	0.84 (0.40–1.78)	0.657
Treatment (RT/HT vs. HT alone)	0.32 (0.28–0.36)	<0.001	1.10 (0.87–1.40)	0.434
Chemotherapy/ Targeted Therapy (Yes vs. No)	4.49 (3.66–5.52)	<0.001	1.73 (1.39–2.16)	<0.001
Ratio of AI (Incremental)	3.16 (2.74–3.64)	<0.001	0.71 (0.61–0.83)	<0.001
Radiotherapy ≥16 Fractions	0.37 (0.32–0.43)	<0.001	1.00 (0.79–1.28)	0.975
Pre-Therapy Variables				
OA Diagnosis Before HT Start (Yes vs. No)	2.13 (1.26–3.62)	0.005	∞ (Not estimable*)	0.288
The Use of NSAID Before HT Start (Yes vs. No)	1.68 (0.63–4.50)	0.298	Not Included	–
Days from First OA Diagnosis to HT Start	0.99 (0.99–0.99)	0.005	1.00 (0.99–1.00)	0.296
00.Days from First NSAID Prescription to HT Start	0.99 (0.99–1.00)	0.305	Not Included	–
Duration of OA Treatment Before HT Start	0.93 (0.71–1.22)	0.622	Not Included	–
Duration of NSAID Treatment Before HT	0.99 (0.98–1.01)	0.987	Not Included	–
Cost of Pre-HT OA Treatment	0.99 (0.99–1.00)	0.734	Not Included	–
Cost of Pre-HT NSAID Use	0.99 (0.99–1.00)	0.913	Not Included	–
Post-Therapy Variables			Not Included	–
OA diagnosis After HT Start (Yes vs. No)	1.14 (0.76–1.72)	0.512	Not Included	–
The Use of NSAID After HT Start	1.58 (0.84–2.94)	0.153	Not Included	–
Days from HT Start to First OA Diagnosis	0.99 (0.99–1.00)	0.518	Not Included	–
Days from HT Start to First NSAID Prescription	0.99 (0.99–0.99)	0.156	Not Included	–
Duration of OA Treatment After HT Start	0.98 (0.96–1.02)	0.498	Not Included	–
Duration of NSAID Treatment After HT Start	1.00 (0.99–1.00)	0.177	Not Included	–
Cost of Post-HT OA Treatment	0.99 (0.99–1.00)	0.516	Not Included	–
Cost of Post-HT NSAID Use	1.00 (0.99–1.00)	0.133	Not Included	–

Abbreviations: ALND, Axillary Lymph Node Dissection; **AI**, Aromatase Inhibitor; **BCS**, Breast-Conserving Surgery; **CI**, Confidence Interval; **HR**, Hazard Ratio; **HT**, Hormone Therapy; **NHI**, National Health Insurance; **OA**, Osteoarthritis; **RT/**

HT, Radiotherapy and Hormone Therapy. *__Note:__ *Hazard ratios could not be reliably estimated due to low event counts in the data.*

Beyond adherence, older age at diagnosis (HR, 1.23; 95 % CI, 1.22 to 1.25; $P < .001$), receiving chemotherapy or targeted therapy (HR, 1.73; 95 % CI, 1.39 to 2.16; $P < .001$), and undergoing mastectomy (HR, 1.23; 95 % CI, 1.03 to 1.47; $P = .022$) emerged as independent predictors of higher mortality. Conversely, residing in a non-capital area was associated with a higher risk of death (HR, 1.26; 95 % CI, 1.01 to 1.45; $P = .001$). While insurance type was significantly associated with survival in the univariate analysis (HR, 3.10; 95 % CI, 2.57 to 3.75; $P < .001$), this association remained significant but attenuated in the multivariate model (HR, 1.35; 95 % CI, 1.11 to 1.63; $P = .002$). The use of radiotherapy with 16 or more fractions did not demonstrate significant independent associations with survival in the multivariate model.

Focusing specifically on OA-related factors, having an OA diagnosis before starting AHT was associated with higher mortality in the univariate analysis (HR, 2.13; 95 % CI, 1.26 to 3.62; $P = .005$). However, this association became statistically insignificant after adjusting for potential confounders in the multivariate analysis, suggesting that other factors may mitigate the impact of OA on survival outcomes.

4. Discussion

This nationwide cohort study identifies several factors associated with discontinuation and low adherence to adjuvant AHT in women with breast cancer, underscoring the significant impact these factors have on survival outcomes. Socioeconomic disparities, comorbid conditions, and treatment-related burdens emerged as major predictors of low adherence and early discontinuation.

The GBTM analysis revealed that 16.6 % of patients fell into the low adherence group, characterized by a rapid decline in the PDC within the first two to three years of therapy. This finding is consistent with similar studies utilizing GBTM to assess AHT adherence, which have reported comparable rates of declining adherence. For example, Wu et al. found that 22.4 % of patients demonstrated decreasing adherence over time, highlighting the critical need for early interventions to prevent long-term discontinuation [17]. Similarly, Garneau et al. identified that approximately 19 % of breast cancer survivors exhibited declining adherence trajectories, associated with worse clinical outcomes [23]. These parallels suggest that a substantial subset of patients are at significant risk of nonadherence, necessitating targeted strategies to support adherence during the initial years of therapy.

Socioeconomic factors were significantly associated with adherence patterns. Patients residing in non-metropolitan areas and those covered by Medical Aid/Veteran insurance were more likely to exhibit low adherence to AHT [9,10]. Nattinger et al. reported that rural breast cancer patients had lower rates of AHT adherence compared to urban counterparts, potentially due to limited access to specialized oncology services and longer travel distances to treatment centers [10]. Furthermore, Ward et al. demonstrated that patients with inadequate insurance coverage, such as those on Medicaid or uninsured, were less likely to initiate and adhere to AHT, likely due to financial constraints and higher out-of-pocket costs [9]. These findings highlight the need to address systemic barriers, including enhancing healthcare accessibility in rural areas and expanding insurance coverage to reduce financial burdens that impede adherence.

Adherence to AHT is critically linked to survival outcomes. In our study, patients in the low adherence group had a 3.56-fold higher risk of mortality compared to those in the high adherence group (HR, 3.56; 95 % CI, 3.09 to 4.09) [1]. This significant association is consistent with prior studies indicating that nonadherence to AHT significantly increases the risk of breast cancer recurrence and mortality. McCowan et al. found that patients with less than 80 % adherence to tamoxifen had a 20 % higher risk of mortality (HR, 1.20; 95 % CI, 1.04 to 1.40) [1]. Similarly, Makubate et al. reported that each 10 % decrease in adherence was associated with a 16 % increase in mortality risk (HR, 1.16; 95 % CI, 1.13 to 1.19) [2]. Hershman et al. observed that early discontinuation of AHT was associated with a 26 % higher risk of mortality (HR, 1.26; 95 % CI, 1.13 to 1.41) [5]. These consistent findings across multiple studies underscore the substantial impact of adherence on survival in breast cancer patients.

The presence of pre-existing OA and prior use of NSAIDs were associated with lower adherence to AHT in our study. Moreover, the significance of the time from initial OA diagnosis to AHT initiation, indicating a history of OA before cancer treatment, suggests that a longer duration of OA may further impede adherence. Gillespie et al. found that patients with a history of OA were 25 % more likely to discontinue AHT compared to those without OA (odds ratio [OR], 1.25; 95 % CI, 1.10 to 1.42) [11]. Similarly, Land et al. reported that breast cancer patients with comorbid OA were 32 % less likely to adhere to their AHT regimen (OR, 0.68; 95 % CI, 0.54 to 0.86) [12]. These studies indicate that comorbid conditions not only influence treatment decisions but also impact adherence and outcomes. Partridge et al. found that patients experiencing musculoskeletal side effects were 50 % more likely to discontinue therapy (OR, 1.50; 95 % CI, 1.12 to 2.00) [13]. Addressing OA symptoms through comprehensive pain management and rehabilitation programs may mitigate these barriers, thereby enhancing AHT adherence [14].

Interestingly, our study also found that the longer time elapsed between AHT initiation and the first NSAID prescription due to OA was associated with a lower risk of AHT discontinuation (subdistribution hazard ratio [SHR], 0.99; 95 % CI, 0.99 to 0.99; $P < .001$). This may suggest that the delayed use of NSAIDs is a marker of less severe OA, which in turn is associated with better adherence, rather than the delayed use itself causing better adherence. Previous research indicates that the timing of side effect onset can influence adherence to therapy. Patients who develop side effects later during treatment may have already established adherence behaviors and coping strategies, making them more resilient to new symptoms [7,16]. For example, Moon et al. found that patients who experienced delayed onset of arthralgia were 20 % less likely to discontinue AHT compared to those who developed symptoms early (HR, 0.80; 95 % CI, 0.67 to 0.95) [16]. Additionally, Murphy et al. reported that early onset of side effects was associated with a higher likelihood of nonadherence, emphasizing the importance of symptom timing in adherence patterns [7]. This suggests that patients who develop OA symptoms later may have had sufficient time to adapt to the treatment regimen and are more motivated to continue AHT despite emerging side effects.

Furthermore, our findings indicate that patients undergoing chemotherapy or targeted therapy were less likely to adhere to AHT, possibly due to the cumulative burden of treatments and their side effects. For example, Henry et al. reported that women undergoing adjuvant chemotherapy were 34 % more likely to discontinue AHT within the first two years (OR, 1.34; 95 % CI, 1.20 to 1.51) [24]. Murphy et al. found that patients receiving both chemotherapy and AHT were 45 % more likely to report nonadherence to AHT after one year (HR, 1.45; 95 % CI, 1.22 to 1.72) [7]. Similarly, Kimmick et al. demonstrated that among women with breast cancer, those who underwent chemotherapy and AHT were 38 % more likely to discontinue AHT early (OR, 1.38; 95 % CI, 1.24 to 1.54) [25]. These results highlight the multifaceted nature of adherence, where both clinical and psychosocial factors play substantial roles in influencing patient behavior.

We also acknowledge the decreasing adherence in the high adherence group after 3–4 years, which suggests that even initially adherent patients may experience challenges in maintaining adherence over the long term. Several factors may contribute to this decline. Late relapses typically refer to recurrences occurring more than 5 years after initial treatment. Especially in hormone receptor-positive breast cancer, the risk of late recurrence is high, and it is closely related to sustained adherence to hormone therapy. Studies have shown that decreased adherence increases the risk of recurrence, emphasizing the importance

of long-term treatment. Chang et al. [26] showed that adherence trajectories influence the risk of recurrence, reporting a higher risk of recurrence in groups with decreasing adherence, which suggests that late recurrence, especially in long-term follow-up. We need to establish an ongoing management strategy, not be satisfied with high adherence rates. Also, fatigue or stress from long-term treatment can reduce adherence [27]. This can affect patients who initially had high adherence. It is important to note that continuous adherence monitoring and management strategies are needed, rather than being satisfied with high adherence rates.

Unfortunately, we were unable to identify enough patients using steroidal AIs in our dataset from 2011 to 2015 for a meaningful comparison. This likely reflects the prescribing patterns during that specific time period in Korea, where non-steroidal AIs were more commonly used in early adjuvant settings. This emphasizes the difficulty in identifying specific subgroups or therapies in older data. Although our cohort is 2011–2015, the latest treatment strategy with CDK4/6 inhibitors could have a large implication. It would be very important to explore and analyze for future study.

While this study benefits from the robustness of a national database encompassing a large sample size and comprehensive clinical information, certain limitations warrant acknowledgment. The potential for residual confounding remains despite rigorous statistical adjustment. Due to the nature of the Korean National Health Insurance Service database used in our study, detailed clinical information, particularly pathological findings and staging data, is unavailable. This is because the data primarily reflects insurance claims for treatments and procedures. Currently, pathological results and basic patient information are not linked across hospitals in Korea. Therefore, although multivariable analysis controlled for all variables available in the claim data, there is potential for residual confounding due to other unmeasured factors such as pathologic stage, grade and hormone receptor status" This limitation will be added to the discussion. Despite this limitation, we leveraged the strengths of the claims data, including the large sample size (approximately 30,000 individuals), treatment duration and timing, and socioeconomic factors. Also, our findings carry significant implications for both clinical practice and health policy. In addition to emphasizing the crucial role of patient education and shared decision-making in promoting adherence, the study highlights the need for tailored interventions and integrated care models that address socioeconomic disparities, manage comorbid conditions like OA, and mitigate the impact of intensive treatment regimens to optimize adherence and outcomes for all patients. Future studies should incorporate detailed clinical and patient-reported data to validate our results and explore underlying mechanisms further.

5. Conclusion

In conclusion, our findings emphasize the critical impact of socioeconomic disparities and comorbidities on AHT adherence and survival outcomes in breast cancer patients. The use of GBTM provided valuable insights into adherence patterns over time, highlighting critical periods where interventions may be most effective. Addressing these disparities through policy changes, enhanced access to healthcare services in non-metropolitan areas, and comprehensive management of comorbid conditions is imperative. By adopting a multifaceted approach, we can improve adherence to life-saving therapies and ultimately enhance survival outcomes for all breast cancer patients.

CRediT authorship contribution statement

B.S. Jang: Writing – review & editing, Writing – original draft, Visualization, Supervision, Formal analysis, Data curation, Conceptualization. **J.H. Chang:** Writing – review & editing, Visualization, Resources, Methodology. **K.H. Shin:** Writing – review & editing, Investigation, Conceptualization.

Data sharing statement

The data used in this study are derived from a nationwide combined big data project and are accessible exclusively to pre-approved researchers at a designated secure analysis center. Consequently, the original individual-level data cannot be shared publicly. Only aggregated results may be extracted. Requests for data access must be submitted to the governing body of the data repository for consideration and must comply with all applicable regulations and approvals.

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Declaration of competing interest

All authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2025.104476.

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