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Treatment Delay and Survival in Patients with Breast Cancer by Stage and Cardiovascular Comorbidity: A Nationwide Korean Cohort Study

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Abstract

Background

The impact of treatment delay on breast cancer survival across disease stages remains inconsistent across studies. We evaluated the association between time to treatment initiation (TTI) and overall survival by disease stage among Korean women with breast cancer.

Methods

A retrospective cohort study was conducted using the Breast Cancer Collaborative Stage-Linked Database (2012–2019), which was established under the Korean Clinical Data Utilization for Research Excellence (K-CURE) project. TTI was categorized as ≤ 30 days (reference), 31–60 days, ≥ 61 days, or no treatment within 1 year. Stage-stratified Cox proportional hazards models were used to estimate adjusted hazard ratios (aHRs) for overall survival. Subgroup analyses were performed according to molecular subtype and comorbidity status.

Results

A total of 16,495 women were included. Among treated patients, TTI was not significantly associated with overall survival in patients with stage I, II, or IV disease. In patients with stage III disease, a delay of ≥ 61 days was associated with a 50% higher risk of death (aHR, 1.50; 95% CI, 1.04–2.16). In the overall cohort, this delay was associated with worse survival among patients with triple-negative breast cancer (aHR, 1.75; 95% CI, 1.10–2.78) and HR+/HER2 + tumors (aHR, 1.41; 95% CI, 1.04–1.92). Among patients with stage III disease, the association was especially pronounced for those with preexisting cardiovascular disease (aHR, 5.28; 95% CI, 1.78–15.68).

Conclusions

Among Korean women with stage III disease, a treatment delay of ≥ 61 days was associated with worse overall survival. The association was more pronounced in aggressive subtypes and in those with preexisting cardiovascular disease, highlighting the need to minimize avoidable delays in these high-risk groups.

Introduction

Breast cancer is the most common malignancy among women worldwide and remains a leading cause of cancer-related mortality [1]. In Korea, the incidence of breast cancer has steadily increased since 2000, making it the most prevalent cancer among Korean women [2]. In 2021 alone, 34,628 women were

newly diagnosed with breast cancer, with the highest incidence occurring in the 40- to 49-year age group [3].

The time elapsed between cancer diagnosis and treatment initiation, typically referred to as time to treatment initiation (TTI), is considered an important determinant of survival outcomes [4]. Prior studies have consistently suggested that treatment delay adversely affects breast cancer outcomes. A meta-analysis of adjuvant chemotherapy studies revealed that a 4-week delay was associated with significantly worse overall survival (HR = 1.13; 95% CI, 1.08–1.19) and disease-free survival (HR = 1.14; 95% CI, 1.05–1.24) [5]. However, the findings across different disease stages remain inconsistent. Some studies have reported no significant differences between early and delayed treatment in terms of overall survival, whereas others have reported that the impact of delay varies substantially by stage and patient age [6, 7, 8, 9]. Importantly, in many prior studies, the analyses were not stratified by disease stage, limiting the interpretability of their findings across different levels of disease severity.

The potential role of preexisting comorbidities in this relationship has also been of interest. A nationwide Korean cohort study reported that a diagnosis-to-first-treatment interval of ≥ 60 days was associated with a higher 5-year mortality risk (HR: 2.09; 95% CI: 1.43–3.06) in patients with early-stage breast cancer, with the association being stronger for patients with a high comorbidity burden [10]. In particular, cardiovascular disease (CVD) has been identified as a leading cause of death among patients with breast cancer, representing a major competing cause of mortality among survivors, with a fully adjusted hazard ratio for non–breast cancer death of 1.87 (95% CI, 1.80–1.93) among patients with preexisting CVD [11]. Patients with preexisting CVD may be especially vulnerable to treatment delays, as their reduced tolerance to cancer therapy and elevated competing risk of noncancer death could amplify the adverse impact of a prolonged time to treatment. However, whether cardiovascular comorbidity affects the association between treatment delay and survival has not been fully examined.

The aim of this study was to examine the association between TTI and overall survival among women with breast cancer in Korea, stratified by disease stage, using a large nationwide linked database. Additionally, we explored whether the association between treatment delay and survival differed by molecular subtype and preexisting CVD.

Methods

Data source. The Breast Cancer Collaborative Stage-Linked Database, a linked dataset constructed by integrating the Breast Cancer Collaborative Stage dataset (Breast CS) from the Korea Central Cancer Registry (KCCR) with administrative and clinical data from the Cancer Public Library Database (CPLD), was utilized [12]. The Breast CS dataset provides detailed tumor-level clinical and pathological information for women newly diagnosed with breast cancer between 2012 and 2019, while the CPLD provides links to nationwide health insurance claims, cause-of-death records, and health screening data. Cause-of-death information, obtained from Statistics Korea, was available through December 2021, whereas other linked data extended through December 2022.

The CPLD was launched in 2022 as part of the Korean Clinical Data Utilization for Research Excellence (K-CURE) project, an initiative of the Ministry of Health and Welfare of Korea, to integrate clinical and population-based cancer data for research. It links data from four major public sources: the Korea National Cancer Incidence Database (KNCI DB) from the KCCR, cause-of-death data from Statistics Korea, the National Health Information Database from the National Health Insurance Service (NHIS), and the National Health Insurance Research Database from the Health Insurance Review and Assessment Service (HIRA). Further details on the CPLD have been described previously [13].

The KCCR has compiled nationwide cancer incidence data into the KNCI DB since 1999 by consolidating hospital-based registries with information from central and regional cancer registration programs. The Breast CS dataset was established by systematically sampling 10% of the breast cancer cases recorded in the KNCI DB, which were then supplemented with detailed clinical and pathological information, including tumor size, regional lymph node status, and molecular subtype, through medical chart reviews [14]. Cancer stage was classified according to the American Joint Committee on Cancer (AJCC) TNM staging system.

Study population. This study employed a retrospective cohort design to examine the association between TTI and overall survival among women with newly diagnosed breast cancer. The database included 16,870 women diagnosed with breast cancer between 2012 and 2019. We excluded patients diagnosed with stage 0 or an unknown stage, male patients, and those whose eligibility could not be verified in the NHIS database. We further excluded patients whose diagnosis and death occurred during the same calendar month, as their survival time could not be reliably determined. After these exclusions, the final study population comprised 16,495 women, who were analyzed separately by disease stage (stages I–IV). The cohort selection process is summarized in Fig. 1.

Treatment and time to treatment initiation. Treatment was defined as any surgery, radiotherapy, or chemotherapy received within one year from the date of breast cancer diagnosis; detailed treatment types are provided in **Supplementary Table 1**. Because all diagnosis dates in the data source were recorded only at the month level, we imputed the day of diagnosis for each patient. For each of the 50 imputations, the diagnosis day was randomly drawn from a uniform distribution spanning the first to the last day of the recorded diagnosis month, generating 50 imputed datasets. Fifty imputations were used to ensure stable estimates, in accordance with prior methodological recommendations [15]. The treatment initiation date was defined as the date of the first treatment received on or after the imputed diagnosis date. The TTI was calculated for each imputed dataset and categorized into four groups: ≤30 days, 31–60 days, ≥ 61 days, and no treatment. The ≤ 30-day cutoff reflects Korean breast cancer treatment guidelines, which recommend initiating treatment within four weeks of diagnosis [16]. Patients who received no surgery, radiotherapy, or chemotherapy within one year of diagnosis were classified into the no-treatment group.

Outcomes and follow-up. The primary outcome was overall survival, defined as death from any cause. Each patient was followed from the date of breast cancer diagnosis until death or the end of follow-up,

whichever occurred first. Although the linked claims and health screening data extended through December 2022, cause-of-death information obtained from Statistics Korea was available only through December 2021. The follow-up period was therefore truncated to December 31, 2021, to ensure complete and uniform ascertainment of mortality across the cohort.

Death dates, like diagnosis dates, were recorded only at the month level. The day of death was imputed using the same approach, yielding 50 datasets per patient, each with a unique combination of imputed diagnosis and death days. Because patients with a diagnosis and death in the same calendar month were excluded, the imputed diagnosis day always preceded the imputed death day.

Covariates. Covariates included demographic, lifestyle, and clinical characteristics. Demographic variables included age at diagnosis (continuous), insurance premium level (upper 50%, lower 50%, and medical aid beneficiaries), and residential area (Seoul vs. other regions). Molecular subtype was determined by joint hormone receptor (HR; estrogen receptor [ER] and/or progesterone receptor [PR]) and HER2 status and was classified into four categories: HR−/HER2− (triple-negative breast cancer [TNBC]), HR−/HER2+ (HER2-enriched), HR+/HER2−, and HR+/HER2+ [17]. Lifestyle factor data, including body mass index (BMI; <25 kg/m² and ≥ 25 kg/m²), smoking history (never vs. ever), alcohol consumption (none, 1–3 times/week, and ≥ 4 times/week), and physical activity (none, 1–3 times/week, and ≥ 4 times/week), were obtained from the National Health Screening database of the NHIS using the most recent records on or before the diagnosis date. Comorbidities included CVD (ICD-10 codes: I20–I25, I47–I49, I50, and I60–I69), diabetes mellitus (ICD-10 codes: E10–E14), chronic kidney disease (ICD-10 codes: N18–N19), and a history of prior malignancy. All diagnostic records before the breast cancer diagnosis date were reviewed without a lookback restriction. To minimize false-positive results, each comorbidity was considered present only when it was recorded as a primary or first secondary diagnosis in at least one claim. For molecular subtype and health screening–derived variables, missing values were retained as a separate category.

Statistical analysis. Baseline characteristics are summarized as means with standard deviations for continuous variables and as frequencies with percentages for categorical variables, separately by disease stage.

The primary analysis was used to estimate the association between TTI and overall survival using stage-specific Cox proportional hazards models, with the ≤ 30-day group as the reference. Two models were fitted: Model 1 adjusted for age only, and Model 2 additionally adjusted for insurance premium, residential area, molecular subtype, BMI, smoking status, alcohol consumption, physical activity, prior malignancy, diabetes mellitus, CVD, and chronic kidney disease. Results are presented as adjusted hazard ratios (aHRs) with 95% confidence intervals (CIs). The proportional hazards assumption was assessed for each treatment delay group using an interaction between the group indicator and log(time). The assumption held for all treated groups (all $p > 0.05$); the no-treatment group violated it and was therefore retained for descriptive purposes only and excluded from hazard ratio estimation. We conducted subgroup analyses to examine effect modification. Analyses by molecular subtype were

performed in the overall cohort to preserve adequate statistical power, whereas analyses by CVD status were performed for patients with stage III disease, where the primary association between treatment delay and survival was observed.

All Cox models were fitted across the 50 imputed datasets, and estimates were pooled using Rubin's rules via PROC MIANALYZE [18, 19]. In a sensitivity analysis, both diagnosis and death dates were fixed to the first day of the recorded month, yielding a single record per patient, and all primary analyses were repeated to assess robustness. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA), with statistical significance defined as a two-sided $p < 0.05$. Figures were generated using R version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria) with the ggplot2 package.

Results

A total of 16,495 women with newly diagnosed breast cancer were included in the final analysis, comprising 7,335 patients with stage I disease (44.5%), 6,554 with stage II disease (39.7%), 1,941 with stage III disease (11.8%), and 665 with stage IV disease (4.0%). The majority of patients were aged 40–59 years across all stages (Table 1). The most common molecular subtype across all stages was HR+/HER2−, accounting for 59.5%, 49.4%, 43.8%, and 38.4% of patients in stages I–IV, respectively. In contrast, the prevalence of TNBC increased with advancing stage.

Table 1
Baseline characteristics of the breast cancer patients by cancer stage

	Stage □ (N = 7,335)		Stage □ (N = 6,554)		Stage □ (N = 1,941)		Stage □ (N = 665)	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Age, years								
< 40	579	7.9	690	10.5	250	12.9	62	9.3
40–49	2,512	34.3	2,259	34.5	623	32.1	170	25.6
50–59	2,316	31.6	1,995	30.4	648	33.4	205	30.8
60–69	1,290	17.6	1,028	15.7	266	13.7	126	19.0
≥ 70	638	8.7	582	8.9	154	7.9	102	15.3
Insurance premium								
Top 50%	4,284	58.4	3,509	53.5	995	51.3	332	49.9
Bottom 50%	2,763	37.7	2,724	41.6	842	43.4	296	44.5
Medical beneficiary	174	2.4	207	3.2	68	3.5	29	4.4
Unknown	114	1.6	114	1.7	36	1.8	8	1.2
Residence area								
Seoul	1,441	19.7	1,282	19.6	393	20.3	129	19.4
Else	5,894	80.4	5,272	80.4	1,548	79.7	536	80.6
BMI, kg/m^2								
< 25	4,065	55.4	3,083	47.1	774	39.9	211	31.7
≥ 25	1,709	23.3	1,601	24.4	480	24.7	105	15.8
Unknown	1,561	21.3	1,870	28.5	687	35.4	349	52.5
Smoking status								
Never	5,372	73.2	4,362	66.6	1,137	58.5	304	45.7
Ever	401	5.5	322	4.9	116	6.0	12	1.8
Unknown	1,562	21.3	1,870	28.5	688	35.5	349	52.5

Abbreviation = N: the number of cases; BMI: body mass index; HR+/-: Hormone Receptor positive/negative, HER2+/-: Human Epidermal growth factor Receptor 2 positive/negative. a. Including facilities such as clinics, convalescent hospitals, public health centers, and subcenters.

	Stage □ (N = 7,335)		Stage □ (N = 6,554)		Stage □ (N = 1,941)		Stage □ (N = 665)	
	N	%	N	%	N	%	N	%
Age, years								
Alcohol consumption, times per week								
0	4,375	59.7	3,492	53.3	911	46.9	255	38.4
1–3	1,292	17.6	1,092	16.7	315	16.2	56	8.4
≥ 4	105	1.4	98	1.5	27	1.4	4	0.6
Unknown	1,563	21.3	1,872	28.5	688	35.5	350	52.6
Physical activity, times per week								
0	2,666	36.4	2,253	34.4	612	31.5	169	25.4
1–3	2,021	27.6	1,631	24.9	437	22.5	89	13.4
≥ 4	1,086	14.8	800	12.2	204	10.5	58	8.7
Unknown	1,562	21.2	1,870	28.5	688	35.5	349	52.5
Pre-exising comorbidities								
Cancer	946	12.9	675	10.3	191	9.8	70	10.5
Diabetes mellitus	1,020	13.9	970	14.8	267	13.8	92	13.8
Cardiovascular disease	734	10.0	563	8.6	195	10.1	61	9.2
Chronic kidney disease	71	1.0	53	0.8	11	0.6	6	0.9
Molecular subtype								
TNBC	700	9.5	1,024	15.6	252	13.0	84	12.6
HER2-enriched	636	8.7	686	10.5	280	14.4	106	15.9
HR+/HER2-	4,361	59.5	3,238	49.4	850	43.8	255	38.4
HR+/HER2+	1,106	15.0	1,151	17.6	404	20.8	128	19.3
Unknown	532	7.3	455	6.9	155	8.0	92	13.8
Type of medical institution								

Abbreviation = N: the number of cases; BMI: body mass index; HR+/-: Hormone Receptor positive/negative, HER2+/-: Human Epidermal growth factor Receptor 2 positive/negative. a. Including facilities such as clinics, convalescent hospitals, public health centers, and subcenters.

	Stage □ (N = 7,335)		Stage □ (N = 6,554)		Stage □ (N = 1,941)		Stage □ (N = 665)	
	N	%	N	%	N	%	N	%
Age, years								
Tertiary hospital	5,183	71.6	4,905	76.1	1,468	76.4	440	70.7
General hospital	1,267	17.5	1,229	19.0	381	19.8	126	20.3
Hospital or belowa	789	10.9	316	4.9	73	3.8	56	9.0
Medical institution area								
Seoul	2,810	38.8	2,600	40.3	756	39.3	233	37.5
Else	4,429	61.2	3,850	59.7	1,166	60.7	389	62.5

Abbreviation = N: the number of cases; BMI: body mass index; HR+/-: Hormone Receptor positive/negative, HER2+/-: Human Epidermal growth factor Receptor 2 positive/negative. a. Including facilities such as clinics, convalescent hospitals, public health centers, and subcenters.

With respect to initial treatment, surgery was the most common first treatment modality in patients with stage I and II disease (91.0% and 74.7%, respectively), whereas chemotherapy was the predominant initial treatment in patients with stage IV disease (70.2%) (**Supplementary Table 2**). In patients with stage III disease, surgery and chemotherapy were both commonly used as initial treatments (52.7% and 38.7%, respectively). When all treatments received within one year of diagnosis were considered, a combination of all three modalities (surgery, radiotherapy, and chemotherapy) was the most common treatment pattern in patients with stage I through III disease (68.9%, 66.6%, and 81.4%, respectively), whereas chemotherapy alone was most frequent in patients with stage IV disease (42.1%).

The associations between TTI and overall survival, stratified by cancer stage, are presented in Fig. 2, and the median follow-up duration by TTI group is provided in **Supplementary Table 3**. Among treated patients, a treatment delay of 31–60 days was not significantly associated with overall survival at any stage. For delays of ≥ 61 days, findings differed by stage. In patients with stage I (aHR, 1.11; 95% CI, 0.57–2.15) and stage II (aHR, 1.31; 95% CI, 0.78–2.21) disease, prolonged delay was not significantly associated with overall survival. In patients with stage III disease, a delay of ≥ 61 days was associated with significantly poorer overall survival (aHR, 1.50; 95% CI, 1.04–2.16). In patients with stage IV disease, treatment delay was not significantly associated with overall survival regardless of duration (31–60 days: aHR, 0.74; 95% CI, 0.53–1.03; ≥61 days: aHR, 1.01; 95% CI, 0.67–1.52). Sensitivity analyses using fixed diagnosis and death dates yielded consistent results (**Supplementary Table 4**).

When analyzed separately by molecular subtype in the overall cohort, a delay of ≥ 61 days was associated with worse overall survival among patients with TNBC (aHR, 1.75; 95% CI, 1.10–2.78) and HR+/HER2 + tumors (aHR, 1.41; 95% CI, 1.04–1.92). In contrast, neither moderate (31–60 days) nor

prolonged (≥ 61 days) delay was significantly associated with overall survival among patients with HER2-enriched or HR+/HER2 − tumors (Fig. 3).

Among the comorbidity subgroups examined, the association between treatment delay and overall survival appeared more pronounced among patients with stage III disease with CVD. In this subgroup, a delay of ≥ 61 days was associated with worse overall survival (aHR, 5.28; 95% CI, 1.78–15.68), whereas no significant association was observed among those without CVD (aHR, 1.30; 95% CI, 0.86–1.97) (Fig. 4).

Discussion

In this nationwide retrospective cohort study, the association between TTI and overall survival among Korean women with breast cancer was examined using a large linked database. Treatment delay beyond 30 days was not significantly associated with overall survival among patients with stage I, II, or IV disease. In contrast, treatment initiation 61 days or more after diagnosis was associated with significantly worse overall survival among patients with stage III breast cancer. In subgroup analyses, this adverse association appeared more pronounced among patients with biologically aggressive tumor subtypes—TNBC and HR+/HER2 + tumors—and among patients with stage III disease with preexisting CVD.

Our findings suggest that the prognostic impact of treatment delay varies according to both disease stage and tumor biology. Although previous meta-analyses have generally reported poorer outcomes associated with delayed surgery, adjuvant therapy, and neoadjuvant treatment [20], the magnitude of these associations has varied considerably across studies. Several studies have reported no significant association between treatment delay and survival after adjustment for disease stage and other prognostic factors [21, 22]. In the present study, no significant association was observed for stage I, II, or IV disease, whereas prolonged treatment delay was associated with worse overall survival in patients with stage III disease. Early-stage breast cancers may exhibit favorable outcomes despite moderate treatment delays because of their relatively limited disease burden, whereas prognosis of metastatic disease is often determined primarily by tumor biology and treatment responsiveness. In contrast, stage III breast cancer typically requires timely multimodal treatment with curative intent, making survival outcomes potentially more sensitive to prolonged delays in treatment initiation.

These subtype-specific findings suggest that the consequences of treatment delay may be greater for biologically aggressive tumors. The association observed in patients with TNBC is consistent with prior evidence: Gagliato et al. reported that a longer time to chemotherapy was associated with worse overall survival, particularly in patients with TNBC and in trastuzumab-treated HER2-positive tumors, and subsequent analyses have similarly identified TNBC as the subtype most sensitive to treatment delay [23, 24]. Because endocrine therapy and HER2-targeted therapeutic options for TNBC are lacking, chemotherapy is the primary systemic treatment, potentially increasing vulnerability to delay. The association observed in HR+/HER2 + tumors is less consistent with earlier reports, some of which

reported no significant effect of delay in HER2-positive disease, possibly reflecting heterogeneity in trastuzumab use and limited subgroup sizes across studies [25]. Because HER2 positivity confers a more proliferative phenotype for which timely systemic and HER2-targeted therapy is important, prolonged delay may still adversely affect outcomes in this subgroup.

Another notable finding was the stronger association between prolonged treatment delay and poor survival among patients with stage III disease and preexisting CVD, although the wide confidence interval (aHR, 5.28; 95% CI, 1.78–15.68) reflects the small number of such patients and warrants cautious interpretation. Several mechanisms may explain why the same delay could be more consequential in this subgroup. Cardiovascular comorbidity may limit the use or intensity of potentially cardiotoxic but effective therapies, including anthracycline-based chemotherapy and HER2-targeted agents, thereby compounding the disadvantage of delayed initiation [26, 27]. CVD is also a major competing cause of mortality among breast cancer survivors and may reduce treatment tolerance [11, 28], and shared inflammatory and immune-related pathways have been proposed to link cardiovascular disease with cancer progression [29, 30]. Because overall survival was the primary outcome, part of the excess mortality in this subgroup may reflect non–breast cancer deaths, as discussed below. Collectively, these observations support the value of integrated cardio-oncology care aimed at minimizing avoidable treatment delays in this high-risk population.

This study has several strengths. First, it utilized a large-scale linked database that integrated detailed cancer registry information with health care utilization and mortality data, enabling comprehensive stage-specific analyses. In addition, uncertainty arising from month-level diagnosis and death dates was addressed through multiple imputation, and the robustness of the findings was supported by sensitivity analyses using fixed dates. Several limitations should be acknowledged. First, residual confounding cannot be excluded despite adjustment for a broad range of demographic, clinical, lifestyle, and comorbidity-related factors. Second, although information on breast cancer-specific mortality was available in the database, the number of breast cancer-specific deaths was relatively limited, particularly within stage- and subtype-specific strata. Consequently, overall survival was used as the primary outcome, and the contribution of noncancer deaths could not be fully distinguished. Third, information concerning the specific causes of treatment delay was unavailable, precluding differentiation between delays attributable to patient, health care system, or clinical factors. Finally, some subgroup analyses involved relatively small numbers of events, resulting in wider confidence intervals and reduced statistical precision.

In conclusion, treatment initiation at 61 days or more after diagnosis was associated with significantly worse overall survival among patients with stage III breast cancer, whereas no significant association was observed for patients with stage I, II, or IV disease. The adverse association of prolonged treatment delay was more pronounced among patients with preexisting CVD and among those with biologically aggressive tumor subtypes. These findings highlight the importance of timely treatment initiation and coordinated multidisciplinary care for patients at the highest risk of adverse outcomes.

Abbreviations

aHR
adjusted hazard ratio
AJCC
American Joint Committee on Cancer
BMI
body mass index
CI
confidence interval
CPLD
Cancer Public Library Database
CS
Collaborative Stage
CVD
cardiovascular disease
ER
estrogen receptor
HER2
human epidermal growth factor receptor 2
HIRA
Health Insurance Review and Assessment Service
HR
hormone receptor
ICD-10
International Classification of Diseases, 10th Revision
IRB
Institutional Review Board
KCCR
Korea Central Cancer Registry
K-CURE
Korean Clinical Data Utilization for Research Excellence
KNCI DB
Korea National Cancer Incidence Database
NHIS
National Health Insurance Service
PR
progesterone receptor
TNBC
triple-negative breast cancer

TNM
tumor-node-metastasis
TTI
time to treatment initiation

Declarations

Ethics approval and consent to participate. This study was exempt from review by the Institutional Review Board (IRB) of Seoul National University Hospital (IRB approval number: E-2412-014-1592), as preexisting, deidentified administrative data were utilized in accordance with applicable ethical guidelines.

Consent for publication. Not applicable.

Availability of data and materials. This study used data from the Korean Clinical Data Utilization Network for Research Excellence (K-CURE). These data are not publicly available due to data use agreements and national privacy regulations. Qualified researchers may request access through the K-CURE data access committee (https://www.kcure.or.kr) with appropriate institutional and ethical approvals.

Competing interests. The authors declare that they have no competing interests.

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Authors' contributions. H.-J.K. designed the study methodology, curated the data, performed the formal analysis, prepared Figures 1–4, and wrote the main manuscript text. J.Y.B. contributed to the investigation, methodology, and validation of the analyses. K.-H.L. validated the clinical interpretation of the findings and critically revised the manuscript. A.S. conceptualized the study, contributed to the methodology, supervised the work, and critically revised the manuscript. All authors reviewed and approved the manuscript.

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Figures

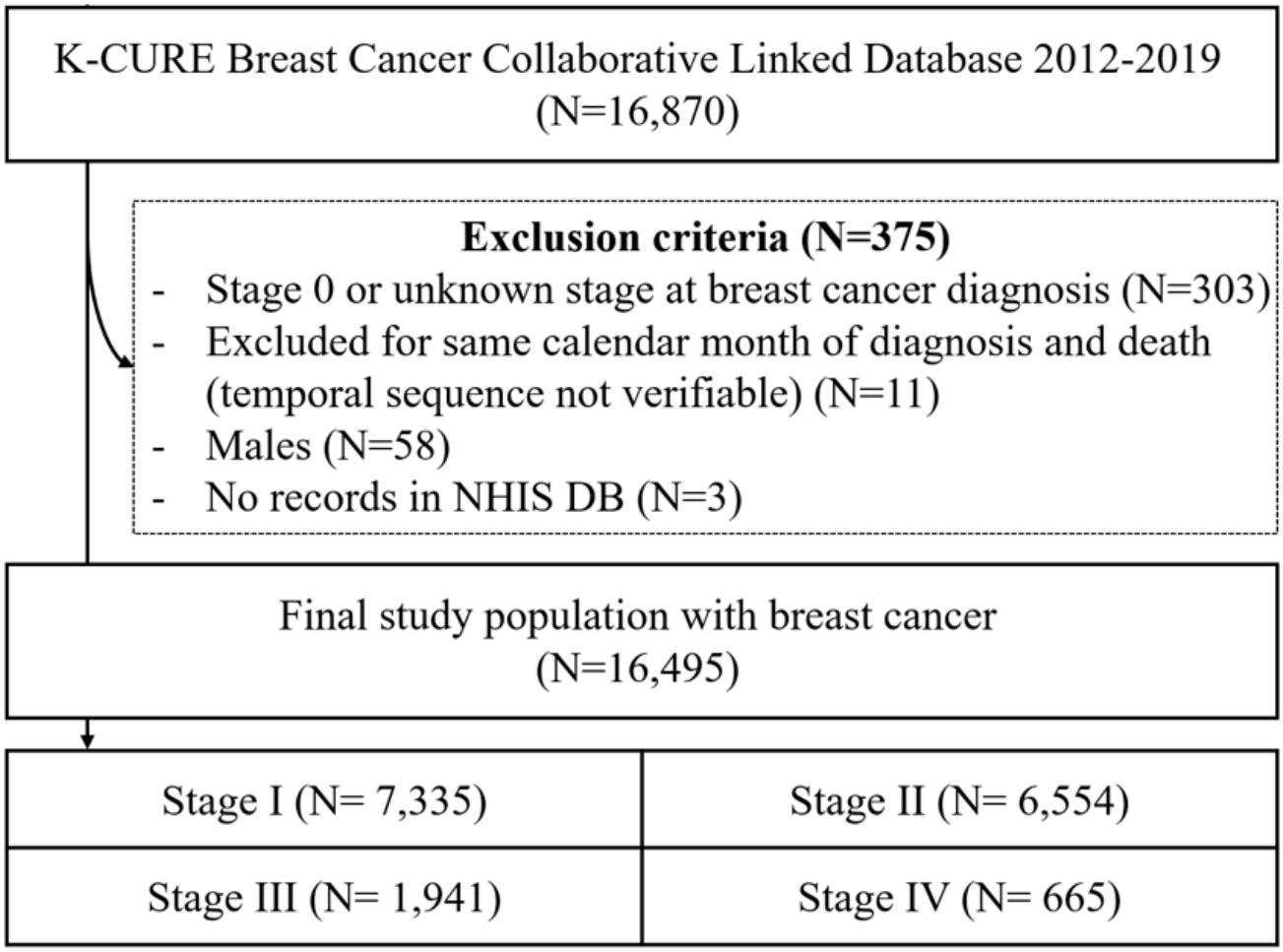


Figure 1

Flow chart of study population.

	Treatment delay	Cases (N)	Deaths (N)	Person years	Model 1[a] aHR (95% CI)	Model 2[b] aHR (95% CI)
Stage I	No treatment	41	7	194.55	6.25 (2.91 – 13.42)	4.55 (2.00 – 10.34)
	<31 days	4,810	132	28014.73	1.00 (Ref)	1.00 (Ref)
	31–60 days	2,039	50	10785.73	0.95 (0.64 – 1.41)	0.97 (0.65 – 1.45)
	≥61 days	446	12	2043.54	1.18 (0.62 – 2.25)	1.11 (0.57 – 2.15)
Stage II	No treatment	74	31	274.95	8.00 (5.47 – 11.72)	6.03 (3.84 – 9.49)
	<31 days	4,362	278	25174.91	1.00 (Ref)	1.00 (Ref)
	31–60 days	1,718	101	8873.71	1.01 (0.76 – 1.33)	1.05 (0.76 – 1.47)
	≥61 days	400	24	1838.58	1.14 (0.71 – 1.81)	1.31 (0.78 – 2.21)
Stage III	No treatment	20	17	49.29	8.13 (4.94 – 13.38)	8.38 (4.98 – 14.10)
	<31 days	1,331	259	7160.45	1.00 (Ref)	1.00 (Ref)
	31–60 days	456	85	2233.26	1.03 (0.75 – 1.40)	1.07 (0.78 – 1.47)
	≥61 days	135	37	588.49	1.69 (1.18 – 2.43)	1.50 (1.04 – 2.16)
Stage IV	No treatment	64	48	119.73	2.06 (1.51 – 2.81)	1.84 (1.33 – 2.56)
	<31 days	414	257	1321.02	1.00 (Ref)	1.00 (Ref)
	31–60 days	141	75	499.06	0.78 (0.57 – 1.06)	0.74 (0.53 – 1.03)
	≥61 days	46	29	146.33	1.02 (0.68 – 1.53)	1.01 (0.67 – 1.52)

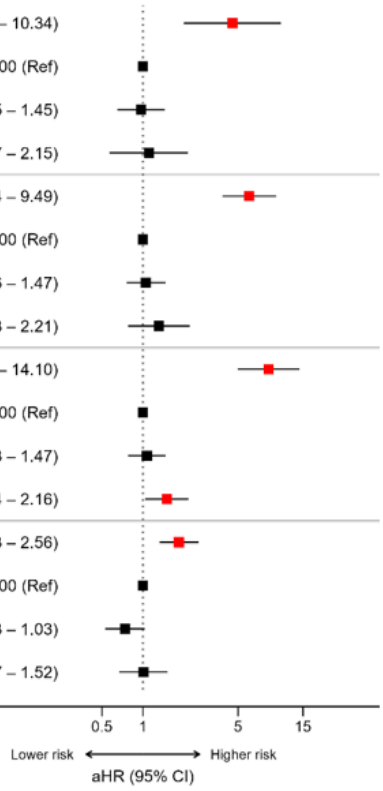


Figure 2

Association between treatment delay and stage-stratified survival among breast cancer patients.

Abbreviation= HR: hazard ratio; CI: confidence interval; aHR: adjusted HR; Ref: reference. [a] Adjusted for age; [b] Adjusted for age, molecular subtype, insurance premium, residence area, body mass index, smoking status, alcohol consumption, physical activity, history of cancer, diabetes mellitus, cardiovascular disease, chronic kidney disease.

Subtype	Treatment delay	Cases (N)	Deaths (N)	Person years	Model 1[a] aHR (95% CI)	Model 2[b] aHR (95% CI)
HR−/HER2− (TNBC)	No treatment	31	24	49.80	12.83 (8.29 – 19.86)	3.61 (2.15 – 6.06)
	<31 days	1,388	197	7495.53	1.00 (Ref)	1.00 (Ref)
	31–60 days	518	70	2553.60	0.99 (0.71 – 1.37)	0.93 (0.67 – 1.31)
	≥61 days	123	27	503.53	1.77 (1.13 – 2.78)	1.75 (1.10 – 2.78)
HR−/HER2+ (HER2-enriched)	No treatment	19	8	57.40	6.02 (2.90 – 12.48)	2.22 (0.97 – 5.10)
	<31 days	1,124	117	6414.36	1.00 (Ref)	1.00 (Ref)
	31–60 days	437	45	2264.44	1.03 (0.68 – 1.57)	1.20 (0.79 – 1.83)
	≥61 days	128	10	551.63	0.93 (0.46 – 1.89)	0.88 (0.43 – 1.79)
HR+/HER2−	No treatment	52	15	207.94	6.74 (4.02 – 11.32)	2.70 (1.58 – 4.63)
	<31 days	5,661	355	31611.29	1.00 (Ref)	1.00 (Ref)
	31–60 days	2,454	119	12529.07	0.83 (0.65 – 1.07)	0.85 (0.66 – 1.11)
	≥61 days	537	33	2417.34	1.18 (0.81 – 1.73)	1.07 (0.72 – 1.57)
HR+/HER2+	No treatment	75	45	196.74	10.28 (7.53 – 14.04)	3.72 (2.64 – 5.24)
	<31 days	4,448	472	25298.57	1.00 (Ref)	1.00 (Ref)
	31–60 days	1,633	166	8403.38	1.00 (0.80 – 1.26)	1.08 (0.87 – 1.35)
	≥61 days	401	55	1790.38	1.49 (1.10 – 2.01)	1.41 (1.04 – 1.92)

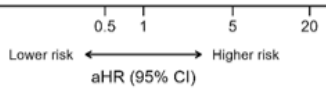


Figure 3

Association between treatment delay and survival among breast cancer patients by molecular subtypes.

Abbreviation= TNBC: triple-negative breast cancer; HR: hormone receptor; HER2-: Human Epidermal growth factor Receptor 2 negative; HR: hazard ratio; CI: confidence interval; aHR: adjusted HR; Ref: reference. [a] Adjusted for age; [b] Adjusted for age, stage, insurance premium, residence area, body mass index, smoking status, alcohol consumption, physical activity, history of cancer, diabetes mellitus, cardiovascular disease, chronic kidney disease.

Group	Treatment delay	Cases (N)	Deaths (N)	Person years	Model 1[a] aHR (95% CI)	Model 2[b] aHR (95% CI)
With CVD	No treatment	4	4	6.78	9.79 (3.21 – 29.80)	9.36 (2.36 – 37.11)
	<31 days	128	30	602.37	1.00 (Ref)	1.00 (Ref)
	31–60 days	38	12	151.67	1.45 (0.64 – 3.28)	1.48 (0.57 – 3.79)
	≥61 days	11	8	34.56	4.23 (1.82 – 9.87)	5.28 (1.78 – 15.68)
Without CVD	No treatment	16	13	42.50	7.89 (4.47 – 13.91)	8.06 (4.46 – 14.55)
	<31 days	1,203	229	6558.08	1.00 (Ref)	1.00 (Ref)
	31–60 days	418	73	2081.59	0.98 (0.71 – 1.36)	1.03 (0.73 – 1.44)
	≥61 days	123	29	553.93	1.45 (0.97 – 2.18)	1.30 (0.86 – 1.97)

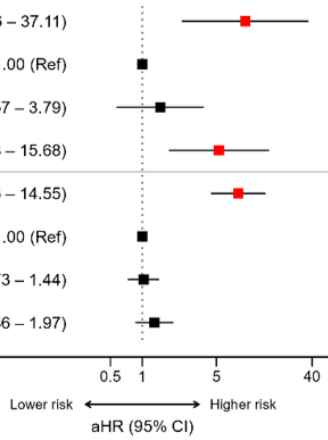


Figure 4

Association between treatment delay and survival, stratified by cardiovascular disease status in Stage III. Abbreviation= CVD: cardiovascular disease; HR: hazard ratio; CI: confidence interval; aHR: adjusted HR; Ref: reference. [a] Adjusted for age; [b] Adjusted for age, molecular subtype, insurance premium, residence area, body mass index, smoking status, alcohol consumption, physical activity, history of cancer, diabetes mellitus, cardiovascular disease, chronic kidney disease.

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