Development and validation of deep learning-based risk prediction model for major adverse cardiovascular events in female long-term breast cancer survivors

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A Dissertation Submitted
to the Department of Medicine
and the Graduate School of Yonsei University
in partial fulfillment of the
requirements for the degree of
Doctor of Philosophy in Medical Science

Si Nae Oh

December 2024

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The Graduate School
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December 2024

ACKNOWLEDGEMENTS

I would like to thank my supervisor, Dr. Jae Yong Shim, for his guidance and feedback throughout this project. I am also grateful to my husband, Sung Won Yoon, and my child, Soo Ho Yoon, for their patience and encouragement.

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ABSTRACT

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Background:

Clinical practice guidelines recommend reassessing the risk of cardiovascular toxicity five years after cancer treatment in asymptomatic adult cancer survivors, including new or pre-existing cardiovascular risk factors and cancer therapy-related cardiovascular toxicity. However, studies providing individualized risk prediction for these populations remain limited. This study aimed to develop and validate deep learning-based prediction models for the risk of major adverse cardiovascular events (MACEs) in long-term breast cancer survivors.

Methods:

We used data from the Korean National Health Insurance Service databases from 2005 to 2021, identifying 5,131 5-year female breast cancer survivors diagnosed in 2006. The study population was split into derivation and validation cohorts in a 4:1 ratio. The primary outcome was the occurrence of MACEs within a 10-year follow-up period. A deep learning survival model (DeepSurv) was developed and compared to a traditional Cox proportional hazards regression (CPH) model. Model performance was evaluated based on discrimination and calibration. Shapley additive explanations were used to rank predictors by importance.

Results:

The cumulative incidence of MACE at the 10-year follow-up was 14.4% in the derivation cohort and 12.1% in the validation cohort. Both models included 23 conventional and breast cancer treatment-related cardiovascular risk factors. In the validation cohort, the DeepSurv model achieved a time-dependent concordance index (C^{td}) of 0.739 (95% CI, 0.701–0.774) and an integrated Brier score (IBS) of 0.049, comparable to the CPH model (C^{td}: 0.737, 95% CI, 0.671–0.804; IBS: 0.045, 95% CI, 0.037–0.053). Key predictors identified using Shapley additive explanations included age, dyslipidemia, prior stroke, anthracycline chemotherapy, hypertension, diabetes mellitus, hemoglobin levels, prior aromatase inhibitor use, and prior radiotherapy.

Conclusions:

We developed and validated a deep learning survival model to predict the 10-year risk of MACEs

in individual 5-year breast cancer survivors. By incorporating both conventional and breast cancer treatment-related cardiovascular risk factors, the model demonstrated good calibration and discrimination.

Key words : breast cancer, cancer survivor, major adverse cardiovascular event, prediction model, machine learning.

1. INTRODUCTION

In recent decades, there has been a consistent decline in cancer-related mortality, accompanied by a significant increase in the number of cancer survivors.[1] Cancer survivors often face a significant burden of chronic health conditions resulting from the long-term effects of cancer and its treatments. As they live longer, the risk of noncancer deaths has begun to exceed that of cancer-related mortality.[2] Besides reducing life expectancy, these might affect their physical and psychosocial health status, and quality of life.[3] In this context, managing treatment-related side effects has taken on greater importance.

Among these side effects, cancer therapy-related cardiovascular toxicity significantly affects long-term morbidity and mortality outcomes in cancer patients, as well as the selection of anticancer therapies they can receive.[4] Before initiating treatments with known cardiovascular toxicity, it is essential to identify and address cardiovascular risk factors and pre-existing cardiovascular diseases (CVDs). Additionally, a comprehensive prevention and surveillance plan should be established to enable the early detection and effective management of potential cardiovascular complications.[5,6] During cancer therapy, the emergence of side effects necessitates careful consideration of the benefits and risks of continuing or modifying treatment.[5,6] In this regard, efforts to predict cardiotoxicity have primarily concentrated on stratifying risk to guide further cancer therapy decisions before and during cancer therapy.[7]

Meanwhile, cardiovascular toxicity risk restratification including evaluation of new or pre-existing cardiovascular risk factors and cardiovascular disease is recommended 5 years after cancer therapy in asymptomatic adult cancer survivors.[6] Based on cardiovascular toxicity risks, long-term follow-up surveillance should be organized and integrated into the overall long-term cancer survivorship care.[5,6] This includes patient education and cardiovascular risk factor optimization for all adult cancer survivors, which can be done in collaboration with primary care or specialist with expertise in cardiovascular risk factor management.[6] For cancer survivors at high risk, regular complementary tests including electrocardiography, natriuretic peptides measurement, and echocardiography is recommended.[5,6]

Clinical practice guidelines have provided risk stratification criteria for long-term follow-up in adult cancer survivors and adult survivors of childhood cancer based on both conventional and cancer treatment related cardiovascular risk factors.[5,6] However, unlike in adult survivors of childhood cancer, the diagnostic value of these criteria has not yet been studied in adult cancer survivors.[8-10] CVD is highly prevalent and poses a greater mortality threat than cancer itself in survivors of several cancer types, such as cancers of the breast, prostate, colorectum, and lung.[11,12] Whereas attention was primarily given to the cardiotoxicity during and early after the cancer treatments in this population, less attention has been directed toward the prediction and prevention of late cardiovascular complications.[13]

Five-year breast cancer survival rates now exceed 80% in most high-income countries, contributing to a global population of over 7.7 million breast cancer survivors.[1,14] Breast cancer survivors have a significantly increased risk of CVD and cardiovascular mortality, resulting from shared risk factors underlying cancer and CVD.[15] Moreover, treatment strategies commonly used

in breast cancer, such as chemotherapy, radiation therapy, and biologic agents, can cause late effects, including cardiovascular toxicity, throughout patients' lives.[15] There is an urgent need of prediction models to estimate individual long-term cardiovascular risk in breast cancer survivors, thereby enabling individualized prevention and surveillance.[7]

The objective of this study was to develop and validate a deep-learning based prediction model for major adverse cardiovascular events (MACEs) in individual long-term breast cancer survivors based on conventional and breast cancer treatment-related cardiovascular risk factors using the Korean National Health Insurance Service (NHIS) databases.

2.Methods

All authors have reviewed and approved this manuscript, and each author believes that the manuscript represents honest work. This study was approved by the Institutional Review Board of National Health Insurance Service Ilsan Hospital (IRB number NHIMC 2021-11-001). As the NHIS database is anonymized, the requirement for informed consent was waived.

2.1.Data sources

We used the NHIS databases between 2005 and 2021. The NHIS operates as a single, non-profit health insurance provider in South Korea, ensuring coverage to the entire population. It maintains a comprehensive computerized database containing healthcare-related information, including inpatient and outpatient claims, medication prescriptions, diagnoses, procedures, and treatments. Upon request, the NHIS provides researchers with a customized dataset containing de-identified information specific to the study population. Additionally, we incorporated data from the National Health Screening Program. This program offers biannual mandatory health screening examinations to all NHIS beneficiaries aged 40 years or older. The screenings include a self-reported questionnaire on lifestyle behviors, anthropometric measurements, blood pressure, and laboratory tests.[14] The validity of NHIS database has been described in previous studies.[15]

2.2.Study design and population

This nationwide population-based retrospective cohort study identified 14,170 patients newly diagnosed with breast cancer between January 1, 2006, and December 31, 2006. New diagnosis was defined by applying a 1-year washout period for 2005. Long-term breast cancer survivors were defined as those who newly diagnosed with breast cancer and survived at least 5 years. We excluded 64 male patients, 1,984 patients who had missing value for age, 6,774 patients without health screening records or not subject to health screening, and 217 patients died before index date (January 1, 2012). Finally, 5,131 participants were enrolled in this study. The cohort selection process is illustrated in Figure 1.

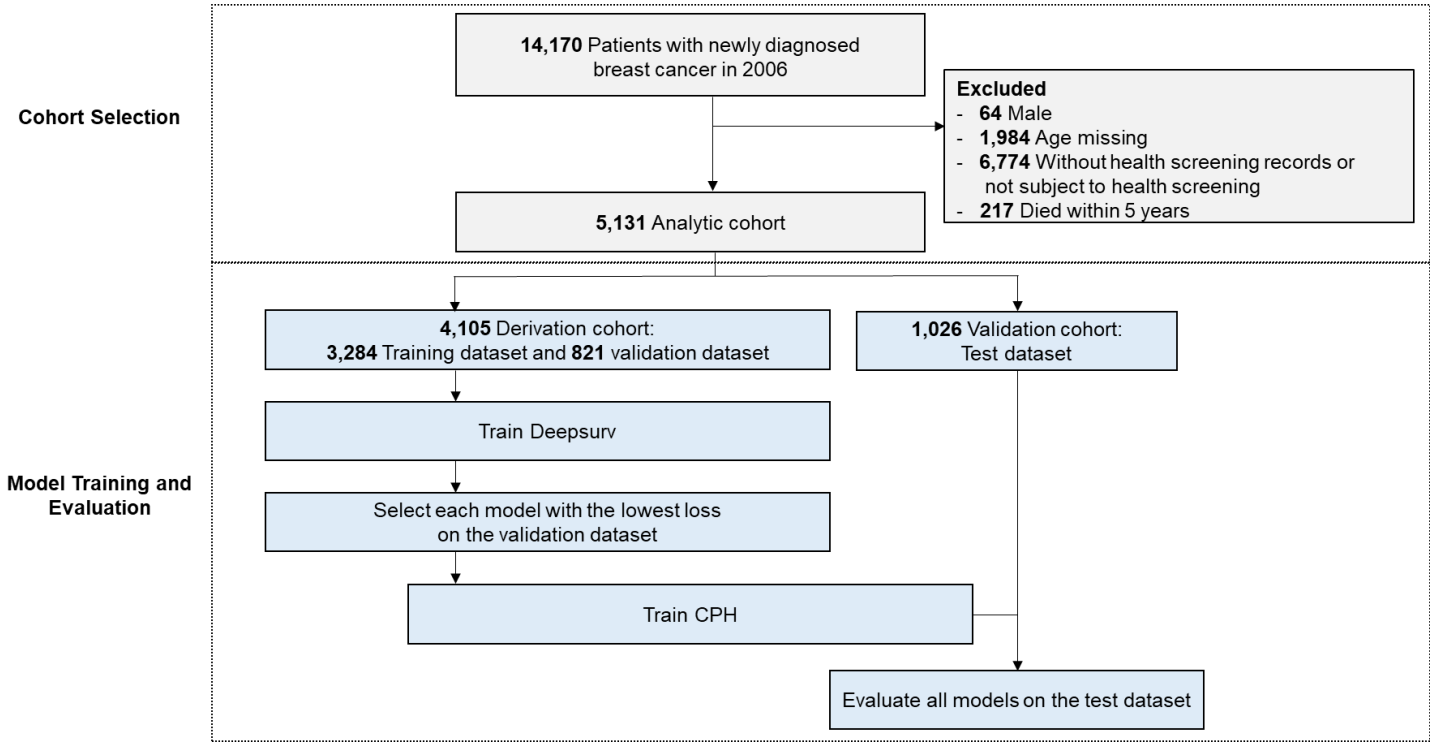

Figure 1. Flow chart of cohort selection and model training and evaluation. Abbreviation: CPH, the Cox proportional hazards model.

2.3.Data collection

To construct the models, we collected socio-demographic characteristics, prior cancer treatment. prior cardiovascular disease, comorbidities, lifestyle behavior, physical examination and laboratory test results. Socio-demographic characteristics included age (years) and household income (upper half or lower half) at the index date. Household income was derived from insurance premiums. Prior cancer treatments included the use of anthracycline (yes or no), trastuzumab (yes or no), tamoxifen (yes or no), aromatase inhibitors (yes or no), and radiotherapy (yes or no). Prior cardiovascular diseases, including myocardial infarction, stroke, congestive heart failure, peripheral artery occlusive disease, and atrial fibrillation, were assessed from the inception of data collection up to the index date. Comorbidities included hypertension (yes or no), diabetes mellitus (yes or no), and dyslipidemia (yes or no), and chronic kidney disease (yes or no) within 2 years of the index date. Lifestyle behavior included cigarette smoking (non-smoker or smoker), alcohol consumption (non-drinker or drinker), and moderate to vigorous physical activity (3 days or more days per week, or fewer than 3days per week) within 2 years of the index date. Physical examination and laboratory tests included body mass index (kg/m2), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), fasting serum glucose (mg/dL), total cholesterol (mg/dL), creatinine (mg/dL), and hemoglobin (g/dL) within 2 years of index date. The body mass index was calculated by dividing the participant's weight in kilograms by their height in meters squared.

The primary outcome was the occurrence of MACE (a composite of acute myocardial infarction, stroke, congestive heart failure, and all-cause death) at any time before the final follow-up at 10 years (31st December 2022).[16] Acute myocardial infarction was defined as hospitalization for primary or secondary diagnosis of the International Classification of Diseases, Tenth Revision (ICD-10) codes I21 and I22. A stroke was defined as hospitalization for primary or secondary diagnosis of ICD-10 codes I60 to I69. Patients were considered to have congestive heart failure if they were hospitalized for primary or secondary diagnosis of ICD-10 codes I50. The ICD-10 codes were derived from the American Heart Association guidelines.[17]

2.4.Model training and performance evaluation

We developed a model based on deep learning survival analysis (DeepSurv) as shown in figure 2. To compare its performance against traditional methods, we also trained a Cox proportional hazard regression (CPH) model using the same data set. DeepSurv model was implemented using the Python module Pycox (version 0.2.3), while the CPH model was implemented with scikit-survival (version 0.21.0). DeepSurv hyperparameters were tuned with Optuna (version 3.5.0) using five-fold cross-validation.

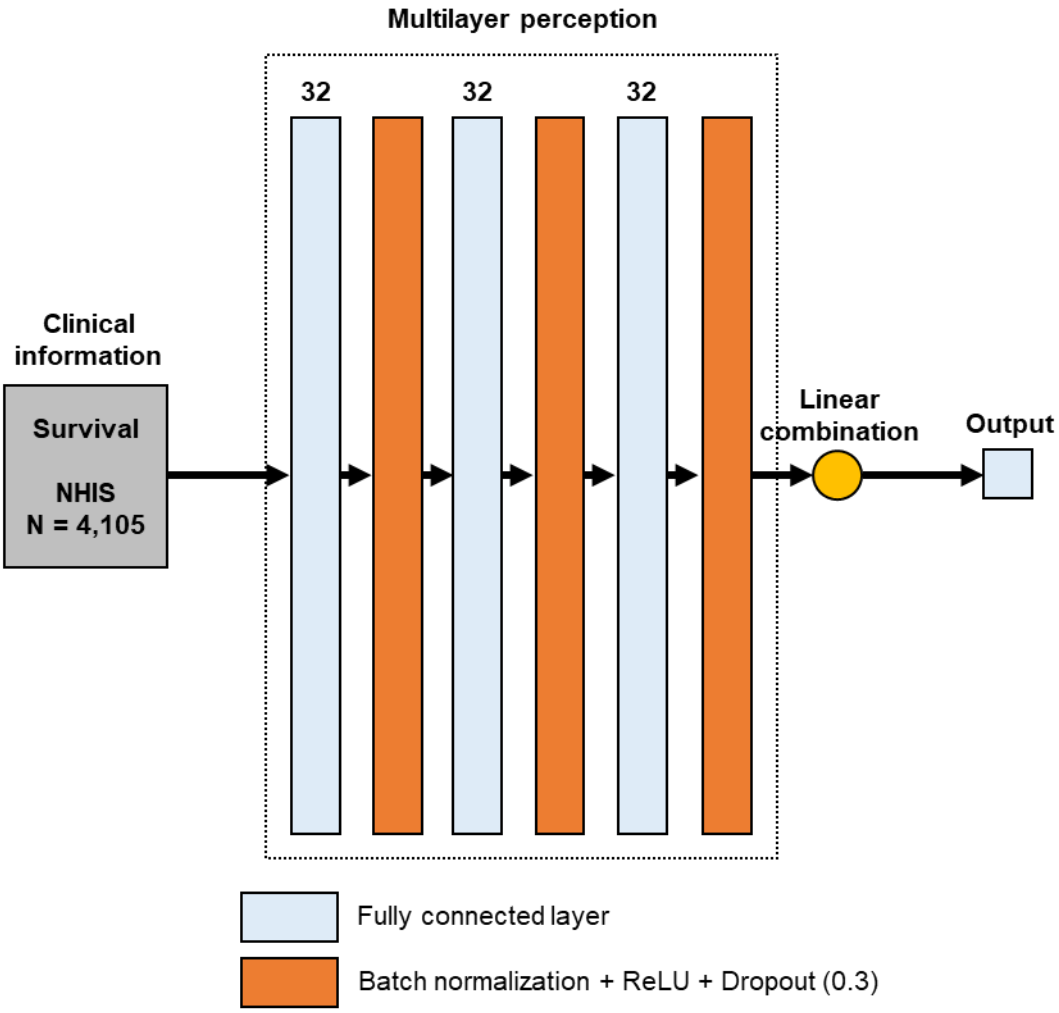

Figure 2. Deep learning model architecture. Clinical information was input into the DeepSurv model, a multi-layer perceptron designed to predict a patient's risk of MACEs. The model's output is a single node representing the patient's log risk, which is subsequently used to parameterize the Weibull survival distribution and calculate the weight *w*, reflecting the individualized survival probability. To enhance model performance and prevent overfitting, weight decay regularization, ReLU activation with batch normalization, dropout, and Adaptive Moment estimation (Adam) optimization were applied.

For feature selection, the permutation feature importance method was employed on the training dataset to prevent data leakage and result bias. This method ranked clinical factors based on their contribution to model predictions, determined by evaluating changes in prediction errors when each

feature was randomly shuffled.[18]

We computed the time-dependent concordance index (Ctd index), an extension of Harrell's concordance index (C index), which is widely recognized as the standard metric for assessing discrimination in survival analysis. A C^{td} index of 0.5 reflects random prediction (equivalent to a coin toss), while a value of 1 indicates perfect predictive accuracy. Additionally, we assessed overall model performance using the integrated Brier score (IBS), which accounts for both discrimination and calibration. An IBS of 0 represents perfect prediction, while a score of 0.25 indicates the threshold for random prediction. Models with IBS values below 0.25 are generally deemed valid. To estimate 95% confidence intervals for these metrics, bootstrap resampling with 1,000 iterations was employed. The model training and evaluation workflow is depicted in Figure 1.

2.5.Model explanation

Shapley Additive exPlanations (SHAP) were employed to quantify the influence of individual features on model predictions using the SHAP Python module (version 0.43.0).[21] Data processing was conducted using SAS (version 9.4), while all analysis codes were implemented and performed in Python (version 3.8).

3.Result

3.1.Baseline characteristics of the cohort

The study involved a total of 5,131 patients who were randomly assigned in a 4:1 ratio to either the derivation or validation cohorts. During the training process, 20% of the derivation cohort was reserved for model evaluation, with the final model assessment performed using the validation cohort. Baseline characteristics of the cohort are presented in Table 1. The mean (SD) population age was 56.2 (9.5) years. 40.1% of the patients received chemotherapy with anthracycline-containing regimens, and 0.7% were treated with antihuman epidermal growth factor receptor antibodies. 39.9% of the patients were treated with tamoxifen and 26.0% received aromatase inhibitors. 47.1% of the patients underwent radiotherapy. The cumulative incidences of MACE at 10-year follow-up were 14.4% and 12.1% in the derivation and validation cohort, respectively.

Table 1.Baseline characteristics

	Total (N = 5,131)	Derivation cohort (N = 4,105)	Validation cohort (N = 1,026)	P-value
Age, y, mean (SD)	56.2 (9.5)	56.2 (9.5)	56.0 (9.6)	0.471
Insurance premium				
Lower half	1,879 (36.6)	1,489 (36.3)	390 (38.0)	0.301
Upper half	3,252 (63.4)	2,616 (63.7)	636 (62.0)	

	Total (N = 5,131)	Derivation cohort (N = 4,105)	Validation cohort (N = 1,026)	P-value
Prior cancer treatment				
Anthracycline	2,056 (40.1)	1,678 (40.9)	378 (36.8)	0.018
Trastuzumab	38 (0.7)	30 (0.7)	8 (0.8)	0.870
Endocrine therapy				
Tamoxifen	2,045 (39.9)	1,635 (39.8)	410 (40.0)	0.939
Aromatase inhibitors	1,333 (26.0)	1,083 (26.4)	250 (24.4)	0.188
Radiotherapy	2,419 (47.1)	1,933 (47.1)	486 (47.4)	0.873
Prior cardiovascular disease				
Myocardial infarction	115 (2.2)	87 (2.1)	28 (2.7)	0.238
Stroke	636 (2.4)	505 (12.3)	131 (12.8)	0.685
Congestive heart failure	173 (3.4)	134 (3.3)	39 (3.8)	0.394
Peripheral artery occlusive disease	805 (15.7)	641 (15.6)	164 (16.0)	0.771
Atrial fibrillation	135 (2.6)	105 (2.6)	30 (2.9)	0.512
Comorbidities				
Hypertension	1,962 (38.2)	1,560 (38.0)	402 (39.2)	0.487
Diabetes mellitus	729 (14.2)	576 (14.0)	153 (14.9)	0.470
Dyslipidemia	2,143 (41.8)	1,730 (42.1)	413 (40.1)	0.272
Chronic kidney disease	356 (6.9)	286 (7.0)	70 (6.8)	0.871
Lifestyle factors				
Cigarette smoking				
Non-smoker	5,060 (98.6)	4,044 (98.5)	1,016 (99.0)	0.210
Smoker	71 (1.4)	61 (1.5)	10 (1.0)	
Alcohol consumption				
Non-drinker	4,587 (89.4)	3,678 (89.6)	909 (88.6)	0.460
1 days/week	374 (7.3)	290 (7.1)	84 (8.2)	
2 days/week	96 (1.9)	80 (2.0)	16 (1.6)	
≥3 days/week	74 (1.4)	57 (1.4)	17 (1.7)	
Moderate-to-vigorous physical activity				

	Total (N = 5,131)	Derivation cohort (N = 4,105)	Validation cohort (N = 1,026)	P-value
None	2,259 (44.0)	1,817 (44.3)	442 (43.1)	0.271
1 day/week	273 (5.3)	220 (5.4)	53 (5.2)	
2 days/week	528 (10.3)	435 (10.1)	93 (9.1)	
≥3 days/week	2,071 (40.4)	1,633 (39.8)	438 (42.7)	
Physical examination and laboratory tests				
BMI, kg/m^2, mean (SD)	23.6 (3.1)	23.6 (3.1)	23.6 (3.1)	0.996
Systolic blood pressure, mmHg, mean (SD)	121 (15.7)	121.3 (15.7)	121.3 (15.9)	0.903
Diastolic blood pressure, mmHg, mean (SD)	75 (10.1)	75.1 (10.2)	75.0 (9.8)	0.8
Fasting serum glucose, mg/dl, mean (SD)	97.9 (21.3)	97.7 (20.5)	98.5 (24.2)	0.284
Total cholesterol, mg/dL, mean (SD)	197.9 (37.4)	197.8 (37.5)	198.1 (37.2)	0.830
Creatinine, mg/dL, mean (SD)	0.8 (0.7)	0.8 (0.7)	0.8 (0.7)	0.948
Hemoglobin, g/dL, mean (SD)	12.8 (1.1)	12.8 (1.1)	12.9 (1.1)	0.212
MACE during follow-up period	714 (13.9)	590 (14.4)	124 (12.1)	0.058
All-cause death	453 (8.8)	372 (9.1)	81 (7.9)	0.239
Myocardial infarction	26 (0.5)	19 (0.5)	7 (0.7)	0.376
Stroke	254 (5.0)	200 (4.9)	54 (5.3)	0.606
Congestive heart failure	60 (1.2)	52 (1.3)	8 (0.8)	0.194

All values are expressed as frequency (%) unless otherwise specified. Abbreviation: SD, standard deviation; BMI, body mass index; and MACE, major adverse cardiovascular event.

3.2.Feature selection

The permutation feature importance analysis identified 23 relevant clinical factors with non-negative feature importance values out of the 26 clinical factors assessed in both the DeepSurv and CPH models (Figure 3 and Table S1).

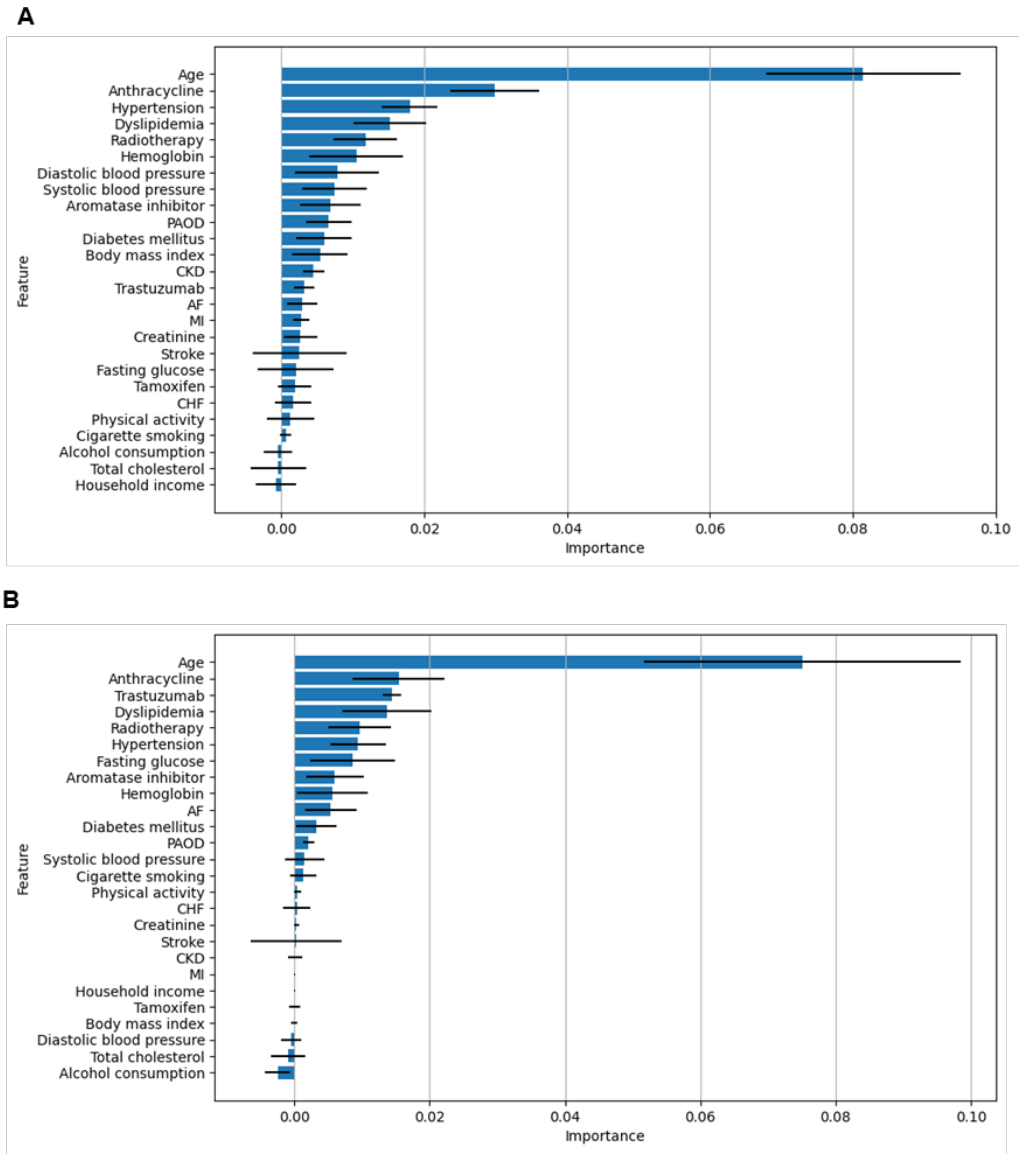

Figure 3. Permutation Feature Importance for all 26 features. Feaure importance provided for the Deepsurv (A) and the Cox proportional hazard model (B). Since the loss functions used by each model vary, the importance levels are relative values. A negative value indicates that when the feature is permuted, the model's performance improves. Abbreviations: AF, atrial fibrillation; CHF, congestive heart failure; CKD, chronic kidney disease; PAOD, peripheral arterial obstructive disease; and MI, myocardial infarction.

3.3.Model performance

To assess the discrimination and overall performance of the DeepSurv and CPH models, we computed the C^{td} index and IBS. Using 23 relevant clinical factors, DeepSurv achieved a C^{td} value of 0.739 (95% CI, 0.701–0.774), which was not significantly higher than the CPH model (C^{td} 0.737 [95% CI, 0.671–0.804]). Both models demonstrated excellent IBS values of 0.049 or less, significantly below the random prediction threshold of 0.25, indicating their reliability (Table 2).

Table 2. Performance comparison of deep learning and traditional model for major adverse cardiovascular event risk prediction among breast cancer survivors at 10 years.

Model	C^{td} (95% CI)	IBS (95% CI)
Derivation cohort		
DeepSurv	0.744 (0.699-0.770)	0.057 (0.047-0.063)
CPH	0.738 (0.710-0.767)	0.054 (0.038-0.056)
Validation cohort		
DeepSurv	0.739 (0.701-0.774)	0.049 (0.043-0.055)
CPH	0.737 (0.671-0.804)	0.045 (0.037-0.053)

Abbreviation: CI, confidence inerval; C^{td}, the time-dependent concordance index; IBS, integrated Brier score; and CPH, the Cox proportional hazards model.

3.4.Model explanation

Figure 4 and Figure S1 show the ranking of the clinical factors used by the DeepSurv and CPH models obtained using the SHAP method. Age, dyslipidemia, prior stroke, anthracycline chemotherapy, hypertension, hemoglobin level, aromatase inhibitor use, and radiotherapy were ranked highly in both DeepSurv and CPH models.

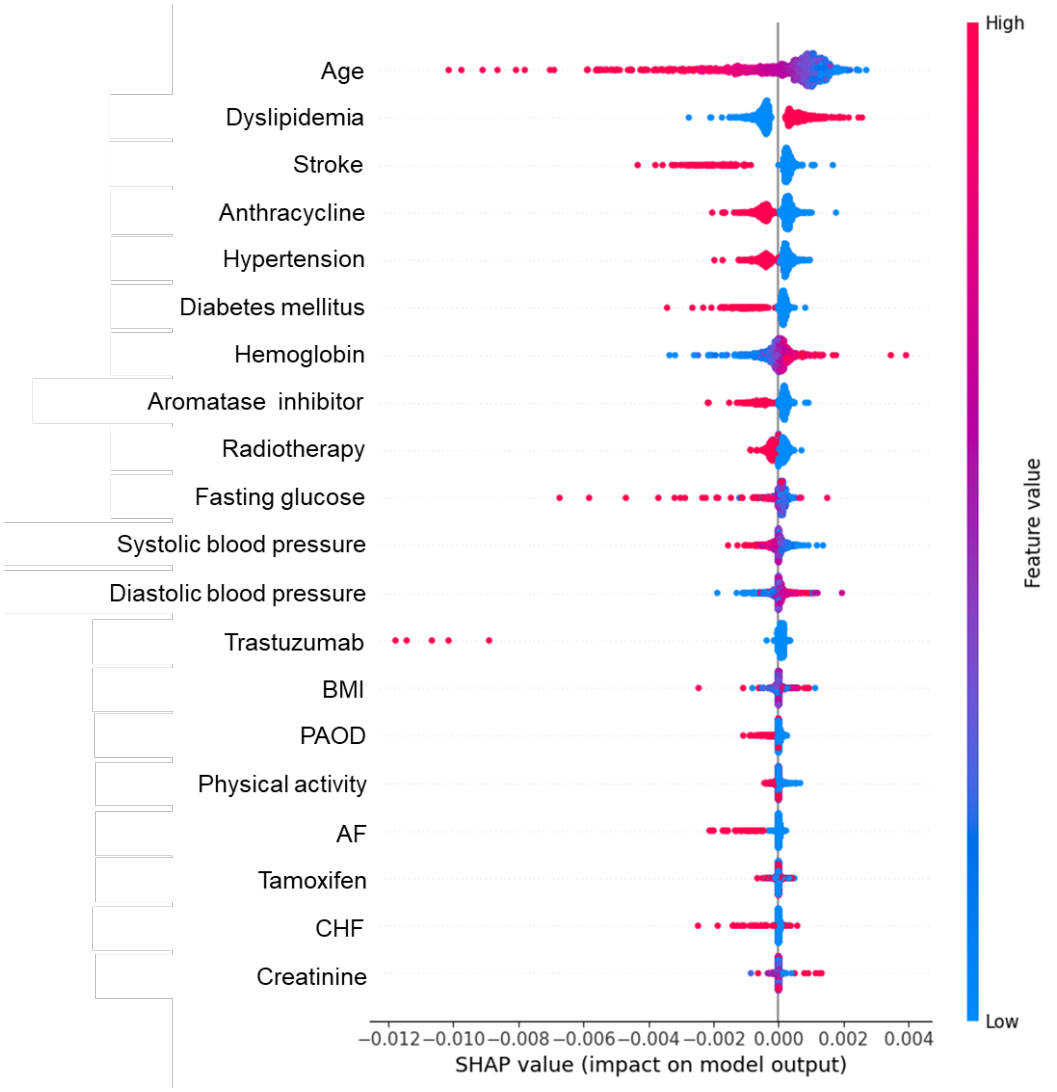

Figure 4. Shapley values in DeepSurv model. The summary plot displays the impact of individual features on the model's predictions, demonstrating the relationship between feature values and their contributions to risk estimation. A negative SHAP value indicates that the feature increases the likelihood of major adverse cardiovascular event (MACE), whereas a positive SHAP value indicates a decreased likelihood of MACE. Abbreviations: AF, atrial fibrillation; BMI, body mass index; CKD, chronic kidney disease; CHF, congestive heart failure; PAOD, peripheral arterial obstructive disease; and SHAP, Shapley Additive exPlanations.

4.Discussion

We developed and validated deep leaning-based prediction models for 10-year MACEs risk in 5-year breast cancer survivors with a good performance, incorporating both conventional and breast cancer therapy-related cardiovascular risk factors in a large population-based cohort. The clinical practice guidelines recommend reassessment of cardiovascular toxicity risk 5 years after therapy to guide long-term follow-up.[5,6] However, the existing risk stratification approach, which includes evaluating new or pre-existing cardiovascular risk factors and cancer therapy-related cardiovascular toxicity, is based on limited evidence and lacks the ability to provide individualized risk predictions. This is the first study to develop prediction models in a large cohort of adult long-term cancer survivors with extended follow-up to estimate individual cardiovascular risk.

4.1.Conventional cardiovascular risk factors in breast cancer survivors

For long-term cardiovascular surveillance in adult cancer survivors, clinical practice guidelines have suggested risk stratification criteria based on both conventional and cancer treatment related cardiovascular risk factors.[5,6] For predicting early cardiotoxicity risk in patients with breast cancer, recent models based on factors such as age, preexisting CVD, conventional cardiovascular risk factors, and/or current cancer treatment have shown good ability to predict MACE.[22,23] These conventional cardiovascular risk factors include medical conditions such as hypertension, diabetes mellitus, dyslipidemia, and chronic kidney disease, as well as lifestyle factors such as smoking, alcohol consumption, physical inactivity, and obesity. Our findings regarding these traditional cardiovascular risk factors are consistent with the existing literature.

Our analysis of Shapley Additive Explanations revealed that the presence of dyslipidemia was associated with a lower risk of MACE (Figure 4). Dyslipidemia cases were defined as individuals prescribed antidyslipidemic medications under ICD-10 code for dyslipidemia. Statins, an essential approach for current lipid-lowering therapies, are well known to improve cardiovascular outcomes. A recent observational study reported that statin therapy was associated with a reduced risk of MACE in patients with breast cancer undergoing breast-conserving surgery and adjuvant whole breast radiotherapy.[24] Further research is warranted to explore the potential role of lipid-lowering therapy in mitigating cardiovascular complications in this population.[25]

Our results also showed that lower diastolic blood pressure was associated with an increased risk of MACE (Figure 4). While high diastolic blood pressure is associated with vascular and organ damage in individuals with preserved vascular compliance, the relationship between diastolic blood pressure and cardiovascular risk becomes more complex in cases of noncompliant vasculature, displaying a U-shaped association.[26] Multiple studies in patients with heart failure with preserved ejection fraction have reported that low diastolic blood pressure, particularly when combined with high systolic blood pressure, is linked to myocardial damage, coronary heart disease, heart failure hospitalization, stroke, and cardiovascular mortality.[27,28,29]

Household income did not contribute to the model predictions in our study. Social deprivation is a well-established cardiovascular risk factor in the general population.[30] In cancer survivors, current evidence indicates that individuals exposed to adverse social determinants of health over their

lifetime are disproportionately affected by cardiovascular side effects of cancer and its therapies.[31] We included household income—available as a social determinant of health in the NHIS dataset—as a predictor. Previous studies have suggested that lower household income contributes to health inequities in cardio-oncology care, likely through associations with resource availability and accessibility. In South Korea, universal insurance coverage ensures healthcare access for the entire population, which may mitigate these health inequities.

Additionally, prior myocardial infarction was not found to contribute to model predictions, and alcohol intake and cigarette smoking were not included as predictors in our models. This discrepancy may be attributed to the significantly lower prevalence of prior myocardial infarction (0.5%), smoking (1.4%), and heavy alcohol consumption (1.4%) in our study participants compared to Western populations.

4.2.Breast cancer therapy-related cardiovascular risk factors

Current cardiovascular toxicity risk stratification schemes for long-term cancer survivors are based on conventional cardiovascular risk factors and a history of anthracycline treatment and radiotherapy.[5,6] However, our approach incorporates endocrine therapy and HER2-targeted therapy into the patient's cancer treatment history, recognizing their critical role in predicting MACEs in breast cancer survivors on an individual basis.

It is well established that anthracycline chemotherapy and HER2-targeted therapies trigger cardiac dysfunction.[6] However, long-term effects of cardiac dysfunction caused by these treatments beyond 10 years among breast cancer survivors are unknown. In our study, both anthracycline and trastuzumab treatments were significant risk factors in the DeepSurv model.

Additionally, we found that radiation therapy was associated with an increased risk for MACEs. Previous studies reported that there was an excess of non–breast cancer deaths after 5 years among patients receiving radiation therapy, mainly due to CVD and lung cancer.[32] Radiation therapy involving the heart within the treatment field carries a risk of long-term coronary artery disease and heart failure, which may emerge as early as five years post-exposure and persist for up to 30 years.[33,34]

Endocrine therapy is widely used in breast cancer treatment, as 65–70% of early and metastatic breast cancer cases are hormone receptor-positive.[35] Tamoxifen is the preferred endocrine therapy for premenopausal women, while treatment options for postmenopausal women include tamoxifen, aromatase inhibitors, or a sequential combination.[36] Adjuvant endocrine therapy is commonly administered for a prolonged period of 5 years or longer, highlighting the importance of comprehensive evaluation of its overall toxicity.[37] A meta-analysis reported that long-term aromatase inhibitors use is associated with an increased risk for hypercholesterolemia and CVD compared with tamoxifen use.[31] Although tamoxifen positively impacts lipid profiles, it has not demonstrated a protective effect on cardiovascular outcomes and has been shown to minimally increase the risk of venous thromboembolism compared to the use of aromatase inhibitors.[38] In our study, treatment with both aromatase inhibitors and tamoxifen were significant risk factors in the DeepSurv model.

4.3.Deep learning in risk prediction modeling

By using CPH and Deepsurv to develop a risk prediction model, we compared traditional statistical approaches with a novel deep learning-based method in survival analysis. DeepSurv extends the CPH model by learning nonlinear relationships among variables, offering the potential to capture complex interactions between covariates without the need for prior specification.[39] However, in our study, the performance of the DeepSurv model was not significantly higher than that of the conventional CPH model in predicting future cardiovascular outcomes for breast cancer survivors. These findings suggest that the impact of nonlinear interactions among predictors in our dataset may be limited. Future research incorporating imaging data, such as electrocardiography and echocardiographic parameters, might further enhance the DeepSurv model's ability to predict cardiovascular outcomes by leveraging its strength in capturing complex relationships.

4.4.Limitations

This study has several potential limitations. First, due to our reliance on administrative data, we were unable to account for certain risk factors like electrocardiography, echocardiographic parameters, blood biomarkers including natriuretic peptides, family history of CVD and genetic variants. Incorporating these parameters could potentially enhance the model's performance. Second, we could not obtain information regarding the dose of anthracycline chemotherapy and radiotherapy. Finally, our prediction model needs external validation before recommending its use as a clinical decision support tool to individualize cardiovascular surveillance and preventive strategies.

5.CONCLUSION

We developed and validated a deep learning-based risk prediction model to estimate the 10-year MACEs risk in 5-year breast cancer survivors using nationwide population-based cohort. The model based on both patient-related and cancer treatment–related risk factors, demonstrated a good performance. However, in our study, the performance of the DeepSurv model was not significantly higher than conventional CPH model. Further research is needed to refine this prediction model, aiming to enhance its performance and customization for tailoring long-term cancer survivorship programs according to individual cardiovascular risk.

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APPENDICES

Figure S1. Shapley values in the Cox proportional hazards model.

Table S1. Performance comparison of deep learning model for cardiovascular disease risk prediction among breast cancer survivors at 10 years (derivation cohort).

Figure S1. Shapley values in the Cox proportional hazards model. The summary plot illustrates the impact of each feature on the model's predictions, highlighting the relationship between feature values and their contributions to risk estimation. A positive SHAP value indicates that the feature increases the likelihood of MACE, while a negative SHAP value indicates a decreased likelihood. Abbreviations: AF, atrial fibrillation; BMI, body mass index; CKD, chronic kidney disease; CHF, congestive heart failure; PAOD, peripheral arterial obstructive disease; and SHAP, Shapley Additive exPlanations.

Table S1. Performance comparison of deep learning model for major adverse cardiovascular event risk prediction among breast cancer survivors at 10 years (inclusion of all 26 factors).

Model	**C^{td} (95% CI)**	**IBS (95% CI)**
DeepSurv	0.736 (0.690-0.771)	0.049 (0.049-0.065)
CPH	0.730 (0.679-0.789)	0.045 (0.038-0.053)

Abbreviation: CI, confidence inerval; C^{td}, the time-dependent concordance index; IBS, integrated Brier score; CPH, the Cox proportional hazards model.

Abstract in Korean

여성 유방암 장기 생존자에서 딥러닝 기반 주요심혈관사건 위험 예측 모델 개발 및 검증

배경:

임상 진료 지침에 따르면, 암 치료 후 5년 시점에서 무증상 성인 암 생존자에 대하여 새로운 또는 기존의 심혈관 위험 요인과 암 치료 관련 심혈관 독성을 평가하는 것을 포함한 심혈관 독성 위험에 대한 재평가가 권장됩니다. 그러나 이를 위해 개별화된 위험도 예측을 제공하는 연구는 제한적입니다. 본 연구는 여성 유방암 장기 생존자에서 개별화된 주요심혈관사건 위험도 예측 모델을 개발하고 검증하는 것을 목표로 하였습니다.

방법:

2005년부터 2021년까지의 국민건강보험공단 데이터베이스를 사용하여 2006년에 진단받고 5년 이상 생존한 5,131명의 여성 유방암 생존자를 포함하였습니다. 연구 대상자는 4:1 비율로 파생 코호트와 검증 코호트에 무작위 배정되었습니다. 주요 결과는 10년 최종 추적 기간 동안 발생한 주요 심혈관 사건(MACEs)이었습니다. 딥러닝 생존 모델(DeepSurv)을 개발하고 이를 Cox 비례위험회귀(CPH) 모델과 비교하여 성능을 평가하였습니다. 모델 성능은 판별력(discrimation)과 보정력(calibration)을 통해 평가되었으며, Shapley 가산 설명을 사용하여 임상 요인의 중요도를 순위화 했습니다.

결과:

10년 추적 관찰 동안 주요심혈관사건의 누적 발생률은 파생 코호트에서 14.4%, 검증 코호트에서 12.1%로 나타났습니다. DeepSurv 및 CPH 모델에는 23개의 일반적인 심혈관 위험 요인과 유방암 치료 관련 요인이 포함되었습니다. 검증 코호트에서 DeepSurv 모델은 시간 의존적 일치 지수(C^{td}) 0.739 (95% CI, 0.701–0.774)와 통합 브리어 점수(IBS) 0.049를 기록하여 CPH 모델(Ctd: 0.737, 95% CI, 0.671–0.804; IBS: 0.045, 95% CI, 0.037–0.053)과 유사한 성능을 보였습니다. Shapley 가산 설명 분석에서 나이는 가장 중요한 요인으로 나타났으며, 이상지질혈증, 뇌졸중 병력, 안트라사이클린 화학요법, 고혈압, 당뇨병, 헤모글로빈 수치, 아로마타제 억제제 사용 병력, 방사선 치료가 그 뒤를 이었습니다.

결론:

5년 이상 생존한 여성 유방암 생존자를 대상으로 10년 주요심혈관사건 위험을 예측하는 딥러닝 기반 생존 모델을 개발 및 검증하였으며, 기존 심혈관 위험 요인과 유방암 치료 관련 요인을 통합하여 좋은 보정력과 판별력을 입증했습니다.

핵심되는 말 : 유방암, 암생존자, 주요심혈관사건, 예측 모형, 기계학습.