Validation of the PREDICT Prognostication Tool in US Patients With Breast Cancer

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ABSTRACT

Background: PREDICT is an online prognostication tool derived from breast cancer registry information on approximately 6,000 women treated in the United Kingdom that estimates the postsurgical treatment benefit of surgery alone, chemotherapy, trastuzumab, endocrine therapy, and/or adjuvant bisphosphonates in early-stage breast cancer. Our aim was to validate the PREDICT algorithm in predicting 5- and 10-year overall survival (OS) probabilities using real-world outcomes among US patients with breast cancer. **Methods:** A retrospective study was performed including women diagnosed with unilateral breast cancer in 2004 through 2012. Women with primary unilateral invasive breast cancer were included. Patients with bilateral or metastatic breast cancer, no breast surgery, or missing critical clinical information were excluded. Prognostic scores from PREDICT were calculated and external validity was approached by assessing statistical discrimination through area under time-dependent receiver-operator curves (AUC) and comparing the predicted survival to the observed OS in relevant subgroups. **Results:** We included 708,652 women, with a median age of 58 years. Most patients were White (85.4%), non-Hispanic (88.4%), and diagnosed with estrogen receptor–positive breast cancer (79.6%). Approximately 50% of patients received adjuvant chemotherapy, 67% received adjuvant endocrine therapy, 60% underwent a partial mastectomy, and 59% had 1 to 5 axillary sentinel nodes removed. Median follow-up time was 97.7 months. The population's 5- and 10-year OS were 89.7% and 78.7%, respectively. Estimated 5- and 10-year median survival with PREDICT were 88.3% and 73.8%, and an AUC of 0.77 and 0.76, respectively. PREDICT performed most poorly in patients with high Charlson-Deyo comorbidity scores (2–3), where PREDICT overestimated OS. Sensitivity analysis by year of diagnosis and HER2 status showed similar results. **Conclusions:** In this prognostic study utilizing the National Cancer Database, the PREDICT tool accurately predicted 5- and 10-year OS in a contemporary and diverse population of US patients with nonmetastatic breast cancer.

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Background

The most common type of cancer diagnosed among women worldwide is breast cancer, with an estimated 2.3 million new cases globally in 2020.[1] In the United States alone, in 2023, an estimated 300,590 new breast cancer cases and 43,700 breast cancer–related deaths are expected.[2] Due to steady progress in early breast cancer diagnosis and treatment, 5-year overall survival (OS) continues to improve.[3]

Accurate estimates of survival and the impact of different adjuvant therapies in early-stage breast cancer are essential for optimal clinical decision-making by medical oncologists.[4] PREDICT is an online clinical tool, developed in the United Kingdom, which has been shown to accurately estimate the relative impact of adjuvant therapies, such as chemotherapy, endocrine therapy, trastuzumab, and bisphosphonates, on OS in patients with breast cancer.[4,5] Provided with basic inputs of an individual patient's clinicopathologic characteristics, PREDICT provides personalized prognostic information displayed as 5- and 10-year OS estimates, both with and without adjuvant therapies.[6]

The PREDICT model was derived from survival data from 5,694 women with breast cancer recorded by the Eastern Cancer Registration and Information Centre (ECRIC) and subsequently validated in 5,468 women from the West Midlands Cancer Intelligence Unit.[4,5] The population from the ECRIC was composed mostly of patients aged 50 to

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64 years, with nodal status 0, tumor size 10 to 19 mm, histologic grade 2 tumors, and estrogen receptor (ER)–positive disease.[5] The key inputs for the PREDICT tool include: age at diagnosis, postmenopausal status, ER status, HER2 status, Ki-67 level, invasive tumor size, tumor grade, positive nodes, and adjuvant treatment options (endocrine therapy, chemotherapy, trastuzumab, and/or bisphosphonates).[5]

Unlike the tool Adjuvant! Online, which is no longer available and previously widely used for adjuvant therapy decision-making, PREDICT is not widely known or used among US medical oncologists. One of the reasons for this may be that PREDICT has never been validated in a US breast cancer cohort, which comprises a more diverse population than the UK cohort used for its development and validation. Thus, the primary objective of this study was to conduct an external validation of the PREDICT UK tool using the National Cancer Database (NCDB) to determine its accuracy in a large cohort of patients with breast cancer treated in the United States.

Methods

Source of Data

Data were obtained from the NCDB 2004–2018 breast cancer dataset. The NCDB, which is jointly sponsored by the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society, is a nationwide oncology outcomes database sourced from hospital registry data that represents >70% of newly diagnosed cancer cases in the United States.[7] The database covers >1,500 CoC-accredited facilities and accounts for approximately 3 million breast cancer cases collected from 2004 through 2017.[7] The high-quality data from a large, diverse patient group with an extensive follow-up availability in the NCDB makes it an ideal source for assessing the validity of the PREDICT tool in the US population.[8–10]

Following Institutional Review Board exemption due to the deidentified data source, a retrospective cohort study using the NCDB was performed. Definitions of the database variables are available from the dictionary in the NCDB Participant User Data File.[11] The CoC's NCDB and the hospitals participating in the CoC NCDB are the source of the deidentified data used herein; they have not verified and are not responsible for the statistical validity of the data analysis or the conclusions derived by the authors.

Study Cohort

Women diagnosed with primary unilateral invasive breast cancer in 2004 through 2012 with at least 5 years of follow-up were included (Figure 1). Only patients aged 25 to 85 years were included to mirror the age group used in the initial PREDICT UK validation. Patients with stage IV breast cancer, no definitive breast surgery, prior neoadjuvant therapy (endocrine therapy or chemotherapy), male sex, and missing critical clinical information (necessary for PREDICT scores calculation) or follow-up data were excluded. Given the inherent inaccuracies in clinical versus surgical staging of breast cancer and that PREDICT does not take into account neoadjuvant chemotherapy or the presence or absence of a complete pathologic response, patients who had chemotherapy prior to definitive curative-intent surgery were therefore excluded in our analyses.

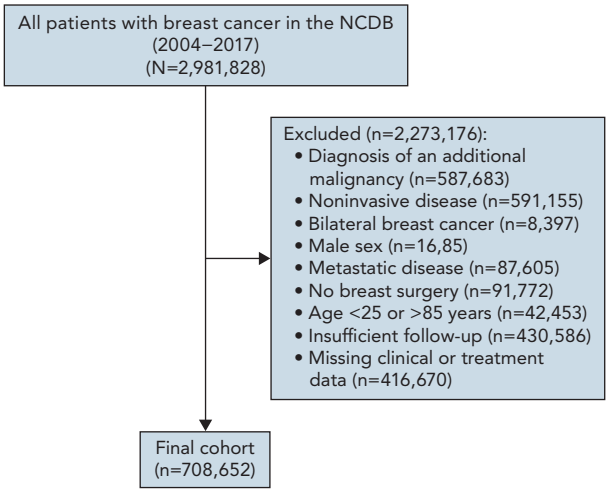

Figure 1. CONSORT diagram for PREDICT validation using the NCDB breast cancer population.
Abbreviation: NCDB, National Cancer Database.

Outcomes

The primary outcomes determined by the PREDICT model are 5- and 10-year OS, which were also the outcomes of this study, considering all-cause mortality.

Covariates

Patient demographics (age, self-reported race [Black, other, and White], self-reported ethnicity [Hispanic and non-Hispanic], insurance status, Charlson-Deyo comorbidity score, and Rural-Urban Continuum Code [RUCC] area), facility type, tumor characteristics (size, histologic grade, hormone receptor status, nodal status, clinical stage, and pathologic stage), and treatment factors (surgery, adjuvant chemotherapy, and endocrine therapy) were collected.[11] The NCDB does not include drug-specific codes (eg, trastuzumab)—for cases diagnosed prior to 2013, trastuzumab was classified as a chemotherapy.[11] Staging was based on TNM classification in the 7th edition of the AJCC Cancer Staging Manual because most of the patients in the dataset had unknown HER2 status.[12]

Prognostic Scores Calculation

Of the key inputs for the PREDICT tool, the variables that are also available in NCDB include age at initial breast cancer diagnosis, number of lymph nodes examined, number of positive lymph nodes, tumor size, histologic grade, ER status, and HER2 status. Scores can be generated with unknown information on menopausal status, HER2 status, and Ki-67 status, or whether breast cancer was detected by screening versus mammogram.

In terms of details about the type of systemic therapy, only categorical (yes/no) information is available in the NCDB with respect to adjuvant chemotherapy, endocrine therapy, or trastuzumab use. No specific information regarding the types of medications used or the duration of therapy is available. Therefore, because neither the exact duration of endocrine therapy nor the specific chemotherapy regimen used in patients is recorded in the NCDB, for modeling purposes, we made 2 key assumptions. First, we assumed that all women who received adjuvant chemotherapy received a second-generation chemotherapy regimen (eg, sequential doxorubicin/cyclophosphamide followed by paclitaxel [AC-T]).[13] Second, we assumed a 5-year duration of adjuvant endocrine therapy for women who received adjuvant endocrine therapy in the NCDB. Likewise, there are scant data in the NCDB on the mode of breast cancer detection; therefore, in our validation, screen detection was used for patients when it was unknown whether breast cancer was self-detected. Because no information on Ki-67 expression is available in the NCDB, it was assigned as "unknown" for all patients.

Prognostic scores from PREDICT were obtained using the R package, nhs.predict.[14] The probability of 5- or 10-year death from all causes was calculated according to the PREDICT tool and compared with the NCDB real-world data on OS.

Statistical Analysis

Population characteristics were presented as absolute values and percentages for categorical variables and as medians and quartiles for continuous variables.

The PREDICT performance was measured via the area under the curve (AUC) of time-dependent receiver operating characteristic curves, a well-established method to graphically display the relationship between sensitivity and specificity for every possible cutoff considering the probabilities to the outcome obtained from a model.[15] In our study, these cutoffs represent the point from which, according to the PREDICT tool's absolute prediction, the patient is considered to have the endpoint of 5- or 10-year death. An AUC of 0.5 reflects random predictions, whereas an AUC of 1 implies perfect predictive performance.[15,16]

Calibration was assessed by comparing the observed 5- and 10-year OS (obtained via Kaplan-Meier estimates) from the NCDB versus the average and median predicted probability from PREDICT. Subgroup analysis was performed according to age, self-reported race, self-reported ethnicity, comorbidity score, facility type, RUCC area, stage, grade, ER status, HER2 status, and systemic therapy. Sensitivity analysis was performed in patients diagnosed after 2010, the year when the NCDB started to collect HER2 status information. A second sensitivity analysis was performed on patients without HER2-positive status, because HER2-targeted therapy was labeled as chemotherapy for cases diagnosed before 2013 according to the NCDB classification.

All analyses were performed using Stata/MP (StataCorp LLC) and RStudio software (RStudio Inc). This study adheres to transparent reporting of a multivariable prediction model for individual prognosis or diagnosis guidelines.[17]

Results

Population

The study cohort included 708,652 women diagnosed with breast cancer (Table 1). The cohort median age was 58 years (IQR, 49–68 years). Most patients were White (85.4%) and non-Hispanic (88.4%), had private health insurance (59.2%) and low comorbidity scores (85.9%), and were from metropolitan areas (86.4%) and diagnosed with ER-positive breast cancer (79.6%). Approximately 50% of patients received adjuvant chemotherapy, 67% received adjuvant endocrine therapy, 60% underwent a partial mastectomy, and 59% had 1 to 5 axillary sentinel nodes removed. Median follow-up time was 97.7 months (IQR, 76.3–125.2 months).

5-Year OS

The 5-year OS was 89.7% (95% CI, 89.7%–89.8%) (Figure 2, Table 2). Using PREDICT, the estimated a 5-year median survival was 88.3% (IQR, 78.9%–93.9%), which corresponds to an AUC of 0.78 at this time point (Figure 3).

For the 5-year estimations, according to each of the subgroups analyzed (Table 2), comparing the observed OS versus the predicted median survival, the PREDICT tool performed better in women aged 51 to 60 years (OS, 92.4% [95% CI, 92.3%–92.6%] vs estimated median survival of 92% [IQR, 82.5%–95.3%]; supplemental eFigure 1); Black patients (OS, 84.3% [95% CI, 84.1%–84.6%] vs estimated median survival of 84.6% [IQR, 74.5%–92.2%]; eFigure 2); non-Hispanic patients (OS, 89.7% [95% CI, 89.7%–89.8%] vs estimated median survival of 88.4% [IQR, 78.9%–93.9%]; eFigure 3); patients from comprehensive facilities (OS, 89.6% [95% CI, 89.5%–89.7%] vs estimated median survival of 88.4% [IQR, 79%–93.8%]; eFigure 4); those from urban areas (OS, 88.3% [95% CI, 88.1%–88.5%] vs estimated median survival of 87.8% [IQR, 78.4%–93.5%]; eFigure 5); those with low (0–1) Charlson-Deyo comorbidity scores (OS, 90.3% [95% CI, 90.

Table 1. Demographic Characteristics From the NCDB Validation Cohort

	NCDB Patients With Breast Cancer n (%)
Total, N	708,652
Follow-up, median (IQR), mo	97.7 (76.3–125.2)
Age, median (IQR), y	58 (49–68)
Self-reported race	
White	599,174 (85.4)
Black	74,464 (10.6)
Other[a]	27,796 (3.9)
Self-reported ethnicity	
Non-Hispanic	626,537 (88.4)
Hispanic	33,947 (4.7)
Insurance status	
Not insured	13,976 (1.9)
Private insurance	416,187 (59.2)
Public insurance	267,901 (38.3)
Charlson-Deyo comorbidity score	
0	609,291 (85.9)
1	81,345 (11.4)
2	14,062 (1.9)
3	3,954 (0.5)
Facility type	
Community	61,114 (9.1)
Comprehensive	314,207 (47)
Academic	192,503 (28.8)
Integrated	99,588 (14.9)
RUCC area	
Metropolitan	596,762 (86.4)
Urban	83,194 (12)
Rural	10,529 (1.5)
ER-positive	564,151 (79.6)
PR-positive	488,483 (68.9)
HER2-positive[b]	38,494 (5.4)
Breast surgical procedure	
Partial mastectomy	422,916 (59.6)
Unilateral mastectomy	214,149 (30.2)
Bilateral mastectomy	71,587 (10.1)

(*continued in next column*)

Table 1. Demographic Characteristics From the NCDB Validation Cohort (cont.)

	NCDB Patients With Breast Cancer n (%)
Axillary surgical procedure	
None	856 (0.1)
SLNB (1–5 nodes)	418,738 (59.4)
ALND (6–10 nodes)	284,396 (40.4)
Chemotherapy	353,987 (49.9)
Endocrine therapy	475,063 (67)
Immunotherapy	5,182 (0.7)

Abbreviations: ALND, axillary lymph node dissection; ER, estrogen receptor; NCDB, National Cancer Database; PR, progesterone receptor; RUC, Rural-Urban Continuum Code; SLNB, sentinel lymph node biopsy.
[a]Race other than Black or White as per the NCDB dictionary (https://www.facs.org/media/brilfbgu/puf-2020-data-dictionary.pdf).
[b]HER2 information was not collected until 2010 in the NCDB.

2%–90.3%] vs estimated median survival of 88.4% [IQR, 79%–93.9%]; eFigure 6); those with stage I breast cancer (OS, 94.5% [95% CI, 94.4%–94.5%] vs estimated median survival of 92.4% [IQR, 85.6%–95.5%]; eFigure 7); those with grade 1 breast cancer (OS, 94.6% [95% CI, 94.5%–94.7%] vs estimated median survival of 94.5% [IQR, 90.1%–96.6%]; eFigure 8); those with ER-positive status (OS, 92% [95% CI, 91.9%–92%] vs estimated median survival of 90.8% [IQR, 83.9%–94.7%]; eFigure 9); those with HER2-negative status (OS, 90.6% [95% CI, 90.5%–90.7%] vs estimated median survival of 89.6% [IQR, 81.2%–94.3%]; eFigure 10); and those receiving adjuvant endocrine therapy only (OS, 93.1% [95% CI, 93%–93.2%] vs estimated median survival of 92.4% [IQR, 86.1%–95.4%]; eFigure 11). The model performed the worst in patients with high (2–3) Charlson-Deyo comorbidity

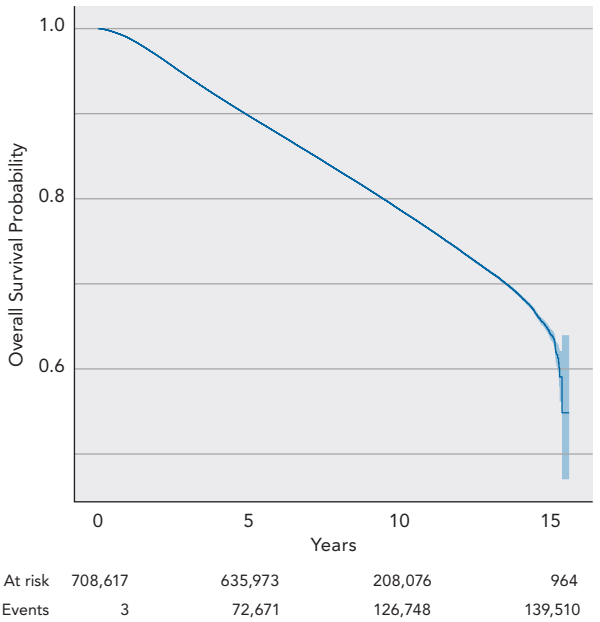

Figure 2. Kaplan-Meier curve demonstrating observed overall survival at 0, 5, 10, and 15 years for the National Cancer Database breast cancer population (2004–2012). Shaded area depicts the 95% CI.

Table 2. Observed 5- and 10-Year OS vs 5- and 10-Year Average and Median Estimated Survival by the PREDICT Tool

		5-Year Survival			10-Year Survival		
			PREDICT			PREDICT	
	n	NCDB Overall (95% CI)	Mean (95% CI)	Median (IQR)	NCDB Overall (95% CI)	Mean (95% CI)	Median (IQR)
All patients	708,652	89.7 (89.7–89.8)	84.4 (84.3–84.4)	88.3 (78.9–93.9)	78.7 (78.6–78.8)	69.4 (69.4–69.5)	73.8 (58.5–84.4)
Age							
<36 y	18,802	88.8 (88.4–89.3)	80.3 (80.1–80.5)	84 (73.6–91.1)	80.5 (79.9–81.2)	66 (65.7–66.3)	71.6 (54.1–81.5)
36–40 y	31,802	91.1 (90–91)	84.9 (84.7–85)	88.2 (79.5–94.9)	84.4 (84–84.9)	73 (72.8–73.2)	76.9 (63.8–87.2)
41–50 y	152,491	93.1 (93.1–93.4)	87.6 (87.6–87.7)	92.3 (83–96.2)	87.8 (87.6–88)	76.9 (76.9–77)	81.5 (69.4–90)
51–60 y	191,434	92.4 (92.3–92.6)	87 (86.9–87.1)	92 (82.5–95.3)	85.7 (85.5–85.9)	75.3 (75.2–75.4)	80.4 (68.3–87.9)
>60 y	314,123	86.3 (86.2–86.4)	81.4 (81.3–81.4)	85 (75.4–90.9)	69.1 (68.9–69.3)	62 (61.9–62.1)	65.6 (50.2–76.9)
Self-reported race							
White	599,174	90.2 (90.1–90.3)	84.7 (84.7–84.8)	88.7 (79.4–94)	79.1 (78.9–79.2)	69.7 (69.7–69.8)	74.2 (58.8–84.62)
Black	74,464	84.3 (84.1–84.6)	81 (80.9–81.1)	84.6 (74.5–92.2)	72.9 (72.5–73.3)	66.3 (66.1–66.4)	70.3 (54.8–81.1)
Other	27,796	93.3 (93–93.6)	85.1 (84.9–85.2)	89.2 (79.8–94.4)	86.1 (85.6–86.6)	71.1 (70.9–71.3)	75.5 (61–85.7)
Self-reported ethnicity							
Non-Hispanic	626,537	89.7 (89.7–89.8)	84.4 (84.4–84.5)	88.4 (78.9–93.9)	78.6 (78.5–78.7)	69.5 (69.4–69.5)	73.9 (58.6–84.4)
Hispanic	33,947	90.8 (90.5–91.1)	83.4 (83.2–83.5)	87.4 (77.6–93.6)	82.2 (81.7–82.7)	68.8 (68.5–69)	73.1 (57.7–83.9)
Charlson-Deyo score							
0–1	690,636	90.3 (90.2–90.3)	84.5 (84.4–84.5)	88.4 (79–93.9)	79.5 (79.4–79.7)	69.6 (69.6–69.7)	74.1 (58.8–84.5)
2–3	18,016	70.1 (69.5–70.8)	80.1 (79.8–80.3)	83.7 (73.1–90.9)	46.2 (45.3–47.1)	61.3 (61–61.6)	64.6 (47.2–77.5)
Facility type							
Community	61,114	86.7 (86.4–87)	83.5 (83.4–83.6)	87.4 (77.6–93.3)	73 (72.6–73.5)	67.5 (67.4–67.7)	71.9 (55.5–83)
Comprehensive	314,207	89.6 (89.5–89.7)	84.5 (84.4–84.5)	88.4 (79–93.8)	78 (77.8–78.2)	69.2 (69.2–69.3)	73.6 (58.2–84.2)
Academic	192,503	90.8 (90.7–91)	84.7 (84.6–84.8)	88.9 (79.4–94.1)	81.1 (80.9–81.4)	70.1 (70.1–70.2)	74.6 (59.7–84.9)
Integrated	99,588	89.9 (89.7–90.1)	84.7 (84.6–84.8)	88.6 (79.2–94)	78.4 (78.1–78.7)	69.8 (69.6–69.9)	74.1 (59–84.6)
RUCC area							
Metropolitan	596,762	90 (89.9–90)	84.4 (84.4–84.5)	88.4 (78.9–93.9)	79.2 (79.1–79.3)	69.6 (69.5–69.6)	74 (58.7–84.5)
Urban	83,194	88.3 (88.1–88.5)	83.9 (83.8–84)	87.8 (78.4–93.5)	75.8 (75.4–76.1)	68.6 (68.4–68.7)	72.8 (57.6–83.4)
Rural	19,499	88.1 (87.7–88.6)	83.6 (83.4–83.8)	87.5 (78.1–93.3)	75.2 (74.5–75.9)	68.1 (67.8–68.4)	72.2 (57.1–83.1)
Stage							
I	359,817	94.5 (94.4–94.5)	89.7 (89.7–89.7)	92.4 (85.6–95.5)	85.2 (85.1–85.4)	77.4 (77.4–77.5)	81 (70.8–88.4)
II–III	314,123	84.7 (84.5–84.8)	78.6 (78.6–78.7)	78.7 (71.4–89.9)	71.7 (71.5–71.9)	60.8 (60.7–60.8)	64.2 (48.2–75.7)
Histologic grade							
1	150,413	94.6 (94.5–94.7)	92.1 (92–92.1)	94.5 (90.1–96.6)	84.6 (84.4–84.8)	80.6 (80.4–80.6)	85.6 (74.9–91)
2	288,897	91.8 (91.7–91.9)	87.2 (87.2–87.3)	90.5 (83.3–94.2)	80 (79.8–80.2)	72.1 (72.1–72.2)	76.7 (63.3–85)
3	230,856	84 (83.8–84.1)	75.5 (75.4–75.5)	79 (68.5–85.8)	73.5 (73.3–73.7)	58.3 (58.3–58.4)	62.6 (46.4–73.1)
Unknown	35,300	90 (89.7–90.3)	87.6 (87.5–87.7)	90.4 (84–93.9)	78.1 (77.6–78.6)	73.1 (72.9–73.3)	77.8 (64.1–85.9)
ER status							
ER-positive	564,151	92 (91.9–92)	87.7 (87.6–87.7)	90.8 (83.9–94.7)	80.3 (80.2–80.4)	71.8 (71.8–71.9)	76.8 (61.7–86.1)
ER-negative	144,501	81.1 (80.9–81.3)	71.5 (71.4–71.6)	75.7 (64.4–82.1)	72.4 (72.1–72.6)	60 (59.9–60.1)	64.2 (49.4–73.5)

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Table 2. Observed 5- and 10-Year OS vs 5- and 10-Year Average and Median Estimated Survival by the PREDICT Tool (cont.)

		5-Year Survival			10-Year Survival		
			PREDICT			PREDICT	
	n	NCDB Overall (95% CI)	Mean (95% CI)	Median (IQR)	NCDB Overall (95% CI)	Mean (95% CI)	Median (IQR)
HER2 status[a]							
HER2-positive	38,494	90.8 (90.5–91.1)	77.6 (77.4–77.8)	81.6 (69.7–90)	80 (78.9–81.2)	60.8 (60.6–61)	64.5 (47.2–76.8)
HER2-negative	229,129	90.6 (90.5–90.7)	86 (85.9–86)	89.6 (81.2–94.3)	77.7 (77.1–78.3)	71.4 (71.3–71.5)	75.7 (61.8–85.2)
Unknown	441,029	89.2 (89.1–89.3)	84.1 (84.1–84.2)	88 (78.4–93.8)	78.2 (78.1–78.3)	69.1 (69.1–69.2)	73.6 (57.9–84.3)
Systemic therapy							
No chemo or endocrine therapy	97,300	84.1 (83.9–84.3)	83.6 (83.5–83.7)	87.1 (76.9–94)	69.6 (69.3–69.9)	67.8 (67.7–67.9)	72.6 (53.7–84.9)
Chemo only	136,289	82.5 (82.3–82.7)	73.9 (73.8–74)	77.6 (66.7–84)	74.5 (74.2–74.7)	61.7 (61.6–61.8)	65.7 (51.4–74.6)
Endocrine only	257,365	93.1 (93–93.2)	89.2 (89.2–89.3)	92.4 (86.1–95.4)	81.1 (80.9–81.3)	74.8 (74.7–74.9)	80.4 (66.2–88)
Chemo + endocrine	217,698	92.8 (92.7–92.9)	85.5 (85.5–85.6)	88.8 (81.3–93.2)	82.6 (82.4–82.8)	68.6 (68.5–68.7)	73.1 (58.6–82.7)
Immunotherapy	5,182	90.7 (89.9–91.5)	77.7 (77.3–78.2)	81.7 (69.7–89.9)	81.7 (80.5–83)	61.6 (61–62.1)	65 (49.2–76.8)

Abbreviations: Chemo, chemotherapy; ER, estrogen receptor; NCDB, National Cancer Database; OS, overall survival; RUCC, Rural-Urban Continuum Code.
[a]HER2 information was not collected until 2010 in the NCDB.

scores (OS, 70.1% [95% CI, 69.5%–70.8%] vs estimated median survival of 83.7% [IQR, 73.1%–90.9%]; eFigure 12), where PREDICT overestimated survival (Table 2).

10-Year OS

The observed 10-year OS for this NCDB cohort was 78.7% (95% CI, 78.6%–78.8%; Figure 2, Table 2), whereas the predicted 10-year median survival was 73.8% (IQR, 58.5%–84.4%), corresponding to an estimated AUC of 0.76 for the 10-year prediction (Figure 3).

According to the subgroup analysis, comparing the observed 10-year OS versus the 10-year predicted median survival by group, PREDICT performed best in women aged >60 years (OS, 69.1% [95% CI, 68.9%–69.3%] vs estimated median survival of 65.6% [IQR, 50.2%–76.9%]; supplemental eFigure 13); Black patients (OS, 72.9% [95% CI, 72.5%–73.3%] vs estimated median survival of 70.3% [IQR, 54.8%–81.1%]; eFigure 14); non-Hispanic patients (OS, 78.6% [95% CI, 78.5%–78.7%] vs estimated median survival of 73.9% [IQR, 58.6%–84.4%]; eFigure 15); patients treated at community-based facilities (OS, 73% [95% CI, 72.6%–73.5%] vs estimated median survival of 71.9% [IQR, 55.5%–83%]; eFigure 16); those from both urban (OS, 75.8% [95% CI, 75.4%–76.1%] vs estimated median survival of 72.8% [IQR, 57.6%–83.4%]; eFigure 17) and rural areas (OS, 75.2% [95% CI, 74.5%–75.9%] vs estimated median survival of 72.2% [IQR, 57.1%–83.1%]; eFigure 18); those with stage I breast cancer (OS, 85.2% [95% CI, 85.1%–85.4%] vs estimated median survival of 81% [IQR, 70.8%–88.4%]; eFigure 19); unknown histologic grade (OS, 78.1% [95% CI, 77.6%–78.6%] vs estimated median survival of 77.8% [IQR, 64.1%–85.9%]; eFigure 20); those with ER-positive status (OS, 80.3% [95% CI, 80.2%–80.4%] vs estimated median survival of 76.8% [IQR, 61.7%–86.1%]; eFigure 21); those with HER2-negative status (OS, 77.7% [95% CI, 77.1%–78.3%] vs estimated median survival of 75.7% [IQR, 61.8%–85.2%]; eFigure 22); and those receiving adjuvant endocrine therapy only (OS, 81.1% [95% CI, 80.9%–81.3%] vs estimated median survival of 80.4% [IQR, 66.2%–88%]; eFigure 23). Conversely, the model performed the worst in patients with high (2–3) Charlson-Deyo comorbidity scores (OS, 46.2% [95% CI, 45.3%–47.1%] vs estimated median survival of 64.6% [IQR, 47.2%–77.5%]; eFigure 24), where PREDICT overestimated survival (Table 2).

Sensitivity Analysis

In patients diagnosed with breast cancer after 2010 (n=180,815), only 5-year survival was analyzed because there are no patients with 10 years of follow-up in this cohort. The tool AUC for 5-year survival was 0.77. The observed 5-year OS for this NCDB cohort was 90.8% (95% CI, 90.6%–90.9%), whereas the predicted 5-year median survival was 88.9% (IQR, 80%–94%).

In patients with HER2-negative or unknown HER2 status (n=669,953), the 5-year OS was 89% (95% CI, 89.6%–89.8%), whereas PREDICT predicted a 5-year median survival of 88.6% (IQR, 79%–94%), performing an AUC of 0.78 at this time point. The observed 10-year OS for these patients was 78.7% (95% CI, 78.5%–78.8%),

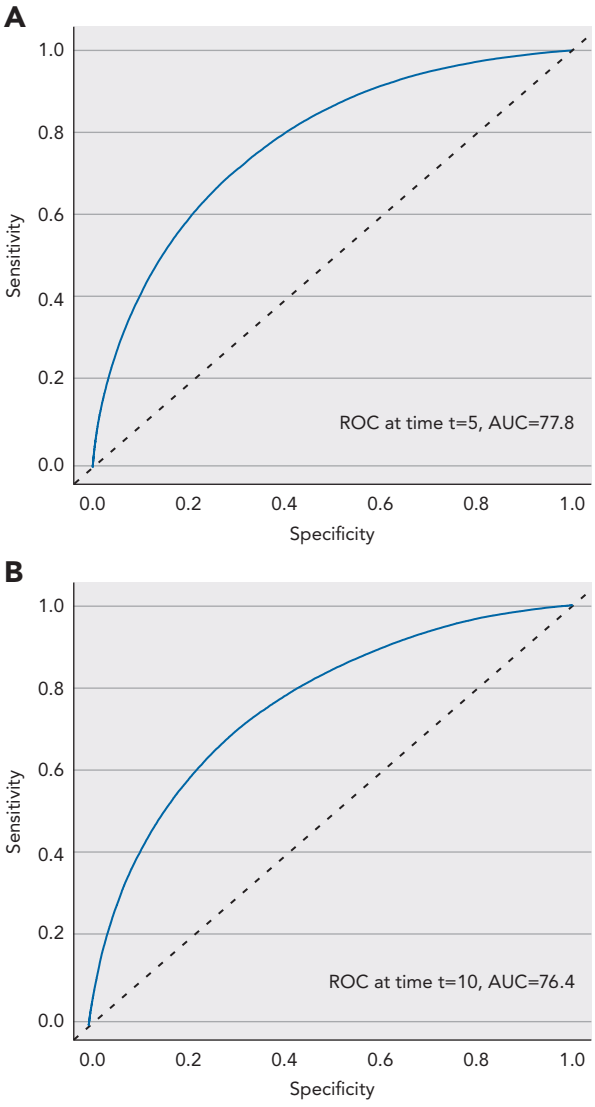

Figure 3. Time-dependent ROC curves for PREDICT—estimated versus actual—and AUC, **(A)** 5-year all-cause mortality and **(B)** 10-year all-cause mortality.
Abbreviations: AUC, area under the curve; ROC, receiver operating characteristic.

whereas the predicted 10-year median survival was 74.3% (IQR, 59.2%–84.7%), giving an AUC of 0.74 for the 10-year prediction.

Discussion

This is the first study to validate the PREDICT UK tool in a large US-based dataset of patients with breast cancer.[18] In routine clinical practice, one of the most common questions that patients with breast cancer and their families have is regarding the relative benefit of adjuvant chemotherapy or endocrine therapy on survival. Therefore, a clinical tool that can accurately estimate the benefit of different systemic therapies is useful for patients and providers alike. Our results, derived from >700,000 patients with breast cancer, confirmed that the PREDICT tool accurately predicted OS in an independent US dataset and can be incorporated into the routine clinical practice of medical oncologists.

In addition to our main findings, we demonstrated that PREDICT performance for both 5- and 10-year survival was worst in patients with high Charlson-Deyo scores, where PREDICT overestimated OS. Furthermore, 5-year OS predictions proved to be more accurate than the 10-year predictions. Moreover, interestingly, the tool performed better in Black patients when compared with White and other races, demonstrating that PREDICT may take into account some of the existing breast cancer health disparities.[19] The sensitivity analysis by year of diagnosis and HER2 status showed similar results from the main cohort.

Prior to the advent of PREDICT UK, Adjuvant! Online was the predominantly used prognostic tool that assisted with adjuvant therapy decision-making in women with early-stage breast cancer.[20] Adjuvant! was derived from SEER data, with estimates on the efficacy of adjuvant therapy based on the 1998 overviews of randomized trials of adjuvant therapy.[21] Prior studies have compared PREDICT to Adjuvant! and shown similar performance, although both were found to underestimate all-cause mortality for women aged ≤40 years in a Dutch dataset.[22] Currently, PREDICT is the only validated breast cancer prognostic model available online for adjuvant therapy decision-making. It is endorsed by the AJCC for having met its criteria for inclusion of risk models used for individualized prognosis in the practice of precision medicine.[23] Despite the endorsement by the AJCC, PREDICT is not widely used by most oncologists in the United States. Our work demonstrated that PREDICT performed well in a US breast cancer cohort as a prognostic tool.

PREDICT has also been validated in other countries and populations. In 2017, a study using data from the nationwide Netherlands Cancer Registry included 8,834 patients and, with an AUC range from 0.78 to 0.80, demonstrated that the tool predicted OS correctly in the majority of Dutch patients with breast cancer.[24] In 2018, with 45,789 records from the Scottish Cancer Registry, and an AUC range from 0.74 to 0.77, the tool was shown to be effective in estimating the benefit of adjuvant therapy and prognosis for women with early-stage breast cancer in the Scottish context.[6] In 2022, using 636 cases from the Kyushu University Hospital (Fukuoka, Japan), researchers concluded that PREDICT accurately estimated the 5- and 10-year OS in the overall Japanese study population.[25] In addition to being validated in other countries, the tool has also validated in older patients with breast cancer and accurately predicted 5-year OS in a cohort of 2012 patients with a median age of 75 years.[26]

Despite good results in multiple countries and populations, PREDICT has limitations. For example, prior

work has shown that PREDICT underestimates breast cancer mortality risk in younger women diagnosed before the age of 40 years, which was corroborated by our work.[27] In previous versions, the model did not approach tumor size or nodal involvement as a continuous mortality risk but as discrete categories (ie, an 18-mm or 19-mm tumor can be predicted to have the same mortality, whereas a 19-mm tumor would have a different risk estimation than a 20-mm tumor), but this has been corrected in later PREDICT versions.[10,28]

Even with the availability of genomic tests, such as Oncotype DX and MammaPrint, tools such as PREDICT that can provide accurate estimates of clinical risk still have value. Genomic tests still require a clinical context for proper interpretation of the overall molecular risk score. In other words, the clinical utility of genomic tests is not that they replace clinicopathologic factors but that they help to refine clinical estimates of breast cancer recurrence risk and better predict which patients are likely to benefit from adjuvant chemotherapy. For example, the MINDACT trial used Adjuvant! to quantify clinical risk.[29] In this regard, genomic tests provide information that is complementary to clinical estimates of breast cancer recurrence or mortality and help identify the population of patients with clinically high-risk breast cancer in whom de-escalation of adjuvant systemic therapy would not impair clinical outcomes. Moreover, PREDICT attempts to cover a broader array of clinical scenarios and treatments than adjuvant chemotherapy. The value of this study, therefore, was to validate the accuracy of PREDICT as a clinical tool in a large and diverse cohort of patients treated in the United States.

Our study has several limitations. First, the NCDB does not include information on local regional recurrence and disease-free survival; thus, OS is the only quantifiable clinical outcome. Second, the NCDB does not collect cancer-specific mortality; therefore, it is impossible to determine whether discrepancies between PREDICT and actual outcomes are due to breast cancer–specific mortality or to non–cancer-related mortality. Third, the NCDB does not provide any detailed granular treatment data regarding the type or duration of either adjuvant chemotherapy or endocrine therapy, which could impact recurrence and survival if the entire treatment regimen was not able to be completed. Ki-67 is also not collected in the NCDB and, therefore, could not be factored into our analyses. However, PREDICT UK does not require input of Ki-67 to estimate recurrence, and functions without Ki-67. Moreover, Ki-67 is not widely used in the United States and remains somewhat controversial as a prognostic factor, with substantial heterogeneity in assessment methods, and may not provide information that is independent of grade.[30,31] In addition, our study excluded patients who received neoadjuvant therapy, which is currently considered the standard of care for most cases involving triple-negative or HER2-positive breast cancer. Despite these limitations, these data suggest that PREDICT UK is a clinically useful and free tool that should be more widely used in the United States for adjuvant therapy decision-making. Additionally, the advantage of using the NCDB for PREDICT validation is the sheer size of this database and long-term follow-up, which enhances the overall generalizability and reliability of the results.

Conclusions

Results of our study show the successful validation of the PREDICT tool in the NCDB dataset of patients with breast cancer and its ability to accurately predict 5- and 10-year OS in a contemporary population of US patients with early-stage breast cancer. Therefore, we have shown that PREDICT is a clinically useful tool that can be routinely used by medical oncologists as part of their decision-making and estimation of clinical risk and the impact of breast cancer adjuvant therapies on OS.

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Supplemental online content for:

Validation of the PREDICT Prognostication Tool in US Patients With Breast Cancer

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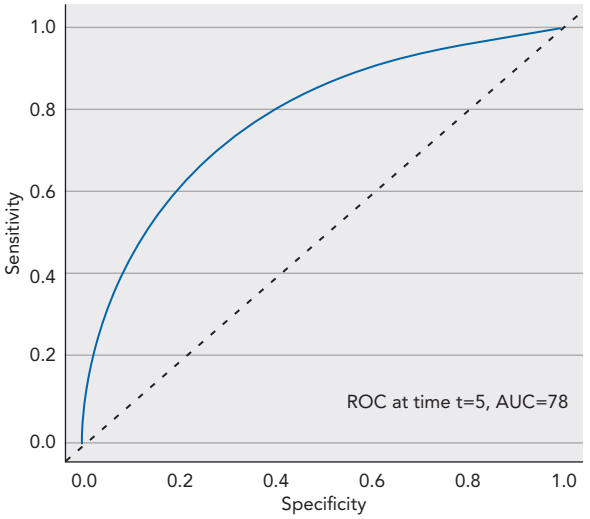
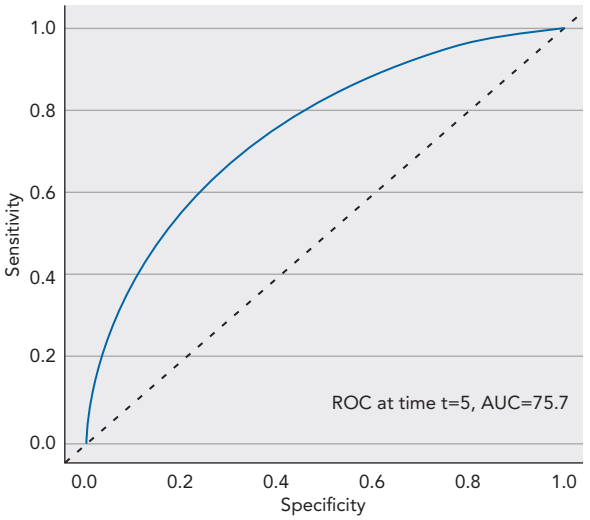
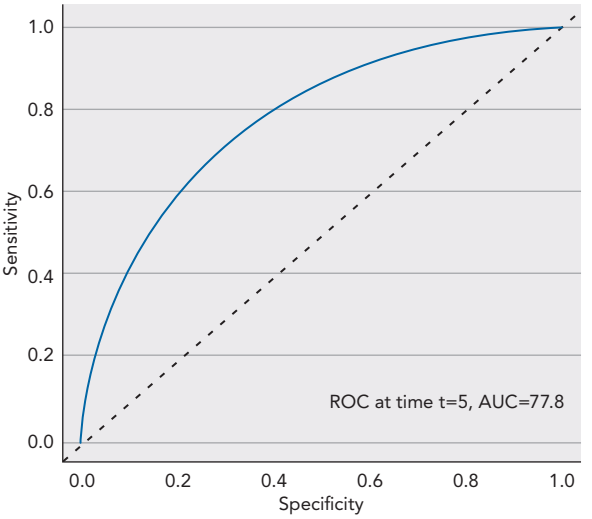


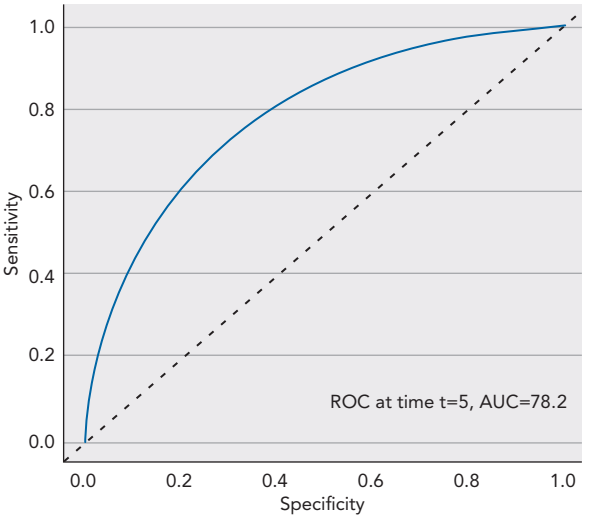
eFigure 1. Time-dependent receiver operating characteristic (ROC) curves for PREDICT—estimated vs actual—and area under the curve (AUC) in women aged 51–60 years, 5-year all-cause mortality.



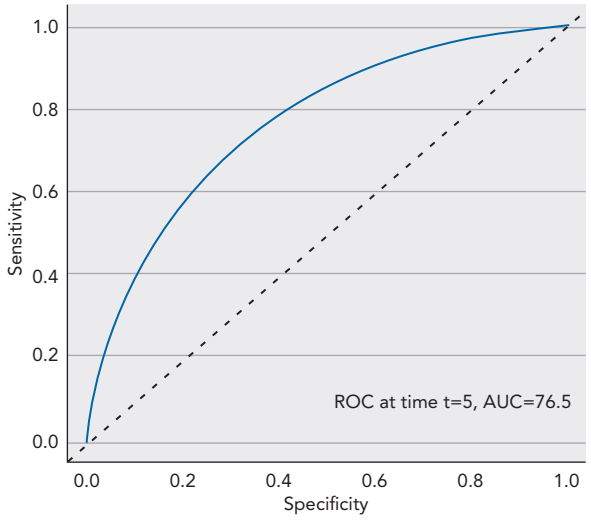
eFigure 2. Time-dependent receiver operating characteristic (ROC) curves for PREDICT—estimated vs actual—and area under the curve (AUC) in Black patients, 5-year all-cause mortality.



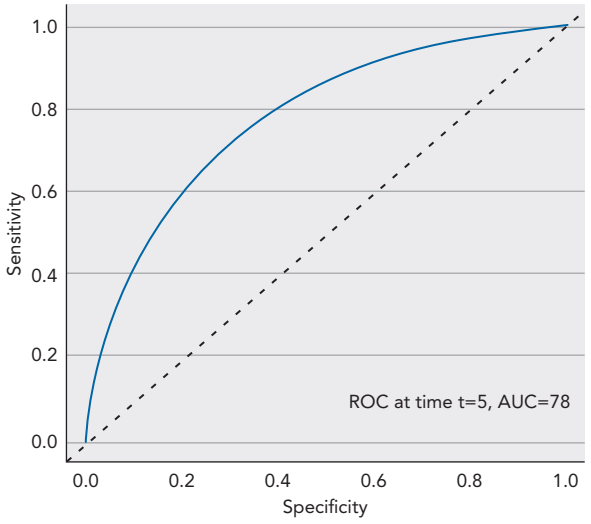
eFigure 3. Time-dependent receiver operating characteristic (ROC) curves for PREDICT—estimated vs actual—and area under the curve (AUC) in non-Hispanic patients, 5-year all-cause mortality.



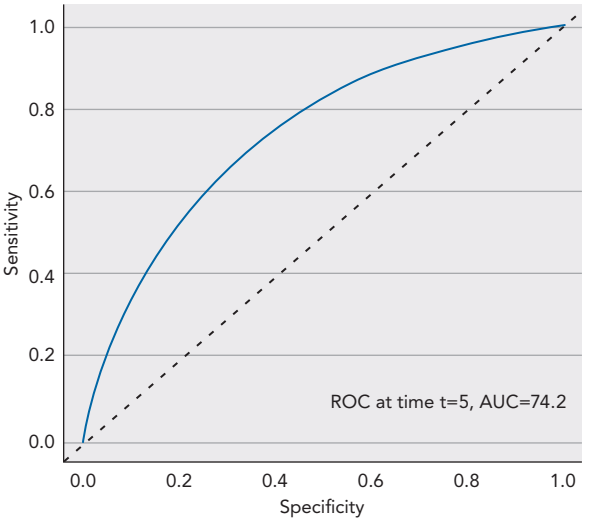
eFigure 4. Time-dependent receiver operating characteristic (ROC) curves for PREDICT—estimated vs actual—and area under the curve (AUC) in patients from comprehensive facilities, 5-year all-cause mortality.



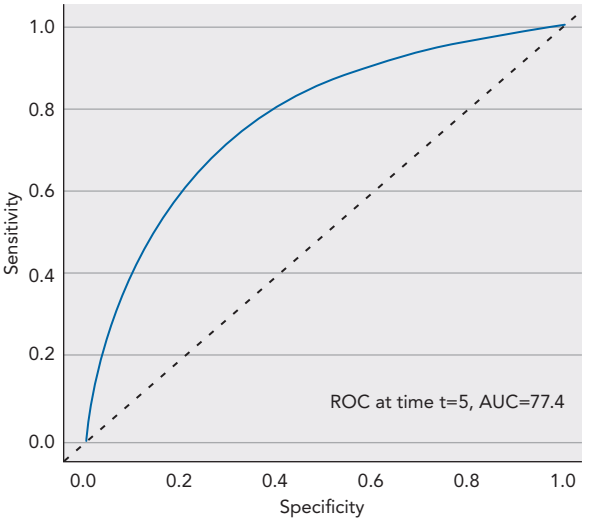
eFigure 5. Time-dependent receiver operating characteristic (ROC) curves for PREDICT—estimated vs actual—and area under the curve (AUC) in patients from urban areas, 5-year all-cause mortality.



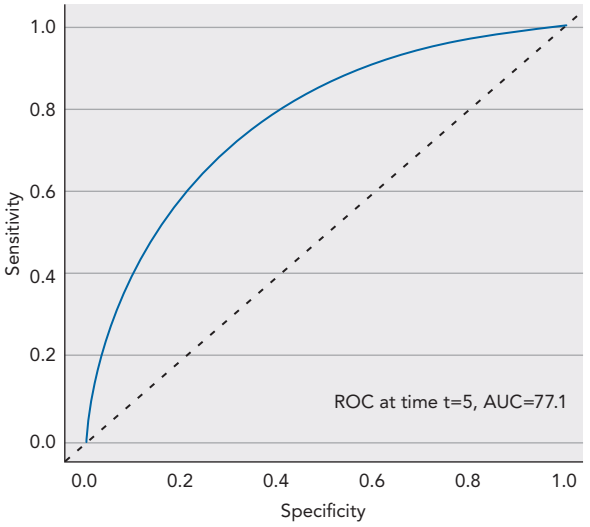
eFigure 6. Time-dependent receiver operating characteristic (ROC) curves for PREDICT—estimated vs actual—and area under the curve (AUC) in patients with low (0–1) Charlson-Deyo comorbidity score, 5-year all-cause mortality.



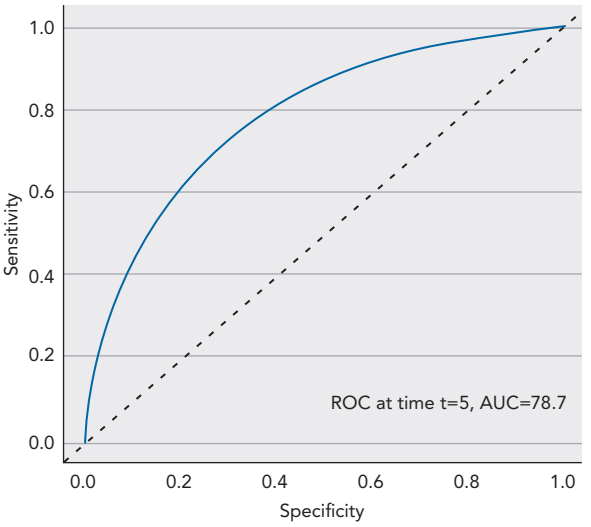
eFigure 7. Time-dependent receiver operating characteristic (ROC) curves for PREDICT—estimated vs actual—and area under the curve (AUC) in patients with stage I breast cancer, 5-year all-cause mortality.



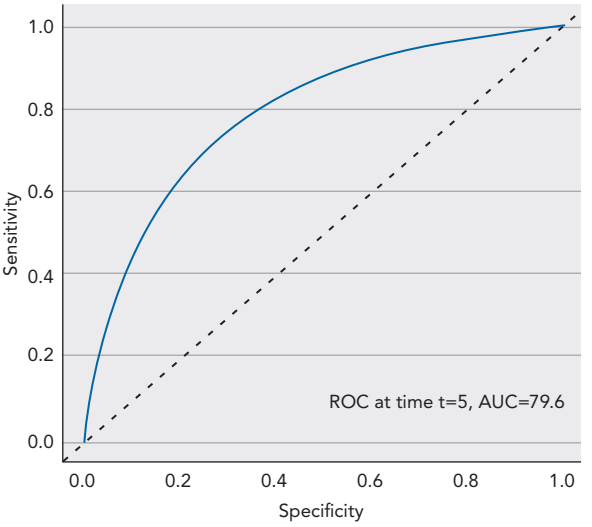
eFigure 8. Time-dependent receiver operating characteristic (ROC) curves for PREDICT—estimated vs actual—and area under the curve (AUC) in patients with grade 1 breast cancer, 5-year all-cause mortality.



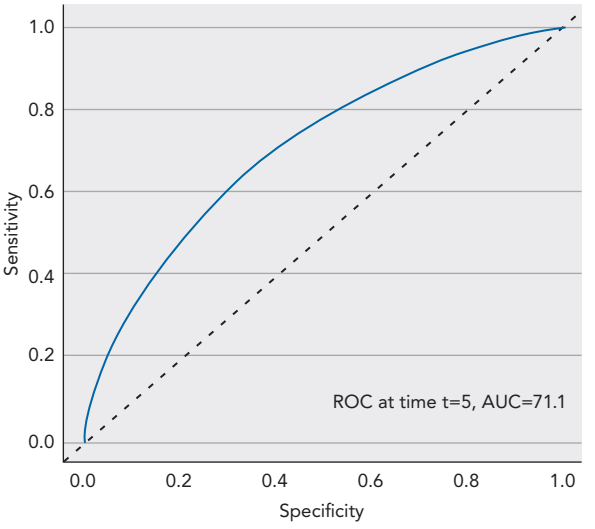
eFigure 9. Time-dependent receiver operating characteristic (ROC) curves for PREDICT—estimated vs actual—and area under the curve (AUC) in patients with estrogen receptor–positive breast cancer, 5-year all-cause mortality.



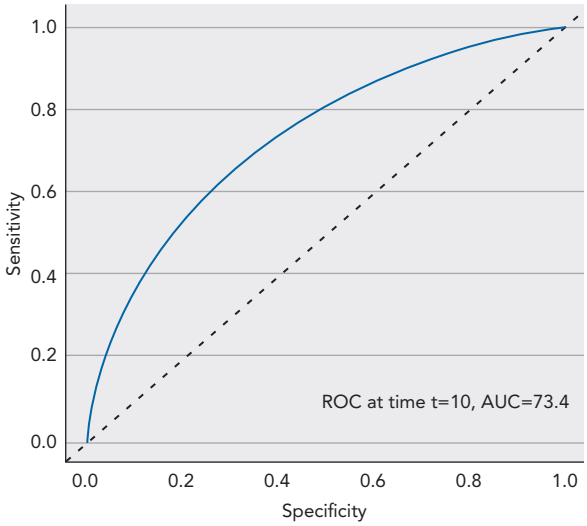
eFigure 10. Time-dependent receiver operating characteristic (ROC) curves for PREDICT—estimated vs actual—and area under the curve (AUC) in patients with HER2-negative breast cancer, 5-year all-cause mortality.



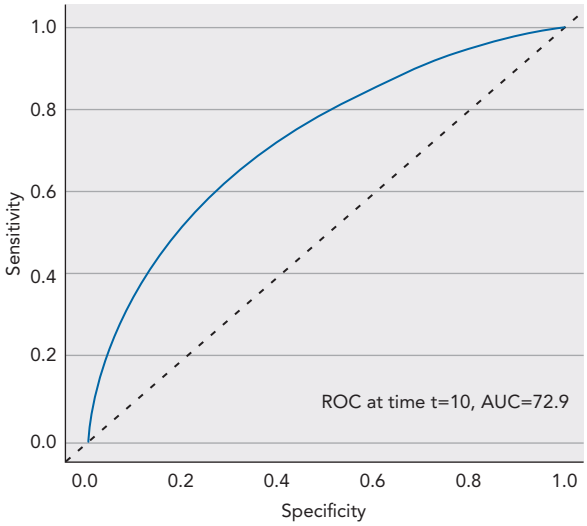
eFigure 11. Time-dependent receiver operating characteristic (ROC) curves for PREDICT—estimated vs actual—and area under the curve (AUC) in patients with breast cancer receiving adjuvant endocrine therapy only, 5-year all-cause mortality.



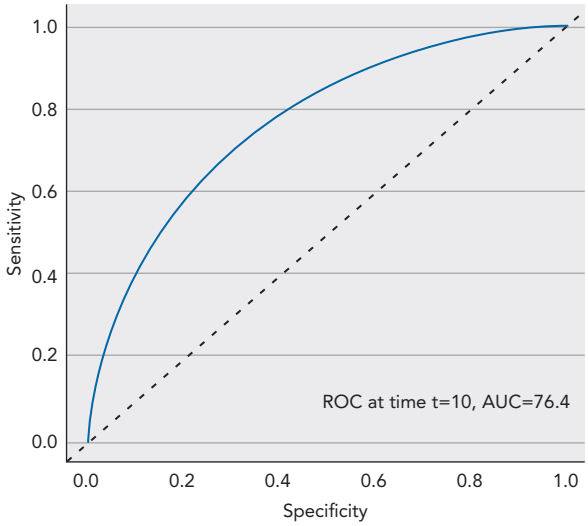
eFigure 12. Time-dependent receiver operating characteristic (ROC) curves for PREDICT—estimated vs actual—and area under the curve (AUC) in patients with high (2–3) Charlson-Deyo comorbidity score, 5-year all-cause mortality.



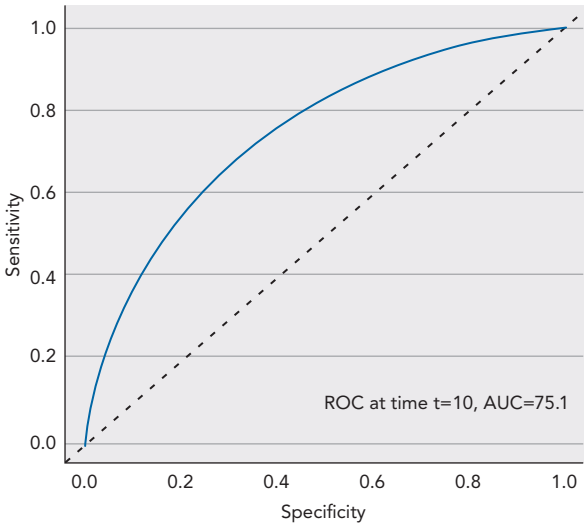
eFigure 13. Time-dependent receiver operating characteristic (ROC) curves for PREDICT—estimated vs actual—and area under the curve (AUC) in women aged >60 years, 10-year all-cause mortality.



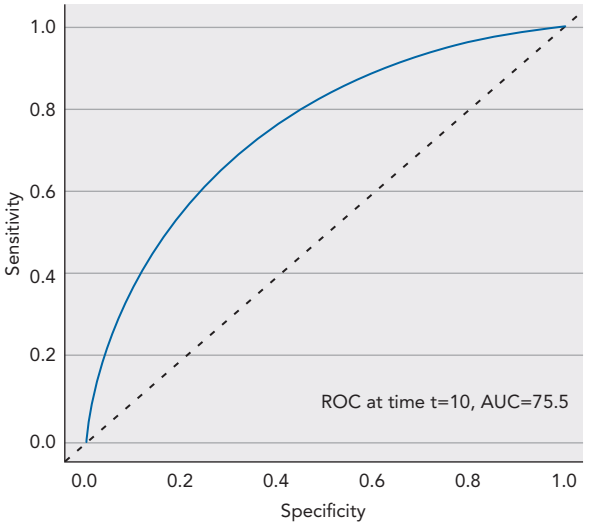
eFigure 14. Time-dependent receiver operating characteristic (ROC) curves for PREDICT—estimated vs actual—and area under the curve (AUC) in Black patients, 10-year all-cause mortality.



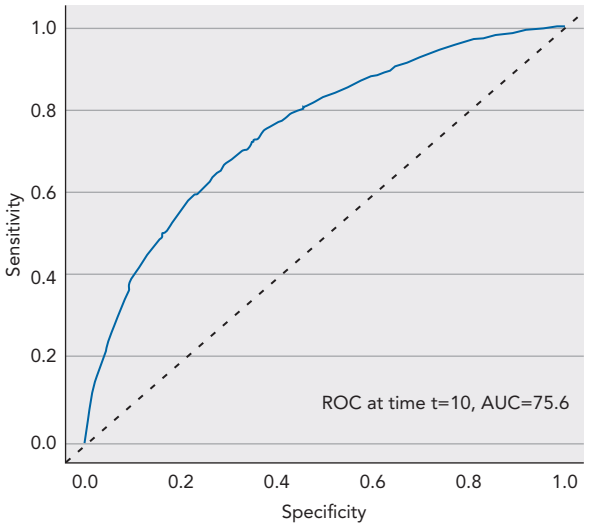
eFigure 15. Time-dependent receiver operating characteristic (ROC) curves for PREDICT—estimated vs actual—and area under the curve (AUC) in non-Hispanic patients, 10-year all-cause mortality.



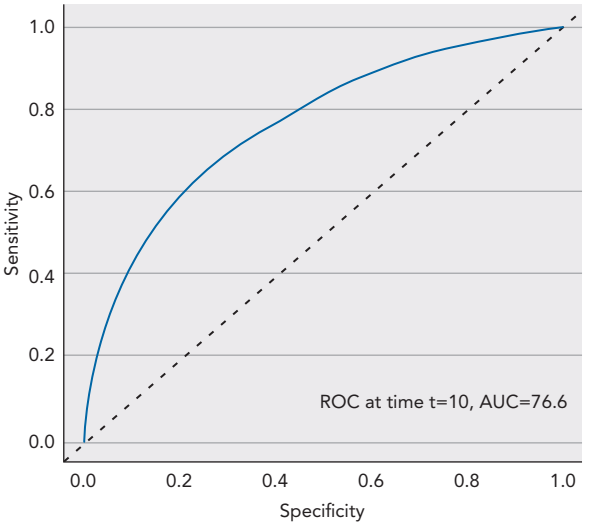
eFigure 16. Time-dependent receiver operating characteristic (ROC) curves for PREDICT—estimated vs actual—and area under the curve (AUC) in patients treated at community-based facilities, 10-year all-cause mortality.



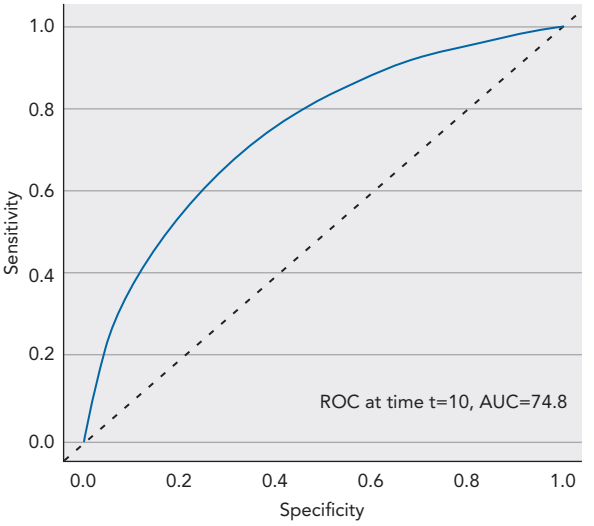
eFigure 17. Time-dependent receiver operating characteristic (ROC) curves for PREDICT—estimated vs actual—and area under the curve (AUC) in patients from urban areas, 10-year all-cause mortality.



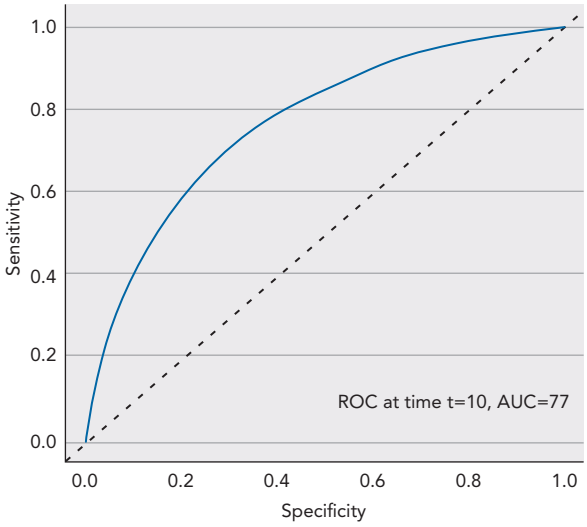
eFigure 18. Time-dependent receiver operating characteristic (ROC) curves for PREDICT—estimated vs actual—and area under the curve (AUC) in patients from rural areas, 10-year all-cause mortality.



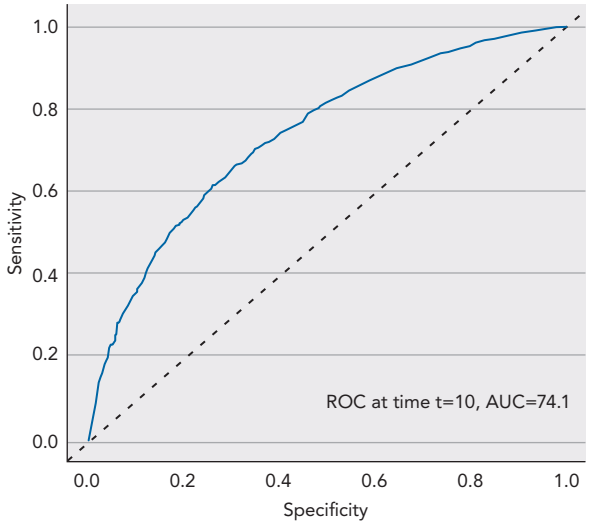
eFigure 19. Time-dependent receiver operating characteristic (ROC) curves for PREDICT—estimated vs actual—and area under the curve (AUC) in patients with stage I breast cancer, 10-year all-cause mortality.



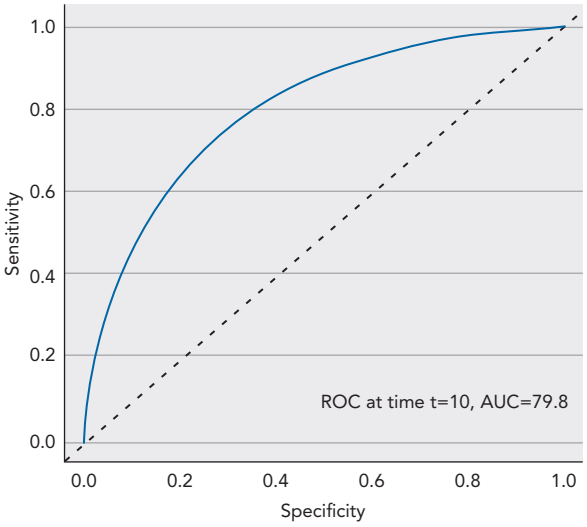
eFigure 20. Time-dependent receiver operating characteristic (ROC) curves for PREDICT—estimated vs actual—and area under the curve (AUC) in patients with unknown-grade breast cancer, 10-year all-cause mortality.



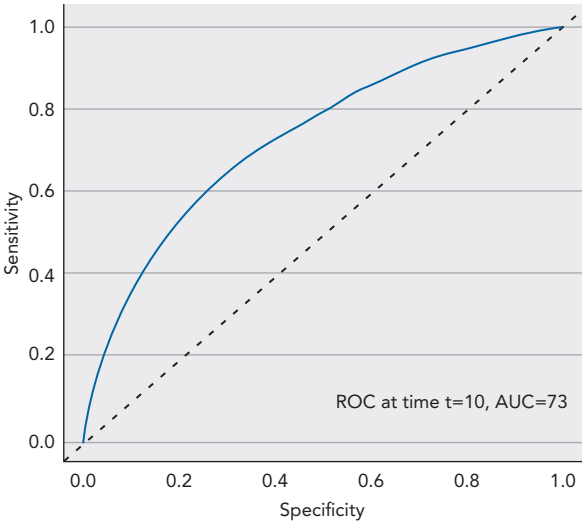
eFigure 21. Time-dependent receiver operating characteristic (ROC) curves for PREDICT—estimated vs actual—and area under the curve (AUC) in patients with estrogen receptor–positive breast cancer, 10-year all-cause mortality.



eFigure 22. Time-dependent receiver operating characteristic (ROC) curves for PREDICT—estimated vs actual—and area under the curve (AUC) in patients with HER2-negative breast cancer, 10-year all-cause mortality.



eFigure 23. Time-dependent receiver operating characteristic (ROC) curves for PREDICT—estimated vs actual—and area under the curve (AUC) in patients with breast cancer receiving adjuvant endocrine therapy only, 10-year all-cause mortality.



eFigure 24. Time-dependent receiver operating characteristic (ROC) curves for PREDICT—estimated vs actual—and area under the curve (AUC) in patients with high (2–3) Charlson-Deyo comorbidity score, 10-year all-cause mortality.