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ORIGINAL ARTICLE

Validation of PREDICT tool v2.2 in patients with early-stage breast cancer enrolled in the GIM and MIG trials

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Background: PREDICT v2.2 is a prognostic tool used to estimate 5- and 10-year overall survival (OS) rates in early-stage breast cancer (BC). While it has been validated in several populations, limited data exist on its performance in cohorts derived from randomized clinical trials.

Materials and methods: This study analyzed individual data from patients with early-stage BC enrolled in five phase III randomized clinical trials conducted by the Gruppo Italiano Mammella (GIM) and Mammella InterGruppo (MIG) between 1992 and 2012. Patients with stage IV disease, prior neoadjuvant therapy, or missing data were excluded. PREDICT v2.2 was used to calculate 5- and 10-year OS predictions. Observed survival was derived using Kaplan—Meier estimates, and the model's calibration and discriminatory accuracy were evaluated.

Results: Among the 6205 patents included, the median predicted 5-year OS was 87.1%, while the observed 5-year OS was 93.0%, resulting in an underestimation of 5.6% [95% confidence interval (CI) 5.0% to 6.3%]. Similarly, the predicted 10-year OS was 73.8%, compared with an observed OS of 82.1%, with an underestimation of 8.3% (95% CI 7.2% to 9.4%). Discrimination was moderate, with area under the curve values of 66.2% (95% CI 63.5% to 68.9%) at 5 years and 63.9% (95% CI 61.7% to 66.1%) at 10 years. Subgroup analyses revealed that underestimations were more pronounced in patients with human epidermal growth factor 2-positive tumors, larger tumor sizes, or older age.

Conclusions: PREDICT v2.2 underestimates 5- and 10-year OS in a clinical trial-derived population of early-stage BC patients. Despite reasonable accuracy, its performance is influenced by specific patient and tumor characteristics. Regular updates are necessary to ensure its applicability in contemporary clinical practice.

Key words: early-stage breast cancer, HER2, prognostic model, PREDICT tool, overall survival, validation study

INTRODUCTION

Breast cancer is the most common cancer worldwide and its incidence has been increasing by ∼0.5% annually in the past 20 years.[1] However, advancements in screening have increased the proportion of cases identified in the early setting, making early therapeutic choices crucial. Consequently, over the years, free online tools have been developed to assist patients and physicians in therapeutic decision making.[2]

PREDICT (http://www.predict.nhs.uk/) is an online, free-access, prognostic tool designed to calculate the potential impact of different post-surgical interventions on patients with early-stage invasive breast cancer. This tool is based on clinical and pathological data and treatment options available to calculate patients' estimated overall survival (OS) rates at 5, 10, and 15 years, both with and without the effect of adjuvant therapies such as systemic chemotherapy, endocrine therapy, trastuzumab, and bisphosphonates.[3]

The first version of the PREDICT tool, version 1.0, was developed in 2010 based on cancer registry data from 5694

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women diagnosed with breast cancer from 1999 to 2003 in East Anglia, UK.[3] Subsequent versions of PREDICT have been improved by incorporating additional features, including other clinical information, histological characteristics, and therapeutic options. The first improvement to the tool integrated the status of human epidermal growth factor 2 (HER2) and accounted for the potential effects of trastuzumab treatment.[4] Later additions included Ki-67,[5] and adjustments were made to refine inputs such as the age at diagnosis, precise tumor size in millimeters, and the number of positive lymph nodes.[6,7] The tool has also expanded to include bisphosphonates as a treatment option and to provide survival outcomes up to 15 years. In the most recent versions of PREDICT (v2.2), a further option was introduced to include the effect of the extended adjuvant endocrine therapy after the first 5 years; moreover, an upcoming update will also incorporate the progesterone receptor status[8] and include the benefit from adjuvant radiotherapy.[9]

Several studies over the past decades have been carried out to validate different versions of the PREDICT tool, highlighting not only its potential but also some limitations, particularly in some subgroups such as young patients or those with HER2-positive disease.[10-12] Few studies, however, have to date attempted to validate the latest version of the PREDICT tool using a patient population collected from randomized clinical trials.

The present study aimed to validate the prognostic performance of PREDICT tool v2.2 using individual data of patients enrolled in five adjuvant randomized clinical trials from the Gruppo Italiano Mammella (GIM) and Mammella InterGruppo (MIG).

MATERIALS AND METHODS

Study design and patients

The current analysis used individual patient-level data from patients diagnosed with early breast cancer enrolled in five adjuvant phase III randomized trials conducted by the MIG and GIM study groups (i.e. MIG1,[13] MIG5,[14] GIM2,[15] GIM3,[16] and GIM6[17] trials). Details of these trials have been previously reported. Briefly, MIG1 was an open-label, multicenter, phase III randomized trial that compared standard versus dose-dense adjuvant anthracycline-based chemotherapy in high-risk early breast cancer patients.[13] MIG5 was a multicenter, randomized phase III trial including patients with node-positive early breast cancer who received either six cycles of fluorouracil, epirubicin, and cyclophosphamide (FEC) or four cycles of epirubicin and paclitaxel (NCT02450058).[14] GIM2 was a multicenter, randomized phase III trial with a 2 $\times$ 2 factorial design, evaluating the efficacy and safety of adjuvant anthracycline and taxane-based chemotherapy with or without the inclusion of fluorouracil. Treatments were administered with a dose-dense schedule or a standard-interval schedule in node-positive breast cancer patients (NCT00433420).[15] GIM3 was a multicenter, randomized phase III trial comparing three aromatase inhibitors (letrozole versus anastrozole versus exemestane) and the upfront versus switch (after 2 years of tamoxifen) treatment strategy in postmenopausal women diagnosed with hormone receptor (HR)-positive early breast cancer (NCT00541086).[16] In the phase III randomized GIM6 trial, premenopausal patients aged 18-45 years with stage I-III early breast cancer candidates for (neo)adjuvant CT were randomly assigned to receive chemotherapy alone or combined with the gonadotropin-releasing hormone agonist triptorelin.[17] Detailed summaries of MIG/GIM trials are presented in Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2025.105924. The independent review boards of all participating centers approved each trial, and all included patients provided written informed consent before study entry. The MIG and GIM steering committees approved the present analysis before its conduction. For the present analysis, we included women diagnosed with primary unilateral invasive breast cancer from 1992 to 2012 enrolled in one of the MIG/GIM trials and who had a minimum of 5 years of follow-up. Because enrollment of each trial was open to patients of any age, we further excluded patients $<$25 or $>$85 years of age as PREDICT is not applicable in these age categories. Further exclusion criteria included individuals with stage IV breast cancer, those who did not undergo definitive breast surgery, patients who received prior neoadjuvant therapy (either endocrine therapy or chemotherapy), males, and those lacking essential clinical data required for calculating PREDICT scores or missing follow-up information.

Objectives and outcomes

The primary objective of this study was to assess the prognostic accuracy of the PREDICT v2.2 model for 5- and 10-year survival outcomes in patients with early-stage breast cancer undergoing adjuvant treatment within an Italian cohort of patients from five MIG/GIM randomized clinical trials. Secondary objectives included evaluating PREDICT v2.2 model for 5- and 10-year outcomes according to breast cancer subtypes (i.e. luminal-like, HER2-positive, and triple-negative breast cancer), body mass index (BMI) categories (BMI $<$ 18.5 kg/m^2: underweight, BMI 18.5-24.9 kg/m^2: normal weight, BMI $\geq$ 25.0 kg/m^2: overweight, BMI $\geq$ 30.0 kg/m^2: obesity), and age groups (i.e. $\leq$40 years, 41-64 years, and $\geq$65 years). Additionally, patients were categorized based on chemotherapy regimen and trastuzumab exposure. Main outcome was the 5- and 10-year OS defined according to the Standardized Definitions for Efficacy Endpoints (STEEP) criteria version 2.0.[18]

Data extraction

PREDICT estimates for each patient were calculated using adapted scripts from the PREDICT v2.2 model, written in R and maintained by Prof. Paul Pharoah. The full implementation is available at https://github.com/WintonCentre. Patient and tumor characteristics, as well as administered adjuvant treatments, were entered in the PREDICT v2.2 program to calculate the predicted 5-year and 10-year OS for each patient according to actual treatment received.

Statistical analysis

This analysis should be considered exploratory, as it was not pre-specified in any of the study protocols. The prognostic performance of the PREDICT model was evaluated using two endpoints: (i) calibration, which assesses the agreement between predicted and observed survival rates, and (ii) discriminatory accuracy, reflecting the model's ability to differentiate between individuals who will survive 5 and/or 10 years and those who will not. This captures the model's capacity to distinguish patients with favorable versus unfavorable prognoses at an individual level. The observation period for each patient was defined from the date of randomization until the occurrence of an OS event. The median predicted OS at 5 and 10 years was calculated using individual predictions from PREDICT v2.2. Calibration was assessed by comparing the median predicted 5-year survival probabilities generated by PREDICT with observed 5-year survival rates derived from Kaplan–Meier estimates. Using the standard error from the Kaplan–Meier estimates, 95% confidence interval (CI) was calculated for the difference between predicted and observed 5- and 10-year survival rates. Calibration plots were constructed to visually compare mean predicted survival with observed outcomes across deciles of predicted probabilities. Discriminatory accuracy was evaluated by calculating the area under the receiver operating characteristic curve (AUC) with a corresponding 95% CI for 5- and 10-year predicted OS. The AUC quantifies the probability that a randomly chosen patient who survived 5 years has a higher predicted survival probability than a patient who did not. Higher AUC values indicate greater model accuracy in identifying patients with favorable survival outcomes. Subgroup analyses were carried out to examine the prognostic utility of PREDICT based on variables such as anti-HER2 treatment type, BMI status, chemotherapy regimen, age at diagnosis, HR status, pathological nodal involvement, and tumor size. Only complete cases were included and no methods for handling missing values were used. All statistical analyses were conduced using R software version 4.4.2 (R Core Team, R Foundation for Statistical Computing, Vienna, Austria; 2024).

RESULTS

Patient and treatment characteristics

Between 1992 and 2012, overall, 8379 patients were randomized in the MIG1, MIG5, GIM2, GIM3, and GIM6 trials. After the exclusion of 2119 patients, 6205 were finally included in the present analysis (Figure 1). Baseline characteristics are reported in Table 1. Overall, the median age at breast cancer diagnosis was 57 years [interquartile range (IQR) 48-65 years]. The majority of patients ($n = 4412$, 71.1%) were postmenopausal at diagnosis, and ductal carcinoma was the most common histological type (81.0%, $n = 4982$). Luminal-like breast cancer was identified in 60.3% ($n = 3743$) of cases, while T1 tumors were the most prevalent ($n = 3726$, 60.0%). Regarding baseline BMI, 40.7% ($n = 2525$) of patients were classified as having a normal weight.

After a median follow-up of 9.3 years (IQR 5.9-14.8 years), 1083 deaths were observed.

Discrimination

The AUC was 66.2% (95% CI 63.5% to 68.9%) in the overall population for the 5-year prediction, and it was 63.9% (95% CI 61.7% to 66.1%) in the overall population for the 10-year prediction (Figure 2A and B). This finding of suboptimal discriminatory accuracy was consistent across all subgroups.

Calibration

Overall, predicted and observed 5-year OS were 87.1% and 93.0%, respectively, with a difference of 5.6% (95% CI 5.0% to 6.3%) (Table 2), indicating that the PREDICT score underestimated 5-year OS (Figure 2C and D). Similarly, predicted and observed 10-year OS were 73.8% and 82.1%, respectively, with a difference of 8.3% (95% CI 7.2% to 9.4%) (Table 2), with 60% and 93% of the expected events, respectively, observed (calibration intercepts −0.50 and −0.08) (Figure 2C and D). PREDICT assigned a higher-risk category to patients who experienced early events in 62% of cases (C-index 0.62, 95% CI 0.58-0.65). The underestimation was consistent across all subgroups, with poorer predictive performance for patients with older age, HER2-positive disease, or larger tumor size (Figure 3). In particular, among patients stratified by subgroup, the largest OS underestimation at 10 years was observed in HER2-positive disease, where the difference between observed and predicted OS was 13.5%. Similarly, for patients with triple-negative breast cancer and HR-positive/HER2-negative disease, the difference was in both cases 7.9%. Among older patients (>60 years of age), the discrepancy was particularly pronounced (12.3%) compared with those aged 41-64 years and <40 years, where the differences were 6.6% and 4.1%, respectively. Additionally, OS underestimation was more evident in obese patients, with a 10-year observed–predicted difference of 8.7%, followed by overweight (7.9%) and normal-weight patients (7.5%). The predicted and observed OS outcomes at 5 and 10 years, stratified by all analyzed subcategories, are reported in Table 2.

DISCUSSION

Our results indicate that PREDICT v2.2 underestimates OS both at 5 and 10 years. We found a consistent pattern of survival underestimation in different cohorts of patients. Specifically, the overall observed 5-year OS rate was 93.0%, higher than the predicted rate of 87.1%; similarly, at 10 years, the observed OS rate of 82.1% exceeded the predicted rate of 73.8% by 8.3%. To the best of our knowledge, this is the largest analysis of a population collected from several prospective clinical trials with the aim of validating the PREDICT model v2.2.

Multiple studies have validated PREDICT across different cohorts of patients with early-stage breast cancer. In the

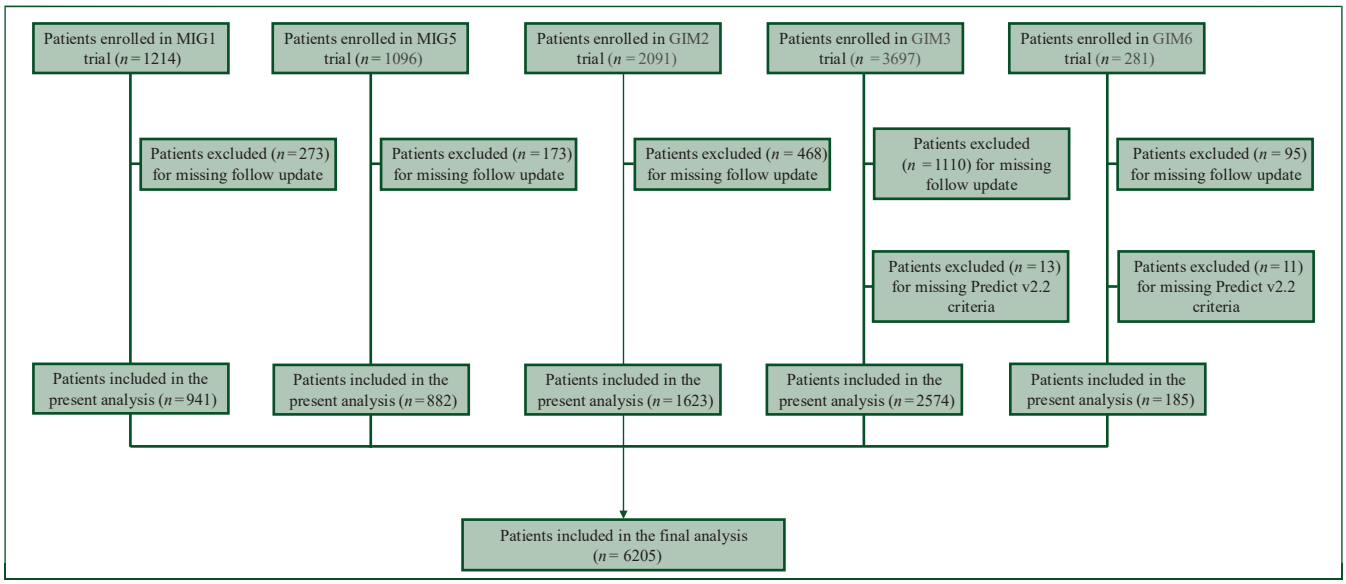

Figure 1. STROBE flowchart representing the patient selection process.
STROBE, Strengthening the Reporting of Observational Studies in Epidemiology; GIM, Gruppo Italiano Mammella; MIG, Mammella InterGruppo.

initial versions of PREDICT, most validation studies revealed an overestimation of predicted OS compared with observed outcomes.[19–21] Contrarily, validation studies utilizing v2.0 or later demonstrated that PREDICT tends to underestimate OS at both 5 and 10 years.[10,12,22–26] Among these, only one study employing v2.0 or later reported observed OS lower than predicted. Notably, in this study, the cohort consisted of only elderly patients (age ≥65 years) recruited between 1997 and 2004; this may explain why in this study PREDICT did overestimate OS.[25] This discrepancy between earlier and more recent versions of PREDICT can be attributed to key updates introduced in v2.0. Specifically, v2.0 incorporated criteria such as the precise tumor size in millimeters, the exact number of positive lymph nodes, the presence of lymph node micrometastases, and an extended follow-up period.

One of the key differences between our study and previous validation studies of PREDICT v2.0 or later versions is that our study included patients enrolled in randomized clinical trials. In contrast, most prior studies involved patients from national registries, thus including a population reflecting more clinical practice. This distinction is significant because patients in clinical trials are candidates for receiving experimental treatments and are closely monitored.[27] While national registries may include a larger number of patients, there is often a substantial variation in patient characteristics within the overall cohort, and treatment protocols can vary significantly between different institutions. Examining specific subgroups, the underestimation of OS appeared to be more pronounced than that observed in the overall cohort.

A key finding of our study is the suboptimal performance of PREDICT in the specific population of patients with HER2-positive disease. Two main aspects might explain this limitation. The first one to consider is whether the population used to validate the PREDICT tool represents the population we usually treat in daily clinical practice. The second one is that the rapid evolution of HER2-targeted therapies has dramatically improved survival outcomes in this patient population, potentially making the tool's predictions less accurate for contemporary cohorts. In this context, we need to consider that only 10.4% of patients included in our analysis were HER2-positive breast cancer patients. This tool was developed incorporating HER2 status based on data from patients not exposed to modern anti-HER2 treatments; moreover, only in the late 2011 version of the PREDICT, the HER2 status was incorporated based on data from 10 179 cases not exposed to anti-HER2 treatment from the Breast Cancer Association Consortium (BCAC).[4] Moreover, the introduction of novel therapeutic approaches, including dual HER2 blockade and antibody—drug conjugates, has significantly altered the natural history of HER2-positive breast cancer, making it crucial to regularly update prognostic tools to reflect these advances.[28,29] However, it should be considered that patients with HER2-positive breast cancer included in the MIG and GIM trials were treated with trastuzumab in 41.5% (4.3% of the overall population) of cases and no one received pertuzumab or trastuzumab emtansine. Agostinetto et al. also reported similar findings in their analysis, focusing specifically on HER2-positive early breast cancer patients recruited in the ALTTO trial. They found that PREDICT underestimated the 5-year OS by ∼6.7% in patients treated with a modern regimen of chemotherapy and anti-HER2 therapies, including trastuzumab. This underestimation was consistent across subgroups, with the most pronounced discrepancies observed in patients with HR-negative disease, nodal involvement, and larger tumors.[10]

Another important aspect emerging from our analysis is the tool's varying performance across different age groups, particularly evident in elderly patients. The predictive accuracy of the model showed notable limitations in geriatric

Table 1. Baseline patients and treatment characteristics in the overall population included

	Overall *n* (%)	MIG1 *n* (%)	MIG5 *n* (%)	GIM2 *n* (%)	GIM3 *n* (%)	GIM6 *n* (%)
Total, *n*	6205 (100)	941 (15.2)	882 (14.2)	1623 (26.2)	2574 (41.8)	185 (3.0)
Age, years						
≤40	591 (9.5)	117 (12.4)	95 (10.8)	247 (15.2)	2 (0.1)	130 (70.3)
41-65	4044 (65.2)	741 (78.7)	663 (75.2)	1213 (74.7)	1372 (53.3)	55 (29.7)
≥65	1570 (25.3)	83 (8.8)	124 (14.1)	163 (10.0)	1200 (46.6)	0 (0.0)
Baseline BMI						
Underweight (<18.5 kg/m^2)	93 (1.5)	13 (1.3)	19 (2.1)	24 (1.4)	21 (0.8)	16 (8.6)
Normal (18.5-24.9 kg/m^2)	2525 (40.6)	524 (55.7)	446 (50.6)	736 (45.3)	691 (26.8)	128 (69.2)
Overweight (25-29.9 kg/m^2)	1826 (29.4)	287 (30.5)	256 (29.0)	519 (32.0)	738 (28.7)	26 (14.1)
Obese (≥30 kg/m^2)	1131 (18.2)	111 (11.8)	142 (16.1)	308 (19.0)	558 (21.7)	12 (6.5)
Missing	630 (10.1)	6 (0.6)	19 (2.1)	36 (2.2)	566 (22.0)	3 (1.6)
Tumor subtype						
Luminal A/B	3743 (60.3)	141 (15.0)	0 (0.0)	59 (3.6)	0 (0.0)	0 (0.0)
HER2 positive	647 (10.4)	83 (8.8)	0 (0.0)	350 (21.6)	214 (8.3)	0 (0.0)
TNBC	200 (3.2)	374 (39.7)	0 (0.0)	1029 (63.4)	2340 (90.9)	0 (0.0)
HR positive/HER2 unknown	1325 (21.3)	220 (23.4)	122 (13.8)	6 (0.4)	0 (0.0)	39 (21.1)
Missing	290 (4.7)	123 (13.1)	882 (14.2)	1623 (26.2)	2574 (41.5)	185 (3.0)
Histology						
Ductal	4982 (81.0)	788 (83.7)	750 (85.0)	1295 (79.8)	1989 (77.3)	160 (86.5)
Lobular	739 (11.9)	80 (8.5)	88 (10.0)	242 (14.9)	323 (12.5)	6 (3.2)
Other	439 (7.1)	72 (7.5)	44 (5.0)	86 (5.3)	233 (9.0)	4 (2.2)
Missing	45 (0.7)	1 (0.1)	0 (0.0)	0 (0.0)	29 (1.1)	15 (8.1)
Tumor size (T)						
pT1	3796 (61.2)	479 (50.9)	475 (53.9)	822 (50.6)	1905 (74.0)	115 (62.2)
pT2	2253 (36.3)	444 (47.2)	386 (43.8)	726 (44.7)	632 (24.6)	65 (35.1)
pT3/4	156 (2.5)	18 (1.9)	21 (2.4)	75 (4.6)	37 (1.4)	5 (2.7)
Nodal status						
pN0	2226 (35.8)	360 (38.3)	0 (0.0)	0 (0.0)	1775 (69.0)	91 (49.2)
pN1	2566 (41.4)	379 (40.2)	609 (69.0)	975 (60.1)	533 (20.7)	70 (37.8)
pN2	1060 (17.1)	193 (20.5)	273 (31.0)	405 (25.0)	165 (6.4)	24 (13.0)
pN3	353 (5.7)	0 (0.0)	0 (0.0)	243 (15.0)	101 (3.9)	0 (0.0)
Grading						
G1	639 (10.3)	57 (6.1)	79 (9.0)	122 (7.5)	371 (14.4)	10 (5.4)
G2	3478 (56.0)	529 (56.2)	482 (54.6)	780 (48.1)	1605 (62.3)	82 (44.3)
G3	2088 (33.6)	355 (37.7)	321 (36.4)	721 (44.4)	598 (23.3)	93 (50.3)
Menopausal status						
Premenopausal	1778 (28.6)	407 (43.2)	391 (44.3)	795 (49.1)	0 (0.0)	185 (100)
Postmenopausal	4412 (71.1)	521 (55.)	489 (55.4)	828 (51.2)	2574 (100)	0 (0.0)
Missing	15 (0.2)	13 (1.4)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Endocrine therapy						
Tamoxifen only	1980 (31.9)	521 (55.4)	691 (78.3)	648 (39.9)	0 (0.0)	120 (64.9)
AI	1692 (27.3)	0 (0.0)	0 (0.0)	389 (24.0)	1300 (50.5)	3 (1.6)
Tamoxifen −−> AI	1676 (27.0)	0 (0.0)	0 (0.0)	389 (23.7)	1274 (49.5)	18 (9.7)
None	857 (13.8)	420 (44.6)	191 (21.7)	202 (12.4)	0 (0.0)	44 (23.8)
Surgery						
Lumpectomy	4240 (68.3)	528 (56.1)	540 (61.2)	982 (60.5)	2071 (80.5)	119 (64.3)
Mastectomy	1953 (32.5)	410 (43.6)	339 (38.4)	641 (39.5)	502 (19.5)	60 (21.4)
Missing	13 (0.2)	2 (0.3)	3 (0.3)	0 (0.0)	1 (0.4)	6 (3.2)
(Neo)adjuvant treatment						
Anthracycline-based	1751 (28.2)	941 (100)	430 (48.7)	0 (0.0)	298 (11.6)	82 (44.3)
Anthracycline + taxanes	2658 (42.8)	0 (0.0)	452 (51.2)	1623 (100)	480 (18.6)	103 (55.7)
Taxane-based	118 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	118 (4.6)	0 (0.0)
No chemotherapy	1678 (27.0)	0 (0.0)	0 (0.0)	0 (0.0)	1678 (65.2)	0 (0.0)
Trastuzumab treatment						
Yes	269 (41.5)	0 (0.0)	0 (0.0)	93 (26.6)	176 (82.2)	0 (0.0)
No	276 (42.7)	0 (0.0)	0 (0.0)	239 (69.2)	37 (17.3)	0 (0.0)
Missing	102 (15.8)	83 (12.8)	0 (0.0)	18 (5.1)	1 (0.5)	0 (0.0)

AI, aromatase inhibitor; BMI, body mass index; GIM, Gruppo Italiano Mammella; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; MIG, Mammella InterGruppo; TNBC, triple-negative breast cancer.

populations (≥65 years of age). This observation likely derives from the limited representation of these patient subgroups in the model's development cohort. Moreover, unlike other prognostic tools such as 'Adjuvant! Online', the current model does not account for coexisting medical conditions in its algorithms. This aspect may underscore a substantial heterogeneity within the elderly breast cancer population, primarily driven by varying comorbidity profiles. Previous research has established comorbidity burden as a crucial determinant of non-cancer mortality outcomes, as demonstrated by Kiderlen et al.[30] These findings emphasize incorporating standardized comorbidity assessments in future prognostic models. Moreover, the elderly population exhibits significant variability in functional

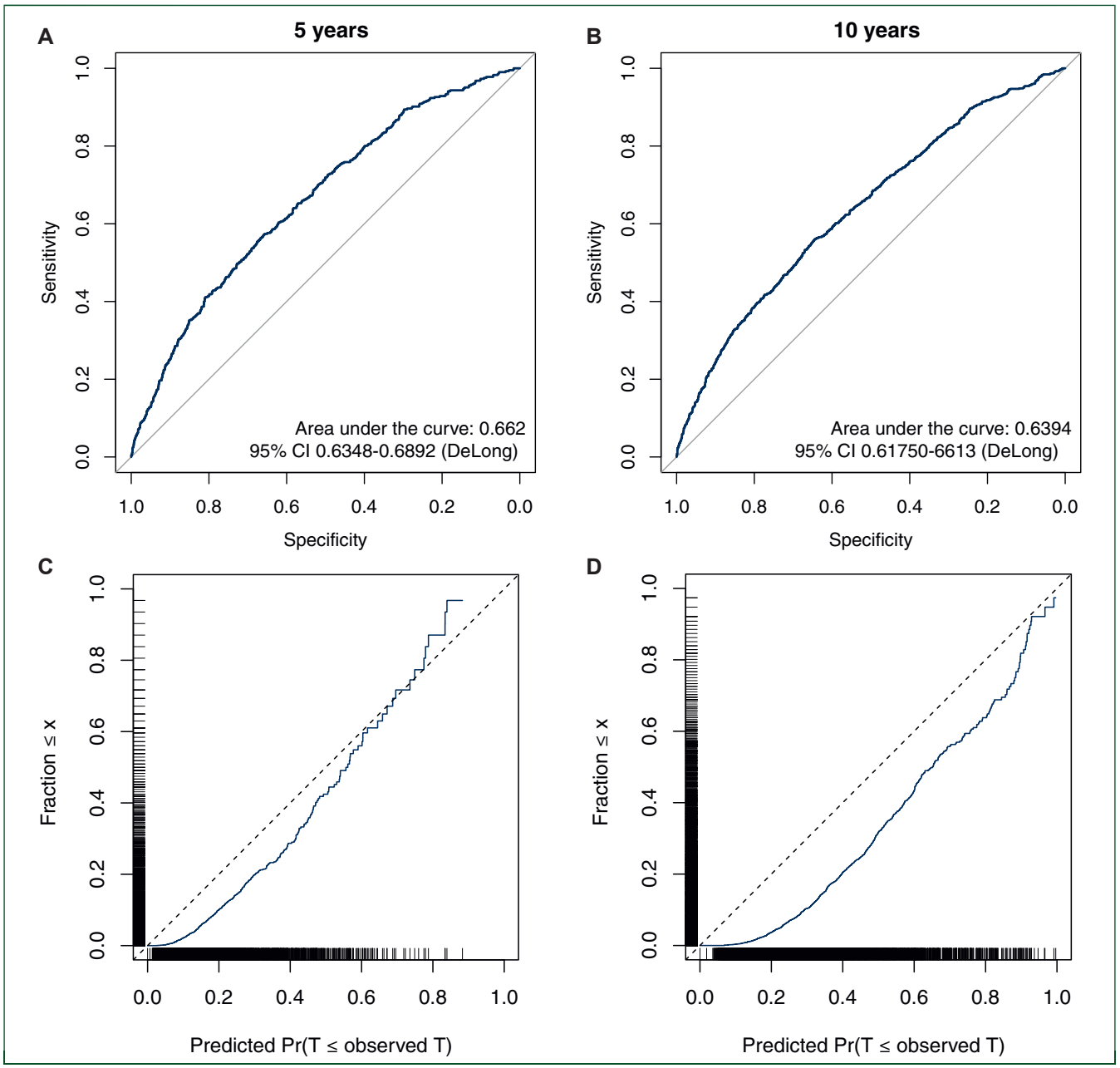

Figure 2. Discriminatory accuracy of PREDICT represented by the AUC and calibration curves. Discriminatory accuracy at (A) 5-year timepoint and (B) 10-year timepoint in the overall population. Calibrations curves for the overall population at (C) 5 years and (D) 10 years.
AUC, area under the receiver operating characteristic curve; CI, confidence interval.

capabilities, cognitive performance, and physiological resilience, further highlighting the need for more comprehensive assessment tools. On the other hand, the young age at diagnosis presents unique prognostic considerations. Previous studies have shown that PREDICT underestimates breast cancer mortality risk in young women.[24,31] Evidence suggests that tumors in younger patients demonstrate increased metastatic potential, even when other prognostic factors appear favorable.[32] Moreover, 10%-15% of young patients are expected to harbor a germline pathogenic variant in breast cancer predisposition genes, particularly in the BReast CAncer (*BRCA*) genes.[33,34] These aspects have historically led to age-based treatment decisions, particularly for patients <40 years, with many clinicians administrating chemotherapy based solely on age; however, this approach potentially exposes a substantial subset of patients to unnecessary treatment-related toxicities without clear therapeutic benefit. A novel finding of our study is the impact of BMI on PREDICT's predictive performance. In the last decade, more importance has been given to the role of BMI as a possible cause of endocrine resistance.[35] Our results suggest that BMI should be considered for future iterations of the tool. This observation aligns with the growing evidence about the prognostic role of BMI in breast cancer. Several studies have demonstrated the impact of obesity on breast cancer outcomes.

Table 2. Predicted probability of 5- and 10-year OS and observed 5- and 10-year OS rate in the study population

	n	5-year OS (%)		Difference (95% CI)	10-year OS (%)		Difference (95% CI)
		Predicted	Observed		Predicted	Observed	
Overall	6205	87.1	93.0	5.16 (5.0-6.3)	73.8	82.1	8.3 (7.2-9.4)
Study							
MIG-1	941	84.3	90.0	5.7 (3.8-7.6)	73.2	79.0	5.8 (3.2-8.5)
MIG-5	882	85.4	88.4	3.0 (0.9-5.1)	72.9	74.7	1.9 (−0.9 to 4.8)
GIM-2	1623	86.0	92.6	6.6 (5.3-7.9)	71.4	81.0	9.7 (7.6-11.8)
GIM-3	2574	89.6	96.0	6.4 (5.6-7.2)	75.3	88.4	13.1 (10.5-15.7)
GIM-6	185	91.3	95.6	4.3 (1.4-7.3)	83.2	89.3	6.0 (1.6-10.7)
Age, years							
≤40	591	86.9	92.5	5.6 (3.5-7.8)	75.4	79.8	4.4 (1.0-7.8)
41-64	4044	88.5	93.2	4.7 (3.9-5.5)	76.7	83.4	6.6 (5.3-8.0)
≥65	1570	84.5	92.4	7.9 (6.5-9.3)	65.8	78.1	12.3 (9.3-15.5)
BMI							
Underweight	93	89.1	92.2	3.0 (−2.4 to 8.8)	78.4	84.3	5.8 (−2.2 to 14.8)
Normal weight	2525	87.8	92.9	5.1 (4.1-6.2)	75.5	83.0	7.5 (5.9-9.2)
Overweight	1826	87.0	92.8	5.8 (4.6-7.0)	73.3	81.2	7.9 (5.7-10.0)
Obese	1131	86.0	92.9	6.8 (5.3-8.4)	70.9	79.7	8.7 (5.8-11.8)
Missing	630	88.5	94.0	5.5 (3.5-7.5)	73.6	85.2	11.6 (5.4-18.3)
Subtype							
TNBC	200	77.9	84.8	6.9 (2.0-12.1)	69.1	78.8	9.7 (4.1-15.7)
Luminal A/B	3743	89.4	95.1	5.7 (5.0-6.5)	75.4	85.1	9.7 (8.1-11.3)
HER2 positive	648	82.0	91.5	9.4 (7.2-11.7)	66.5	80.0	13.5 (9.9-17.2)
HR positive/HER2 unknown	1325	88.4	90.8	2.5 (0.9-4.1)	75.5	78.6	3.1 (0.9-5.4)
Missing	289	74.7	86.1	11.4 (7.5-15.5)	65.3	72.5	7.2 (2.1-12.7)
Tumor size							
pT1	3796	90.8	95.5	4.8 (4.1-5.5)	79.5	87.3	7.8 (6.5-9.2)
pT2	2253	82.9	89.3	6.4 (5.0-7.7)	66.4	75.1	8.7 (6.7-10.8)
pT3/T4	156	67.5	83.6	16.1 (10.3-22.3)	44.2	66.9	22.7 (15.1-31.4)
Nodal status							
N0	2226	91.3	97.0	5.7 (4.9-6.4)	79.8	92.0	12.1 (10.5-13.8)
N1	2566	89.3	94.2	4.9 (4.0-5.8)	77.6	84.0	6.5 (4.9-8.1)
N2	1060	80.5	86.4	6.0 (3.9-8.1)	62.7	69.9	7.2 (4.3-10.3)
N3	353	68.5	79.1	10.6 (6.2-15.2)	42.4	58.9	16.5 (10.6-23.1)
(Neo)adjuvant treatment							
Anthracycline-based	1751	85.9	91.1	5.2 (3.9-6.6)	74.1	79.6	5.5 (3.5-7.6)
Anthracycline + taxanes	2658	86.3	92.1	5.8 (4.7-6.8)	72	80.8	8.8 (7.1-10.5)
Taxane-based	118	86.9	88.9	2.0 (−4.1 to 8.5)	69.7	60.7	−9.0 (−29.9 to 23.0)
Trastuzumab use[a]							
No	360	78.4	90.7	12.3 (9.3-15.4)	62.1	76.6	14.4 (9.8-19.3)
Yes	269	86.8	93.1	6.3 (3.1-9.6)	72.3	88.1	15.8 (11.1-20.8)
Unknown	19	83.9	81.4	−2.4 (−19.4 to 16.1)	68.8	74.7	5.9 (−12.9 to 31.0)

AI, aromatase inhibitor; BMI, body mass index; CI, confidence interval; GIM, Gruppo Italiano Mammella; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; MIG, Mammella InterGruppo; OS, overall survival; TNBC, triple-negative breast cancer.
[a]Analysis among HER2-positive breast cancer patients.

For instance, Chan et al. showed that obesity is associated with worse OS in both early-stage and metastatic breast cancer patients, with a hazard ratio of 1.4 (95% CI 1.3-1.5) in early-stage disease.[36] Similarly, a study presented at 2024 San Antonio Breast Cancer Symposium analyzed data from 206 904 early breast cancer patients and confirmed that overweight and obesity are linked to a moderate increase in distant recurrence and breast cancer mortality across all patient groups with a hazard ratio per 5 kg/m^2 BMI increment of 1.06 overall.[37] The biological mechanisms underlying this association include altered hormone levels, chronic inflammation, and potential differences in drug metabolism, all of which could affect treatment efficacy and overall prognosis.[38]

In this context, it is worth highlighting that a multitude of prognostic models have been developed for early breast cancer, each leveraging different types of data (e.g. clinicopathological and genomic) and serving distinct purposes in treatment planning. A comprehensive overview of these models, including their clinical applications and integration within guidelines,[39,40] is provided in Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2025.105924, to assist clinicians in selecting the most appropriate tool for individual patient profiles.

Our study has several limitations that should be acknowledged. A key consideration is the temporal context of patient enrollment (1992-2012), which precedes several major advances in adjuvant breast cancer therapy.[29,41–44] While a large proportion of our cohort received regimens still considered standard, such as anthracycline and taxane-based chemotherapy (58.7%, 2658 out of 4527) and aromatase inhibitor-based endocrine therapy (66.5%, 3368 out of 5068), none received more recent agents including adjuvant cyclin-dependent kinase 4 and 6 inhibitors or poly (ADP-ribose) polymerase inhibitors. Therefore, the discrepancy between

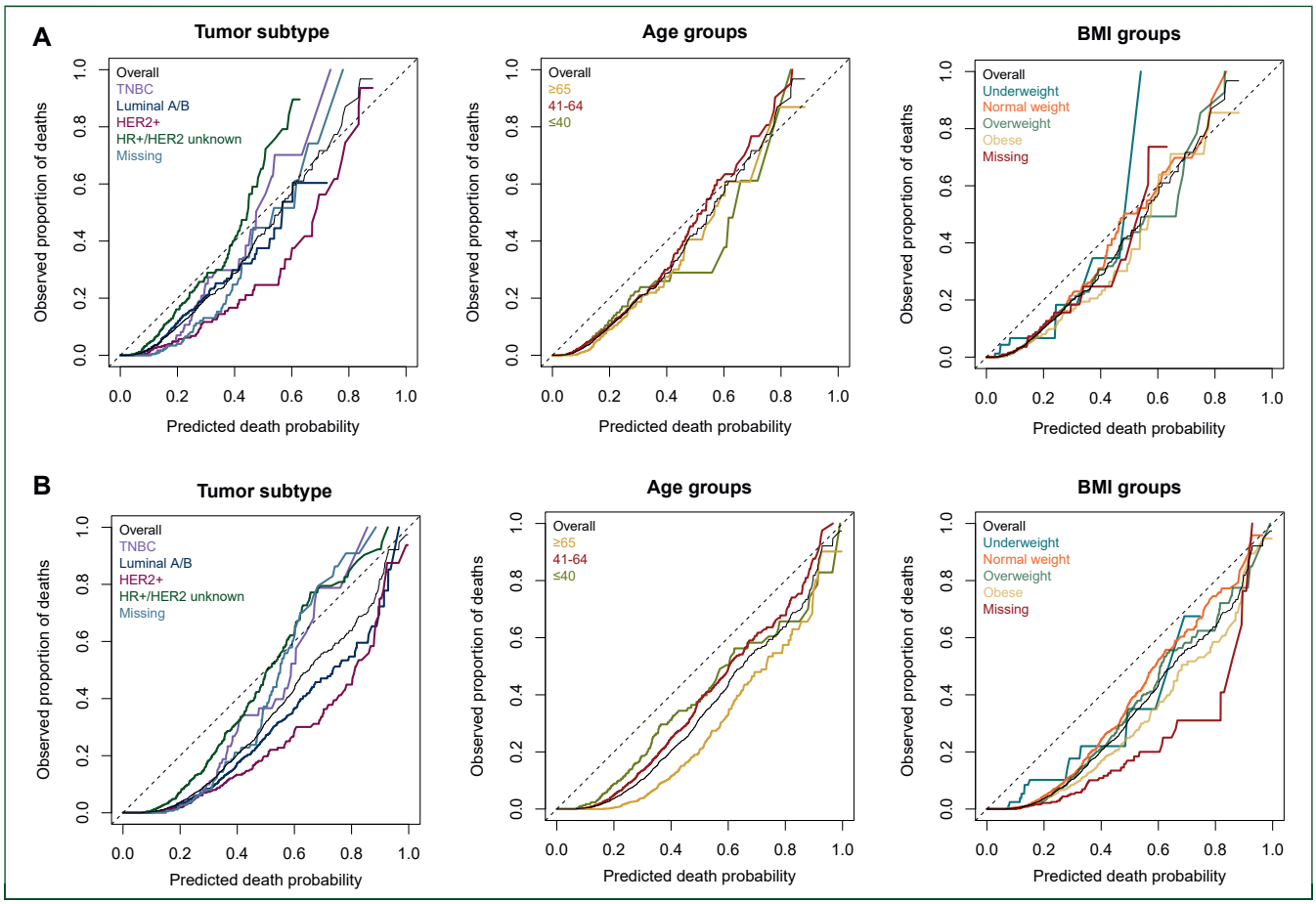

Figure 3. Calibration curves. Calibration curves divided by subgroup (i.e. tumor subtype, age, and BMI) for the overall population at (A) 5 years and (B) 10 years. BMI, body mass index; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; TNBC, triple-negative breast cancer.

predicted and observed survival rates might be even more pronounced in current clinical practice. Moreover, the discrepancy between trial outcomes and real-world results warrants careful consideration. Clinical trials, while methodologically rigorous, may not accurately represent real-world patient populations. Their rigid selection criteria often exclude patients with comorbidities, advanced age, or poor health status. This selective process can result in trial participants showing better survival outcomes than in broader real-world clinical settings. Consequently, the findings from these trials may not fully generalize to the diverse and more complex patient groups encountered in routine medical practice.

CONCLUSIONS

In conclusion, our pooled analysis of five adjuvant randomized clinical trials found that PREDICT underestimates 5- and 10-year OS in a clinical trial-derived population of early-stage breast cancer patients. While PREDICT remains a useful tool for prognostication and treatment decision making, regular updates are crucial to align with evolving therapies. Future versions of PREDICT should consider incorporating additional prognostic factors such as BMI and better represent extreme age groups to improve its accuracy. The improvements in breast cancer survival outcomes achieved through therapeutic advances highlight the need for dynamic prognostic tools that can adapt to these changes while maintaining their clinical utility.

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