Original Article

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Assessment High-Risk Breast Cancer in Older Patients: A Comparative Analysis of PREDICT Scores and TAILORx Risk Categorization

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ABSTRACT

Objective: This study aimed to evaluate the relationship between PREDICT tool overall survival (OS) scores and high-risk patients according to TAILORx risk categorization in elderly hormone reseptor (HR) positive human epidermal growth factor negative early breast-cancer patients.

Materials and Methods: We conducted a retrospective study, extracting data from medical records of 64 patients diagnosed with breast cancer. A retrospective analysis was performed on all patients who had Oncotype Dx Recurrence Scores across five medical centers between 2017 and 2022. PREDICT scores were defined as calculated 10-year OS rates via PREDICT tool.

Results: The median age of the patients was 67, with a range between 65–75 years. Low-risk patients had a slightly higher two PREDICT scores compared to high-risk patients (78% *vs.* 73%), (81% *vs.* 77%), which were statistically significant. The progesterone receptor (PR) level was significantly lower in the high-risk group (3.5% *vs.* 80%). A unit decrease in the PREDICT scores was associated with a 11% increase in the odds of being in the high-risk group. However, these effects weren't statistically significant in the multivariate analysis. A unit decrease in the PR level was significantly associated with increased odds (by 5% in the multivariate analysis) of being in the high-risk group.

Conclusion: Our study underscores the importance of using a combination of tools, including the PREDICT tool, PR levels, and TAILORx risk categorization, for a comprehensive risk assessment in these patients, especially in the older population. Accurate risk assessment is crucial for tailoring the treatment and optimizing outcomes in this vulnerable population. Future studies are warranted to further validate these findings in larger cohorts and to explore additional biomarkers and genomic signatures that may aid in the risk assessment and management of breast cancer in older patients.

Keywords: Breast cancer; PREDICT tool; oncotype DX recurrence score; TAILORx risk categorization

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Key Points

- This is first study in the literature to investigate the relationship between ODx-RS and PREDICT tool OS scores in HR-positive HER-2 negative early breast-cancer elderly patients.
- A unit decrease in PREDICT scores and PR levels was associated with increased odds of being classified as high-risk, but only the PR levels association was statistically significant in the multivariate analysis.
- Despite the PREDICT tool indicating higher survival scores for low-risk patients compared to high-risk patients, the tool did not demonstrate significant predictive value in the multivariate analysis, indicating alone its limited utility as a standalone predictive measure for high-risk classification in older patients.

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Introduction

Breast cancer has now overtaken lung cancer as the most commonly diagnosed cancer globally, with 2.3 million new cases diagnosed annually (1). In Turkey, breast cancer remains the dominant cancer among women, with 24,175 cases, or 23.9%, recorded in 2020 (1, 2). This prevalence has underscored the need for tools that can provide personalized prognostic insights, aiding clinicians in formulating treatment strategies tailored to individual patient profiles. The PREDICT tool and the Oncotype Dx Recurrence score (ODx-RS) have emerged as being important in this field (1, 3), designed to deliver nuanced prognoses by combining both tumor-specific and patient-specific factors (3). However, their efficacy and applicability, specifically in the older population (≥65 years) with breast cancer, warrants further exploration.

The PREDICT tool, originating from UK research, is geared towards forecasting post-surgical survival for invasive breast cancer. PREDICT considers variables such as tumor size, nodal status, grade, and biomarkers such as human epidermal growth factor-2 (HER-2) and Ki-67 (3-9). Several studies have highlighted its validity across a variety of patient cohorts, particularly in age-specific groups (9-14). Given that PREDICT is free, user friendly, and easily accessible, it may provide an economically feasible option to guide adjuvant chemotherapy decision-making in resource-limited settings. PREDICT is a web-based prognostication tool, which estimates the probability of survival for individual patients with breast cancer and the impact of systemic treatment choices on their survival probability (http://www.predict.nhs.uk/).,Als Furthermore, PREDICT has been endorsed by the American Joint Committee on Cancer (13). Notably, a recent study by van der Plas-Krijgsman et al. (15) introduced the PORTRET tool–a prognostic model explicitly designed for older patients (≥65 years) with breast cancer in the Netherlands. This need for the development of this tool undelines the significance of age-specific prognostic models.

The Oncotype Dx (ODx) test (Genomic Health, Redwood City, CA, USA) examines a 21-gene expression profile. It has been authenticated for patients with HR-positive, HER-2 negative, and lymph node negative breast cancer. This score segments patients into risk categories (low, intermediate, or high) primarily concerning recurrence in hormone receptor-positive breast cancer, thereby aiding the decision-making process around the need for adjuvant chemotherapy (1, 16-18). As the realm of oncology shifts towards more patient-focused care, comprehending the impact and implications of these tools, specifically for the older demographic (≥65 years), becomes increasingly important.

This study was designed to investigate the possible correlations between the PREDICT tool and the TAILORx risk classification in an older cohort of patients with hormone receptor positive/HER2 negative breast cancer, focusing on their combined prognostic value.

Materials and Methods

Study Design and Patient Population

This was a retrospective study, with data extracted from the medical records of patients diagnosed with breast cancer. A retrospective analysis was performed on all patients who had available ODx-RS across five medical centers between 2017 and 2022. The study eventually included women aged 65 years and above who were diagnosed with hormone receptor positive, HER-2 negative, early-stage breast cancer (pT1-2, pN0-N1mic, M0). These patients were treated in five different hospitals across Turkey and had ODx-RS assessments to inform the decision for adjuvant chemotherapy.

Patient demographic, clinical, and pathological details, including age, tumor size, histological grade, estrogen receptor (ER) and progesterone receptor (PR) status, Ki-67 index, and lymph node status were recorded retrospectively. The ODx-RS was examined using tissue sections taken from surgically removed, formalin-fixed, paraffin-embedded samples in a centralized laboratory. If nuclear staining was moderate to strong in at least 1% of tumor cells upon immunohistochemical (IHC) testing, ER and/or PR were considered positive. HER-2 expression was evaluated using IHC staining. A score of 0 or 1 on the IHC staining was interpreted as negative for HER-2. In cases where the IHC score was 2, further assessment was conducted using a Fluorescence *In Situ* Hybridization (FISH) test. Only those with a negative FISH test result were included in the study. Patients were divided into two groups according to ODx-RS: 0-25 and ≥26. An oncotype score cut-off value of 26 for chemotherapy administration was used, based on the TAILORx study (19, 20).

Even with the known ODx scores, the choice of adjuvant therapy was determined at a weekly tumor board meetings. Patients were split into two categories: those who received hormone therapy alone and those who received chemotherapy (taxane-based and/or adriamycin-based regimens) in combination with hormone therapy (aromatase inhibitors or tamoxifen).

Predicted 10-Year OS (PREDICT Score)

PREDICT scores were defined as calculated OS rates using the PREDICT tool. In the present study the predicted OS was calculated for each patient using version 2 of the PREDICT tool. For each patient, data on age (continuous), tumor size (continuous), number of involved lymph nodes (continuous), ER status (positive, negative, undefined), tumor grade (grade 1, grade 2, grade 3, undefined), HER-2 status (positive, negative, undefined), Ki-67 status (entered as undefined for all patients), and adjuvant chemotherapy regimen (no chemotherapy, second-generation chemotherapy, third-generation chemotherapy) were manually entered. For every entry, the program predicted 10-year OS for three different scenarios. These were, survival with no adjuvant treatment, benefit of adjuvant hormone therapy, and additional benefit of adding adjuvant chemotherapy (ChT) to adjuvant hormone therapy. We used the second and third scenarios for every patients and OS scores were recorded for each patient [(2-OS score via PREDICT only adding hormonotherapy (HT); 3- OS score via PREDICT adding combine therapy (ChT + HT)]. The survival probability corresponding to the actual treatment received by the individual patient was recorded. PREDICT score was defined as calculated OS rate derived from the PREDICT tool. In order to ensure accuracy, all the PREDICT scores were calculated by two research personnel, and further audited.

The study protocol was reviewed and performed in accordance with İstanbul Bilgi University Ethics Committee. (project number: 2023-40162-053, date: 30.03.2023).

Statistical Analysis

Data were analyzed using SPSS, version 22.0 (IBM Inc., Armonk, NY, USA). Descriptive statistics were used to summarize patient demographics and tumor characteristics in both age groups. Mean and standard deviation or median and range were computed for continuous variables as appropriate, while frequencies and percentages

were calculated for categorical variables. The Student's t-test was used in cases where the numerical demographic and clinical properties met with the standard distribution hypothesis. In cases where these criteria were not met, the Mann-Whitney U test was used to compare the distribution of ODx risk categories (high risk *vs.* not high risk). Boxplot analysis was used to evaluate the distribution of PREDICT scores between the high-risk and non-high-risk groups To control for potential confounders, a multivariate linear regression analysis was conducted with the TAILORx high risk score (ODx-RS ≥26) as the dependent variable and the PREDICT scores, tumor size, Ki-67, and tumor grade as independent variables. A *p*-value of less than 0.05 was considered statistically significant.

Table 1. Characteristics of the patients at baseline

(n = 64)	n (%)/median (min-max)
Age	67 (65–75)
PREDICT score* (only hormonotherapy)	78% (57–85)
PREDICT score* (chemoterapy + hormonotherapy)	80% (63–86)
The histological subtype	
IDC	47 (73.4%)
Other subtypes#	17 (26.6%)
ODx-RS	15 (1–37)
Ki-67	18.5 (5–50)
Histologic grade	
Grade 1	6 (9.4%)
Grade 2	41 (64.1%)
Grade 3	17 (26.6%)
Tumor diameter	1.6 (0.6–4)
PR status	
PR>10	47 (73.4%)
PR≤10	17 (26.6%)
Ki-67 status	
Ki-67 <20	33 (51.6%)
Ki-67 ≥ 20	Ki-67 <20
Ki-67 ≥ 20	
0-10	18 (30.0%)
11–25	31 (51.7%)
≥26	11 (18.3%)
pT stage	
pT1	36 (56.3%)
pT2	28 (43.8%)
pN stage	
pN0	
pN1mic	55 (85.9%)
pM	9 (14.1%)
Adjuvant treatment	
HT	48 (75.0%)
ChT+HT	16 (25.0%)

All the values presented as n (%), IDC: invasive ductal carcinoma; #: invasive lobuler carcinoma, mucinous, metaplastic, micropapiller, cribriform, papiller; *PREDICT scores were defined as calculated overall survival rates via PREDICT tool; min: minimum; max: maximum

Results

The median (range) age of the patients was 67 (65-75) years. The majority of tumors were histological grade 2 (64.1%) followed by grade 3 (26.6%) and grade 1 (9.4%). In terms of treatment, 75% received HT while 25% received combined ChT + HT. Clinicopathological details of the patients are summarized in Table 1.

Low-risk patients had slightly but significantly higher PREDICT scores compared to high-risk patients (78% *vs.* 73% and 81% *vs.* 77%, for HT only or combined ChT + HT, respectively. The PR level was significantly lower in the high-risk group (3.5% *vs.* 80%) (Table 2) (Figure 1).

A unit decrease in the PREDICT scores was associated with an 11% increase in the odds of being in the high-risk group (Table 3). However, these effects lost significance in the multivariate analysis. A unit decrease in the PR level was significantly associated with increased odds (by 5% in the multivariate analysis) of being in the high-risk group. Grade 3 tumors were about 3.72 times more likely to be high risk compared to grade 1–2 tumors in univariate analysis.

Discussion and Conclusion

The aim of this study was to categorize the risk of HR positive/HER-2 negative, early stage breast cancer patients, focusing on high-risk *vs.* not high-risk classification using the TAILORx risk categorization and the PREDICT tool for OS scores, focussing on older patients. The results revealed that low-risk patients had slightly higher PREDICT scores compared to high-risk patients, which was a significant difference. Moreover, a unit decrease in the PREDICT scores and PR level was associated with an increase in the odds of being in the high-risk group. However, the effects of PREDICT scores did not remain significant on multivariate analysis, whereas a unit decrease in the PR level continued to be significantly associated with increased odds of being in the high-risk group (14, 15).

The PREDICT tool has been previously validated in the Dutch breast cancer population (14) and our study further supports its utility in predicting the risk group of breast cancer patients. The PREDICT tool, along with other genomic signatures, such as the 21-gene recurrence score, are essential in guiding decisions on adjuvant systemic therapy for women with early-stage, invasive breast cancer (21). The 21-gene recurrence score, in particular, has been shown to be useful in determining the benefit of chemotherapy among women of different age groups with HR-positive, HER-2-negative, node-negative breast cancer (22). Our study also highlighted the significance of PR levels in determining the risk group, supporting the use of biomarkers in guiding decisions on adjuvant systemic therapy (21).

The present study is particularly relevant for older patients, as the management of breast cancer in this population presents unique challenges. Older patients often have comorbidities and may experience more side effects from chemotherapy, making it even more important to accurately assess the risk and tailor the treatment accordingly (23, 24). While many studies have reported a heightened risk of endometrial carcinoma in postmenopausal breast cancer patients undergoing tamoxifen treatment, a study by Chiofalo et al. (25), involving 1199 patients, found no significant difference in risk between those treated with tamoxifen and those either treated

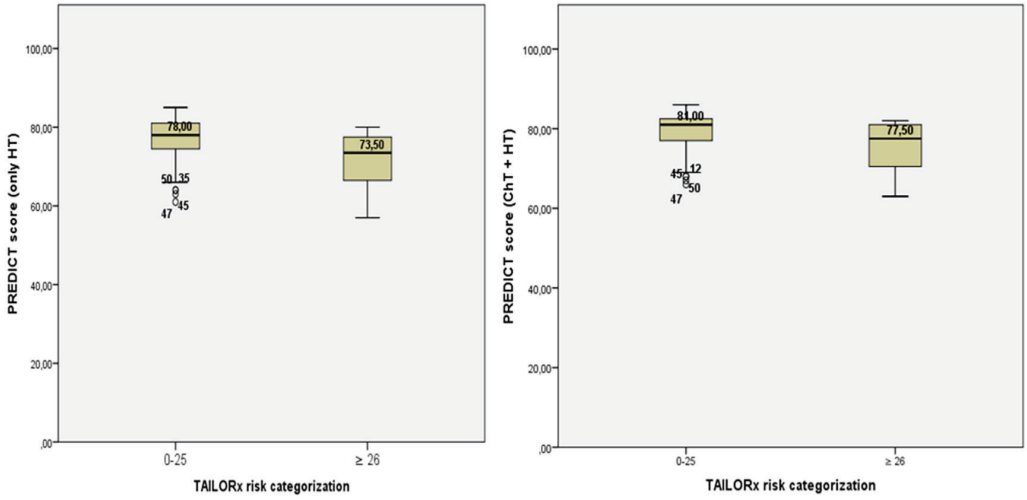

Figure 1. a. PREDICT scores (with only HT treatment) according to TAILORx risk categorization (ODX-RS<26 ODX-RS and ODX-RS ≥26) (left), 1b. PREDICT scores (with combine treatment) according to TAILORx risk categorization (right)

Table 2. Association between clinicopathological characteristics according to risk groups

	Low-risk group (n = 52) median (min-max)	High-risk group (n = 12) median (min-max)	*p*-value
PREDICT (only hormonotherapy)*	78 (61–85)	73 (57–80)	**0.02**
PREDICT (chemoterapy + hormonotherapy)*	81 (66–86)	77 (63–82)	**0.03**
Tumor size (cm)	1.65 (0.6–4.0)	1.85 (1.3–3.6)	0.21
Ki-67 level (%)	18 (5–50)	25 (10–40)	0.10
PR level (%)	80 (0–100)	3.5 (0–80)	**<0.001**

*PREDICT scores were defined as calculated overall survival rates via PREDICT tool; min: minimum; max: maximum

Table 3. Regression models of potential prognostic variables associated with the high-risk group (≥65 years)

All patients	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value
PREDICT score* (only hormonotherapy)	0.89	0.81–0.97	**0.02**	0.72	0.25–2.03	0.53
PREDICT score* (chemoterapy + hormonotherapy)	0.89	0.80–0.99	**0.04**	1.22	0.39–3.82	0.72
Tumor size	1.20	0.57–2.51	0.62			
Ki-67	1.06	0.99–1.13	0.08			
ER	0.96	0.91–1.02	0.96			
PR	0.96	0.93–0.98	**0.002**	0.95	0.92–0.98	**0.002**
Grade 1-2 vs. grade 3	3.72	1.01–13.8	**0.04**	3.57	0.53–23.8	0.18

*PREDICT scores were defined as calculated overall survival rates via PREDICT tool; CI: confidence interval; OR: odds ratio

with aromatase inhibitors or receiving no treatment (26). Previous studies have shown that the use of the 21-gene recurrence score was of variable utility among older women of different races (27), and our study adds to this body of literature by highlighting the importance of using a combination of tools, such as the PREDICT scores, PR levels, and TAILORx risk categorization for a more comprehensive risk assessment in older patients (28, 29).

Interestingly, the present study found that grade 3 tumors were more likely to be high risk compared to grade 1–2 tumors in univariate analysis, although this lost significance in the multivariate analysis. This finding is in line with previous studies that have highlighted the association between higher tumor grade and worse outcomes (30, 31). The clinical utility of genomic signatures in young breast cancer patients has been previously documented (32), and our study extends these findings to older patients, underlining the importance

of incorporating genomic signatures and tools such as PREDICT in the risk assessment and management of breast cancer in older patients.

However, it is important to acknowledge certain limitations of the study. These include the relatively small sample size and the retrospective nature of the analysis. Additionally, the study did not assess the impact of these tools on clinical outcomes, such as recurrence-free survival, which would be important to evaluate in future studies.

In conclusion, the present study underscores the importance of using a combination of tools, including the PREDICT tool, PR levels, and TAILORx risk categorization, for a comprehensive risk assessment in HR positive/HER-2 negative, early stage breast cancer in older breast cancer patients. Accurate risk assessment is crucial for tailoring the treatment and optimizing outcomes in this vulnerable population. Future studies are warranted to further validate these findings in larger cohorts and to explore additional biomarkers and genomic signatures that may aid in the risk assessment and management of breast cancer in older patients.

Ethics Committee Approval: The study method was reviewed and performed in accordance with İstanbul Bilgi University Ethics Committee. (project number: 2023-40162-053, date: 30.03.2023).

Informed Consent: Retrospective study.

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Authorship Contributions

Concept: Ç.Ü.; Design: Ç.Ü.; Data Collection or Processing: E.G., M.Ö., K.N.P., C.U., H.K., O.D., V.Ö., Ç.Ü.; Analysis or Interpretation: Ç.Ü., Ç.O., T.D.; Literature Search: Ç.Ü., Ç.O., V.Ö.; Writing: Ç.Ü., Ç.O.; Editing: Ç.Ü., T.Ö., Ç.O., V.Ö.

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