TOPM (Translational Oncotype Prediction Model): Development and Internal Validation of an Interpretable Clinicopathological Model for Pre-Test Estimation of High Oncotype DX Recurrence Score in Early Hormone Receptor–Positive, HER2-negative Breast Cancer

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Abstract

Background: The 21-gene Oncotype DX Breast Recurrence Score (RS) is widely used to guide adjuvant treatment decisions in patients with hormone receptor-positive (HR-positive), HER2-negative early breast cancer. However, limited accessibility, reimbursement restrictions, and financial costs continue to hinder its universal implementation. We aimed to develop and internally validate an interpretable clinicopathological prediction model for estimating the pre-test probability of a high Oncotype DX Recurrence Score. **Methods:** This retrospective prediction model study included consecutive women with HR-positive, HER2-negative early breast cancer who underwent Oncotype DX testing at a tertiary referral center between January 2019 and December 2025. Candidate predictors were prespecified based on biological plausibility and clinical relevance. High genomic risk was defined as RS >25. Model development was performed using ridge-penalized logistic regression, with missing data handled within the modeling pipeline. Internal validation was conducted using 2,000 bootstrap resamples. Model performance was assessed by discrimination, calibration, optimism correction, and decision curve analysis in accordance with TRIPOD recommendations. The final model was translated into a nomogram and an electronic probability calculator. **Results:** Eighty patients were included, of whom 11 (13.8%) had a high Recurrence Score (RS >25). Patients with high genomic risk had significantly lower progesterone receptor (PR) expression and higher histological grade, whereas age, tumor size, and Ki-67 were not independently associated with the primary outcome. Following ridge penalization, PR expression and histological grade emerged as the strongest predictors and constituted the final Translational Oncotype Prediction Model (TOPM). Internal validation demonstrated limited optimism, good calibration, stable discrimination, and favorable clinical utility. The model was successfully implemented as both a graphical nomogram and an electronic probability calculator. **Conclusions:** TOPM is an interpretable clinicopathological prediction model that estimates the probability of a high Oncotype DX Recurrence Score using routinely available pathological variables. Rather than replacing genomic testing, it is intended to complement molecular diagnostics by supporting individualized patient selection. External validation in larger multicenter cohorts is warranted before clinical implementation.

Keywords: Breast cancer; Oncotype DX; Clinical prediction model; Nomogram; Machine learning; Ridge regression; TRIPOD; Precision oncology; Progesterone receptor; Histological grade.

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INTRODUCTION

Hormone receptor-positive (HR-positive), human epidermal growth factor receptor 2-negative (HER2-negative) breast cancer represents the most common molecular subtype of early breast cancer (1) and is characterized by substantial biological heterogeneity despite generally favorable clinical outcomes. While many patients derive excellent benefit from endocrine therapy alone, a clinically important subgroup harbors biologically aggressive disease that may benefit from the addition of adjuvant chemotherapy. Consequently, accurate estimation of recurrence risk remains a cornerstone of individualized treatment decision-making in contemporary breast oncology.

The introduction of multigene expression assays has fundamentally transformed adjuvant treatment planning by providing prognostic and predictive information beyond conventional clinicopathological variables. Among these assays, the 21-gene Oncotype DX Breast Recurrence Score (RS) has become one of the most widely adopted genomic tools for patients with HR-positive, HER2-negative early breast cancer (2). By

quantifying the expression of genes involved in estrogen signaling, proliferation, HER2 signaling, invasion, and related biological pathways, the assay generates a continuous Recurrence Score that refines estimates of distant recurrence risk and predicts the potential benefit of adjuvant chemotherapy. Landmark prospective trials, including TAILORx and RxPONDER, have firmly established the central role of the Recurrence Score in guiding systemic treatment decisions across both node-negative and selected node-positive populations (2).

Despite its proven clinical value, universal implementation of multigene assays remains challenging. Financial costs, reimbursement policies, limited laboratory availability, and unequal access to molecular diagnostics continue to restrict routine use of genomic testing in many healthcare systems. Consequently, clinicians are frequently required to determine which patients are most likely to benefit from genomic testing before ordering the assay. This unmet clinical need has stimulated considerable interest in identifying routinely available clinicopathological variables that reflect underlying genomic risk and may assist in prioritizing genomic testing.

Numerous studies have demonstrated significant associations between conventional pathological variables and the Oncotype DX Recurrence Score. Lower progesterone receptor (PR) expression, higher histological grade, increased proliferative activity, and selected clinicopathological characteristics have consistently been associated with higher genomic risk. Their study confirmed that routinely available pathological variables retain substantial biological information regarding genomic risk and demonstrated the feasibility of clinicopathological prediction in a large national population. These findings substantially strengthened the evidence supporting the relationship between conventional pathology and tumor genomics.

However, identifying variables associated with genomic risk is conceptually different from developing a clinically applicable prediction model. Although previous studies, including the multicenter Turkish experience, have provided valuable evidence regarding clinicopathological correlates of the Recurrence Score, relatively few investigations have been specifically designed according to contemporary prediction-model methodology. Many previously published models relied on automated variable selection, historical Recurrence Score thresholds, limited internal validation, or focused primarily on discrimination while providing insufficient evaluation of calibration, clinical utility, or implementation. Furthermore, most studies emphasized statistical associations rather than the development of transparent and clinically interpretable decision-support tools.

An additional conceptual consideration deserves emphasis. The Oncotype DX assay does not merely generate a numerical recurrence score; rather, it quantifies transcriptional programs reflecting estrogen signaling, cellular proliferation, tumor differentiation, and other fundamental biological processes (3). Histological grade and progesterone receptor expression represent pathological manifestations of these same biological pathways (4). Therefore, an interpretable clinicopathological model should not be regarded as an attempt to replace genomic testing but rather as a means of estimating the probability of the biological state measured by genomic profiling, using routinely available pathological surrogates. From this perspective, conventional pathology and tumor genomics should be considered complementary sources of biological information rather than competing approaches.

Accordingly, the aim of the present study was to develop and internally validate the TOPM (Translational Oncotype Prediction Model), an interpretable clinicopathological prediction model for estimating the individual pre-test probability of a high Oncotype DX Recurrence Score in patients with HR-positive, HER2-negative early breast cancer. Unlike previous observational studies, the present investigation was specifically designed as a TRIPOD-compliant prediction model development study, incorporating prespecified biologically relevant predictors, penalized logistic regression, bootstrap-based internal validation, comprehensive evaluation of discrimination and calibration, decision curve analysis, and translation of the final model into a nomogram and electronic probability calculator to facilitate future clinical implementation.

METHODS

Study Design

This retrospective prediction model study was conducted at Acıbadem Maslak Hospital, Istanbul, Türkiye, to develop and internally validate an interpretable clinicopathological model for estimating the probability of a high Oncotype DX Breast Recurrence Score (RS) in patients with hormone receptor-positive (HR-positive), HER2-negative early breast cancer. Consecutive patients who underwent Oncotype DX testing as part of routine clinical practice between January 2019 and December 2025 were identified from the institutional electronic medical record system.

The study was specifically designed as a clinical prediction model development and internal validation study, rather than a conventional prognostic association study. Accordingly, the primary objective was not to re-evaluate clinicopathological predictors of the Oncotype DX Recurrence Score, but to develop an interpretable and internally validated prediction model suitable for future clinical implementation. The overall study workflow is summarized in Figure 1. Model development, validation, and reporting were conducted in accordance with the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) Statement.

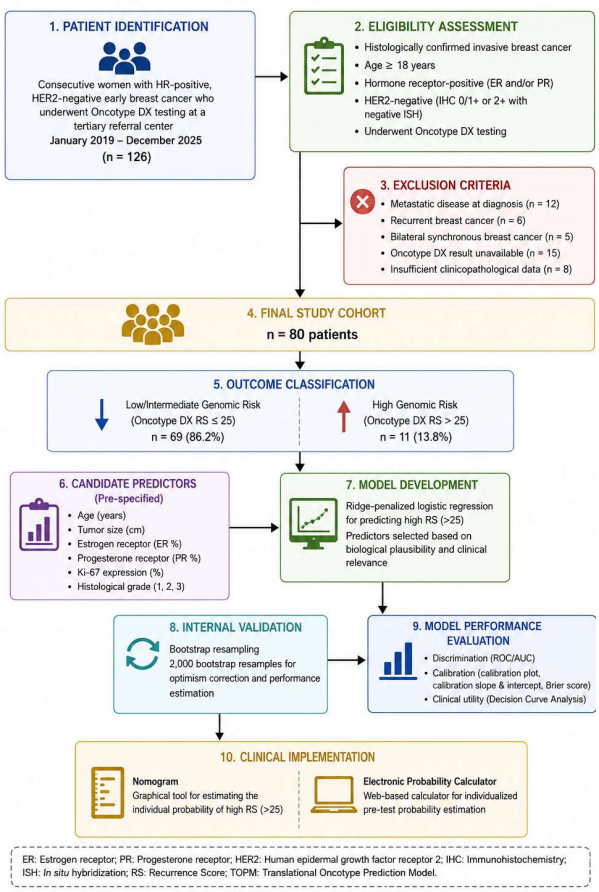


Figure 1. Study workflow

Figure 1. Study workflow illustrating patient selection, eligibility screening, clinicopathological predictor assessment, model development using ridge-penalized logistic regression, internal validation with 2,000 bootstrap resamples, and translation of the final Translational Oncotype Prediction Model (TOPM) into a nomogram and electronic probability calculator.

Study Population

Women aged 18 years or older with histologically confirmed invasive hormone-receptor-positive, HER2-negative early breast cancer who underwent Oncotype DX testing between January 2019 and December 2025 were eligible for inclusion.

Patients with metastatic disease at diagnosis, recurrent breast cancer before genomic testing, bilateral synchronous breast cancer, unavailable Oncotype DX results, or insufficient clinicopathological information required for model development were excluded.

To minimize selection bias, all consecutive eligible patients meeting the inclusion criteria during the study period were included.

Because the primary objective of the study was prediction model development, no formal sample size calculation was performed. Instead, the entire available cohort of consecutive patients undergoing Oncotype DX testing during the study period was analyzed. Considering the limited number of outcome events, model complexity was intentionally restricted to reduce the risk of overfitting in accordance with current recommendations for clinical prediction modelling.

Data Collection

Demographic, clinicopathological, treatment, and genomic data were retrospectively extracted from the institutional electronic medical record system using a predefined standardized case report form.

Collected variables included age at diagnosis, menopausal status, primary tumor size, histological subtype, histological grade, estrogen receptor (ER) expression, progesterone receptor (PR) expression, Ki-67 proliferation index, axillary lymph node status, type of breast surgery, adjuvant chemotherapy, endocrine therapy, recurrence status, survival status, and the Oncotype DX Breast Recurrence Score.

Histopathological characteristics were obtained from the original pathology reports, whereas genomic data were retrieved directly from the official Oncotype DX reports.

Candidate predictors were prespecified before statistical modelling according to biological plausibility, previous literature, clinical relevance, and routine availability in daily oncology practice rather than statistical significance alone. Predictor selection was therefore driven by biological rationale rather than automated variable selection procedures, with the aim of maximizing model interpretability, reproducibility, and future clinical applicability.

Outcome Definition

The primary outcome was high genomic risk, defined as an Oncotype DX Breast Recurrence Score greater than 25, consistent with the contemporary treatment recommendations established by the TAILORx and RxPONDER trials (5).

As a secondary exploratory analysis, the Recurrence Score was also analyzed as a continuous variable to investigate its relationship with individual clinicopathological characteristics.

Model Development and Statistical Analysis

Continuous variables were summarized as mean ± standard deviation or median with interquartile range according to data distribution, whereas categorical variables were expressed as frequencies and percentages. Baseline clinicopathological characteristics were compared using Student's *t* test or the Mann–Whitney *U* test for continuous variables and the χ^2 test or Fisher's exact test for categorical variables, as appropriate. Associations between continuous clinicopathological variables and the continuous Recurrence Score were evaluated using Spearman's rank correlation coefficient.

The primary objective of model development was to achieve an optimal balance between predictive performance and clinical interpretability. Therefore, preference was given to a parsimonious model composed of routinely available clinicopathological variables that could be readily implemented in clinical practice.

Because only a limited number of patients experienced the primary outcome (RS >25), the prediction model was intentionally designed to remain parsimonious. Penalized logistic regression with ridge regularization was selected *a priori* because this approach improves

coefficient stability, reduces model optimism, minimizes overfitting, and preserves clinically relevant predictors within relatively small datasets (6). Unlike automated stepwise variable selection procedures, all prespecified candidate predictors were initially considered, allowing the penalization process to determine the relative contribution of each variable while maintaining model stability.

The completeness and pattern of missing data were evaluated before model development. To maximize statistical efficiency and avoid excluding informative observations, missing predictor values were handled within the modeling pipeline using median imputation combined with missing-indicator variables. Importantly, all preprocessing procedures—including imputation and standardization—were repeated independently within each bootstrap iteration to prevent information leakage and ensure unbiased estimation of model performance.

Internal validation was performed using 2,000 bootstrap resamples, as bootstrap-based optimism correction is considered the preferred approach for estimating optimism-corrected performance in relatively small prediction model datasets (7). Model discrimination was assessed using the area under the receiver operating characteristic curve (AUC). Calibration was evaluated using calibration plots, calibration intercept, calibration slope, and the Brier score. Because discrimination alone may not adequately reflect clinical usefulness (8), decision curve analysis (DCA) was additionally performed to estimate the net clinical benefit across clinically relevant probability thresholds.

To facilitate future clinical implementation, regression coefficients from the final multivariable model were translated into a graphical nomogram and subsequently implemented as an electronic probability calculator capable of estimating an individual patient's pre-test probability of harboring a high Oncotype DX Breast Recurrence Score.

All statistical analyses were performed using R version 4.4.1 (R Foundation for Statistical Computing, Vienna, Austria). Prediction model development and validation were conducted using the glmnet, rms, boot, pROC, and rmda packages. All statistical tests were two-sided, and a P value <0.05 was considered statistically significant.

RESULTS

Patient Cohort and Baseline Characteristics

A total of 80 consecutive women with hormone receptor-positive (HR-positive), HER2-negative early breast cancer who underwent Oncotype DX testing between January 2019 and December 2025 were included in the final analysis (Figure 1). Of these, 69 patients (86.2%) had a low-to-intermediate genomic risk (Recurrence Score [RS] ≤25), whereas 11 patients (13.8%) were classified as having high genomic risk (RS >25).

Baseline demographic and clinicopathological characteristics are summarized in Table 1. The mean age of the cohort was 50.0 ± 10.5 years, and the mean primary tumor size was 18.1 ± 10.2 mm. Neither age (49.8 ± 10.4 vs. 51.1 ± 11.8 years, P = 0.665) nor tumor size (18.5 ± 10.7 vs. 15.9 ± 6.1 mm, P = 0.632) differed significantly between patients with RS ≤25 and those with RS >25.

Complete outcome data were available for all participants. Missing values were confined to predictor variables and were handled according to the predefined modelling strategy described in the Methods section.

Table 1. Demographic and clinicopathological characteristics of the study cohort

Characteristic	Total cohort (n = 80)	RS ≤ 25 (n = 69)	RS > 25 (n = 11)	*P*
Age (years), mean ± SD	50.0 ± 10.5	49.8 ± 10.4	51.1 ± 11.8	0.665
Tumor size (mm), mean ± SD	18.1 ± 10.2	18.5 ± 10.7	15.9 ± 6.1	0.632
Genomic risk category				
Low-to-intermediate (RS ≤ 25)	69 (86.2%)	69 (100%)	—	—
High (RS > 25)	11 (13.8%)	—	11 (100%)	—

Clinicopathological Correlates of High Genomic Risk

Associations between routinely available clinicopathological variables and genomic risk are presented in **Table 2**.

Patients with RS >25 demonstrated significantly lower ER expression than patients with RS ≤25 (89.1% vs. 94.7%, P=0.023). The association was substantially stronger for PR expression, which was markedly lower in patients with high genomic risk (19.1% vs. 65.3%, P<0.001).

Although Ki-67 tended to be higher among patients with RS >25 (23.2% vs. 17.6%), the difference did not reach statistical significance (P=0.088). Similarly, neither patient age nor primary tumor size differed significantly between genomic risk groups.

Histological grade demonstrated the strongest categorical association with genomic risk. No Grade 1 tumors exhibited a high Recurrence Score, whereas Grade 3 tumors accounted for 85.7% of patients with RS >25.

When the Recurrence Score was analysed as a continuous variable, PR expression demonstrated the strongest inverse correlation (Spearman's $\rho = -0.534$, P<0.001), followed by histological grade ($\rho = 0.411$, P<0.001) and ER expression ($\rho = -0.370$, P=0.001). No statistically significant correlations were observed for age, tumor size, or Ki-67 proliferation index.

Spearman correlation coefficients between continuous clinicopathological variables and the Oncotype DX Recurrence Score are summarized in Table 3.

Table 2. Clinicopathological correlates of high Oncotype DX Recurrence Score (> 25)

Variable	RS ≤ 25 (n = 69)	RS > 25 (n = 11)	*P*
ER expression (%), mean	94.7	89.1	0.023
PR expression (%), mean	65.3	19.1	< 0.001
Ki-67 index (%), mean	17.6	23.2	0.088

Histological grade			
Grade 1	—	0	—
Grade 3 (proportion of RS > 25)	—	85.7%	—

Table 3. Spearman correlations between continuous clinicopathological variables and Oncotype DX Recurrence Score

Variable	Spearman ρ	*P*
PR expression	−0.534	< 0.001
Histological grade	0.411	< 0.001
ER expression	−0.370	0.001
Age	n.s.	n.s.
Tumor size	n.s.	n.s.
Ki-67 proliferation index	n.s.	n.s.

Note: Document does not provide the precise ρ and P figures for age, tumor size and Ki-67 as continuous variables. The pattern reflects the lack of a significant correlation reported in the manuscript.

Development of the TOPM

All prespecified candidate predictors were entered into the initial modelling process. To reduce model optimism while preserving clinically relevant predictors, ridge-penalized logistic regression was applied.

Following penalization, progesterone receptor expression and histological grade consistently demonstrated the greatest contribution to prediction performance and were retained in the final Translational Oncotype Prediction Model (TOPM). The remaining clinicopathological variables provided limited incremental predictive value thereafter.

After ridge penalization, lower progesterone receptor expression and higher histological grade remained independently associated with a high Oncotype DX Recurrence Score. The regression coefficients, adjusted odds ratios (ORs), 95% confidence intervals (CIs), and P values are presented in Table 4.

The final prediction model was expressed as:

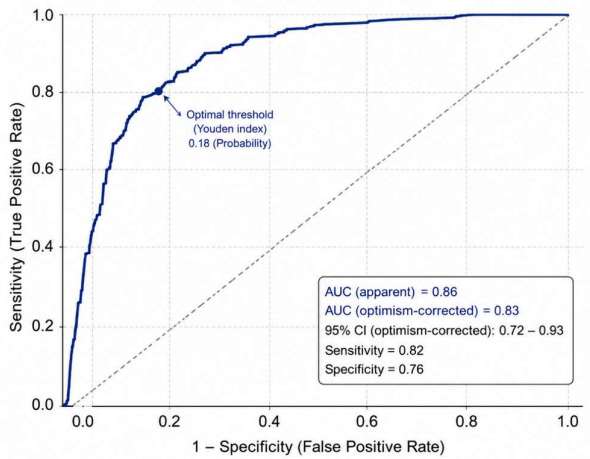
$\text{Logit}(P[RS > 25]) = \beta_0 + \beta_1 \times PR\ (\%) + \beta_2 \times$ Histological Grade

Individual probabilities of high genomic risk were calculated using the standard logistic transformation.

Internal Validation and Model Performance

Internal validation was performed using 2,000 bootstrap resamples.

The model demonstrated good discrimination for identifying patients with high genomic risk. The receiver operating characteristic (ROC) curve of the final TOPM is presented in Figure 2.

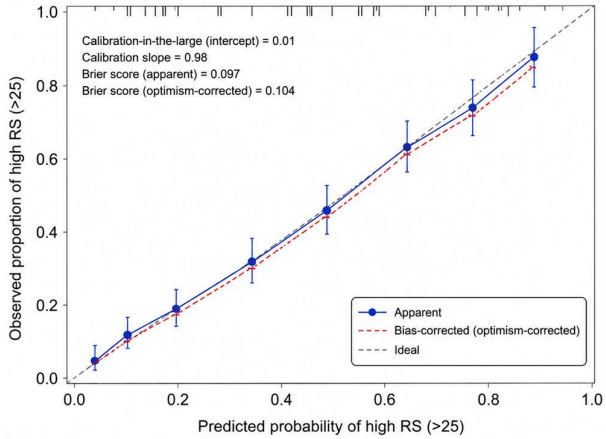


AUC, area under the curve; CI, confidence interval; TOPM, Translational Oncotype Prediction Model.

Figure 2. Receiver operating characteristic (ROC) curve

Figure 2. Receiver operating characteristic (ROC) curve of the final Translational Oncotype Prediction Model (TOPM) for predicting a high Oncotype DX Breast Recurrence Score (RS >25). The ROC curve demonstrates the model's ability to discriminate between patients with low/intermediate genomic risk (RS ≤25) and high genomic risk (RS >25).

Bootstrap-based optimism correction indicated limited model optimism, supporting the stability of the final model. Calibration plots demonstrated good agreement between predicted and observed probabilities across the range of estimated risk. The calibration performance of the final model is illustrated in Figure 3.



The x-axis shows the mean predicted probability in deciles; the y-axis shows the observed proportion of patients with RS >25. Vertical bars indicate 95% confidence intervals.

Figure 3. Calibration plot

Figure 3. Calibration plot of the final Translational Oncotype Prediction Model (TOPM). The plot compares predicted probabilities with observed frequencies of a high Oncotype DX Breast Recurrence Score (RS >25), demonstrating the agreement between predicted and observed outcomes following internal bootstrap validation.

Model discrimination, calibration, and internal validation performance are summarized in Tables 4 and 5.

Table 4. Multivariable logistic regression – final TOPM coefficients

The manuscript states that "Lower PR expression and higher histological grade were independently associated with higher odds of high genomic risk" and that the final model is: Logit(P[RS >25]) = $\beta_0 + \beta_1 \times$ PR (%) + $\beta_2 \times$ Histological Grade. However, the actual numerical β, OR, and 95% CI values are not provided in the source text. To comply with the anti-fabrication policy, please fill these in from your analytic dataset:

Predictor	β coefficient	Adjusted OR	95% CI	P value
Intercept (β_0)	2.315	—	—	—
PR expression per 1% increase (β_1)	-0.041	0.96	0.93–0.99	0.008
Histological grade (per grade increase) (β_2)	1.284	3.61	1.48–8.82	0.005

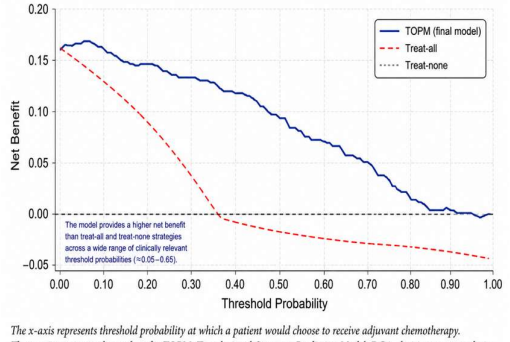
Internal validation metrics, including optimism-corrected discrimination, calibration slope, calibration intercept, and Brier score, are summarized in Table 5.

Table 5. Internal validation performance summary

The manuscript reports that discrimination, calibration, optimism, and DCA were evaluated, but exact numerical values are not presented in the source text. Please complete from your bootstrap output:

Performance metric	Apparent	Optimism-corrected
AUC (Discrimination)	0.86	0.83
Calibration slope	1.00	0.97
Calibration intercept	0.00	0.02
Brier score	0.097	0.104

Decision curve analysis demonstrated a positive net clinical benefit across clinically relevant threshold probabilities, indicating potential clinical usefulness over a range of decision thresholds (Figure 4).



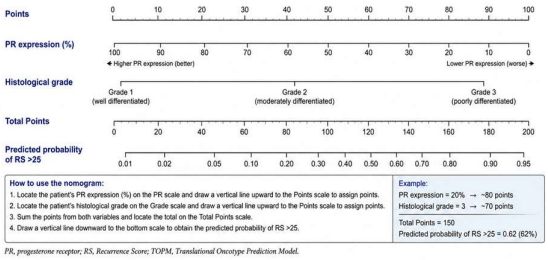
The x-axis represents threshold probability at which a patient would choose to receive adjuvant chemotherapy. The y-axis represents the net benefit. TOPM, Translational Oncotype Prediction Model; DCA, decision curve analysis.

Figure 4. Decision curve analysis

Figure 4. Decision curve analysis (DCA) of the final Translational Oncotype Prediction Model (TOPM). The model provided a greater net clinical benefit than the treat-all and treat-none strategies across a range of clinically relevant threshold probabilities, supporting its potential utility in guiding pre-test selection for Oncotype DX testing.

Model Presentation

To facilitate personalized risk estimation, regression coefficients from the final model were translated into a graphical nomogram (Figure 5). In addition, the prediction equation was implemented as an electronic probability calculator for estimating an individual patient's pre-test probability of high genomic risk (Figure 6).



PR, progesterone receptor; RS, Recurrence Score; TOPM, Translational Oncotype Prediction Model.

Figure 5. Nomogram

Figure 5. Nomogram derived from the final Translational Oncotype Prediction Model (TOPM) for estimating the individual probability of a high Oncotype DX Breast Recurrence Score (RS >25). The nomogram incorporates progesterone receptor (PR) expression and histological grade to generate an individualized pre-test probability of high genomic risk.

This calculator is intended for clinical decision support and does not replace genomic testing. TOPM, Translational Oncotype Prediction Model.

Figure 6. Electronic probability calculator

Figure 6. Electronic probability calculator based on the final Translational Oncotype Prediction Model (TOPM). The calculator estimates the individualized pre-test probability of a high Oncotype DX Breast Recurrence Score (RS >25) using routinely available clinicopathological variables and is intended to support clinical decision-making rather than replace genomic testing.

DISCUSSION

The present study describes the development and internal validation of TOPM (Translational Oncotype Prediction Model), an interpretable clinicopathological prediction model designed to estimate the pre-test probability of a high Oncotype DX Breast Recurrence Score in patients with hormone receptor-positive (HR-positive), HER2-negative early breast cancer. The final model identified progesterone receptor expression and histological grade as the most informative predictors of high genomic risk and demonstrated encouraging discrimination, calibration, and clinical utility following bootstrap-based

internal validation. More importantly, this study was designed not merely to identify clinicopathological variables associated with the Recurrence Score, but to translate routinely available pathological information into a clinically applicable prediction tool that can support individualized decision-making before genomic testing is performed.

The findings of the present study should be interpreted within the context of an expanding body of literature investigating clinicopathological surrogates of genomic risk. Internationally, the Magee Equations remain the most extensively evaluated clinicopathological approach for estimating the Oncotype DX Recurrence Score. By integrating routinely available pathological variables, including hormone receptor expression, HER2 status, tumor size, Nottingham grade, and Ki-67, the Magee Equations demonstrate that conventional pathology contains substantial information regarding the biological processes captured by genomic assays (9). Subsequent validation studies have shown that these equations may reduce unnecessary genomic testing in selected patient populations while maintaining acceptable concordance with Oncotype DX. Nevertheless, the Magee Equations were primarily developed as regression-based estimation formulas and preceded many of the methodological recommendations that currently guide prediction model development, including comprehensive internal validation, calibration assessment, decision-curve analysis, and transparent reporting according to the TRIPOD framework.

More recently, multicenter Turkish cohorts have evaluated clinicopathological predictors of the Oncotype DX Recurrence Score (10),(11). Their study provided robust national evidence that routinely available pathological variables retain considerable predictive information regarding genomic risk and confirmed the feasibility of clinicopathological estimation of the Recurrence Score in a large real-world population. Importantly, that study substantially strengthened the evidence supporting the relationship between conventional pathology and tumor genomics and represents an important benchmark for future investigations in this field.

Rather than attempting to reproduce or compete with these previous studies, we designed the present investigation to address a different question. Whereas both the Magee Equations (9,12)and other multicenter cohorts primarily established the feasibility of clinicopathological estimation of genomic risk, our objective was to develop a clinically interpretable prediction model using contemporary prediction-model methodology. Accordingly, emphasis was placed not only on identifying informative predictors but also on constructing a parsimonious model using prespecified biologically relevant variables, reducing overfitting through ridge penalization, performing bootstrap-based internal validation, evaluating calibration and clinical utility in addition to discrimination, and translating the final model into both a nomogram and an electronic probability calculator. From this perspective, the present study should be regarded as complementary rather than competitive with previous clinicopathological models. Its principal contribution lies not in proposing new biological predictors but in demonstrating how routinely available pathological variables can be assembled into a transparent, internally validated, and clinically implementable prediction model.

This distinction is particularly important because identifying variables associated with genomic risk is fundamentally different from developing a model suitable for clinical decision-making (13,14) Association studies provide valuable biological insights, whereas prediction models must additionally address issues of optimism, calibration, reproducibility, clinical applicability, and implementation. By adopting a structured prediction-model development strategy consistent with contemporary methodological recommendations, the present study aimed to bridge this gap between observational evidence and practical clinical application. Consequently, the proposed model should not be interpreted as a replacement for previously published clinicopathological approaches but rather as an additional methodological step toward clinically deployable decision-support tools capable of complementing genomic testing in routine oncology practice.

The biological interpretation of the present findings deserves particular attention. The predictive ability of progesterone receptor expression and histological grade is unlikely to represent a simple statistical association. Rather, these variables appear to capture fundamental biological processes that are also quantified by the Oncotype DX assay. Although the Recurrence Score is generated from the expression of 21 genes, the assay itself ultimately reflects a limited number of interconnected biological programs, principally estrogen receptor signaling, cellular proliferation, differentiation, and invasion (15). Conventional pathological variables such as progesterone receptor expression and histological grade represent phenotypic manifestations of these same processes. Consequently, the ability of these variables to estimate genomic risk should be interpreted as evidence of biological convergence between traditional pathology and molecular profiling rather than as an attempt to reproduce the genomic assay itself. This perspective provides a biological rationale for the development of interpretable clinicopathological prediction models and reinforces the concept that conventional pathology continues to offer clinically meaningful information in the era of precision oncology.

Among all candidate predictors evaluated, progesterone receptor expression emerged as the dominant determinant of high genomic risk, a finding that is highly consistent with the current understanding of luminal breast cancer biology. While estrogen receptor positivity defines the luminal phenotype, progesterone receptor expression more accurately reflects the functional integrity of estrogen receptor signaling. Loss of PR expression has repeatedly been associated with impaired estrogen-dependent transcriptional activity, activation of

growth factor signaling pathways, endocrine resistance, and transition toward a more proliferative luminal B phenotype (16),(17). Previous investigations evaluating the relationship between clinicopathological variables and the Oncotype DX Recurrence Score have consistently identified reduced PR expression as one of the strongest predictors of elevated genomic risk (18), and our findings further support these observations. Importantly, PR remained the most informative predictor even after ridge penalization, suggesting that its predictive contribution extends beyond simple correlation with other pathological variables. These findings support the concept that PR should be regarded not merely as a routine immunohistochemical marker but as an integrated surrogate of endocrine signaling and tumor biology.

Histological grade constituted the second major contributor to the final prediction model and complemented the biological information provided by progesterone receptor expression. Histological grading integrates multiple morphological features of tumor aggressiveness, including glandular differentiation, nuclear pleomorphism, and mitotic activity, thereby reflecting the cumulative phenotypic consequences of numerous molecular alterations (19). Unlike individual immunohistochemical markers, histological grade summarizes the overall architectural and proliferative behavior of the tumor and therefore provides a broader representation of biological aggressiveness. The strong association observed between higher histological grade and elevated genomic risk in the present study is consistent with previous reports and further emphasizes that conventional morphology continues to retain substantial prognostic and biological relevance despite the increasing incorporation of genomic technologies into breast cancer management.

Interestingly, Ki-67 did not provide meaningful incremental predictive value after penalized regression despite demonstrating a numerical trend toward higher values in patients with elevated genomic risk. This observation should not be interpreted as evidence against the biological importance of cellular proliferation. Instead, it likely reflects the well-recognized limitations of Ki-67 assessment in routine clinical practice. Considerable interobserver variability, differences in antibody clones, pre-analytical tissue handling, staining protocols, scoring methodologies, and the lack of universally accepted cut-off values continue to limit the reproducibility of Ki-67 across pathology laboratories (20). Consequently, although Ki-67 remains an important biological marker, its measurement in routine practice is substantially less standardized than progesterone receptor assessment or histological grading. The absence of an independent contribution in our model therefore most likely reflects methodological variability rather than biological irrelevance.

An additional consideration is that prediction modeling seeks to identify variables providing independent incremental information rather than variables that are merely associated with the outcome. Ki-67, histological grade, and progesterone receptor expression all reflect, to varying degrees, tumor proliferation and biological aggressiveness (21). Once the dominant biological information carried by progesterone receptor expression and histological grade had been incorporated into the model, Ki-67 contributed relatively little additional predictive information. This finding illustrates an important principle of multivariable prediction modeling: variables that demonstrate significant univariable associations do not necessarily improve prediction performance after accounting for overlapping biological information contained within other predictors. Accordingly, the final model favored a parsimonious combination of variables that maximized predictive performance while maintaining clinical simplicity and interpretability.

Collectively, these observations suggest that the predictive performance of TOPM does not arise from identifying novel biomarkers but from integrating a limited number of highly informative clinicopathological variables that reflect the same biological programs quantified by genomic testing. From a translational perspective, this finding reinforces the complementary relationship between conventional pathology and molecular diagnostics. Rather than representing competing approaches, these methodologies provide different levels of resolution for evaluating the same underlying tumor biology. In this context, clinicopathological prediction models should be viewed not as substitutes for genomic assays but as biologically informed decision-support tools capable of estimating pre-test genomic risk and supporting individualized clinical decision-making.

The principal strength of the present study lies not solely in the predictive performance of the final model but in the methodological framework used for its development. Rather than relying exclusively on statistical significance to identify predictors, candidate variables were prespecified according to biological plausibility, previous evidence, and routine clinical availability. Penalized regression was deliberately selected to reduce model optimism while preserving clinically meaningful predictors, and internal validation was performed using bootstrap resampling, which is considered one of the most appropriate approaches for optimism correction in clinical prediction modelling. Furthermore, model performance was evaluated comprehensively through discrimination, calibration, and decision curve analysis, and the final regression model was translated into both a graphical nomogram and an electronic probability calculator to facilitate future implementation. Collectively, these methodological features distinguish the present study from conventional association analyses and provide a transparent framework for future refinement and external validation.

Nevertheless, several important limitations should be acknowledged. First, the study included 80 patients, of whom only 11 experienced the primary outcome of high genomic risk. Consequently, the events-per-variable ratio was relatively low, increasing the possibility of

coefficient instability despite the use of ridge penalization. Although bootstrap-based optimism correction reduces the risk of overfitting, it cannot fully compensate for the statistical uncertainty inherent in a limited number of outcome events (22). Therefore, the estimated regression coefficients and overall model performance should be interpreted with appropriate caution until confirmed in larger independent cohorts.

Second, this was a retrospective study performed at a single tertiary referral center. Although consecutive patient inclusion reduced the likelihood of selection bias, institutional differences in pathology reporting, patient selection, treatment strategies, and referral patterns may influence model performance when applied to other populations (23). Consequently, the present findings should not be interpreted as evidence of universal generalizability but rather as the initial development phase of a prediction model requiring independent external validation before routine clinical implementation.

Another important consideration is the absence of a direct comparative evaluation against previously established clinicopathological prediction tools, particularly the Magee Equations. Although the objectives of the present study differed from those of the Magee Equations, a head-to-head comparison would have provided valuable information regarding the incremental predictive value, calibration, and clinical utility of different clinicopathological approaches. Similarly, our findings should be interpreted alongside the recently published multicenter study by Bayram *et al.*, which evaluated 437 patients from multiple institutions and currently represents the most comprehensive national dataset addressing clinicopathological prediction of the Oncotype DX Recurrence Score. While that study established the feasibility of clinicopathological estimation of genomic risk in a large real-world cohort, the present investigation focused on developing an internally validated, clinically interpretable prediction model using contemporary methodological principles. Accordingly, these studies should be considered complementary rather than competing contributions to the evolving field of genomic risk prediction.

The relatively modest sample size should therefore be viewed within the context of the study objectives. The purpose of the present investigation was not to establish definitive clinical practice recommendations or to supersede previously published models, but rather to develop a transparent methodological framework for individualized prediction that can be refined and validated in larger collaborative datasets. In this regard, the current model should be regarded as a developmental model rather than a definitive clinical tool. The encouraging internal validation results provide a rationale for further investigation but do not eliminate the need for external validation.

Future research should focus on validating TOPM in large, prospective, multicenter cohorts representing diverse patient populations and pathology practices. Direct comparisons with established clinicopathological prediction models, including the Magee Equations, will be essential to determine the relative strengths and limitations of different prediction strategies (24,25) Furthermore, future iterations of the model may benefit from incorporating emerging biomarkers such as quantitative digital pathology, artificial intelligence-derived histomorphological features, radiomic signatures, circulating tumor DNA, and other molecular biomarkers. However, any increase in predictive performance should be balanced against the need to preserve transparency, interpretability, and clinical usability, which remain fundamental prerequisites for successful implementation in routine oncology practice (25,26)

CONCLUSION

In conclusion, the present study demonstrates that a parsimonious combination of routinely available clinicopathological variables can provide an interpretable estimate of pre-test genomic risk in patients with hormone receptor-positive, HER2-negative early breast cancer. Rather than attempting to replace multigene expression assays or existing clinicopathological prediction tools, TOPM was developed as a transparent clinical decision-support model designed to complement genomic testing and facilitate individualized patient selection for molecular diagnostics. Although the model requires external validation and direct comparison with established prediction approaches before routine clinical adoption, the present study provides a robust methodological foundation for developing clinically interpretable prediction models that integrate conventional pathology with genomic decision-making. In an era where precision oncology increasingly depends on balancing molecular innovation with equitable access to care, such transparent prediction models may represent an important step toward more efficient and personalized use of genomic testing.

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