BREAST CANCER

Individualized Chemotherapy Benefit Prediction by EndoPredict in Patients With Early Breast Cancer in an Indian Cohort

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PURPOSE There are new advancements in the modulation of the treatment of patients with early-stage breast cancer, including the use of several molecular profiling tests to identify or select those patients who require additional adjuvant chemotherapy together with hormonal therapy on the basis of a recurrence score. One such tool is EndoPredict (Myriad Genetics; Salt Lake City, UT), which provides support in clinical decision making. The objective of this analysis was to study the landscape of absolute chemotherapy benefit and the likelihood of recurrence within 5 to 15 years in Indian patients with breast cancer who are undergoing EndoPredict testing.

PATIENTS AND METHODS This study included 308 patients with hormone-positive, human epidermal growth factor receptor 2–negative early breast cancer. Their postsurgical blocks were analyzed using the EndoPredict test. The MEDCALC statistical tool (Panum Education; Seoul, Republic of Korea) was used to estimate the correlation coefficient and to conduct multiple regression analysis.

RESULTS On the basis of the EndoPredict EPclin Risk Score, 52.12% of patients were classified as being in the low-risk category and could safely forgo adjuvant chemotherapy. For every unit increase in the EPclin Risk Score, the percentage increase in absolute chemotherapy benefit was 6.82%. Similarly, the correlation between the likelihood of recurrence within 5 to 15 years and the EPclin Risk Score suggested that there is a 10.34% increase in recurrence for each unit of EPclin Risk Score.

CONCLUSION The EPclin Risk Score has good prognostic and predictive power; it also provides the range of chemotherapy benefit for Indian patients.

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INTRODUCTION

In patients with early breast cancer, the natural progression of disease over time and the chance of recurrence are determined by various clinicopathologic factors. The specific treatment strategies for breast cancer depend on various pathologic factors such as the tumor size and grade and the lymph node status, as well as protein biomarkers such as estrogen receptor (ER), progesterone receptor, and human epidermal growth factor receptor 2 (HER2). The level of expression of these biomarkers helps in the selection of the targeted therapies for the patients, such as endocrine therapy in the case of ER-positive expression and/or anti-HER2–targeted therapies such as trastuzumab, pertuzumab, trastuzumab emtansine, or neratinib (in the case of HER2 overexpression/amplification).[1] These clinicopathologic factors help physicians understand the prognosis of the disease and the potential benefit from treatment strategies such as additional adjuvant chemotherapy.

Treatment modalities for patients with early-stage breast cancer have been advancing increasingly. In the past few years, there has been increased availability of molecular profiling tests, which have enabled physicians to determine the course of disease and also to estimate the efficiency of certain specific treatment modalities such as the administration of chemotherapy after surgery. This has been possible mainly because of advancements in technologic platforms such as the clinical use of genomics and sequencing methods. All these test are now included in almost all international breast cancer treatment guidelines such as those of the National Comprehensive Cancer Network and ASCO, despite the fact that they use different platforms for analysis and also that they have been validated in distinct cohorts. However, physicians still have many unanswered questions about using these tests for achieving better outcomes and about incorporating them into routine use. Another area of discussion for physicians is the selection of the best test to use and what its advantages are over other tests.

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

Will the EndoPredict test help in the optimization of treatment of patients with early breast cancer in India?

Knowledge Generated

The EndoPredict test highlighted the benefit of chemotherapy and use of gene expression results together with tumor size and nodal status in Indian patients with breast cancer.

Relevance

This can definitely help in the optimization of chemotherapy administration in Indian patients and can also help guide extended endocrine therapy.

In women with early-stage, ER-positive, HER2-negative breast cancer, recurrence rates during and after treatment are substantially reduced by the administration of endocrine therapy for 5 years. To further reduce the chance of recurrence, adjuvant endocrine therapy is often extended beyond the 5 years.[2] For all their proven benefit, prolonging life with adjuvant endocrine therapy can negatively affect the quality of that life, with adverse effects such as menopausal symptoms, arthropathy, and potential life-threatening problems including pulmonary embolism and endometrial cancer.[2,3] The findings of some clinical trials have suggested that patients gain no additional benefit from continuing endocrine therapy for more than 5 years.[4,5] Standard treatments may lead to significant differences in clinical outcome among patients with similar clinical and pathologic characteristics. Biologic heterogeneity and molecular differences in the tumors influence the chances of recurrence in early breast cancer. Therapy selection must be based on the specific indicative prognostic and predictive factors of the patient.[6] Gene expression profiling, which has come into clinical use in recent years, is beneficial in selecting therapy for luminal breast cancer cases. The primary concern in patients with early-stage breast cancer is to avoid recurrence, and one of the measures taken to do so is to treat the patient with chemotherapy. However, outcomes differ. Chemotherapy also has various adverse effects associated with it that must be considered when measuring it against its potential benefit. In recent times, the therapy selection for luminal-type breast cancer has been based on the clinical use of gene expression profiling. Using this approach, physicians can differentiate between patients who require endocrine therapy only and those who require additional adjuvant chemotherapy together with it.

The EndoPredict test is a second-generation multigene assay that integrates clinical variables together with the molecular characteristics of the tumor. It can accurately determine the risk of recurrence for up to 15 years among ER-positive, HER2-negative (ER+/HER2–) patients with early-stage breast cancer. EndoPredict was established and validated in two independent clinical validation studies (ABCSG6 and ABCSG8).[7-9] It provides prognostic information beyond all common clinicopathologic parameters[7,8] and clinical guidelines.[9,10] The EndoPredict test analyzes the RNA expression of a panel of eight target genes (*BIRC5*, *DHCR7*, *UBE2C*, *AZGP1*, *IL6ST*, *MGP*, *RBBP8*, and *STC2*) from the tumor specimen using reverse transcription polymerase chain reaction, and normalization genes (*CALM2*, *OAZ1*, *RPL37A*) are measured by real-time quantitative polymerase chain reaction. These target genes encode for proteins, such as apoptosis, cholesterol biosynthesis, and ubiquitin-proteasome system, to name a few, that are known to modulate biochemical mechanisms implicated in tumorigenesis within the cell.[11-13] The test result—the EPclin Risk Score—is then combined with tumor size and nodal status, resulting in the EP score.[9,10] It helps predict the benefit of chemotherapy and the 15-year risk of distant recurrence. The EPclin Risk Score is a continuous value (1.0-6.0) and allows for individualized adjuvant treatment decisions with regards to chemotherapy. A differentiation can be made between patients for whom endocrine treatment only would be adequate and those who should also receive chemotherapy in addition to endocrine treatment.

In this study, we believe that for the first time the whole range of chemotherapy benefits for Indian patients with early-stage breast cancer has been studied, and correlations have been validated between the EPclin Risk Score and various factors to establish the prognostic capability of the gene expression testing tool EndoPredict in the Indian population.

PATIENTS AND METHODS

A prospective database of EndoPredict (Myriad Genetics, Salt Lake City, UT) was maintained, and data between October 2015 and September 2019 were analyzed. During this time period, we received a total of 308 diagnostic requests to conduct the EndoPredict assay, which were sent to Myriad Genetics.. The formalin-fixed paraffin-embedded tissue samples were derived from female patients with primary breast cancer. All were ER-positive and HER2-negative tumors. The clinicopathologic data (tumor size, pathologic tumor size, nodal status, grading, and Ki67) were extracted from the pathology reports. Because this was a data collection analysis, the study was exempt from

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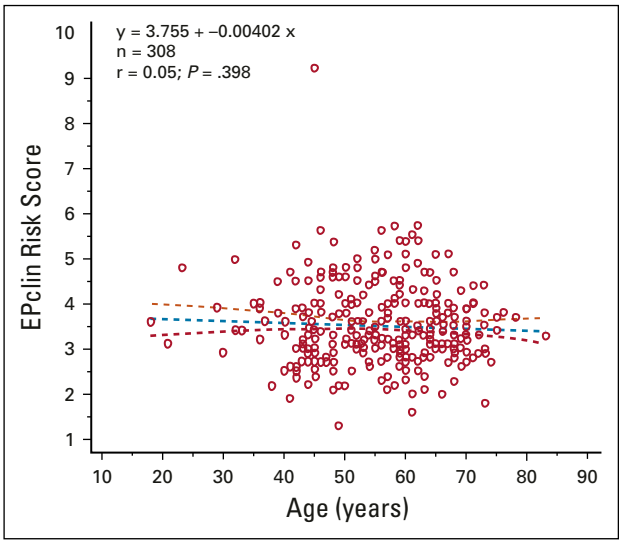

FIG 1. Relationship between EPclin Risk Score and age.

ethics committee approval. For the statistical analysis, tools from MedCalc were used. Multiple regression analysis was performed to determine the correlation between various factors and EPclin Risk Score, and the correlation coefficient was also calculated. All the graphical representations were created using MedCalc.

RESULTS

A total of 308 patients with early-stage breast cancer were considered for this study. Out of the total study population, 259 tumors (84.09%) were node negative and 49 tumors (15.90%) were node positive. There were 63 premenopausal women (19.48%) and 248 postmenopausal women (80.51%). Tumor size stratification in this cohort was as follows: T1 (n = 121, 39.28%); T2 (n = 183, 59.41%); and T3 (n = 4, 01.29%).

We then stratified patients on the basis of their EndoPredict EPclin Risk Score, which revealed that in the case of node-negative patients (n = 259), 124 (47.87%) were classified as high risk and 135 (52.12%) were classified as low risk. Furthermore, Figure 1 shows that on the basis of their gene expression score (EP score) only, 191 patients (73.74%) were stratified as high-risk patients; this demonstrates that 67 patients (25.87%) would have been misclassified if stratification and treatment decision were taken only on the basis of gene expression score.

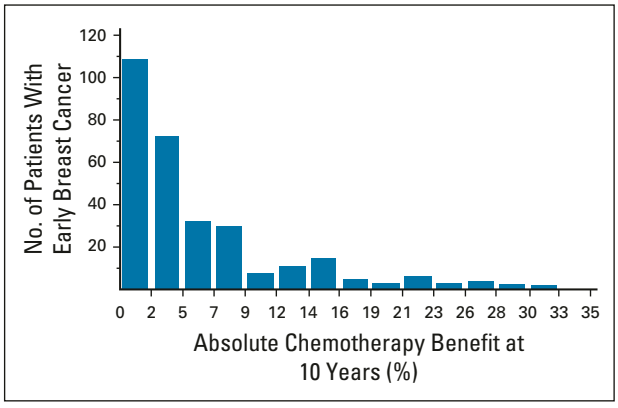

FIG 2. Distribution of absolute chemotherapy benefit at 10 years.

As for the tumor type classification of patients on the basis of EPclin Risk Score, it was observed that out of T1 N0 patients (n= 100), 31 (31.00%) were classified as high risk and 69 (69.00%) had a low risk score. In addition, among T2 N0 patients (n = 156), 93 (59.61%) had a high risk score and 63 (40.38%) were classified as low risk. In the next category, T3 N0 (n = 3), none of the patients were found to have a high risk of recurrence (all three patients [100%] had a low EPclin Risk Score). Furthermore, among T1cN1 patients (n = 21), 15 patients (71.42%) were classified as high risk and six (28.57%) as low risk. In the T2N1 patient category (n = 27), 27 (100%) were found to have a high risk score. In the last category, T3N1 (n = 1), no patient was found to be in the low risk category (EPclin high risk = 1 [100%]).

Absolute Chemotherapy Benefit at 10 Years

One of the major objectives of this study was to understand the range of absolute chemotherapy benefit in the Indian population, because the use of adjuvant additional chemotherapy depends on various clinicopathologic factors as well as on socioeconomic factors. According to these data, the average absolute chemotherapy benefit among patients with early-stage breast cancer was 6.06% ± 6.50%, with a range of 0% to 31%. Figure 2 clearly indicates the variation in the distribution of adjuvant chemotherapy in patients with early-stage breast cancer.

Correlation Between EPclin Risk Score and Absolute Chemotherapy Benefit at 10 Years in Node-Negative Patients With Early-Stage Breast Cancer

In this study, the correlation between EPclin Risk Score and absolute chemotherapy benefit at 10 years in the node-negative group was also analyzed as shown in Figure 3. During this regression analysis, absolute chemotherapy benefit was considered the dependent factor and EPclin Risk Score as the independent factor. The following regression equation was observed:

$$y = 6.82x - 17.9,$$

where y is the absolute chemotherapy benefit and x is the EPclin Risk Score.

This regression analysis revealed that in patients with early-stage breast cancer, for every 1 unit increase in EPclin Risk Score, the absolute chemotherapy benefit at 10 years increases by 6.82%. This establishes the validation of the relationship between EPclin Risk Score and absolute

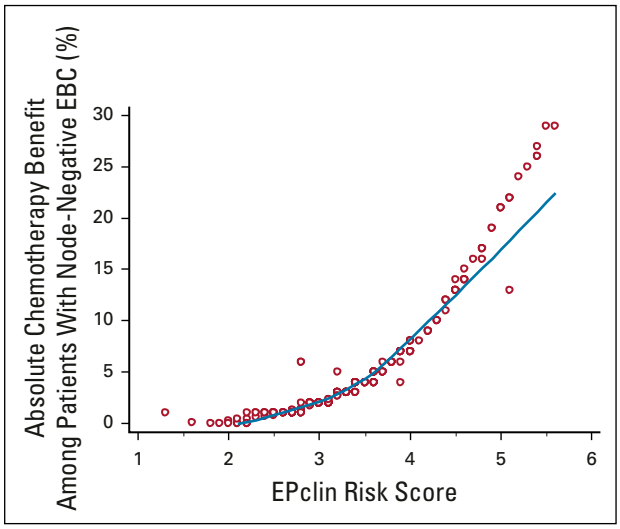

FIG 3. Distribution of absolute chemotherapy benefit among node-negative patients with early-stage breast cancer (EBC).

chemotherapy benefit in the Indian population. In addition to the regression analysis, the correlation coefficient (r) was calculated as $r = 0.92$ with a significant P value ($P < .0001$).

Likelihood of Recurrence in 5 to 15 Years With Extended Endocrine Therapy

Another important prediction from EndoPredict testing is the estimation of the likelihood of recurrence in 5 to 15 years with extended endocrine therapy in node-negative patients with early-stage breast cancer. The likelihood of recurrence between 5 and 15 years gives the estimation of late metastasis, which is important in understanding the prognosis of this disease and its likelihood of recurrence. Figure 4 shows the distribution of the likelihood of recurrence, which was found to be in the range of 1% to 54%; the average likelihood of recurrence in 5 to 15 years

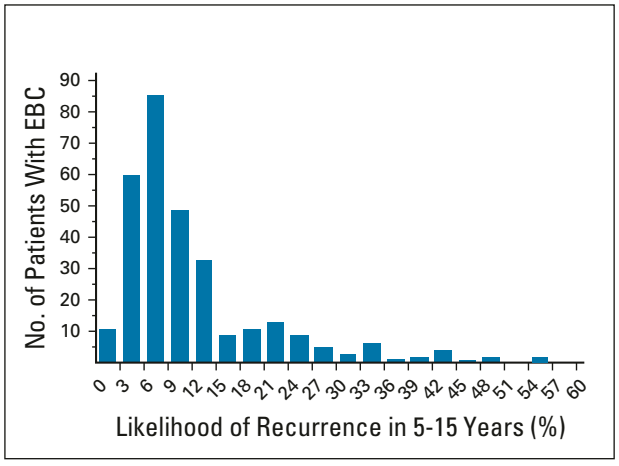

FIG 4. Distribution of likelihood of recurrence in 5 to 15 years. EBC, early-stage breast cancer.

with extended endocrine therapy was 11.77% ± 9.8%; and the median likelihood of recurrence was 8%.

Correlation Between EPclin Risk Score and Likelihood of Recurrence in 5 to 15 Years With Extended Endocrine Therapy in Node-Negative Patients With Early-Stage Breast Cancer

The analysis of the correlation between EPclin Risk Score and the likelihood of recurrence in 5 to 15 years with extended endocrine therapy in node-negative early breast cancer was performed using a regression tool with the likelihood of recurrence in 5 to 15 years as the dependent variable and EPclin Risk Score as the independent variable. The regression equation obtained is as follows:

$$y = 10.34x - 24.67,$$

where y is the likelihood of recurrence in 5 to 15 years and x is the EPclin Risk Score.

As depicted in Figure 5, this regression analysis revealed that for every 1 unit increase in EPclin Risk Score, the likelihood of recurrence in 5 to 15 years with extended endocrine therapy in node-negative patients with early-stage breast cancer increases by 10.34%. This gives the degree of relationship between these two factors. In addition, the coefficient of correlation was calculated as $r = 0.92$, with a significant P value ($P < .0001$).

Relationship of EPclin Risk Score With Different Factors

As discussed, various demographic and clinicopathologic factors, including age, tumor size, nodal status, and gene expression score (EP score), contribute in the determination of the risk of patients with early-stage breast cancer having a recurrence. The first factor that we analyzed was age. When the association of age with EPclin Risk Score was calculated, as shown in Figure 1, it was found that that age was not significantly correlated with EPclin Risk Score, with a correlation coefficient $r = 0.05$ and an insignificant P value of .398. This indicates that age is not a predicting factor in calculating EPclin Risk Score and it does not have any effect on the absolute chemotherapy benefit. Figure 6 depicts the next factor—the gene expression score—or EP score; we found that EPclin Risk Score is significantly dependent on gene expression score with a factor of 0.295, $r = 0.86$, and a significant P value of $< .001$. Furthermore, clinicopathologic factors such as nodal status were evaluated as shown in Figure 7, where it was found that EPclin Risk Score is significantly dependent on nodal status with a factor of 0.793, $r = 0.33$, and a significant P value of $< .001$. Finally, in Fig 8, another important clinicopathologic factor tumor size, EPclin Risk Score, was found to be significantly dependent, with a factor of 0.412, $r = 0.24$, and a significant P value of $< .001$.

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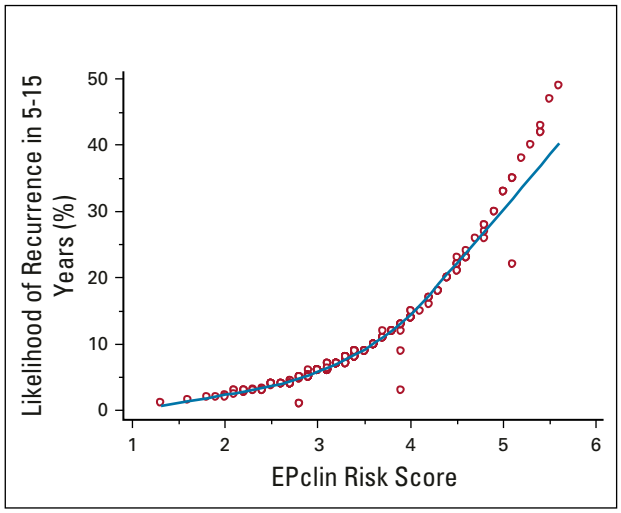

FIG 5. Distribution of likelihood of recurrence in 5 to 15 years among patients with node-negative early-stage breast cancer.

We also applied the multiple regression together, to validate the correlation factor. It was confirmed, with the multiple regression equation as follows:

$$\text{EPclin Risk Score} = 0.92 + 0.29(\text{EP score}) + 0.41(\text{tumor size}) + 0.79(\text{nodal status})$$

The P value for this association is $P < .0001$.

DISCUSSION

The current treatment strategy for patients with early-stage breast cancer includes the administration of adjuvant chemotherapy as standard practice, as indicated by early National Surgical Adjuvant Breast and Bowel Project studies. However, in the case of ER-positive, HER 2-negative and node-negative patients, most suffer from being overtreated because the clinical decisions for adjuvant chemotherapy are made only on the basis of the

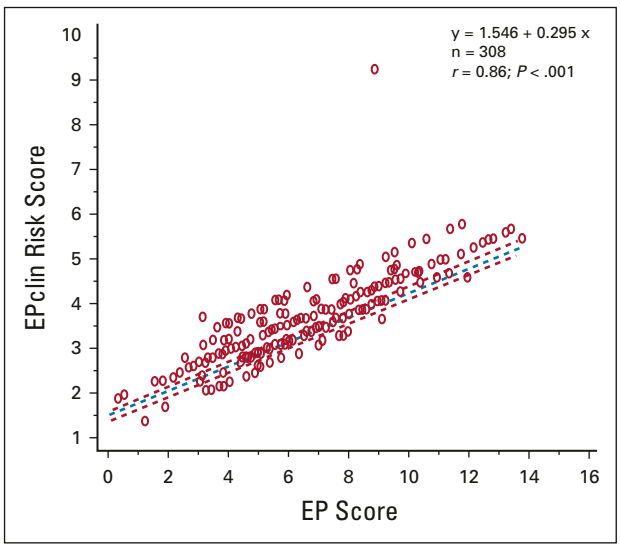

FIG 6. Relationship between EPclin Risk Score and EP score.

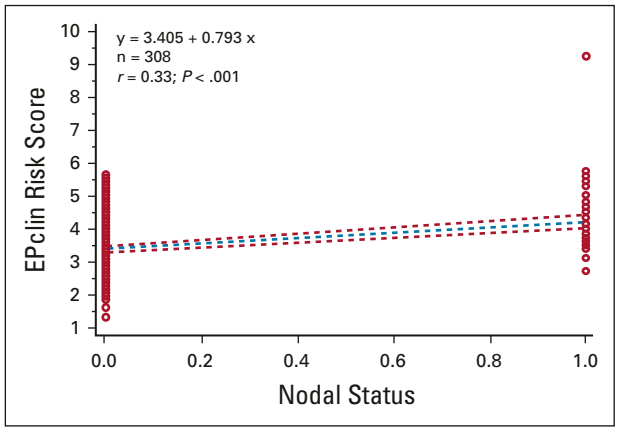

FIG 7. Relationship between EPclin Risk Score and nodal status.

histopathologic and clinical features of the tumor.[14] The Cochrane Review compiled data from 14 randomized clinical trials that included 5,600 women suffering from breast cancer. Data from this study showed that higher doses of chemotherapy did not indicate increased survival in these patients with early-stage breast cancer.[15] One of the best ways to improve the quality of life of patients is to strike a balance between the risk and benefit of chemotherapy. In the Indian scenario, various factors come into play when deciding on the use of gene expression testing for selecting patients to undergo adjuvant chemotherapy. On the patient front, there is a lack of awareness and difficulty in getting access to adequate health care facilities. It has also been proposed that there might be variations in breast cancer pathologic characteristics and disease etiology because India reports a greater number of patients having triple-negative breast cancers (ie, 30%, which is much higher than the reported 12% to 15% in Western countries).[16]

In the current study, an effort was made to initiate and establish the use of the second-generation gene expression test EndoPredict in Indian patients with early-stage breast cancer. To our knowledge, this study is the first multicenter prospective effort to monitor and validate the use of EndoPredict in Indian patients with breast cancer who are hormone positive. This test has an application not only in postmenopausal females, but also in premenopausal patients, because 19.48% of the patients tested belonged to the latter category. There were some interesting findings in the case of T1 node-positive patients, because 28.57% were classified as low risk, whereas in the case of T2 node-positive patients, none were classified as low risk. This establishes the superiority of EndoPredict over first-generation multigene prognostic tests, which do not include tumor size and nodal status in their algorithm. This same result has been observed in the various clinical validation studies conducted for EndoPredict as reported in the following trials: ABCSG6,[17] ABCSG8,[18] and TRANSATAC (ClinicalTrials.gov identifiers: NCT00309491, NCT00291759, and NCT03503799, respectively.[19]

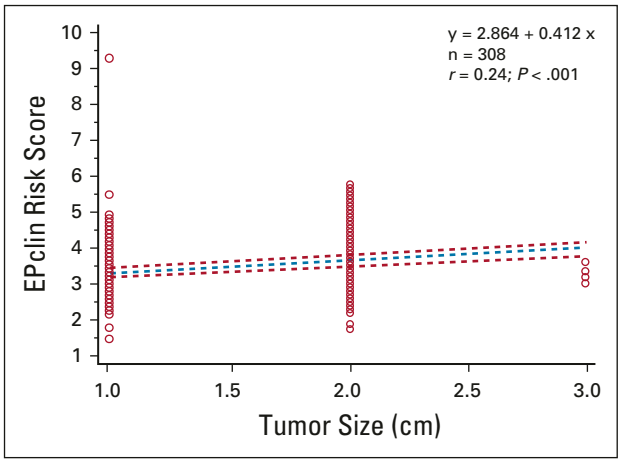

FIG 8. Relationship between EPclin Risk Score and tumor size.

To our knowledge, this is the first instance in which absolute chemotherapy benefit was analyzed in Indian patients with early-stage breast cancer, and the average absolute chemotherapy benefit was observed to be 6.06% ± 6.50%. In the current study, it was found that for every 1 unit increase in EPclin Risk Score, the absolute chemotherapy benefit at 10 years increased by 6.82%. This demonstrates the correlation of absolute chemotherapy benefit and EPclin Risk Score in the Indian population, as illustrated in Figure 3. This finding definitely supports the data from the study presented by Sestak et al,[20] which included 3,746 women and which showed, in an indirect analysis, that a high EPclin Risk Score can predict absolute chemotherapy benefit in patients with early-stage breast cancer who are ER positive and HER2 negative.

Similarly, we analyzed the distribution of the likelihood of recurrence in 5 to 15 years with extended endocrine therapy in patients with early-stage breast cancer, As shown in Figure 3, it was found that the average likelihood of recurrence in 5 to 15 years with extended endocrine therapy was 11.77% ± 9.8%. In addition, the same correlation with EPclin Risk Score revealed that for every 1 unit increase in EPclin Risk Score, the likelihood of recurrence in 5 to 15 years with extended endocrine therapy in node-negative patients with early-stage breast cancer increased by 10.34%. This also supports the latest data, which show that EPclin Risk Score can identify patients at low risk of early or late recurrence who may safely forgo adjuvant chemotherapy or extended endocrine therapy.[21]

In conclusion, this study indicates the clinical usefulness of EndoPredict testing over the use of single approaches (ie, only gene expression score or only using clinicopathologic features such as tumor size, nodal status, ki67, and so forth) to select patients for adjuvant chemotherapy and extended endocrine therapy. EndoPredict provides a comprehensive and holistic approach toward all clinical decisions in an optimized manner. It ensures the best outcome for patients with early-stage breast cancer. However, the follow-up and data collection of these patients is still an on-going process to establish the prospective aspect and their disease recurrence. This study is a beginning point for initiating and establishing the concrete usefulness of molecular profiling in the clinical management of hormone-positive and HER2-negative patients with early-stage breast cancer.

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Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Fatma Islahi
Employment: Positive Bioscience

No other potential conflicts of interest were reported.

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