Clinical Treatment Score Post-5 Years as a Tool for Risk Estimation of Late Recurrence in Thai Patients With Estrogen-Receptor-Positive, Early Breast Cancer: A Validation Study

Thitiya Dejthevaporn[1] and Panchanin Patanayindee[1,2]

[1]Division of Medical Oncology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand. [2]Medical Oncology Unit, Department of Medicine, Faculty of Medicine, Thammasat University, Bangkok, Thailand.

ABSTRACT

BACKGROUND: The risk of late distant recurrence (LDR) of estrogen receptor (ER)-positive breast cancer continues even after 5 years of endocrine treatment. Clinical Treatment Score after 5 years (CTS5) was developed and validated as a tool to assess the risk of LDR using data from Tamoxifen, Arimidex Alone or in Combinations (ATAC) and Breast International Group 1-98 (BIG1-98) trials. This study aimed to externally validate CTS5 in a real-world cohort of patients treated at an academic center in Thailand.

METHODS: The study was a retrospective analytical research study of early-stage, ER-positive breast cancer patients. The primary end-point was LDR. The risk of LDR was determined using the CTS5 calculator. Cox regression model and Kaplan-Meier survival analysis were applied for prognostic validation of CTS5. Calibration was performed by comparing observed LDR to expected LDR using the Hosmer-Lemeshow (H-L) test.

RESULTS: A total of 323 women were included with a median follow-up period of 11.6 years. The rate of LDR was 10.8%. The CTS5 was prognostic for LDR. C-index of the area under the ROC curve was 0.672. There was no significant difference between actual and expected numbers of LDR with an observed (O) LDR events to expected (E) number of LDR events ratio of 0.99 (0.86-1.12) (H-L P = .79) indicating a proper calibration in this cohort.

CONCLUSIONS: Our study validated that CTS5 is accurate in predicting the risk of LDR in ER-positive breast cancer cases in Thai patients. Its performance seemed to be better in postmenopausal patients. CTS5 could be applied in routine clinical practice to improve decisions regarding prolonged endocrine therapy, particularly in resource-limited countries where molecular profiling are inaccessible.

KEYWORDS: Hormone receptor positive breast cancer, CTS5, late distance relapse, endocrine treatment

Introduction

Incidence of breast cancer has increased worldwide over recent years. It has been one of the leading causes of death in women for more than 10 years. In Thailand, the age-standardized incidence rate of breast cancer per 100,000 population has increased from 28.5 in 1995 to 2012 to 31.4 in the years 2013 to 2015. Breast cancer is the most common cancer among Thai women.[1]

Breast cancer screening has led to an improvement in breast cancer outcomes as more early-stage cancers are detected. Improvements in systemic chemotherapy including endocrine treatment for estrogen receptor (ER)-positive breast cancer have reduced the risk of recurrence and death. ER-positive breast cancer is the predominant breast cancer subtype. Even with the standard 5 years of adjuvant endocrine therapy (ET), late distant relapse occurs. Pan et al[2] reported a steady rate of recurrence over years 5 to 20 following completion of the first 5 years of adjuvant ET. The risk of recurrence is associated with tumor size, nodal stage, and histological grade and ranges from 10% to 41%.

Strategies to overcome this persistent risk of late relapse by extending ET beyond 5 years have shown only modest benefits, primarily in disease-free survival. The trials that evaluated the use of extended ET included ATLAS,[3] aTTOm,[4] NCIC CTG MA 17,[5] National Surgical Adjuvant Breast and Bowel Project B-33,[6] IDEAL,[7] GIM-2,[8] and DATA.[9] In addition to the lack of clear survival improvement, prolonged use of anti-hormonal drugs carries a risk of side effects such as thromboembolism, endometrial cancer, osteoporosis, and cardiovascular diseases.[10-12] Therefore, one should exercise caution while using such strategy.

Progress has been made in the field of risk prediction for distant recurrence (DR) in ER-positive early breast cancer (EBC), based on molecular profiling and/or clinicopathological features. Examples are OncotypeDx Recurrence Score (RS),[13] Breast Cancer Index (BCI),[14,15] PAM50 Prosigna Risk of Recurrence score,[16,17] EndoPredict (EPclin),[18] and Clinical Treatment Score after 5 years (CTS5).[19] The aforementioned tools except OncotypeDx RS have been shown to predict late

recurrence 5 to 10 years after diagnosis in ER-positive breast cancer cases. CTS5 was built from only basic information of the tumor and was validated with large BIG1-98 and ATAC cohort studies.[19] Compared to BCI,[20] which is a more costly molecular-based assay, CTS5 has a moderate concordance rate. In this study, we externally validated the performance of CTS5 in a real-world practice setting in Thai patients with ER-positive breast cancers, in both premenopausal and postmenopausal women. This study was conducted in a single cancer center in one of the major academic centers in Bangkok, Thailand.

Method

Patients and study design

This was a retrospective analytical research. Patients were identified through a computer-based search of Ramathibodi Hospital Cancer Registry Database. The inclusion criteria were stage I-III EBC with ER-positive patients who were relapse-free after completion of 4.5 to 5.5 years of any adjuvant ET (tamoxifen, aromatase inhibitor [AI], or both) and sufficient pathological data for CTS5 calculation (tumor size, nodal status, and tumor grade). Patients with any Human Epidermal Growth Factor Receptor-2 (HER2) status were included. Patients were excluded if they had de novo metastasis, noninvasive breast cancer, DR during adjuvant ET, incomplete clinical data (such as absence of details on ET or chemotherapy, surgery, or lost to follow-up), or had received extended duration of ET. All patients included in the study were diagnosed between June 2003 and June 2012 to allow for at least 8 years of follow-up after the initial diagnosis. Clinical data were collected from electronic medical records. The study was approved by the Ethics Committee of Ramathibodi Hospital (COA. MURA2020/1528).

CTS5 calculation

The CTS5 calculator is freely available at http://www.cts5-calculator.com. The final model, based on the combined ATAC and BIG 1-98 data set, is[19]

- CTS5 = 0.438 × nodes + 0.988 × ([0.093 × size] − [0.001 × size 2] + [0.375 × grade] + [0.017 × age])
- Risk of late distance recurrence at 5 to 10 years* = 1 − ([baseline risk]$^{\text{linear prediction CTS5}}$)

*Proportional assumptions were verified using Schoenfeld residuals.

Statistical analysis

The primary endpoint was late distant recurrence (LDR), which was defined as any distant metastasis, excluding contralateral disease and locoregional and ipsilateral recurrences, that occurred after completion of 5 years of adjuvant ET, as well

as second primary cancers. The primary objective of the study was to test the discriminative value of CTS5 and whether the predicted risk was properly calibrated in our patient cohort. The secondary objective was to explore the performance of CTS5 in subgroups of premenopausal and postmenopausal women.

Risk stratification was defined as low risk if the mean 5- to 10-year DR risk was <5%; intermediate risk if it was 5% to 10%; and high risk if it was >10%. The CTS5 score was calculated for each patient. Patients were then stratified into the three risk groups using the following CTS5 cutoffs: low risk < 3.13, intermediate risk 3.13 to 3.86, and high risk > 3.86.[19]

Sample size estimation

According to the development data set of CTS5, the rate of DR after 5 years was 7%, and the mean 5- to 10-year distant relapse risk of the low-risk group was 2.5%.[19] In order to detect the estimated 1.6-fold and 4-fold increases in LDR in the intermediate-risk and high-risk groups, respectively, a sample size of 306 patients was required. With this assumption, LDR events of 26 cases would achieve 80% power at α significance level of 0.05.

The baseline clinical characteristics were reported using descriptive statistics. The endpoint of LDR was censored at the last follow-up visit or at death before a DR event. The Kaplan-Meier method was used to estimate the time to LDR for the three risk groups and to assess the discriminative property of CTS5. Hazard ratio (HR) and 95% confidence intervals (95% CI) between low-intermediate risk and low-high risk were calculated using Cox proportional-hazards model. Log-rank test was applied to compare the Kaplan-Meier survival estimates among the 3 risk categories. The 5- to 10-year LDR risk was calculated using the aforementioned algorithm. The discriminative ability of CTS5 was evaluated by determining the area under the receiver operating characteristic (ROC) curve of LDR of the entire cohort, the postmenopausal cohort, and the premenopausal cohort (C-index).

To evaluate the calibration of CTS5, the observed (O) LDR events and expected (E) number of LDR events were compared (O/E ratio) in a six quantiles of expected events using Hosmer-Lemeshow (H-L) test. A P value of >.1 indicated appropriate calibration.[21] All analyses were performed with STATA software (version 16, STATA, College Station, TX).

Result

Baseline characteristics

Between June 2003 and June 2012, 4 845 patients with EBC were identified by searching the electronic patient records in the Ramathibodi Hospital Cancer Registry Database. There were 2 948 patients who were ER-negative or unknown or who
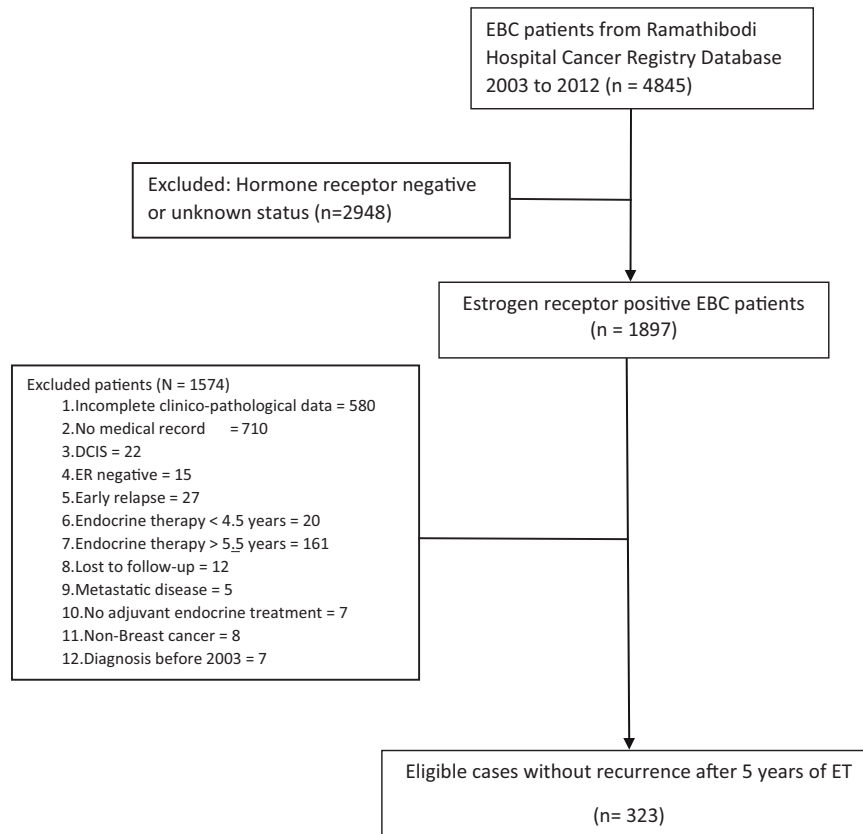
Figure 1. Schematic diagram of patient selection. A total of 323 patients who were free of distant relapse after 5 years of endocrine treatment were eligible for final analysis. EBC indicates early breast cancer; ET, endocrine therapy; DCIS, ductal carcinoma in situ; ER, estrogen receptor.

had no records of prescriptions for ET from the hospital pharmacy. Among the 1897 women with ER-positive EBC, 1574 cases were excluded, mainly due to inadequate clinicopathological information (absence of details on tumor size/nodes/tumor grade needed for CTS5 calculation, or no details of ET or chemotherapy) and unavailability of medical records. Other reasons for exclusion were less than 4.5 years or longer than 5.5 years of ET and early distant relapse during adjuvant ET (Figure 1).

The remaining 323 women were included in the final analysis. The median follow-up time was 11.6 years (95% CI: 11.2-11.8) from the initial diagnosis. Patient baseline characteristics are summarized in Table 1. There were 175 postmenopausal women (54.2%), 144 premenopausal women (44.6%), and 4 (1.2%) perimenopausal women in the cohort. The median age was 60 years in the postmenopausal group and 45 years in the premenopausal group ($P < .001$). The overall tumor characteristics were comparable in both groups with a median tumor size of 20 mm. Two-thirds of the patients were axillary node negative, and 14% had 4 or more nodal metastases (N2-3). The majority of the tumors (68%) were of grade 2. All the tumors were ER positive. HER2 positivity rate was 10.4%, and only 18% (6/34) received adjuvant trastuzumab. (Neo)adjuvant chemotherapy was given to 194 (60.1%) patients with a non-significantly higher proportion of premenopausal women receiving adjuvant chemotherapy (66% vs 55.4%, $P = .06$). The ET prescribed was significantly different between the 2 groups.

Nearly all (95.1%) the premenopausal women received tamoxifen, whereas in the postmenopausal cohort, 63% received 5 year therapy of AI or AI switching and only one-third received 5 years of tamoxifen ($P < .001$).

After a median follow-up time of 11.6 years, LDR was observed in 35 patients (10.8%), evenly distributed between premenopausal and postmenopausal patients. The most common metastatic sites were lung/pleura followed by bone. The rate of LDR among the 503 excluded patients with adequate follow-up was 5% while no data could be retrieved from the remaining 710 patients whose medical records were unavailable. The mean CTS5 score of the total population was 3.3 ± 0.9, with a significantly higher mean CTS5 score in the postmenopausal group (3.45 ± 0.88) than that in the premenopausal group (3.12 ± 0.9) ($P = .0009$). More postmenopausal than premenopausal patients were categorized under intermediate risk and high risk (33.1% and 26.3% vs 22.9% and 19.4%, respectively) ($P = .01$).

Overall, the tumors were well-classified into CTS5 risk groups (Table 2), with larger tumors, nodal metastases, and higher-grade tumors seen more in the intermediate- and high-risk groups than in the low-risk group. Interestingly, only two-thirds of lymph node-negative patients (214 cases) were classified as low risk. More patients in the intermediate- and high-risk groups received adjuvant chemotherapy than those in the low-risk group (77%, 85.5%, and 43.9%, respectively, $P < .001$).

Table 1. Baseline patient characteristics (n = 323).

CHARACTERISTIC	ENTIRE COHORT, N = 323 (%)	POSTMENOPAUSAL, N = 175[a]	PREMENOPAUSAL, N = 144[a]	*P* VALUE
Age (median, years)	51	60	45	<.001
Nodal status (no. of positive nodes)				
Negative	214 (66.3)	118 (67.4)	95 (66.0)	.86
1	38 (11.7)	19 (10.9)	19 (13.2)	
2-3	25 (7.7)	13 (7.4)	11 (7.6)	
4-9	33 (10.2)	19 (10.9)	12 (8.3)	
>9	13 (4.02)	6 (3.4)	7 (4.9)	
Grade				
1	64 (19.8)	29 (16.6)	35 (24.3)	.21
2	221 (68.4)	123 (70.3)	94 (65.3)	
3	38 (11.8)	23 (13.1)	15 (10.4)	
Tumor size (mm)				
<10	36 (11.2)	14 (8)	20 (13.9)	.30
10-20	135 (41.8)	79 (45.1)	56 (38.9)	
21-30	91 (28.2)	51 (29.1)	39 (27.1)	
>30	61 (18.9)	31 (17.7)	29 (20.1)	
Median (IQR)	20 (15)	20 (13)	20 (16.0)	
Hormone status				
ER-positive, PR-positive	275 (85.1)	146 (83.4)	126 (87.5)	.31
ER-positive, PR-negative	48 (14.9)	29 (16.6)	18 (12.5)	
HER2 status[b]				
Positive	34 (10.5)	19 (10.9)	13 (9.0)	.84
Negative	248 (76.8)	135 (77.1)	112 (77.8)	
IHC 2 + & unconfirmed FISH	41 (12.7)	21 (12.0)	19 (13.2)	
Type of surgery				
BCT	78 (24.1)	37 (21.1)	39 (27.0)	.40
Mastectomy	245 (75.9)	138 (78.9)	105 (72.1)	
(Neo)adjuvant chemotherapy[c]	194 (60.1)	97 (55.4)	95 (66)	.06
(Neo)adjuvant chemotherapy regimen[d]				
CMF	28 (14.4)	17 (17.5)	11 (11.6)	.57
AC	118 (60.8)	57 (58.8)	60 (63.2)	
Taxane-based (AC-T, TAC, TC)	42 (21.6)	21 (21.6)	20 (21.1)	
Others	6 (3.1)	2 (2)	4 (4.2)	
Adjuvant trastuzumab	6/34 (17.6)	5/19 (26.3)	1/13 (7.7)	.23
Hormonal treatment				
Tamoxifen 5 years	202 (62.5)	65 (37.1)	137 (95.1)	<.001
Aromatase inhibitor 5 years	83 (25.7)	81 (46.3)	2 (1.4)	
Tamoxifen/AI switching for 5 years total	38 (11.8)	29 (16.6)	5 (3.5)	
Late distant recurrence	35 (10.9)	18 (10.3)	16 (11.1)	.81
Local/regional recurrence	12 (3.7)	5 (2.9)	7 (4.9)	.36
Contralateral breast cancer	4 (1.2)	2 (1.1)	2 (1.4)	>.999

(Continued)

Table 1. (Continued)

CHARACTERISTIC	ENTIRE COHORT, N = 323 (%)	POSTMENOPAUSAL, N = 175[a]	PREMENOPAUSAL, N = 144[a]	*P* VALUE
CTS5 score				
Low risk	155 (48.0)	71 (40.6)	83 (57.6)	.01
Intermediate risk	92 (28.5)	58 (33.1)	33 (22.9)	
High risk	76 (23.5)	46 (26.3)	28 (19.4)	
Score, mean ± SD	3.3 ± 0.9	3.5 ± 0.9	3.1 ± 0.9	.001
Median F/U time (year)	11.6	11.7	11.5	.21

Abbreviations: IQR, interquartile range; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor recptor 2; IHC, immunohistochemistry; FISH, Fluorescence in situ hybridization; BCT, breast conservation therapy; CMF, cyclophosphamide-methotrexate-fluorouracil; AC, adriamycin-cyclophosphamide; AC-T, adriamycin-cyclophosphamide-taxanes; TAC, docetaxel-adriamycin-cyclophosphamide; TC, docetaxel-cyclophosphamide; AI, aromatase inhibitor; CTS5, Clinical Treatment Score after 5 years; SD, standard deviation; F/U, follow-up.
[a]Excluded 4 perimenopausal women.
[b]HER2 status: positive = either IHC 3 + or FISH HER2 positive, negative = IHC 0-1 + or confirmed FISH HER2 negative regardless of IHC, FISH HER2 was performed in 81 cases.
[c]Two perimenopausal women received (neo)adjuvant chemotherapy.
[d]The denominator was numbers of patients who received (neo)adjuvant treatment.

Table 2. Clinicopathological data and late distant relapse of patients in each CTS5 risk group.

CHARACTERISTIC	ENTIRE COHORT, N = 323(%)	LOW RISK, N = 155 (%)	INTERMEDIATE RISK, N = 92 (%)	HIGH RISK, N = 76 (%)	*P* VALUE
Age (median, years)	51	49	56	54	
Menopausal status					
Premenopausal	144 (44.6)	83 (53.6)	33 (35.9)	28 (36.8)	.03
Postmenopausal	175 (54.1)	71 (45.8)	58 (63.0)	46 (60.5)	
Perimenopausal	4 (1.2)	1 (0.7)	1 (1.1)	2 (2.6)	
Nodal status (no. of positive node)					
Negative	214 (66.3)	142 (66.4)	68 (31.8)	4 (1.9)	
1	38 (11.7)	13 (34.2)	16 (42.1)	9 (23.7)	
2-3	25 (7.7)	0 (0)	6 (2)	19 (76.0)	
4-9	33 (10.2)	0 (0)	2 (6.1)	31 (93.9)	
>9	13 (4.02)	0 (0)	0 (0)	13 (100)	
Grade					
1	64 (19.8)	57 (89.1)	7 (10.9)	0 (0)	
2	221 (68.4)	91 (41.0)	72 (32.4)	58 (26.6)	
3	38 (11.8)	7 (18.4)	13 (34.2)	18 (47.4)	
Tumor size (mm)					
<10	36 (11.2)	34 (94.4)	2 (5.6)	0 (0)	
10-20	135 (41.8)	100 (74.1)	25 (18.5)	10 (7.4)	
21-30	91 (28.2)	18 (19.8)	44 (48.4)	29 (31.9)	
>30	61 (18.9)	3 (4.8)	21 (33.9)	37 (61.3)	
(Neo)adjuvant chemotherapy					
Yes	194(60.0)	65 (41.9)	69 (75.0)	60 (78.9)	<.001
Late distant recurrence	35	10	8	17	.001

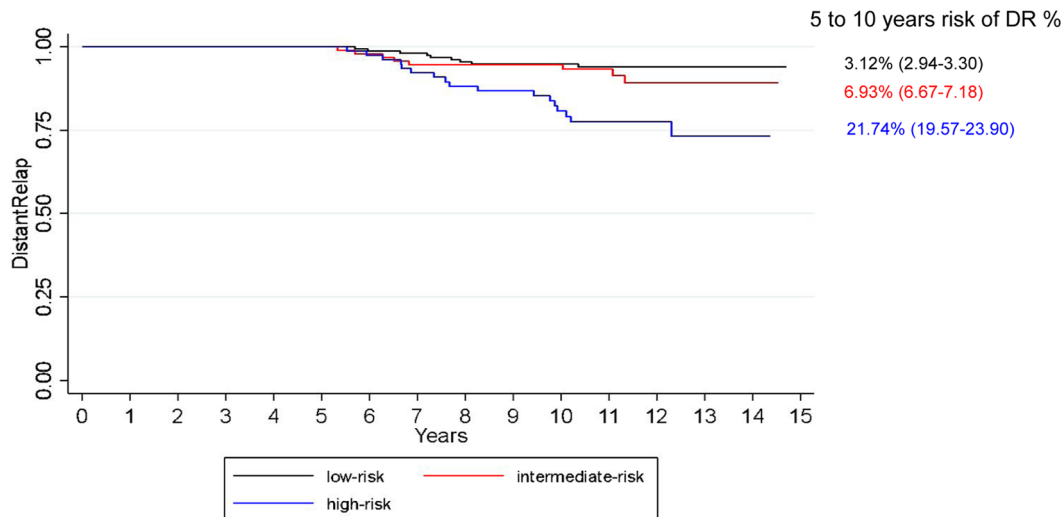Abbreviation: CTS5, Clinical Treatment Score after 5 years.

Figure 2. The Kaplan-Meier curve of observed late distant recurrence-free survival according to risk stratification by CTS5 score, indicating discriminative value of the CTS5 in the study population (log-rank, $P < .001$). The black, red, and blue lines represent low-risk, intermediate-risk, and high-risk subsets, respectively. Low risk, n = 155; intermediate, n = 92; and high, n = 76. CTS indicates Clinical Treatment Score.

Validation of the performance of CTS5 score

Discrimination. From the Kaplan-Meier analysis of LDR-free survival, CTS5 was able to separate the patients into 3 groups with different outcomes (log-rank, $P < .001$) (Figure 2). The mean 5- to 10-year DR risk in low-, intermediate-, and high-risk groups were 3.1%, 6.9%, and 21.7%, respectively (Figure 2). CTS5 as a continuous variable was prognostic for LDR (HR 2.1, 95% CI 1.37-3.18, $P = .001$) (Table 3).

Patients in the high-risk group had a 4.20-fold higher risk of LDR than those in the low-risk category ($P = .001$). Patients in the intermediate-risk group had a 1.55-fold higher risk of LDR than those in the low-risk group, but the difference was not statistically significant (95% CI 0.6-4.01, $P = .37$). The C-index of the CTS5 performance was 0.672, indicating that CTS5 had a moderate discrimination value. ROCs were plotted separately for premenopausal and postmenopausal cohorts. The discriminative performance of CTS5 in the postmenopausal women was better (with C-index of 0.720) than that in premenopausal women (C-index 0.620) (Figure 3).

Calibration. The current data set was divided into six quantiles (54 patients per quantile), and the number of observed (O) distant relapses was compared with the number of expected (E) distant relapse events calculated by CTS5. Based on the H-L method, there was no significant difference between actual and expected numbers of LDR events in all intervals (H-L, $P = .79$) (Figure 4) indicating an appropriate calibration. The overall O/E ratio was 0.99 (95% CI 0.86-1.12). Similar findings were observed when the premenopausal and postmenopausal patients were analyzed separately.

Discussion

The risk of recurrence in ER-positive breast cancer can persist for up to 20 years after diagnosis. Extended adjuvant ET

Table 3. Cox regression analysis of late distant relapse according to CTS5 as a continuous variable and as risk group stratification (N = 323).

CTS5 SCORE	HR (95% CI)	P VALUE
CTS5 score (continuous)	2.1 (1.4-3.2)	.001
CTS5 score category		
Low	Reference	
Intermediate	1.6 (0.6-4.0)	.37
High	4.2 (1.9-9.4)	.001

Abbreviation: CTS5, Clinical Treatment Score after 5 years; HR, hazard ratio; CI, confidence interval.

beyond 5 years has been shown to reduce such relapses with modest survival gain.[22,23] CTS5 score, based on nodal status, tumor size, grade, and patient age, is predictive of late distant relapse. Since its initial validation study,[19] this tool has been externally validated by other groups. Currently, it is freely available online at http://www.cts5-calculator.com. Overall, it is considered prognostic although variable results on its accuracy in predicting outcomes were noted.[24-30]

Our results also demonstrated that CTS5 performed well as a prognostic tool in estimating the risk of LDR in early-stage ER-positive breast cancer. The C-index of the entire cohort of 323 patients was acceptable (0.672) and was even better when only postmenopausal women were analyzed. It was able to discriminate patients into 3 risk categories ($P = .0004$) although it could not clearly distinguish between the intermediate- and low-risk groups. Nevertheless, this finding was in line with results from others, particularly in nontrial populations and in trials that included premenopausal and postmenopausal patients as their validation cohorts.[25-27,29,30] As CTS5 was originally developed upon data sets of postmenopausal women in ATAC
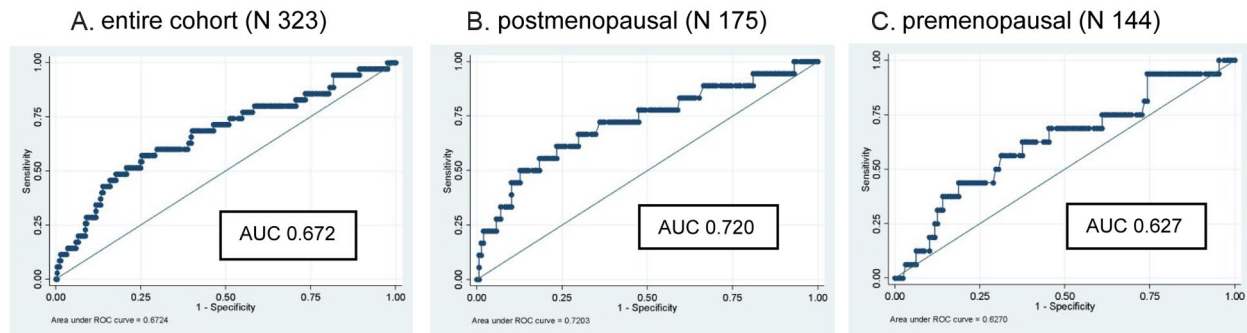
Figure 3. Receiver operating characteristic (ROC) curves of the prediction of late distant relapse using CTS5 with corresponding AUC of (A) entire cohort, N = 323, (B) postmenopausal women, N = 175, and (C) premenopausal cohort, N = 144, showing a better discriminative performance of CTS5 in the postmenopausal women. AUC indicates area under curve; CTS5, Clinical Treatment Score after 5 years.

and BIG1-98 trials, its application to premenopausal patients has been questioned. This was addressed by several investigators including Richman et al,[27] Villasco et al,[30] Lee et al,[28] and Wang et al,[26] which supported the prognostic value of CTS5 scores in premenopausal women. Our study, while smaller in sample size, also included a mix of premenopausal and postmenopausal patients and confirmed a consistent prognostic property of CTS5 in both populations. Of note, the patients' clinicopathologic characteristics in this study were nearly comparable to those previously reported. In contrast, Sestak et al recently reported that CTS5 was less prognostic in node-negative premenopausal women younger than 50 years who participated in a large Trial Assigning Individualized Options for Treatment (TAILORx) study.[31] However, the patient population was different from other studies (node negative only in Sestak et al vs a combination of nodal status in others), and follow-up in Sestak study was relatively short given that more events may arise upon longer follow-up in ER-positive breast cancers.

Calibration of CTS5 in our cohort showed a rather strong agreement between the observed and expected events, both in the overall population and in the premenopausal and postmenopausal subgroups. The patients in our study differed from the development cohort[19] in that ours had larger tumor sizes (T2 tumor 57% vs 30/35% in ATAC/BIG1-98, respectively) and a more advanced nodal status (N2-3 14.2% vs 7.5%) with higher rates of late distant relapse (10.9% vs 5.5%-7%). Furthermore, more chemotherapy was given in our cohort (63.1% vs 19.5%-24%) than in the original data set. In developing the CTS5 model, the type of endocrine treatment was not significant in their univariate analysis, and adding chemotherapy in their model did not improve its performance.[19] We also incorporated chemotherapy in the Cox regression, and it was not an independent factor in the multivariate analysis (data not shown). This finding indicated that CTS5 is a valid instrument that could be applied to clinical settings where variable adjuvant chemotherapy and conventional 5-year ET are used. It is noteworthy that CTS5 may not be accurate in predicting LDR in patients who received extended endocrine treatment as it was developed from patients who received only

5 years of therapy.[24,27,32] Another issue that is still unresolved and requires further validation is the use of CTS5 in HER2-positive patients. Wang et al investigated this in a Surviellance, Epidemiology and End Results (SEER) database[26] and found that it was not consistently prognostic for survival in a subset of HER2-positive women, a different endpoint from most validation studies of CTS5. As HER2 was not routinely tested at the time ATAC and BIG1-98 were conducted, the impact of HER2 upon model performance remains unknown, and further studies are warranted before routine use in luminal B HER2-positive patients. More recently, Pai et al[33] reported that CTS5 could not discriminate outcomes in HER2-positive patients who received trastuzumab. In our study, 10.6% of the patients had proven HER2-positive tumors, and trastuzumab treatment was administered to only 17.6%. Due to a small number of HER2-positive patients, no further analysis was performed in our cohort. An obvious advantage of CTS5 over genomic profiling for risk stratification is that it utilizes basic clinicopathological data that are already available for most patients without additional expense. Given that it has been validated by several independent investigators across multiple ethnicities, including ours, this strengthens its value particularly where 5 years of hormonal treatment is given. Those at intermediate risk will need to engage in shared decision-making to decide whether extended treatment would be in their best interest, while for those at high risk, lengthening adjuvant hormonal therapy seems to be reasonable. Caveats described earlier include application to HER2-positive patients and application to premenopausal patients. In addition, with emerging data on potential benefits of adjuvant cyclin-dependent kinase 4/6 (CDK4/6) inhibitors[34] and poly(ADP-ribose) polymerase (PARP) inhibitors,[35] the validity of CTS5 in these patients will need to be proven as well.

Our study had several limitations. First, due to the retrospective nature of this study, selection bias is a concern. Pathological grade and exact tumor size were missing in a large proportion of screened population as they were not routinely recorded in the past, and archival tissues were no longer available for review. Adding to this were patients who were lost to follow-up, which
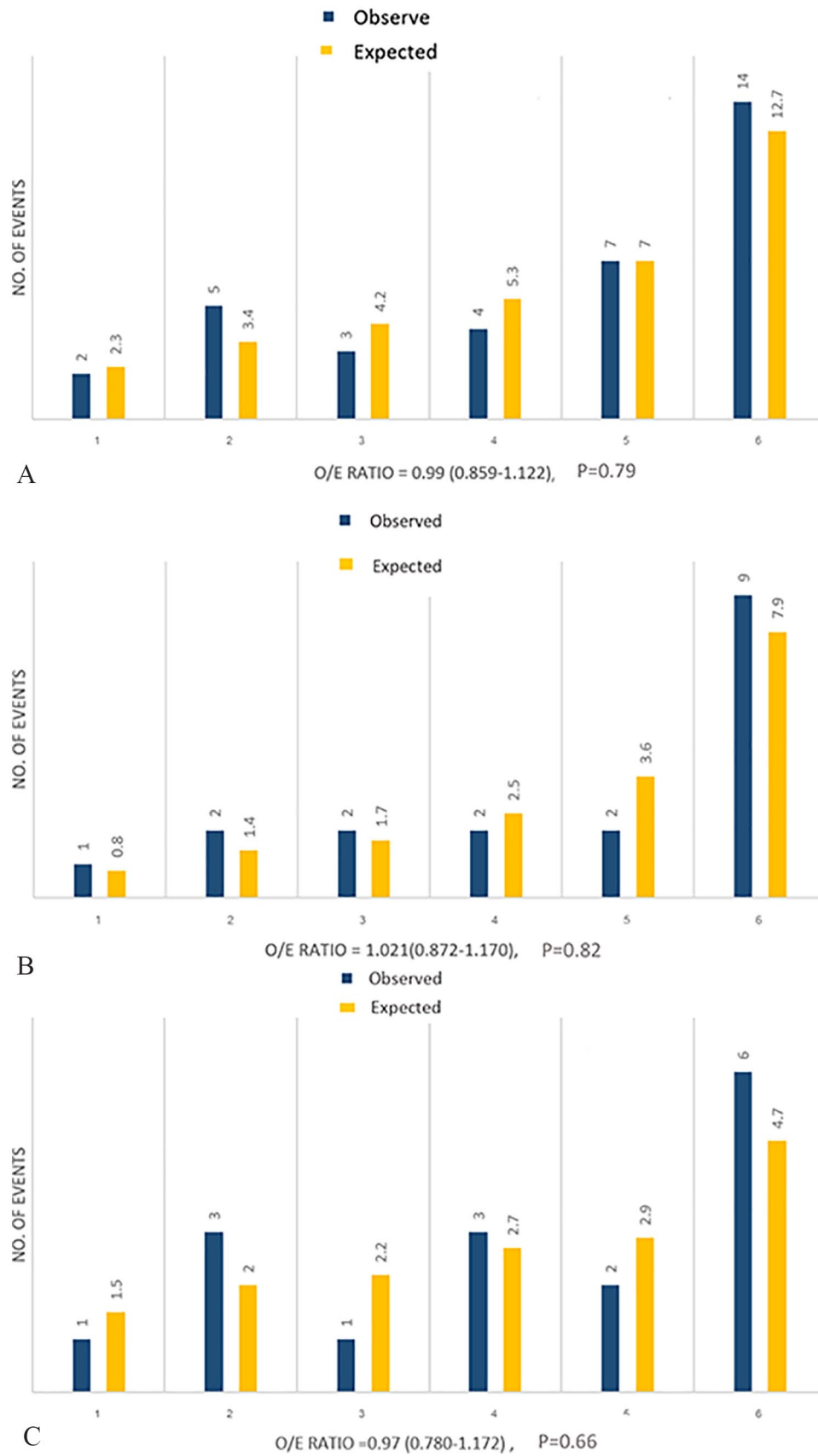
Figure 4. Observed versus expected the number of late DR and chi-square values according to 6-quantiles of CTS5 for (A) total population, (B) postmenopausal women, and (C) premenopausal women, showing no differences in observed and expected numbers of LDR. CTS5 indicates Clinical Treatment Score after 5 years; DR, distant recurrence; LDR, late distant recurrence.

may have been due to distant relapse, and hence the underestimation of events. The LDR of 5% in the excluded patients with adequate follow-up indirectly supported that speculation. Second, the sample size of postmenopausal women was small with the admixture of premenopausal patients within our cohort; this was different from the developing data set. Nevertheless, the results of our study were consistent with BIG1-98/ATAC and others despite those limitations. The strengths of our study were a long follow-up time (median of 11.6 years), which was sufficient to observe for LDRs, and it was a representation of real-world practice data in an upper-middle-income country where routine genomic profiling was not easily accessible and hence strengthened the role of CTS5 in decision-making in routine practice.

Conclusion

This study validated that CTS5 effectively discriminated long-term recurrence risk in ER-positive Thai patients. It accurately estimated LDR in both premenopausal and postmenopausal women. CTS5 could be applied in routine clinical practice to assist in decisions regarding prolonged ET in intermediate- and high-risk patients, particularly in resource-limited countries where molecular profiling is inaccessible.

Declarations

Ethical Approval and Consent to Participate

The ethics approval was granted by Human Research Ethics Committee, Faculty of Medicine Ramathibodi Hospital, Mahidol University (COA. MURA2020/1528). The committee approved a waiver of consent for this study as it is a retrospective chart review. The research involves no more than minimal risk to the subject and does not adversely affect the rights and welfare of the subjects. All patient identifications were protected according to the Good Clinical Practice guideline and not published in the manuscript. All procedures performed in this study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent for publication

Not applicable.

Author Contributions

Thitiya Dejthevaporn: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Supervision; Validation; Writing—original draft; Writing—review & editing.
Panchanin Patanayindee: Data curation; Formal analysis; Investigation; Methodology; Validation; Writing—original draft; Writing—review & editing.

Availability of Data and Materials

The data sets used and/or analyzed during the current study is available from the corresponding author on reasonable request.

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