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ORIGINAL ARTICLE – BREAST ONCOLOGY

The Prognostic Significance of the Oncotype DX Recurrence Score in $T_{1\text{-}2}N_1M_0$ Estrogen Receptor-Positive HER2-Negative Breast Cancer Based on the Prognostic Stage in the Updated AJCC 8th Edition

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ABSTRACT

Background. This study aimed to evaluate the prognostic significance of the Oncotype DX recurrence score (RS) in $T_{1\text{-}2}N_1M_0$ estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer based on the prognostic stage in the updated American Joint Commission on Cancer, 8th edition.

Methods. The Surveillance, Epidemiology, and End Results database was searched to identify ER-positive invasive ductal breast cancer in $T_{1\text{-}2}N_1M_0$ with RS results diagnosed between 2004 and 2012. Patients with RS were categorized into low-risk (RS $<$ 11), intermediate-risk (RS 11–25), and high-risk (RS $>$ 25) groups. The distributions of clinical-pathological characteristics were compared among the RS risk groups using Pearson's Chi square. Breast cancer-specific survival (BCSS) and overall survival (OS) were estimated using the Kaplan–Meier method and compared across RS groups using the log-rank statistic. Cox models were fitted to assess the factors independently associated with survival.

Results. The study enrolled 4059 cases categorized into prognostic stages IA to IIB. The RS risk groups were positively correlated with pathological prognostic stages ($P < 0.001$). The RS risk groups differed significantly in terms of BCSS and OS ($P < 0.001$). According to the multivariate analysis, RS risk group was an independent prognostic factor for BCSS and OS together with the pathological prognostic stage. The subgroup analysis showed similar survival rates across pathological prognostic stages in the RS low-risk group but significant differences in survival rates among pathological prognostic stages in the RS intermediate-risk group. The survival rates among the RS risk groups also differed significantly in pathological prognostic stage IA.

Conclusions. Oncotype DX RS provided independent prognostic significance to complement the prognostic staging system.

The breast cancer staging system has always been based on anatomic factors. However, advances in breast cancer biology have resulted in identification and validation of biologic markers to describe the prognosis and treatment benefit.[1] The prognostic stage system in the American Joint Committee on Cancer (AJCC), 8th edition for breast cancer is a milestone that incorporates contemporary biologic factors such as estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor-2 (HER2), and histologic grade into the traditional anatomic staging system. The updated edition was provided online in November 2017.

Over the years, several multigene assays that provide additional prognostic information have been commercially available. The 21-gene expression assay (Oncotype DX) was developed for hormone receptor (HR)-positive, HER2-negative, and lymph node (LN)-negative breast cancer. Studies have validated that the recurrence score (RS) of Oncotype DX predicts the prognosis and benefits of adjuvant chemotherapy independently of clinical-pathological characteristics.[2–7] In the AJCC 8th edition, Oncotype DX is the only multigene assay that classifies the prognostic

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stage. Cases of $T_{1\text{-}2}N_0M_0$ cancer that are ER-positive and HER2-negative with an RS lower than 11 should be classified as pathological prognostic stage IA.

However, evidence supporting Oncotype DX application in the LN-positive population is limited despite studies with promising results.[8–10] Therefore, it was unclear whether Oncotype DX could provide complementary prognostic information to the prognostic staging system in the AJCC 8th edition for LN-positive cases.

Thus, we conducted a retrospective study to evaluate the prognostic significance of Oncotype DX in this subgroup of patients stratified into the $T_{1\text{-}2}N_1M_0$ ER-positive, HER2-negative category based on the pathological prognostic stage in the updated AJCC 8th edition using the Surveillance, Epidemiology, and End Results (SEER) 18 database.

MATERIALS AND METHODS

Patient Population

This population-based study used data derived from the National Cancer Institute's limited use SEER 18 registry databases released in November 2017. Cases in the SEER database were linked to RS results from assays performed by Genomic Health. All cases with RS had negative HER2 per Oncotype DX test via reverse transcription polymerase chain reaction (RT-PCR). We identified female ER-positive invasive ductal carcinoma cases in $T_{1\text{-}2}N_1M_0$ stage with Oncotype RS results diagnosed between 2004 and 2012. Patients with RS were categorized into low-risk (RS < 11), intermediate-risk (RS 11–25), and high-risk (RS > 25) groups.

The study excluded patients with more than one primary cancer, diagnosis at death or autopsy alone, unknown histologic grade or PR status, no surgery performed or no record of surgery, or less than 6 months of follow-up evaluation. Anatomic tumor-node-metastasis (TNM) stage was based on a derived AJCC 6th edition (2004–2009) or 7th edition (2010–2012). The pathological prognostic stage for these cases was based on the updated AJCC 8th edition. Poorly differentiated and anaplastic histologic grades were considered grade 3 disease.

We obtained permission to access the files of SEER program custom data with additional treatment fields such as radiation therapy, chemotherapy, and Oncotype DX RS results. Informed consent was not required because personal identifying information was not involved. This study was reviewed and approved by the Institutional Review Board of Obstetrics and Gynecology Hospital of Fudan University.

Statistical Analysis

The distributions of clinical-pathological characteristics among the RS risk groups were compared using Pearson's Chi square with Fisher's exact test. The follow-up cutoff was 31 December 2015. Breast cancer-specific survival (BCSS) was computed from the time of breast cancer diagnosis to the time of death from breast cancer or the last follow-up evaluation with patients still alive at the last censored follow-up. Overall survival (OS) was computed from the time of diagnosis to the time of death from any cause or the last follow-up evaluation with patients still alive at the last censored follow-up.

Both BCSS and OS were estimated using the Kaplan-Meier method and compared across RS groups using the log-rank statistic. Adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated using the Cox model to assess the factors independently associated with survival. A two-sided P value lower than 0.05 was considered statistically significant. All the statistical analyses were performed using the SPSS 22.0 software package (SPSS, Chicago, IL, USA).

RESULTS

Clinical-Pathological Characteristics Among $T_{1\text{-}2}N_1M_0$ ER-Positive, HER2-Negative Breast Cancer Patients Receiving Oncotype DX Testing

The study enrolled 4059 patients who met the inclusion criteria. Of these patients, 2898 (71.4%) had stage T_1 cancer, 1854 (45.7%) had stage N_{1mic} cancer, 743 (18.3%) had grade 3 cancer, and 3746 (92.3%) had positive PR status. The median patient age was 59 years.

In this study, 2573 patients (63.4%) were undergoing breast-conserving surgery (BCS), and 1499 patients (36.9%) were receiving chemotherapy. Altogether, 2781 patients (68.5%) had pathological prognostic stage IA cancer, 829 patients (20.4%) had stage IB cancer, 360 patients (8.9%) had stage IIA cancer, and 89 patients (2.2%) had stage IIB cancer. Of the 4059 patients, 794 (19.6%) were in the RS low-risk group, 2667 (65.7%) were in the RS intermediate-risk group, and 598 (14.7%) were in the RS high-risk group.

The higher RS risk groups tended to have younger patients, larger tumors, a higher proportion of grade 3 disease, negative PR status and advanced anatomic TNM stage, and more frequent use of chemotherapy ($P < 0.001$). The RS risk groups did not differ significantly in terms of race, N stage, surgery, or radiation (Table 1).

The findings showed a positive correlation between the RS risk groups and pathological prognostic stages ($P < 0.001$). The proportion of patients in the higher RS risk

TABLE 1 Clinical-pathological characteristics of the recurrence score (RS) risk groups

	Total population		RS risk groups						*P* Value
			Low		Intermediate		High		
	N	%	*n*	%	*n*	%	*n*	%	
Age stage (years)									< 0.001
< 60	2143	52.8	355	44.7	1447	54.3	341	57.0	
≥ 60	1916	47.2	439	55.3	1220	45.7	257	43.0	
Race									0.199
White	3435	84.6	680	85.6	2271	85.2	484	80.9	
Black	296	7.3	53	6.7	185	6.9	58	9.7	
Asian or Indian	316	7.8	58	7.3	204	7.6	54	9.0	
Unknown	12	0.3	3	0.4	7	0.3	2	0.3	
Histologic grade									< 0.001
1	1144	28.2	271	34.1	830	31.1	43	7.2	
2	2172	53.5	461	58.1	1450	54.4	261	43.6	
3	743	18.3	62	7.8	387	14.5	294	49.2	
T stage									< 0.001
T_1	2898	71.4	607	76.4	1959	73.5	332	55.5	
T_2	1161	28.6	187	23.6	708	26.5	266	44.5	
N stage									0.161
N_{1mic}	1854	45.7	346	43.6	1247	46.8	261	43.6	
N_1	2205	54.3	448	56.4	1420	53.2	337	56.4	
Anatomic TNM stage									< 0.001
IB	1422	35.0	278	35.0	983	36.9	161	26.9	
IIA	1476	36.4	329	41.4	976	36.6	171	28.6	
IIB	1161	28.6	187	23.6	708	26.5	266	44.5	
PR status									< 0.001
Negative	313	7.7	13	1.6	171	6.4	129	21.6	
Positive	3746	92.3	781	98.4	2496	93.6	469	78.4	
Surgery									0.090
BCS	2573	63.4	492	62.0	1721	64.5	360	60.2	
Mastectomy	1486	36.6	302	38.0	946	35.5	238	39.8	
Radiation									0.056
No or unknown	1730	42.6	343	43.2	1107	41.5	280	46.8	
Yes	2329	57.4	451	56.8	1560	58.5	318	53.2	
Chemotherapy									< 0.001
No or unknown	2560	63.1	643	81.0	1766	66.2	151	25.3	
Yes	1499	36.9	151	19.0	901	33.8	447	74.7	
Pathological prognostic stage									< 0.001
IA	2781	68.5	618	22.2	1932	69.5	231	8.3	
IB	829	20.4	147	17.7	522	63.0	160	19.3	
IIA	360	8.9	26	7.2	178	49.4	156	43.3	
IIB	89	2.2	3	3.4	35	39.3	51	57.3	

TNM tumor-node-metastasis, *BCS* breast-conserving surgery

groups was increasing, and the proportion in the lower RS risk groups was decreasing with the escalation of pathological prognostic stage. The percentage of the RS low-risk group decreased from 22.2% in pathological prognostic stage IA to 3.4% in stage IIB, whereas the percentage of the RS high-risk group increased from 8.3% in stage IA to 57.3% in stage IIB (Table 1).

The Prognostic Significance of RS Based on the Pathological Prognostic Stage

The median follow-up period was 57 months (range, 7–142 months). The RS risk groups differed significantly in BCSS and OS ($P < 0.001$) (Fig. 1). In the univariate analysis, earlier pathological prognostic stage, lower RS risk group, and reception of chemotherapy were associated with favorable BCSS. Younger age, earlier pathological prognostic stage, and lower RS risk group were associated with favorable OS. According to Cox multivariate analysis, RS risk group was an independent prognostic factor for BCSS and OS together with pathological prognostic stage (Table 2).

In the subgroup analysis, the survival outcomes were similar ($P = 0.890$ for BCSS and $P = 0.737$ for OS) among the different pathological prognostic stages within the RS low-risk group (794 cases). In this subgroup, 618 patients (77.8%) were in pathological prognostic stage IA, 147 cases (18.5%) in stage IB, 26 cases (3.3%) in stage IIA, and 3 cases (0.4%) in stage IIB. Survival rates differed significantly among the pathological prognostic stages ($P < 0.001$ for BCCS vs $P = 0.009$ for OS) in the RS intermediate-risk group (2667 cases), with the survival rates inversely correlated with the escalation of pathological prognostic stages (Fig. 2). Similar trends were observed in the RS high-risk group (598 cases), but without statistical significance ($P = 0.062$ for BCCS and $P = 0.075$ for OS).

Altogether, 2781 patients (68.5%) were in pathological prognostic stage IA, with 618 patients (22.2%) in the RS low-risk group, 1932 patients (69.5%) in the RS intermediate-risk group, and 231 patients (8.3%) in the RS high-risk group. The findings showed significant differences in BCSS ($P < 0.001$) and OS ($P < 0.001$) among the RS risk groups in pathological prognostic stage IA, with the survival rates inversely correlated with increasing RS risks (Fig. 3). Similar trends could be observed but without statistical significance in stage IB (829 cases: $P = 0.088$ for BCSS and $P = 0.132$ for OS), stage IIA (360 cases: $P = 0.167$ for BCSS and $P = 0.192$ for OS), and stage IIB (89 cases: $P = 0.385$ for BCSS and $P = 0.339$ for OS).

DISCUSSION

A more precise cancer staging system can better partition patients into cohorts with similar survival outcomes, which improves predictive outcome accuracy and guides optimal treatments. In the era of personalized care, tumor burden and biology are equally considered. The pathological prognostic stage system in the AJCC 8th edition for the first time incorporated nearly all the important biologic factors together with anatomic TNM factors. It would be the most accurate predictor of outcome in cases of discordance between anatomic TNM stage and tumor biology.

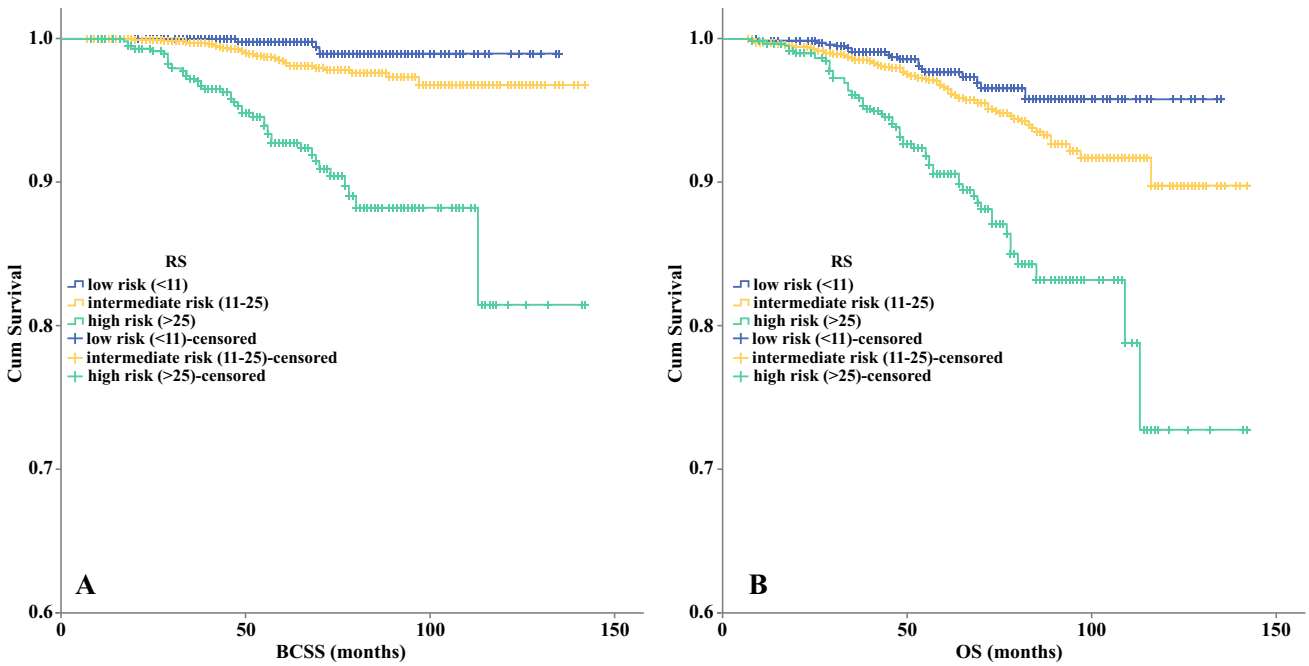

FIG. 1 Kaplan-Meier survival curves among recurrence score (RS) risk groups for $T_{1\text{-}2}N_1M_0$ estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancers. **a** Breast cancer-specific survival (BCSS). **b** Overall survival (OS)

TABLE 2 Multivariate analysis of prognostic factors in $T_{1\text{-}2}N_1M_0$ estrogen receptor (ER)-positive human epidermal growth factor receptor 2 (HER2)-negative breast cancer

	BCSS			OS		
	P value	HR	95% CI	*P* value	HR	95% CI
Age (years)						
≥ 60 versus < 60	–	–	–	< 0.001	2.108	1.552–2.864
RS group	< 0.001			< 0.001		
Intermediate vs low risk	0.036	3.516	1.082–11.423	0.044	1.680	1.015–2.779
High versus low risk	< 0.001	13.037	3.846–44.196	< 0.001	3.825	2.200–6.650
Pathological prognostic stage	0.001			0.005		
IB versus IA	0.151	1.514	0.859–2.669	0.138	1.325	0.914–1.922
IIA versus IA	0.017	2.104	1.142–3.876	0.021	1.685	1.081–2.626
IIB versus IA	< 0.001	4.403	2.139–9.063	0.001	2.622	1.452–4.736
Chemotherapy						
Yes versus no or unknown	0.822	0.947	0.591–1.518	–	–	–

BCSS breast cancer-specific survival, *OS* overall survival, *HR* hazard ratio, *CI* confidence interval

Over the years, multigene assays have been developed rapidly for the purpose of treatment guidance under precise prediction. The 21-gene expression assay (Oncotype DX) is the most widely used and has been incorporated into major international guidelines.[11–14]

Oncotype DX also is applied in the pathological prognostic stage system. In this staging system, cases with ER-positive, HER2-negative $T_{1\text{-}2}N_0M_0$ and an RS lower than 11 are classified as stage IA. However, to date, the significance of Oncotype DX has not been fully evaluated in terms of improving the pathological prognostic stage classification for LN-positive cases. Our study served as a pilot study in this respect.

In our study, 65% of the patients had their RS in the intermediate-risk group, similar to the percentage in other studies.[6,10] In addition, aggressive clinical-pathological characteristics were observed more frequently in the higher RS risk groups (i.e., higher proportion of younger patients, larger tumor, grade 3 disease, and PR-negative status). As a result, the findings showed an increasing proportion of patients in the RS high-risk group and a decreasing proportion in the RS low-risk group with the escalation of prognostic stages. Such a trend also was observed in previous studies irrespective of LN status.

The TAILORx trial for LN-negative cases found a significant difference between the low and midrange RS groups with regard to histologic grade, age, and PR expression but not tumor size.[6] In the WSG PlanB trial for LN-positive cases, RS had a positive correlation with grade and a negative correlation with PR status.[10] It might be expected that increasing clinical risk is in accord with increasing genetic risk in most cases despite some discordances.

Limited studies have evaluated the prognostic significance of RS in LN-positive cancers, mostly in N_1 stage disease, considering the potential eligibility for the application of Oncotype DX in cases with a low LN burden. Among previous retrospective studies, SWOG 8814 confirmed the prognostic value of RS for tamoxifen-treated LN-positive patients.[8] TransATAC indicated that RS was an independent predictor of distant recurrence for LN-positive hormone receptor (HR)-positive patients treated with anastrozole.[9] The study of Stemmer et al.[15] demonstrated that only RS and tumor size were significantly associated with distant recurrence risk.

Two studies evaluated RS in LN-positive patients based on the SEER database and indicated that 5-year BCSS differed significantly among RS groups and was excellent for patients with an RS lower than 18.[16,17] However, both studies included all patients from stage N_1 to stage N_3, and the median follow-up period of 30 months was relatively short.

More recently, the WSG PlanB trial found similar 5-year disease-free survival (DFS) rates between pN_0 and pN_1 subgroups (94.2% vs 94.4%), and RS was further validated as a prognostic indicator.[10,18] In the PACS-01 trial, RS remained a significant predictor of survival because few distant recurrence events occurred in patients with one to three LNs and a low RS (< 18).[19] Currently, the Rxponder trial still is underway to evaluate the use of the 21-gene assay for HR-positive, HER2-negative breast cancer patients with one to three positive LNs.[20]

Our study differed significantly from previous studies in several aspects. First, the RS cutoffs used in our study referred to those used in the recent RCTs such as the TAILORx[5,6] and WSG PlanB trials,[10,18] which differed from those originally defined as low (RS < 18), intermediate (RS 18–30), and high (RS > 30) in many

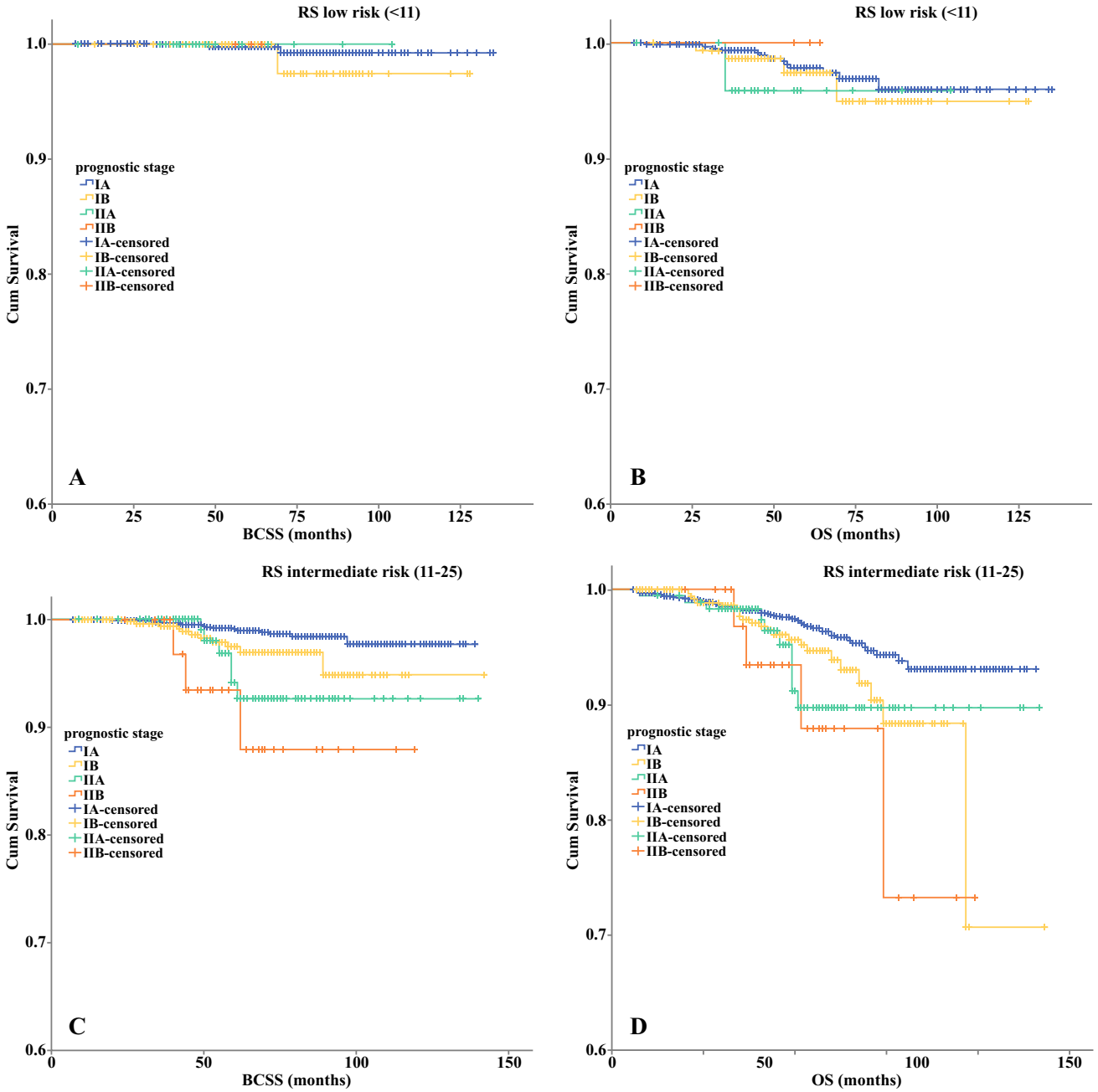

FIG. 2 Kaplan-Meier survival curves among pathological prognostic stages stratified by recurrence score (RS) risk groups. **a** Breast cancer-specific survival (BCSS) in the RS low-risk group. **b** Overall survival (OS) in the RS low-risk group. **c** BCSS in the RS intermediate-risk group. **d** OS in the RS intermediate-risk group

retrospective and population-based studies.[16,17,21] Previous studies showed that the risk of distant recurrence 10 years after diagnosis could be as low as 2–3% among patients with an RS lower than 11 that was not likely to be affected by adjuvant chemotherapy.[2,4,6,21] In the pathological prognostic stage system, the cutoff of RS lower than 11 was accepted as low risk in the staging of LN-negative cases. As a result, it might be a reasonable choice to assign RS lower than 11 and RS higher than 25 as the cutoffs.

Second, in the study of Roberts et al.,[17] LN-positive cases from N_1 to N_3 were included. However cases with four or more positive lymph nodes were considered as high risk of relapse and had a poor survival outcome. As a result, multiple treatments such as chemotherapy and radiation could generally not be omitted, and Oncotype DX RS had limited value in guiding treatments.

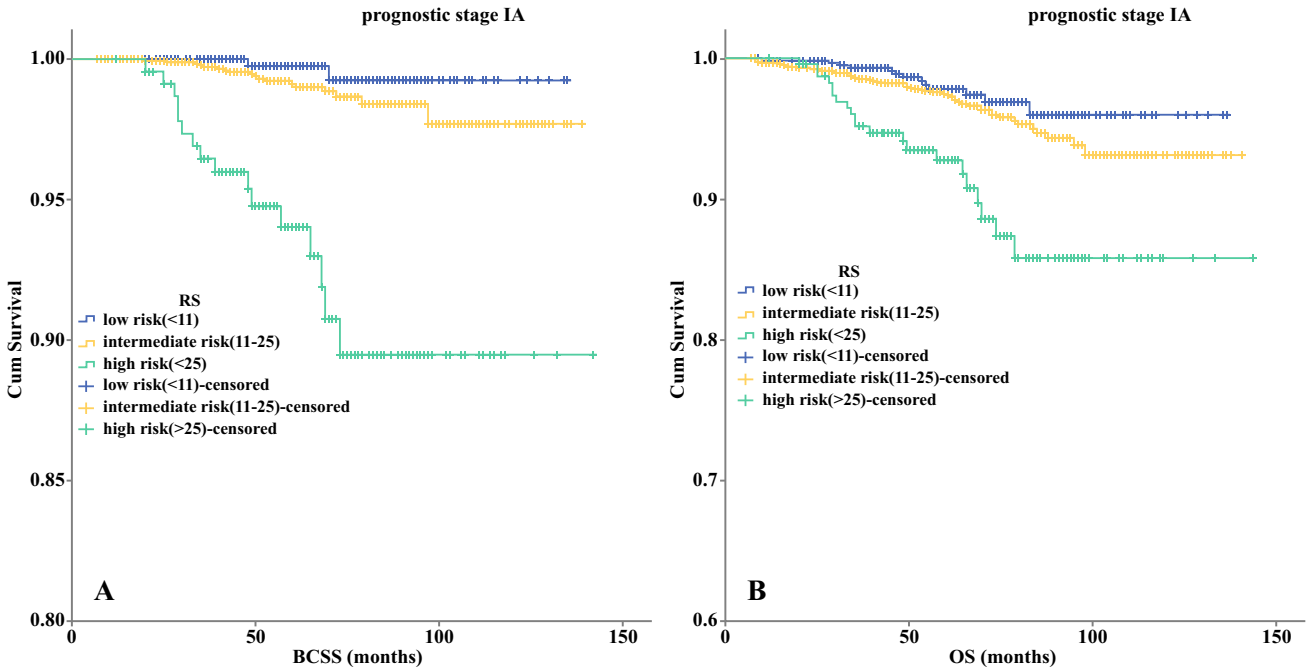

FIG. 3 Kaplan-Meier survival curves among the recurrence score (RS) risk groups in pathological prognostic stage IA. **a** Breast cancer-specific survival (BCSS). **b** Overall survival (OS)

Roberts et al.[17] also indicated that RS was strongly predictive of BCSS only among patients with stage N_1 disease.[17] Therefore, our study focused specifically on stage N_1 breast cancer just as recent RCTs like WSG PlanB[10,18] and Rxponder.[20] Evaluation of RS significance has more rationality and practical value for precise classification of tumor stage and optimal guidance of treatment for disease with a low LN burden.

Finally, previous studies have evaluated the prognostic significance of RS in LN-positive cases. However, N stage is only one among the various clinical-pathological factors related to breast cancer survival. The new pathological prognostic stage system in the AJCC 8th edition incorporates all the characteristics into one comprehensive staging system. This system is believed to be the most accurate predictor of survival outcome. However, it combined multigene assays results only in LN-negative cases. The significance of RS was of value to complement this staging system for LN-positive disease.

Our study was among the first studies to evaluate the prognostic significance of RS based on the pathological prognostic stage system in LN-positive cases for the purpose of accurate outcome prediction and optimal treatment guidance. Our findings showed that RS was an independent prognostic factor for BCSS and OS together with the pathological prognostic stage. This was the highlight of our study.

In clinical practice, genomic testing is best used in combination with clinical-pathological factors because discordance exists sometimes between clinical and genomic risk assignment. On the one hand, BCSS and OS differed significantly in our study among the RS risk groups in 2781 cases with pathological prognostic stage IA cancer. A certain proportion of patients in the low clinical risk group had a relatively poor survival outcome. Genetic testing could help to distinguish the discordance cases, leading to more accurate prediction and precise treatment.

On the other hand, the survival outcomes were similar among the various pathological prognostic stages in cases with RS lower than 11, whereas the survivals were inversely correlated with the escalation of pathological prognostic stages in cases with higher RS risk. In our study, the discordance rate in the RS low-risk group was nearly 23%. In the MINDACT trial, the rate was 32%, and women with high clinical risk and low genomic risk had relatively lower risk of recurrence.[22]

It might be postulated that the prognostic relevance of multi-gene assay characteristics overrides that of clinical-pathological factors in cases with low genomic risk such as an RS lower than 11 in terms of treatment decisions and survival outcomes among N_1 patients. Moreover, this already has been confirmed in LN-negative cases according to the AJCC 8th edition, in which patients with $T_{1\text{-}2}N_0M_0$, ER positivity, HER2 negativity and an RS lower than 11 all were categorized as pathological prognostic stage IA. It

might be concluded that the low-risk RS was predictive for selection of patients from various pathological prognostic stages with one to three positive LNs who had a favorable outcome to be classified at a lower stage, whereas among cases with higher-risk RS, the pathological prognostic stage still had an accurate prognosis prediction.

Oncotype DX RS has a significant impact on reducing chemotherapy use for N_1 and ER-positive breast cancer patients.[23] According to Torres et al.,[24] treatment recommendations changed for 36% of their patients, with the most significant change observed in the RS low-risk group. In this study, the higher RS-risk group had a higher proportion of chemotherapy, but it was not an independent prognostic factor for BCSS. We did not compare the survival outcomes stratified by chemotherapy treatment among RS risk groups, although we did report the percentage of patients for whom chemotherapy was reported as "yes" versus "no/unknown" in various subgroups. First, the patients were not randomized to treatment, and the treatment decision was heavily influenced by RS result. Most patients were in an earlier prognostic stage (stage IA). Second, a 30% relative under-ascertainment of chemotherapy use in the SEER database was reported, which potentially introduced bias and confounding factors that could not be fully controlled.

Several limitations of our study should be recognized. First, the retrospective design had an intrinsic bias despite a large sample size. Second, the median follow-up period of 57 months might have been relatively too short for the differences in survival outcome to be determined between pathological prognostic stages IA and IB, although it was adequate for comparison among the RS risk groups. Third, chemotherapy use is known to be under-reported in SEER, as discussed previously. Further studies should incorporate treatment data into survival analyses among the RS risk groups. Finally, the SEER database does not collect information on distant recurrence, although it is the main cause of breast cancer-specific death.

In conclusion, to date, our study was the largest to explore the prognostic significance of RS specifically in $T_{1\text{-}2}N_1M_0$ ER-positive, HER2-negative breast cancers registered in the SEER database based on the pathological prognostic stage in the updated AJCC 8th edition. Our findings have added to increasing evidence that RS results provide independent prognostic significance to complement the prognostic staging system, as was the case for LN-negative cancer. It might be expected that $T_{1\text{-}2}N_1M_0$ ER-positive, HER2-negative breast cancer with an RS lower than 11 would be classified as a lower stage of disease. Further prospective research and a longer follow-up period are warranted.

CONFLICT OF INTEREST There are no conflicts of interest.

REFERENCES

1. Giuliano AE, Edge SB, Hortobagyi GN. Eighth edition of the AJCC cancer staging manual: breast cancer. *Ann Surg Oncol.* 2018;25:1783–5.
2. Paik S, Shak S, Tang G, et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. *N Engl J Med.* 2004;351:2817–26.
3. Kwa M, Makris A, Esteva FJ. Clinical utility of gene-expression signatures in early stage breast cancer. *Nature Rev Clin Oncol.* 2017;14:595–610.
4. Paik S, Tang G, Shak S, et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. *J Clin Oncol.* 2006;24:3726–34.
5. Sparano JA, Gray RJ, Makower DF, et al. Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. *N Engl J Med.* 2018;379:111–21.
6. Sparano JA, Gray RJ, Makower DF, et al. Prospective validation of a 21-gene expression assay in breast cancer. *N Engl J Med.* 2015;373:2005–14.
7. Curtit E, Mansi L, Maisonnette-Escot Y, Sautiere JL, Pivot X. Prognostic and predictive indicators in early-stage breast cancer and the role of genomic profiling: focus on the Oncotype DX([R]) breast recurrence score assay. *Eur J Surg Oncol.* 2017;43:921–30.
8. Albain KS, Barlow WE, Shak S, et al. Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, oestrogen-receptor-positive breast cancer on chemotherapy: a retrospective analysis of a randomised trial. *Lancet Oncol.* 2010;11:55–65.
9. Dowsett M, Cuzick J, Wale C, et al. Prediction of risk of distant recurrence using the 21-gene recurrence score in node-negative and node-positive postmenopausal patients with breast cancer treated with anastrozole or tamoxifen: a TransATAC study. *J Clin Oncol.* 2010;28:1829–34.
10. Gluz O, Nitz UA, Christgen M, et al. West German Study Group Phase III PlanB Trial: first prospective outcome data for the 21-gene recurrence score assay and concordance of prognostic markers by central and local pathology assessment. *J Clin Oncol.* 2016;34:2341–9.
11. NCCN Clinical Practice Guidelines in Oncology. Breast Cancer. Version 1. 2018. Retrieved at http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed 20 Mar 2018.
12. Harris LN, Ismaila N, McShane LM, et al. Use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol.* 2016;34:1134–50.
13. Senkus E, Kyriakides S, Ohno S, et al. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up. *Ann Oncol.* 2015;26(Suppl 5):v8–30.
14. Coates AS, Winer EP, Goldhirsch A, et al. Tailoring therapies: improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015. *Ann Oncol.* 2015;26:1533–46.
15. Stemmer SM, Steiner M, Rizel S, et al. Clinical outcomes in ER+ HER2 -node-positive breast cancer patients who were treated according to the Recurrence Score results: evidence from a large prospectively designed registry. *NPJ Breast Cancer.* 2017;3:32.
16. Petkov VI, Miller DP, Howlader N, et al. Breast cancer-specific mortality in patients treated based on the 21-gene assay: a SEER population-based study. *NPJ Breast Cancer.* 2016;2:16017.
17. Roberts MC, Miller DP, Shak S, Petkov VI. Breast cancer-specific survival in patients with lymph node-positive hormone receptor-positive invasive breast cancer and Oncotype DX

Recurrence Score results in the SEER database. *Breast Cancer Res Treat.* 2017;163:303–10.
18. Nitz U, Gluz O. Reducing chemotherapy use in clinically high-risk, genomically low-risk pN0 and pN1 early breast cancer patients: five-year data from the prospective, randomised phase 3 West German Study Group (WSG) PlanB trial. *Breast Cancer Res Treat.* 2017;165:573–83.
19. Penault-Llorca F, Filleron T, Asselain B, et al. The 21-gene Recurrence Score(R) assay predicts distant recurrence in lymph node-positive, hormone receptor-positive, breast cancer patients treated with adjuvant sequential epirubicin- and docetaxel-based or epirubicin-based chemotherapy (PACS-01 trial). *BMC Cancer.* 2018;18:526.
20. Wong WB, Ramsey SD, Barlow WE, Garrison LP Jr, Veenstra DL. The value of comparative effectiveness research: projected return on investment of the RxPONDER trial (SWOG S1007). *Contemp Clin Trials.* 2012;33:1117–23.
21. Sparano JA, Paik S. Development of the 21-gene assay and its application in clinical practice and clinical trials. *J Clin Oncol.* 2008;26:721–8.
22. Cardoso F, van't Veer LJ, Bogaerts J, et al. 70-Gene Signature as an aid to treatment decisions in early-stage breast cancer. *N Engl J Med.* 2016;375:717–29.
23. Stemmer SM, Klang SH, Ben-Baruch N, et al. The impact of the 21-gene Recurrence Score assay on clinical decision making in node-positive (up to 3 positive nodes) estrogen receptor-positive breast cancer patients. *Breast Cancer Res Treat.* 2013;140:83–92.
24. Torres S, Trudeau M, Gandhi S, et al. Prospective evaluation of the impact of the 21-gene recurrence score assay on adjuvant treatment decisions for women with node-positive breast cancer in Ontario, Canada. *Oncologist.* 2018;23:768–75.