Validation of a Clinical-Genomic Model for Patients With Early-Stage Breast Cancer Enrolled in a Taiwanese Multicenter Study

Nicolas Pennarun (nicolas.pennarun@gmail.com)
Amwise Diagnostics Pte. Ltd. https://orcid.org/0000-0002-4876-2288
Yi-Hsuan Lee
National Taiwan University Hospital
Ling-Ming Tseng
Taipei Veterans General Hospital
Po-Sheng Yang
Mackay Medical College
Ji-An Liang
China Medical University Hospital
Chia-Ming Hsieh
Taiwan Adventist Hospital
Yuan-Ching Chang
Mackay Medical College
Ming-Yang Wang
National Taiwan University Hospital
Chiun-Sheng Huang
National Taiwan University Hospital
Kuan-Hui Shih
Amwise Diagnostics Pte. Ltd.

Research article

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Abstract

Background

Numerous prospective studies, predominantly in the Caucasian population, have proven the clinical utility of using multigene expression tests to prevent overtreatment in early-stage breast cancer patients with early-stage disease. In this study, we used an Asian population to validate a clinical-genomic assay (RecurIndex®) for estimating the risk of distant recurrence and relapse in early-stage breast cancer patients.

Methods

A total of 298 patients with early-stage breast cancer, luminal-like subtype (85.6%) and HER2-enriched/ triple-negative subtype (14.4%), was enrolled in a retrospective study across five participating medical centers in Taiwan. The inclusion criteria were as follows: women (1) who underwent primary surgery without prior induction treatments, (2) with an early pathologic N stage and (3) who received either mastectomy or breast-conserving surgery. Kaplan Meier method and Cox proportional hazards model were used to, respectively, identify independent prognostic factors and calculate the 5- and 10-year survival rates of patients in the low- and high-risk groups assigned by the diagnostic test. A forest plot was produced to assess hazard ratios and 95% confidence intervals. The primary endpoint was distant recurrence-free survival (DRFS) and the secondary endpoint was relapse-free survival (RFS).

Results

The 10-year DRFS rate was significantly higher in the good prognosis group than in the poor prognosis group (91.9% [95% CI, 86.1-98.1%] versus 62.9% [95% CI, 49.8-79.4%]). The overall hazard ratio for distant recurrence was 1.031 [95% CI, 1.017 - 1.046] per unit Recurrence index-distant recurrence (RI-DR) score increment.

Conclusions

The present study provides robust evidence of the clinical utility of using the RI-DR score to accurately predict clinical outcomes. RecurIndex® could be used to determine the utility of adjuvant chemotherapy in Asian patients, especially those having hormone-receptor positive tumors, leading to a meaningful reduction in adjuvant chemotherapy recommendations.

Background

Breast cancer is the most common malignancy in women around the world. In Taiwan, the incidence of the disease is rising continuing and 12,672 new invasive breast cancer cases have been diagnosed in 2016 according to the Ministry of Health and Welfare, R.O.C (Taiwan)[1]. However, it is known that incidence rates of the disease differ in parts of the world: in Taiwan and, more generally, in Asia, these

percentages have been historically lower than those in Europe and North America[2,3]. Similarly, the American Cancer Society, through the Surveillance, Epidemiology, and End Results (SEER) program, found that the characteristics of breast cancer patients within the American population vary by race/ethnicity: women of Asian ancestry have the lowest incidence and death rates of the malignancy compared to non-Hispanic white and non-Hispanic black populations[4]. Besides, several studies have shown the earlier age of onset of the disease in Asia: women in Western countries have their peak-disease between 55 and 60 years old in contrast with those in Asia, which fall within the range of 45–50 years old[5]. Other than geographic location, factors that may contribute to these cancer health disparities include genomic heterogeneity, biologic diversity, environment and choice of lifestyle[5, 6]. As a result, this variation in the incidence and in the proportion across age groups could lead to different outcomes in patients treated for a breast cancer in Asia from those in Western countries. It is therefore still an ongoing challenge for predicting prognosis and for determining the optimal treatment strategy in breast cancer patients.

Other than selecting the most appropriate treatment, another current key challenge of improving breast cancer outcomes come by early detection and diagnosis as overdiagnosis could result in overtreatment and bring unnecessary burden to patients. Hence, several commercially available multi-gene expression panels have been developed in the past two decades to predict distant recurrence (DR) in early-stage breast cancer (EBC) patients, and particularly the potential benefit of adjuvant chemotherapy. The current most widely used test is the Oncotype DX 21-gene recurrence score (RS)[7]. Since then, numerous studies, such as the Trial Assigning IndividuaLized Options for Treatment (TAILORx), have proved the clinical utility of this gene-expression profiling assay, involving mainly patients being identified as Caucasian (84.3%)[8] and post-menopausal women (69%)[9]. However, the utility of the assay in patients under 50 years old is still under investigation. At the same time, the percentage of Asian patients being enrolled in this trial was less than 5% among around 10,000 women[8]. As differences in overall and age-specific incidences and survival persist among women with breast cancer, despite similar disease stage and treatment, the clinical utility of Oncotype DX is not yet maximized for all population projections and the findings of the assay should be accordingly interpreted with caution for non-Caucasian populations and for patients with age less than 50 years. Recent studies have similarly shown that non-Hispanic black women were greater than two times more likely to be categorized as high-risk and more likely to receive adjuvant chemotherapy than non-Hispanic white counterparts even if they had a low RS [10–12].

To overcome the clinical heterogeneity of the disease, RecurIndex® is another accessible breast cancer recurrence risk test, which is based on a genomic database of predominantly Asians. The multigene panel has been developed using fresh frozen tissues or formalin-fixed paraffin embedded (FFPE) tumor tissues, on a quantitative reverse-transcription-polymerase chain reaction (RT-qPCR) system. The target population is Asian women, who have an early-stage invasive breast cancer, estrogen or progesterone receptors (ER/PR+) and are negative for human epidermal growth factor receptor type 2 (HER2-). The assay evaluates six clinical factors and the expression of a panel of 18 genes, created from a genomic model. A continuous Recurrence index-distant recurrence (RI-DR), ranging from 0-100, is then derived from each patient's gene expression data. Women are classified as low- (RI-DR score < 29) or high-risk (RI-

DR score ≥ 29) of distant recurrence. A previous study from a single center database has shown that the gene-expression profiling test is a viable prognostic biomarker to estimate the DR risk in breast cancer patients[13]. Another recent study revealed that the assay is a reliable tool to predict low- and high-risk of 10-year DR in both negative and positive lymph nodes (LNs) in Asian endocrine-responsive breast cancer patients[14].

In this multicenter, retrospective, observational study, we tested the RI-DR score using archived breast cancer tissue samples of patients admitted to five medical institutions in Taiwan to determine the clinical utility of the assay among Asian women.

Patients And Methods

Patients' selection

Figure 1 shows the CONsolidated Standards Of Reporting Trials (CONSORT) flow diagram of the study. All participants gave written informed consent to use their FFPE tissue samples from the pathology departments and agreed to future retrospective analysis of their data for research purposes. The protocol and informed consent documents were reviewed and approved by the institutional review board (IRB) of the participating hospitals in Taiwan. The inclusion criteria for the study were female patients: (a) being diagnosed with a primary, invasive breast cancer of grade I-III, (b) who underwent primary surgery without prior induction treatments, (c) with a pathologic N stage 0-II, with metastases in 0–9 axillary lymph nodes, and (d) who received either mastectomy or breast-conserving surgery (BCS). Patients who had preoperative chemotherapy, pN3, pT4, and/or M1 disease were excluded. Breast cancer subtypes were determined based on the hormone receptor (HR) and HER2 protein status of the tumor of a patient: HR+/HER2- (luminal A-like), HR+/HER2+ (luminal B-like), HR-/HER2+ (HER2-enriched) and HR-/HER2- (triple negative). Patients with any recurrence within 10 years following primary surgery and patients with disease-free, but not receiving adjuvant chemotherapy, were the preferred patients to take part in this retrospective study. Demographic, clinical and pathological information were obtained from hospital medical records.

Study endpoint definition

The primary endpoint was distant recurrence-free survival (DRFS), defined as the length of time between the primary surgery and the occurrence of distant recurrence and metastasis. The secondary endpoint was relapse-free survival (RFS), expressed as the duration between the primary surgery and any disease recurrence (local, regional or distant) from breast cancer. In the absence of an event, patients were censored at date of last follow-up visit.

Statistical analyses

The current study aimed to retrospectively predict the survival rates of low- and high-risk female patients with EBC at 5-year and 10-year follow-up after the primary surgery. Baseline characteristics of the study

population were compared using χ^2 test for categorical variables and t-test for continuous variables. Survival analyses for primary endpoint DRFS and secondary endpoint RFS were estimated by the Kaplan-Meier method and corresponding log-rank tests were applied for the statistical comparison of the two RI-DR risk groups. Since breast cancer molecular subtypes have already revealed critical difference in survival[15], analyses were stratified into two subtype groups: luminal-like and non-luminal-like. After testing the proportional hazard assumption, univariate and multivariate Cox proportional hazards regression models were used to select independent prognostic factors. RI-DR score, as a linear covariate, was predicted to estimate the 10-year risk of DR, by using the logarithm of the baseline cumulative hazard function derived from Royston and Parmar survival models[16]. These models offer a more flexible approach than the classical parametric models. A forest plot was produced to visually assess hazard ratios (HRs) and 95% confidence intervals (CIs) per RI-DR score increment of each prognostic factor's effect on DRFS. Statistical analyses were performed with R software version 4-0-2. All statistical tests were two-sided. Statistical significance was defined as p-value < 0.05.

Results

A total of 298 women who underwent surgery between April 2004 and March 2019 was enrolled in this validation study. Demographic and clinicopathological features of the patients at baseline by RI-DR risk category are shown in Table 1. According to the criteria of the gene expression assay, 145 (48.7%) patients had a RI-DR score below 29, which means a low-risk of having distant recurrence, and 153 (51.3%) patients had a RI-DR score of greater than or equal to 29, which means a high-risk of having distant recurrence. With an overall median follow-up time of 47.4 (IQR 29.4–71.7) months, 36 patients were identified as having a distant recurrence event during the period study (respectively, 7 and 29 in the low- and high-risk group). The relapse event occurred in an additional 24 patients with, respectively, 10 and 14 patients being assigned in the good and poor prognosis group. A majority of patients were older than 50 years at surgery (54.4%), had luminal-like subtype (85.6%), N0 stage (60.8%), cancer grade I-II cancer (81.5%), no prominent lymphovascular invasion (83.4%) and were not treated with adjuvant chemotherapy (66.9%). In the high-risk group, patients were more likely to undergo a mastectomy (p-value = 0.0187), to have nodal metastasis (p-value $\leq$ 0.0001), a high cancer grade (p-value $\leq$ 0.0001), prominent lymphovascular invasion (p-value $\leq$ 0.0001), a negative ER/PR status (p-values $\leq$ 0.0001) and to carry the overexpressed HER2-receptor protein (p-value = 0.0018). In a multivariate Cox proportional hazards model in which distant recurrence was evaluated in relation to the RI-DR score, N stage, cancer grade, lymph vessel invasion, adjuvant chemotherapy and RI-DR risk group were not statistically significant (Table S1).

Table 1
Baseline characteristics of the subjects by risk level of distant recurrence (n = 298)

Variable	Low-risk of DR (n = 145)	High-risk of DR (n = 153)	P-value
Median follow-up time (months), IQR	47.1 (26.7–70.1)	47.7 (29.9–72.0)	0.7105
Age (years)			
<=50 (n = 136)	65 (47.8)	71 (52.2)	0.7846
>50 (n = 162)	80 (49.4)	82 (50.6)	
N stage			
N0 (n = 180)	122 (67.8)	58 (32.2)	**≤ 0.0001**
N1 (n = 80)	21 (26.2)	80 (73.8)	
N2 (n = 15)	0 (0.0)	15 (100.0)	
Unknown (n = 2)	2	0	
Cancer grade			
I (n = 51)	36 (70.6)	15 (29.4)	**≤ 0.0001**
II (n = 191)	101 (52.9)	90 (47.1)	
III (n = 55)	7 (12.7)	48 (87.3)	
Unknown (n = 1)	1	0	
Molecular subtype			
Luminal-like (n = 255)	141 (55.3)	114 (44.7)	**≤ 0.0001**
HER2/TNBC (n = 43)	4 (9.3)	39 (90.7)	
Axillary lymph node			
Negative (n = 180)	122 (67.8)	58 (32.2)	**≤ 0.0001**
Positive (n = 118)	23 (19.5)	95 (80.5)	
Lymphovascular invasion			
Absent/focal (n = 242)	142 (58.7)	100 (41.3)	**≤ 0.0001**
Prominent (n = 48)	2 (4.2)	46 (95.8)	
Unknown (n = 8)	1	7	
Estrogen receptor			

Variable	Low-risk of DR (n = 145)	High-risk of DR (n = 153)	P-value
Negative (n = 29)	0 (0.0)	29 (100.0)	**≤ 0.0001**
Positive (n = 269)	145 (53.9)	124 (46.1)	
Progesterone receptor			
Negative (n = 49)	7 (14.3)	42 (85.7)	**≤ 0.0001**
Positive (n = 249)	138 (55.4)	111 (44.6)	
HER2 overexpression (IHC score (+))			
Negative (n = 275)	141 (51.3)	134 (48.7)	**0.0018**
Positive (n = 23)	4 (17.4)	19 (82.6)	
Surgical treatment			
Mastectomy (n = 162)	69 (42.6)	93 (57.4)	**0.0187**
BCS (n = 135)	76 (56.3)	59 (43.7)	
Unknown (n = 1)	0	1	
Adjuvant chemotherapy			
No (n = 190)	121 (63.7)	69 (36.3)	**≤ 0.0001**
Yes (n = 94)	17 (18.1)	77 (81.9)	
Unknown (n = 14)	7	7	
Adjuvant hormone therapy			
No (n = 40)	9 (22.5)	31 (77.5)	**≤ 0.0001**
Yes (n = 244)	136 (55.7)	108 (44.3)	
Unknown (n = 14)	0	14	
PMRT & RNI			
No (n = 134)	71 (53.0)	63 (47.0)	0.9511
Yes (n = 97)	51 (52.6)	46 (47.4)	
Unknown (n = 67)	23	44	
Locoregional recurrence			
Free (n = 267)	135 (50.6)	132 (49.4)	0.0536
Yes (n = 31)	10 (32.3)	21 (67.7)	

Variable	Low-risk of DR (n = 145)	High-risk of DR (n = 153)	P-value
Distant recurrence			
Free (n = 262)	138 (52.7)	124 (47.3)	**0.0002**
Yes (n = 36)	7 (19.4)	29 (80.6)	

Table S1
Univariate and multivariate Cox proportional hazards analysis of demographics and clinicopathological factors of patients associated with the likelihood of distant recurrence (n = 298)

	Crude model		Adjusted model	
Variable	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (years)				
>50 vs. ≤50	1.045 (0.54–2.02)	0.8948		
N stage				
N1/N2 vs. N0	2.1493 (1.10–4.21)	**0.0259**	0.758 (0.31–1.88)	0.5527
Cancer grade				
II vs. I	4.251 (1.00–18.16)	0.0507	3.272 (0.75–14.23)	0.1163
III vs. I	**7.096 (1.58–31.81)**	**0.0105**	3.303 (0.65–16.80)	0.1499
Lymph vessel invasion				
Prominent vs. Absent/focal	**3.331 (1.70–6.53)**	**0.0005**	2.224 (0.99–4.98)	0.0513
Adjuvant chemotherapy				
Yes vs. No	**2.442 (1.26–4.72)**	**0.0080**	1.487 (0.63–3.53)	0.3720
PMRT & RNI				
Yes vs. No	1.698 (0.83–3.48)	0.1490		
Adjuvant hormone therapy				
Yes vs. No	0.537 (0.24–1.20)	0.1300		
RI - DR risk group				
Low vs. high	**0.278 (0.12–0.64)**	**0.0024**	0.483 (0.18–1.31)	0.1520

Table 1. Baseline characteristics of the subjects by risk level of distant recurrence (n = 298)

Tables 2a and 2b show the 5- and 10-year Kaplan-Meier DRFS and RFS rates of female patients in the good and poor prognosis groups. Figure S1 illustrates the Kaplan-Meier curves of primary and secondary outcomes.

Table 2. Estimated survival rates at 5 and 10 years according to RI-DR risk classification

(2a) Primary outcomes: DRFS estimates

Risk group by population	5-year DRFS, % (95% CI)	10-year DRFS, % (95% CI)	P-value	Crude HR (95% CI)
All patients (n = 298)			**0.0012**	
Low-risk (n = 145)	91.9 (86.1–98.1)	91.9 (86.1–98.1)		—
High-risk (n = 153)	83.1 (76.6–90.1)	62.9 (49.8–79.4)		**3.59 (1.57–8.20)**
Luminal-like patients (n = 255)			**0.0210**	
Low-risk (n = 141)	91.6 (85.5–98.1)	91.6 (85.5–98.1)		—
High-risk (n = 114)	88.8 (82.4–95.7)	65.3 (50.3–84.8)		**2.71 (1.12–6.53)**
HER2/TNBC patients (n = 43)			0.2500	
Low-risk (n = 4)	100.0	100.0		—
High-risk (n = 39)	70 (56.4–86.7)	61.2 (43.6–85.9)		—
Abbreviations: HR hazard ratio, CI confidence interval				

Bold values denote statistical significance at the $p < 0.05$ level.

(2b) Secondary outcomes: RFS estimates

Risk group by population	5-year RFS, % (95% CI)	10-year RFS, % (95% CI)	P-value	Crude HR (95% CI)
All patients (n = 298)			**0.0025**	
Low-risk (n = 145)	84.3 (77.0-92.2)	78.2 (68.2–89.8)		—
High-risk (n = 153)	72.7 (65.2–81.0)	53.6 (41.6–69.2)		**2.32 (1.32–4.07)**
Luminal-like patients (n = 255)			**0.0082**	
Low-risk (n = 141)	85.5 (78.3–93.4)	79.3 (69.2–91.0)		—
High-risk (n = 114)	76.5 (68.1–86.0)	54.2 (40.3–72.8)		2.**28 (1.22–4.26)**
HER2/TNBC patients (n = 43)			0.7000	
Low-risk (n = 4)	50.0 (18.8–100)	50.0 (18.8–100)		—
High-risk (n = 39)	63.5 (49.8–80.8)	55.5 (38.9–79.3)		0.75 (0.17–3.31)
Abbreviations: HR hazard ratio, CI confidence interval				

Bold values denote statistical significance at the $p < 0.05$ level.

Patients with less favorable prognosis had worse outcomes than patients with good prognosis in all populations, with, respectively, a 10-year DRFS of 62.9% [95% CI, 49.8–79.4%] and 91.9% [95% CI, 86.1–98.1%] in the two groups (p-value = 0.0012). Women in the high-risk group had statistically significantly an increasing risk of distant recurrence related to women classified in the low-risk group (crude HR = 3.59 [95% CI, 1.57–8.20]). The same observation was valid when considering only luminal-like subtype patients in the analysis; however, the sample size of non-luminal-like breast cancer patients was too small to draw a confident conclusion. The relapse-free survival rates – the secondary endpoint – for all patients were 72.7% [95% CI, 65.2–81.0%] at 5 years and 53.6% [95% CI, 41.6–69.2%] at 10 years in the high-risk group of distant recurrence. Compared to the low-risk group, the two survival curves were statistically significantly different from each other when considering all patients and luminal-like subtype patients (p-values of 0.0025 and 0.0082, respectively).

Figure 2a shows the observed distribution of distant recurrence events by RI-DR score interval in all patients and Fig. 3 the predicted probability of distant recurrence for each RI-DR score. As a large group of patients (63.7%) not being treated with adjuvant chemotherapy were assigned in the low-risk group (Table 1), the observed probability of distant recurrence in this subpopulation were calculated and displayed in Fig. 2b.

Figure 2. Histogram of the frequency distribution of distant recurrence by RI-DR score interval in patients with EBC. X-axis stands for the RI-DR score, with a 10-score interval in each column; Y-axis is the frequency of distant recurrence and distant recurrence-free events. The blue color represents DR; the

orange color displays DR-free. The study sample is stratified by (2a) all patients (n = 298) and (2b) patients without adjuvant chemotherapy treatment (n = 190).

(2a) All patients (n = 298)

(2b) Patients without adjuvant chemotherapy treatment (n = 190)

The observed 5-year distant recurrence-free rate was more than 97% for patients with a RI-DR score < 11 and decreased to 87.5% for those having with a RI-DR score above 30. In the subset of patients having a RI-DR score greater than 50, the distant recurrence-free rate dropped to around 50% (Fig. 2a). For patients not receiving adjuvant chemotherapy (n = 190), the risk of having distant recurrence still notably increased for patients with a higher RI-DR score (Fig. 2b).

Through Royston-Parmar modeling, the risk of distant recurrence rose constantly with increasing RI-DR score. The predicted 10-year risk of developing DR in patients with breast cancer was nearly up to 80% when the RI-DR score reaches its maximum value (Fig. 3). In addition, as shown in the forest plot (Figure S2), the overall HR for distant recurrence was 1.031 [95% CI, 1.017–1.046] per unit RI-DR score increment. For each increment of the RI-DR score, most prognostic factors were associated with a worse DRFS.

Discussion

In the current study, we tested the RI-DR score on 298 female patients to determine the clinical utility of the gene-expression profiling test (RecurIndex®) among Asian women. Five medical centers joined the study in order to ensure a good representation of the patient population. The analysis demonstrated that the RI-DR assay is reliable in identifying EBC patients with good and poor prognosis of relapse and distant recurrence in long-term follow-up care. This is particularly true in luminal-like subtype breast cancer patients (p-values of 0.0082 and 0.0210, respectively, comparing the relapse and distant recurrence-free survival in the two RI-DR risk groups). This study also showed that the 10-year DRFS and RFS rates of low-risk patients are in overall, respectively, 91.9% [95% CI, 86.1–98.1%] and 78.2% [95% CI, 68.2–89.8%], versus 62.9% [95% CI, 49.8–79.4%] and 53.6% [95% CI, 41.6–69.2%] for patients classified in the high-risk group (p-values = 0.0012 and 0.0025). The study validates therein the clinical utility of the assay. With this clinical-genomic assay, the decision for a clinician of whether to give to a patient as treatment adjuvant chemotherapy or not will be easier to make.

To date in other Asian countries, only a Korea research team has developed a gene expression assay GenesWell Breast Cancer Test (BCT) for breast cancer patients in Asia. The comparison of the BCT score with Oncotype DX recurrence score (RS) revealed that the score from BCT classify more low-risk patients than RS in patients aged 50 years or less (68.1% versus 44.4%)[17]. Since a substantial proportion of women treated for a breast cancer in Asia are pre-menopausal at diagnosis, further studies, including our model, are necessary in order to identify which clinical-genomic assay is more appropriate in this population.

However, this study has several limitations that must be considered when interpreting the results. First, this is a retrospective observational study: clinicians randomly selected a subset of patients among all available patients. An unintended selection bias might have occurred because patients being not treated with adjuvant chemotherapy were more likely to be enrolled. Therefore, these patients might be over-represented and might tend to be classified as low-risk of distant recurrence due to their clinicopathological features. As a result, few non-luminal-like breast cancer patients (HER2-enriched and TNBC subtypes) who did not undergo adjuvant chemotherapy treatment, were included in this research and we could not draw a clear conclusion for these patients assigned in the low-risk group. In this latter case, a larger sample size would be necessary to prove the clinical utility of this subpopulation.

Conclusions

In conclusion, the study provides a robust evidence that RecurIndex® is an accurate gene expression profiling test to identify Asian EBC patients at high-risk of relapse and distant recurrence at 5-and 10-year follow-up time and can distinguish patients who would benefit from adjuvant chemotherapy and those who would not. The use of the assay will lessen a significant proportion of patients with unnecessary over treatment and burden of needless treatment. However, some investigations remain open in the application of the RI-DR score in HER2-enriched and TNBC patients.

Abbreviations

SEER, Surveillance, Epidemiology, and End Results; DR, distant recurrence; EBC, early-stage breast cancer; RS, recurrence score; TAILORx, Trial Assigning IndividuaLized Options for Treatment; FFPE, formalin-fixed paraffin embedded; RT-qPCR, quantitative reverse transcription-polymerase chain reaction; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; RI-DR, Recurrence index-distant recurrence; LN, lymph node; CONSORT, CONsolidated Standards Of Reporting Trials; IRB, institutional review board; BCS, breast-conserving surgery; pN, regional lymph node; pT, primary tumor; M, distant metastasis; HR, hormone receptor; DRFS, distant recurrence-free survival; RFS, relapse-free survival; HR, hazard ratio; CI, confidence interval; IQR, interquartile range; TNBC, triple-negative breast cancer; IHC, immunohistochemistry; PMRT, post-mastectomy radiation therapy; RNI, regional nodal irradiation; BCT, Breast Cancer Test.

Declarations

Ethics approval and consent to participate: the study protocol was approved by the IRB of each participating site, including the Radiation Oncology department of China Medical University Hospital (CMUH106-REC1-151), MacKay Memorial Hospital (17CT040be), National Taiwan University Hospital (201610066RINA), Taiwan Adventist Hospital (107-E-05) and Taipei Veterans General Hospital (2020-09-004AC). These committees waived documentation of informed consent due to the observational nature of the investigation.

Consent for publication: not applicable.

Availability of data and materials: the datasets used and analyzed during the current study are not publicly available due to privacy and ethical restrictions but are available from the corresponding author on reasonable request.

Competing interests: Nicolas Pennarun and Kuan-Hui Shih are respectively a consultant and an employee of Amwise Diagnostics Pte. Ltd. All other authors have no competing interests.

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Authors' contributions: NP conducted the statistical analysis, interpreted the data and drafted the manuscript. YHL, LMT, PSY, JAL, CMH, YCC, MYW and CSH made substantial contributions to the acquisition and interpretation of data and provided important comments on the contents and final draft. KHS formulated research goals and aims, provided funding acquisition, project administration and resources, participated in the initial conception and design of this research study, collected data, supervised the research activity planning and contributed in revising the manuscript for important intellectual content. All authors read and approved the final manuscript.

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Figures

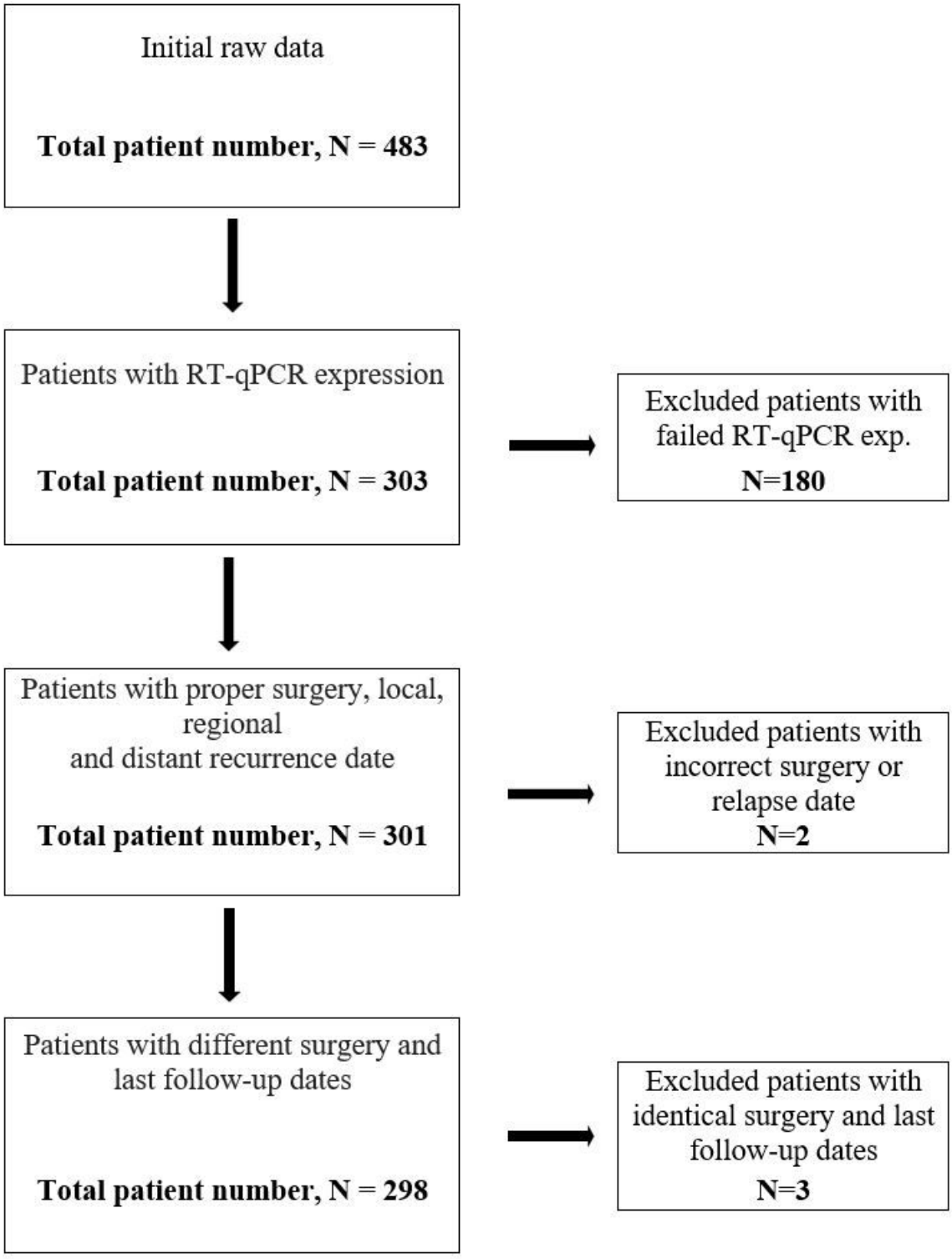
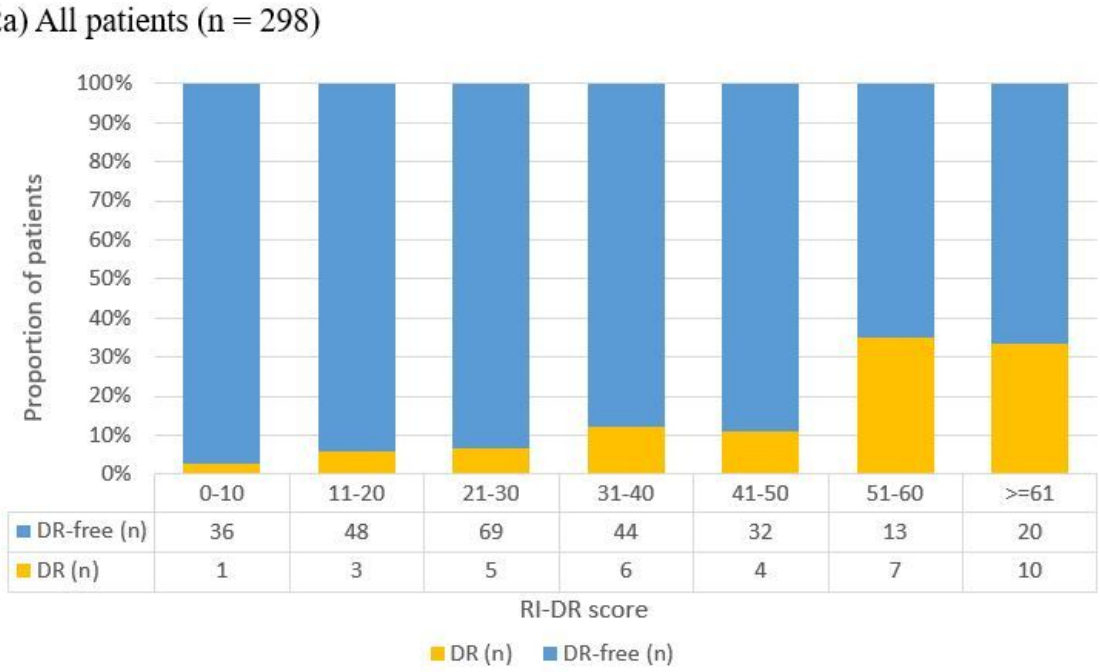


Figure 1

CONSORT flow diagram



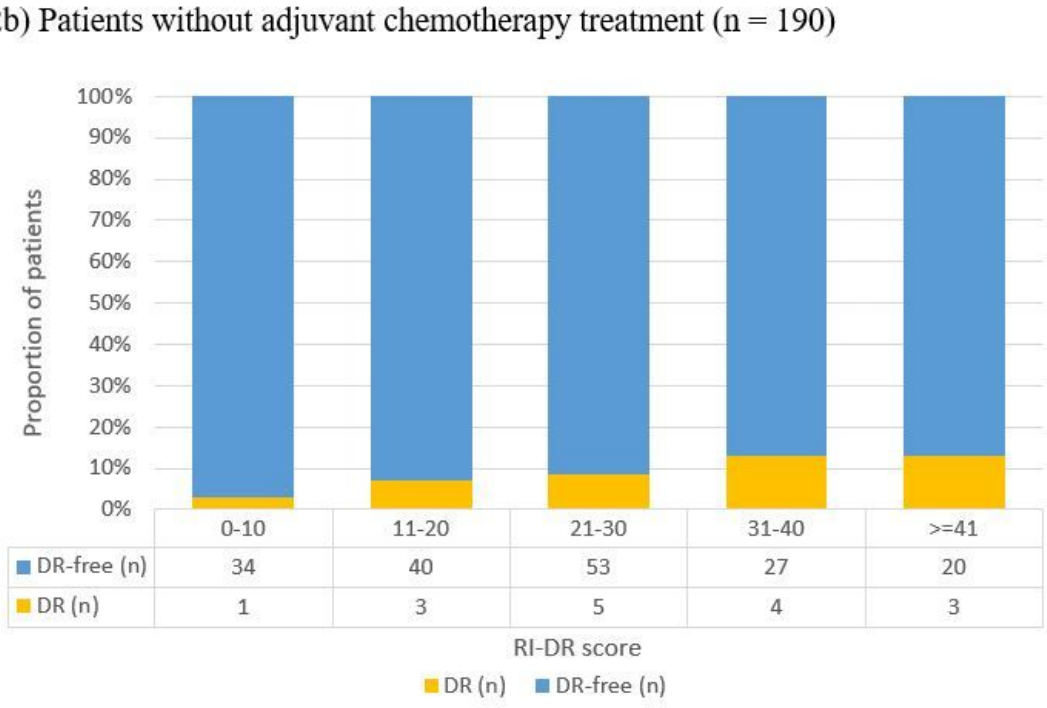


Figure 2

Histogram of the frequency distribution of distant recurrence by RI-DR score interval in patients with EBC. X-axis stands for the RI-DR score, with a 10-score interval in each column; Y-axis is the frequency of

distant recurrence and distant recurrence-free events. The blue color represents DR; the orange color displays DR-free. The study sample is stratified by (2a) all patients (n = 298) and (2b) patients without adjuvant chemotherapy treatment (n = 190).

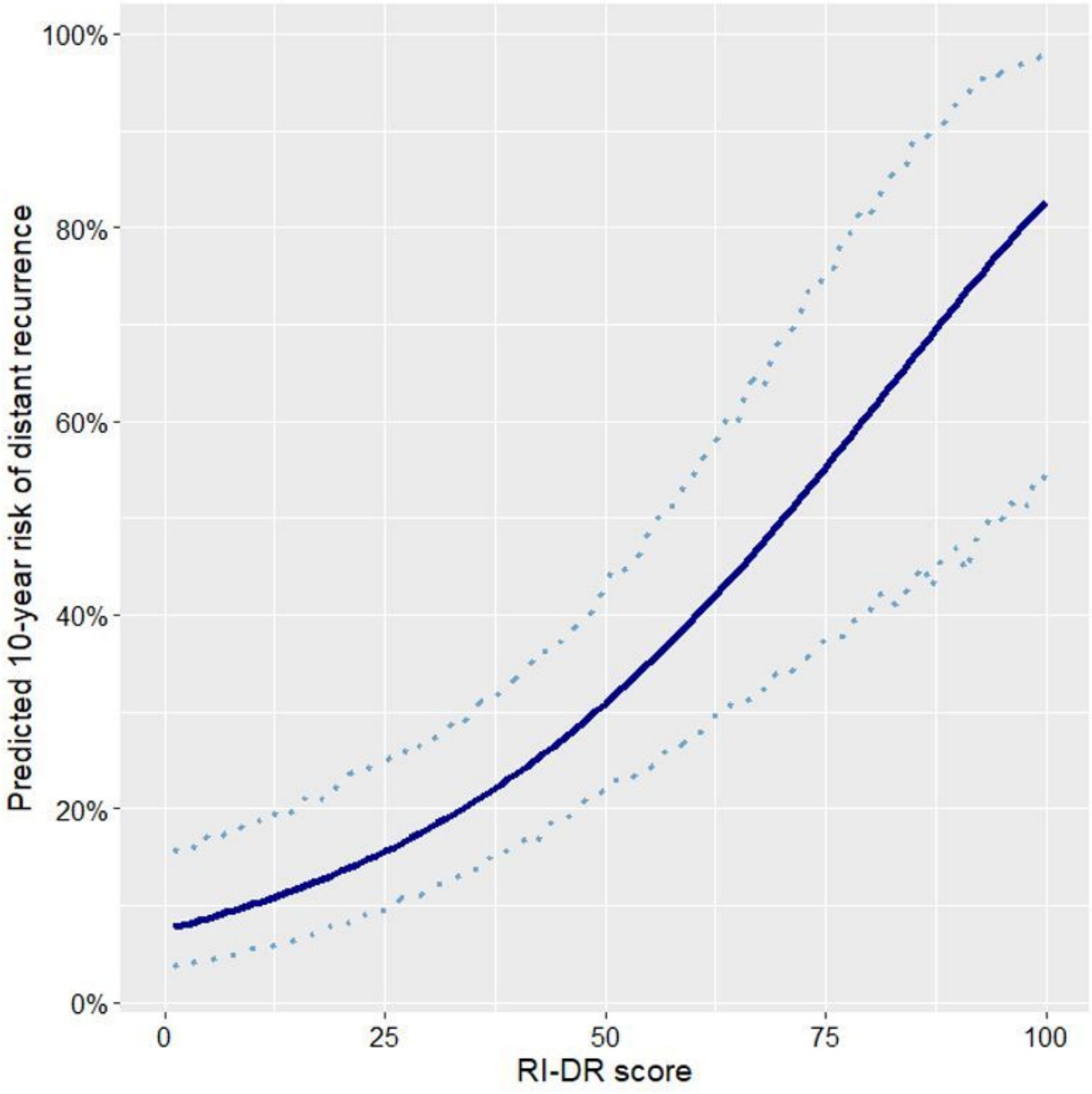


Figure 3

Predicted cumulative hazard plot using Royston-Parmar models: score distribution and probability of distant recurrence. X-axis represents the RI-DR score; Y-axis stands for the probability of distant recurrence predicted by RI-DR score. Dash lines represent the 95% confidence interval.

Supplementary Files

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