Title: Survival of HER2-positive primary breast cancer patients treated by neoadjuvant chemotherapy plus trastuzumab: a multicenter retrospective observational study (JBCRG-C03 study)

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ABSTRACT

Purpose: We investigated the disease-free survival (DFS) of HER2-positive primary breast cancer patients treated with neoadjuvant chemotherapy plus trastuzumab, as well as predictive factors for DFS and pathologic response.

Patients and methods: Data from 829 female patients treated between 2001 and 2010 were collected from 38 institutions in Japan. Predictive factors were evaluated using multivariate analyses.

Results: The 3-year DFS rate was 87% (95% confidence interval [CI] 85-90). The pathologic complete response (pCR: ypT0/is + ypN0) rate was 51%. The pCR rate was higher in the ER/PgR-negative patients than in the ER/PgR-positive patients (64% vs 36%, $P < 0.001$). Patients with pCR showed a higher DFS rate than patients without pCR (93% vs 82%, $P < 0.001$). Multivariate analysis revealed 3 independent predictors for poorer DFS: advanced nodal stage (hazard ratio [HR] 2.63, 95%CI 1.36-5.21, $P = 0.004$ for cN2-3 vs cN0), histological/nuclear grade 3 (HR 1.81, 95%CI 1.15-2.91, $P = 0.011$), and non-pCR (HR 1.98, 95%CI 1.22-3.24, $P = 0.005$). In the ER/PgR-negative dataset, non-pCR (HR 2.63, 95%CI 1.43-4.90, $P = 0.002$) and clinical tumor stage (HR 2.20, 95%CI 1.16-4.20, $P = 0.017$ for cT3-4 vs cT1-2) were independent predictors for DFS, and in the ER/PgR-positive dataset, histological

grade of 3 (HR 3.09, 95%CI 1.48-6.62, *P* = 0.003), clinical nodal stage (HR 4.26, 95%CI 1.53-13.14, *P* = 0.005 for cN2-3 vs cN0), and young age (HR 2.40, 95%CI 1.12-4.94, *P* = 0.026 for ≤40 vs >40) were negative predictors for DFS. Strict pCR (ypT0 + ypN0) was an independent predictor for DFS in both the ER/PgR-negative and -positive datasets (HR 2.66, 95%CI 1.31-5.97, *P* = 0.006 and HR 3.86, 95%CI 1.13-24.21, *P* = 0.029, respectively).

Conclusions: These results may help assure a more accurate prognosis and personalized treatment for HER2-positive breast cancer patients.

Key words: Breast cancer, HER2, neoadjuvant chemotherapy, pathologic complete response, prognostic factors, trastuzumab

INTRODUCTION

Amplification or overexpression of human epidermal growth factor receptor-2 (HER2) is associated with a high risk of breast cancer recurrence and metastasis [1]. Adjuvant use of cytotoxic chemotherapy and trastuzumab, a recombinant humanized monoclonal antibody that targets HER2, improves the overall survival (OS) and disease-free survival (DFS) of patients with HER2-positive primary breast cancer [2,3].

Neoadjuvant chemotherapy (NAC) reduces tumor size, which improves the rate of breast-conserving surgery, and provides information about chemosensitivity that helps with the design of postoperative therapy. Several meta-analyses have revealed that patients with a pathologic complete response (pCR) after NAC had higher survival rates than those without pCR, indicating that pCR represents a surrogate prognostic indicator [4-6].

Adding trastuzumab to NAC doubles the rate of pCR in patients with HER2-positive primary breast cancer [7-9]. The NOAH trial showed better 3-year event-free survival for chemotherapy plus trastuzumab versus chemotherapy alone [8]. In the TECHNO trial, patients with pCR after NAC plus trastuzumab showed better 3-year DFS than patients without pCR [10]; however, predictors for pCR and survival after treatment are unknown.

This multicenter retrospective study investigated the survival after NAC with trastuzumab

among patients with HER2-positive primary breast cancer in efforts to identify predictive factors.

PATIENTS AND METHODS

Patients

In this multicenter retrospective cohort study, the inclusion criteria were female sex, histologically confirmed HER2-positive invasive breast cancer diagnosed between 2001 and 2010, no distant metastasis, age 20-70 years, and received NAC containing trastuzumab. Eligible patients were identified from the institutional databases. Data were managed by the data center of the Japan Breast Cancer Research Group (JBCRG).

The study protocol was approved by the Institutional Review Board at Kyoto University Hospital and participating institutions. All patient data were anonymized and allocated numbers according to Japanese ethics guidelines for epidemiologic research.

Pathological assessment

Pathology specialists at each institution performed the pathological investigation.

HER2-positive status was defined as 3+ overexpression by immunohistochemical testing or HER2 amplification by fluorescent in situ hybridization (HER2/CEP17 ratio ≥ 2.0). At each institution, surgical specimens obtained following NAC were serially sectioned, stained with haematoxylin and eosin (H&E), and diagnosed by experienced pathologists. pCR was defined as the absence of residual invasive cancer cells in the breast and axillary lymph nodes (ypT0/is + ypN0). Strict pCR (spCR), another pCR definition, was defined as no invasive and non-invasive residuals in the breast and axillary nodes (ypT0 + ypN0).

Statistical analysis

All survival outcomes were measured from the date of starting NAC to the date of first event. The primary survival outcome was DFS defined as time to occurrence of recurrence, secondary malignancy (including contralateral breast cancer, hematological malignancy, and sarcoma), or death as a result of any cause. Secondary survival outcomes were OS defined as time to death as a result of any cause, distant recurrence-free survival (DRFS) defined as time to any recurrence except for ipsilateral breast or regional lymph node, and death as a result of any cause.

The Kaplan-Meier method was used to estimate survival outcomes. χ^2 tests for categorical data and log-rank tests for time-to-event endpoints provided two-sided p values, and p values < 0.05 were considered statistically significant. Cox proportional hazards regression analysis was

used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). Logistic regression was used to estimate odds ratios (ORs) and 95% CIs. Covariates used in the multivariate model were age, body mass index, clinical tumor stage, clinical nodal stage, estrogen receptor (ER)/progesterone receptor (PgR) status, histological/nuclear grade, pCR/spCR, surgery type, radiation therapy, adjuvant hormonal therapy, adjuvant chemotherapy, and adjuvant trastuzumab. Menopausal status was not included in the model because of collinearity with age. Patients with missing data were excluded from the multivariate analysis (e.g. patients whose adequate pathologic responses were not confirmed due to insufficient local therapy or lack of information regarding local therapy type). All statistical analyses were performed using JMP® (ver. 10.0.2, SAS Institute Inc. Cary, NC). All analyses were supervised by a statistician (SM).

RESULTS

Patient characteristics

Data of 829 patients from 38 institutions in Japan were collected. Among them, 53 did not meet the inclusion criteria and were excluded, leaving a total of 776 patients for analysis (whole dataset). HER2-positive tumors could be subdivided into ER/PgR positive and negative, and we

therefore divided the patients into an ER/PgR-positive dataset (*N* = 334) and ER/PgR-negative dataset (*N* = 439) and also performed the analyses for each dataset (Figure 1).

Baseline characteristics and treatment of the whole dataset are summarized in Table 1. Median age was 53 (range 25-70) years. Most patients had tumor stage T2 (61%) and were clinically node positive (67%). ER and PgR were negative in 57% of the patients. Most patients received anthracycline- and taxane-containing chemotherapy (87%), and trastuzumab was administered concurrently with taxane (80%). Breast-conserving surgery was performed in 64% of the patients, most of whom (91%) received radiation therapy. Radiation therapy was performed in 35% of the patients who received mastectomy. Adjuvant hormonal therapy was performed in 86% of the ER/PgR-positive patients. Most patients received adjuvant trastuzumab (90%).

Clinical outcomes

The median follow-up period was 42 (interquartile range 30-58) months. For the whole dataset, the 3-year DFS rate was 87% (95%CI 85-90) (Figure 2A). Three-year OS and DRFS were 97% (95%CI 96-98) and 91% (95%CI 89-93), respectively. pCR was achieved in 399 (51%) patients and spCR in 240 (31%) patients.

The 3-year DFS rate was almost the same among patients in the ER/PgR-positive and

-negative datasets (87% vs 88%, *P* = 0.888) (Figure 2B). The pCR and spCR rates were higher in the ER/PgR-negative patients than in the ER/PgR-positive patients (64% vs 36% for pCR, *P* < 0.001; 38% vs 23% for spCR, *P* < 0.001, respectively).

Prognostic factors for survival outcomes

The results of Cox proportional hazard regression performed to evaluate the prognostic effect of baseline characteristics and pathologic tumor response to NAC with trastuzumab are shown in Table 2. In the whole dataset, independent predictors for poorer DFS were advanced clinical nodal stage (adjusted HR 2.63, 95%CI 1.36-5.21, *P* = 0.004 for cN2-3 vs cN0; adjusted HR 1.64, 95%CI 0.91-3.09, *P* = 0.100 for cN1 vs cN0), histological/nuclear grade 3 (adjusted HR 1.81, 95%CI 1.15-2.91, *P* = 0.011), and failure to achieve pCR (adjusted HR 1.98, 95%CI 1.22-3.24, *P* = 0.005). Neither age nor ER/PgR status was an independent predictor for DFS. Multivariate analysis including spCR yielded the same results. The DFS rate was higher among patients with pCR than those without pCR (93% vs 82%, *P* < 0.001) (Figure 3A). Patients who achieved spCR had a higher DFS rate than those who did not (96% vs 84%, *P* < 0.001) (Figure 3B).

In the ER/PgR-positive dataset, independent predictors for poorer DFS were advanced clinical nodal stage, histological/nuclear grade 3, young age (≤40), and not achieving spCR. pCR was not an independent predictor for DFS on multivariate analysis (Table 2; Figure 3C, D).

For the ER/PgR-negative dataset, clinical tumor stage and both pCR and spCR were independent predictors for DFS (Table 2; Figure 3E, F).

Predictors for other survival outcomes are listed in Supplementary Table S1. Predictors for OS were clinical nodal stage, histological/nuclear grade, and spCR, but pCR was not an independent predictor. Predictors for DRFS were clinical nodal stage, histological/nuclear grade, young age, pCR, and spCR.

Predictive factors for pCR

The association of baseline characteristics with pCR/spCR following NAC plus trastuzumab was evaluated by multivariate logistic regression (Table 3). In the whole dataset, independent predictors for pCR were negative ER/PgR status (adjusted OR 3.42, 95%CI 2.42-4.86, $P < 0.001$) and clinical tumor stage T1-2 compared with T3-4 (adjusted OR 1.88, 95%CI 1.27-2.79, $P = 0.002$). Histological/nuclear grade 3 showed a statistically marginal association with pCR (adjusted OR 1.39, 95%CI 0.99-1.95, $P = 0.060$). The same factors were selected as independent predictors in the multivariate model for spCR.

In the ER/PgR-positive dataset, clinical tumor stage was a predictor for pCR and spCR. In the ER/PgR-negative dataset, clinical tumor stage was an independent predictor for both pCR and spCR. Histological/nuclear grade was marginally predictive of pCR and spCR.

DISCUSSION

In this analysis, we assessed survival after NAC plus trastuzumab among patients with HER2-positive breast cancer. Although clinical nodal status, histological/nuclear grade, and pCR/spCR were independent predictors for DFS, the prognostic impact differed depending on ER/PgR status. pCR was a predictor for DFS particularly in patients with ER/PgR-negative tumor, and spCR—a stricter definition of pCR—was an independent prognostic factor regardless of ER/PgR status.

Our data included more patients with clinical tumor stage T2 or higher (89%) and clinically node positive (67%). In this population, a three-year DFS rate of 87% was relatively good; however, a considerable number of patients experienced disease relapse during the follow-up period. Risk factors associated with disease relapse need to be clarified to conduct a clinical trial aimed at improving these patients' prognosis.

In two phase III trials in which patients with HER2-positive disease were randomly allocated to NAC with trastuzumab or NAC only, the addition of trastuzumab to NAC resulted in a higher pCR rate and improved DFS [11,8]. The pCR rate in our study (51%) is comparable to those reported in previous trials of NAC with trastuzumab (30-67%) [7,8,12,10,13-15,9]. In our study,

ER/PgR status was the strongest predictor for pCR or spCR. Our results were consistent with those of two meta-analyses in which the pCR rate of NAC with trastuzumab was about 50% for patients with ER/PgR-negative disease and 30% for those with ER/PgR-positive disease [16,6].

In the TECHNO trial, a phase II trial of 217 patients with HER2-positive disease who received NAC with trastuzumab, failure to achieve pCR was a significant predictor for DFS in the multivariate analysis[10]. Kim et al. retrospectively investigated the prognostic value of pCR using data from 229 patients with HER2-positive tumor who were treated with NAC with trastuzumab [12]. They reported that pCR, clinical tumor stage, and lymphovascular invasion were independent predictors for DFS. In our study, pCR and spCR were predictors for DFS; in addition, conventional prognostic factors such as nodal stage and histological/nuclear grade were predictors for DFS.

In this study, the association of age with DFS was not statistically significant in the whole dataset, consistent with the results of the TECHNO trial and Kim et al. Partridge et al. reported that young age was not associated with worse DFS in patients with HER2-positive disease using large cohort data from the HERA trial [17]. When we divided the patients into ER/PgR-positive and -negative groups, multivariate analysis showed that young age (age $\leq$ 40) was an independent predictor for poorer DFS in the ER/PgR-positive dataset. Our result was consistent with earlier studies showing that younger age is an independent predictor for worse DFS,

especially in patients with ER/PgR-positive disease [18,19].

After dividing the patients into ER/PgR-positive and -negative datasets, we performed multivariate analysis for DFS using each dataset. About 30-40% of HER2-enriched subtype tumors are reported to be ER positive [20,21]. Among clinically HER2-positive tumors, up to 60% are classified as the HER2-enriched subtype, with the rest classified as luminal B, luminal A, or basal-like [22]. Adjuvant systemic therapy differs according to ER/PgR status [23]. Therefore, it seemed reasonable to perform the analysis based on ER/PgR status; however, the results should be interpreted carefully because of the relatively small event rate in each dataset.

In relation to the two aforementioned meta-analyses, pooled analysis from the German study group [6] indicated that pCR was a prognostic factor for the HER2-positive non-luminal subgroup, but not for those in the HER2-positive luminal subgroup. In the meta-analysis from the Collaborative Trials in Neoadjuvant Breast Cancer (CTNeoBC) [16], there was a stronger association of pCR with event-free survival in the HER2-positive non-luminal subgroup compared with those in the HER2-positive luminal subgroup. In our study, pCR was an independent predictor for DFS in the ER/PgR-negative dataset, but not ER/PgR-positive dataset, and spCR was an independent predictor for DFS regardless of ER/PgR status.

The limitations of this study include its retrospective design. Adjustment using multivariate analysis is mandatory to minimize selection bias. The relatively short observation period may

also limit the interpretation of our results. The median follow-up period of our study (42 months) covered the time when recurrence risk is high in HER2-positive disease [24]. A strength of our study was the large number of patients, which allowed us to conduct multivariate analysis separately according to ER/PgR status.

In conclusion, pCR/spCR, nodal status, and grade were predictors for DFS in patients with HER2-positive disease treated with NAC plus trastuzumab. Response to therapy and prognostic impact of the factors differed according to ER/PgR status. Our results may help identify patients who are not likely to achieve pCR or whose outcome would otherwise be unfavorable. New treatment approaches, such as the incorporation of novel anti-HER2 drugs, are needed for patients with high-risk disease.

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CONFLICT OF INTEREST

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Table 1. Patient, disease, and treatment characteristics

Factors	n	(%)
All cases	**776**	**(100)**
Age		
Median (Min-Max)	53	(25-70)
BMI		
Median (Min-Max)	22.0	(15.0-47.3)
Unknown	2	(0.3)
Menopausal status		
Pre-menopausal	335	(43.2)
Post-menopausal	422	(54.4)
Unknown	19	(2.4)
Clinical tumor size		
T1b	9	(1.2)
T1c	77	(9.9)
T2	476	(61.3)
T3	122	(15.7)

T4	91	(11.7)
Unknown	1	(0.1)
Clinical nodal status		
N0	252	(32.5)
N1	366	(47.2)
N2	103	(13.3)
N3	54	(7)
Unknown	1	(0.1)
ER/PgR status		
Positive	334	(43)
Negative	439	(56.6)
Unknown	3	(0.4)
Histological/Nuclear grade		
1	107	(13.8)
2	184	(23.7)
3	350	(45.1)
Unknown	135	(17.4)
NAC regimen		

Anthracycline and taxane	676	(87.1)
Taxane only	78	(10.1)
Anthracycline only	7	(0.9)
Others	1	(0.1)
Unknown	14	(1.8)
Local therapy		
Mastectomy+XRT	96	(12.4)
Mastectomy alone	181	(23.3)
BCS+XRT	449	(57.9)
BCS alone	44	(5.7)
Needle biopsy+XRT	1	(0.1)
Needle biopsy alone	1	(0.1)
Unknown	4	(0.5)
pCR (ypT0/is+ypN0)		
Yes	399	(51.4)
No	365	(47)
Unknown	12	(1.5)
spCR (ypT0+ypN0)		

Yes	240	(30.9)
No	525	(67.7)
Unknown	11	(1.4)
Adjuvant hormonal therapy		
Yes	281	(36.2)
No	440	(56.7)
Unknown	55	(7.1)
Adjuvant trastuzumab therapy		
Yes	697	(89.8)
No	65	(8.4)
Unknown	14	(1.8)
Adjuvant chemotherapy		
Yes	45	(5.8)
No	720	(92.8)
Unknown	11	(1.4)

BMI, body mass index; ER/PgR, estrogen receptor/progesterone receptor; NAC, neoadjuvant chemotherapy; XRT, radiation therapy; BCS, breast-conserving surgery; pCR, pathologic complete response.

Table 2. Adjusted hazard ratios of factors predicting DFS

	pCR (ypT0/is+ypN0)			spCR (ypT0+ypN0)		
Factor	HR	95%CI	p-value	HR	95%CI	p-value
Whole dataset						
Age						
≤40 vs >40	1.67	(0.95-2.81)	0.074	1.63	(0.93-2.75)	0.088
BMI						
25≤ vs <22	1.31	(0.74-2.24)	0.351	1.31	(0.74-2.24)	0.348
22≤, <25 vs <22	0.96	(0.56-1.61)	0.891	1.00	(0.58-1.67)	0.993
Clinical tumor size						
T3-4 vs T1-2	1.53	(0.93-2.49)	0.093	1.42	(0.87-2.32)	0.160
Clinical nodal status						
N2-3 vs N0	2.63	(1.36-5.21)	0.004	2.58	(1.34-5.12)	0.004
N1 vs N0	1.64	(0.91-3.09)	0.100	1.73	(0.96-3.26)	0.070
ER/PgR						
Negative vs positive	0.97	(0.47-2.08)	0.933	0.93	(0.46-1.96)	0.842
Histological/Nuclear grade						

3 vs 1&2	1.81	(1.15-2.91)	0.011	1.77	(1.12-2.84)	0.014
pCR/spCR						
non-pCR vs pCR	1.98	(1.22-3.24)	0.005	2.90	(1.57-5.90)	<0.001
ER/PgR-positive dataset						
Age						
≤40 vs >40	2.40	(1.12-4.94)	0.026	2.33	(1.08-4.80)	0.031
BMI						
25≤ vs <22	1.49	(0.63-3.38)	0.354	1.54	(0.66-3.45)	0.313
22≤, <25 vs <22	0.69	(0.25-1.67)	0.419	0.69	(0.25-1.68)	0.433
Clinical tumor size						
T3-4 vs T1-2	0.83	(0.35-1.88)	0.653	0.69	(0.28-1.62)	0.399
Clinical nodal status						
N2-3 vs N0	4.26	(1.53-13.14)	0.005	4.54	(1.62-14.13)	0.004
N1 vs N0	2.55	(0.99-7.43)	0.053	2.83	(1.08-8.39)	0.034
Histological/Nuclear grade						
3 vs 1&2	3.09	(1.48-6.62)	0.003	3.14	(1.49-6.85)	0.003
pCR/spCR						
non-pCR vs pCR	1.20	(0.57-2.69)	0.634	3.86	(1.13-24.21)	0.029

ER/PgR-negative dataset						
Age						
≤40 vs >40	0.95	(0.35-2.18)	0.913	1.01	(0.38-2.28)	0.979
BMI						
25≤ vs <22	0.94	(0.39-2.05)	0.886	0.97	(0.40-2.11)	0.942
22≤, <25 vs <22	1.10	(0.56-2.08)	0.774	1.10	(0.56-2.08)	0.779
Clinical tumor size						
T3-4 vs T1-2	2.20	(1.16-4.20)	0.017	2.11	(1.11-4.04)	0.024
Clinical nodal status						
N2-3 vs N0	2.04	(0.85-5.07)	0.112	1.73	(0.73-4.27)	0.217
N1 vs N0	1.49	(0.70-3.38)	0.306	1.39	(0.66-3.13)	0.398
Histological/Nuclear grade						
3 vs 1&2	1.33	(0.74-2.48)	0.354	1.29	(0.72-2.41)	0.393
pCR/spCR						
non-pCR vs pCR	2.63	(1.43-4.90)	0.002	2.66	(1.31-5.97)	0.006

BMI, body mass index; ER/PgR, estrogen receptor/progesterone receptor; pCR, pathologic complete response; spCR, strict pathologic complete response; HR, hazard ratio.

Table 3. Adjusted odds ratios of factors predicting pCR

	pCR (ypT0/is+ypN0)			spCR (ypT0+ypN0)		
Factor	OR	95%CI	p-value	OR	95%CI	p-value
Whole dataset						
Age						
>40 vs ≤40	0.97	(0.60-1.58)	0.907	1.45	(0.84-2.63)	0.191
BMI						
25≤ vs <22	1.22	(0.78-1.91)	0.388	1.31	(0.80-2.11)	0.280
22≤, <25 vs <22	1.38	(0.94-2.04)	0.100	1.47	(0.98-2.21)	0.062
Clinical tumor size						
T1-2 vs T3-4	1.88	(1.27-2.79)	0.002	2.16	(1.39-3.41)	0.001
Clinical nodal status						
N0 vs N2-3	0.65	(0.40-1.07)	0.093	0.98	(0.57-1.71)	0.942
N1 vs N2-3	0.83	(0.53-1.31)	0.435	1.44	(0.88-2.39)	0.152
ER/PgR status						
Negative vs positive	3.42	(2.42-4.86)	<0.001	2.27	(1.55-3.35)	<0.001
Histological/Nuclear grade						

3 vs 1&2	1.39	(0.99-1.95)	0.060	1.29	(0.90-1.88)	0.169
ER/PgR-positive dataset						
Age						
>40 vs ≤40	0.74	(0.40-1.39)	0.343	1.22	(0.56-2.89)	0.622
BMI						
25≤ vs <22	1.65	(0.85-3.20)	0.140	1.27	(0.56-2.81)	0.559
22≤, <25 vs <22	1.43	(0.77-2.61)	0.253	1.46	(0.71-2.97)	0.296
Clinical tumor size						
T1-2 vs T3-4	1.76	(0.94-3.43)	0.078	2.95	(1.28-7.72)	0.010
Clinical nodal status						
N0 vs N2-3	0.98	(0.46-2.11)	0.954	0.89	(0.36-2.32)	0.810
N1 vs N2-3	0.80	(0.39-1.67)	0.547	0.93	(0.39-2.35)	0.869
Histological/Nuclear grade						
3 vs 1&2	1.22	(0.73-2.05)	0.454	1.00	(0.54-1.86)	0.991
ER/PgR-negative dataset						
Age						
>40 vs ≤40	1.43	(0.68-2.94)	0.344	1.73	(0.80-4.08)	0.170
BMI						

25≤ vs <22	0.95	(0.52-1.76)	0.871	1.29	(0.69-2.36)	0.422
22≤, <25 vs <22	1.35	(0.81-2.27)	0.248	1.47	(0.89-2.43)	0.132
Clinical tumor size						
T1-2 vs T3-4	1.93	(1.17-3.20)	0.010	1.89	(1.13-3.24)	0.016
Clinical nodal status						
N0 vs N2-3	0.48	(0.24-0.92)	0.027	0.98	(0.49-1.95)	0.943
N1 vs N2-3	0.89	(0.48-1.61)	0.692	1.75	(0.97-3.26)	0.065
Histological/Nuclear grade						
3 vs 1&2	1.53	(0.97-2.42)	0.068	1.50	(0.94-2.40)	0.087

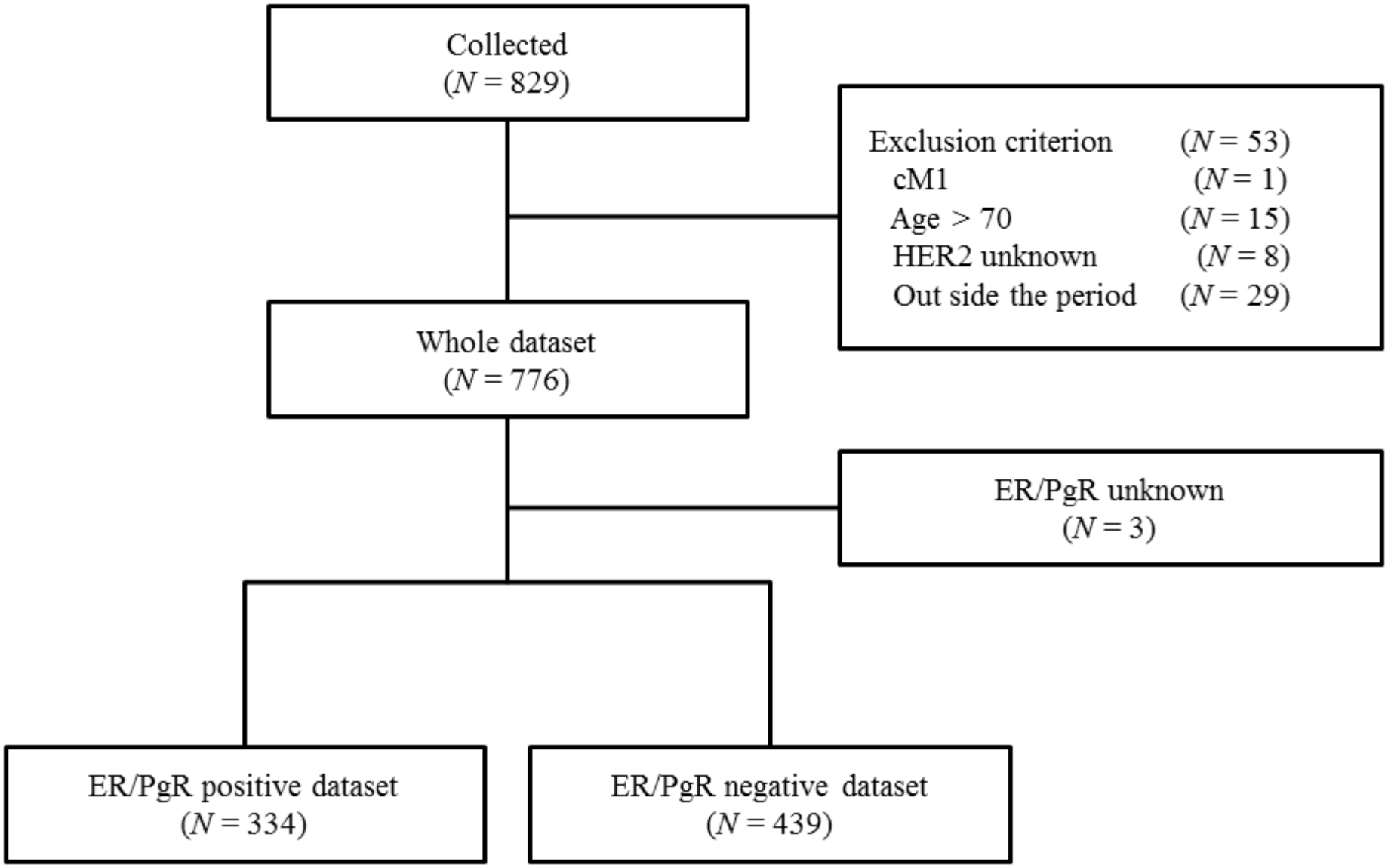
BMI, body mass index; ER/PgR, estrogen receptor/progesterone receptor; pCR, pathologic complete response; spCR, strict pathologic complete response; OR, odds ratio.

FIGURE LEGENDS

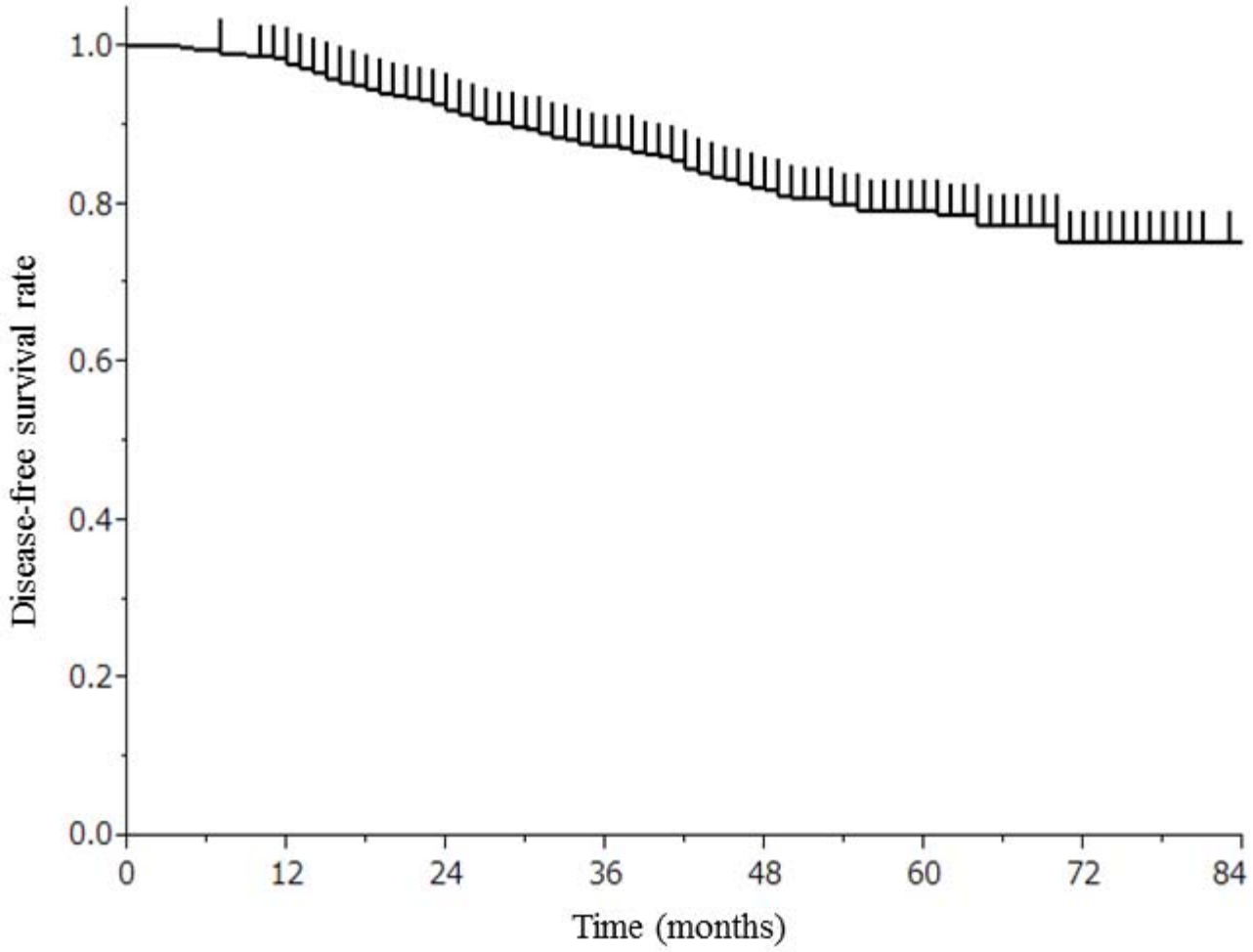
Figure 1. Flowchart of data collection and analysis

Figure 2. DFS curves of the (A) whole dataset and (B) ER/PgR-positive and -negative datasets

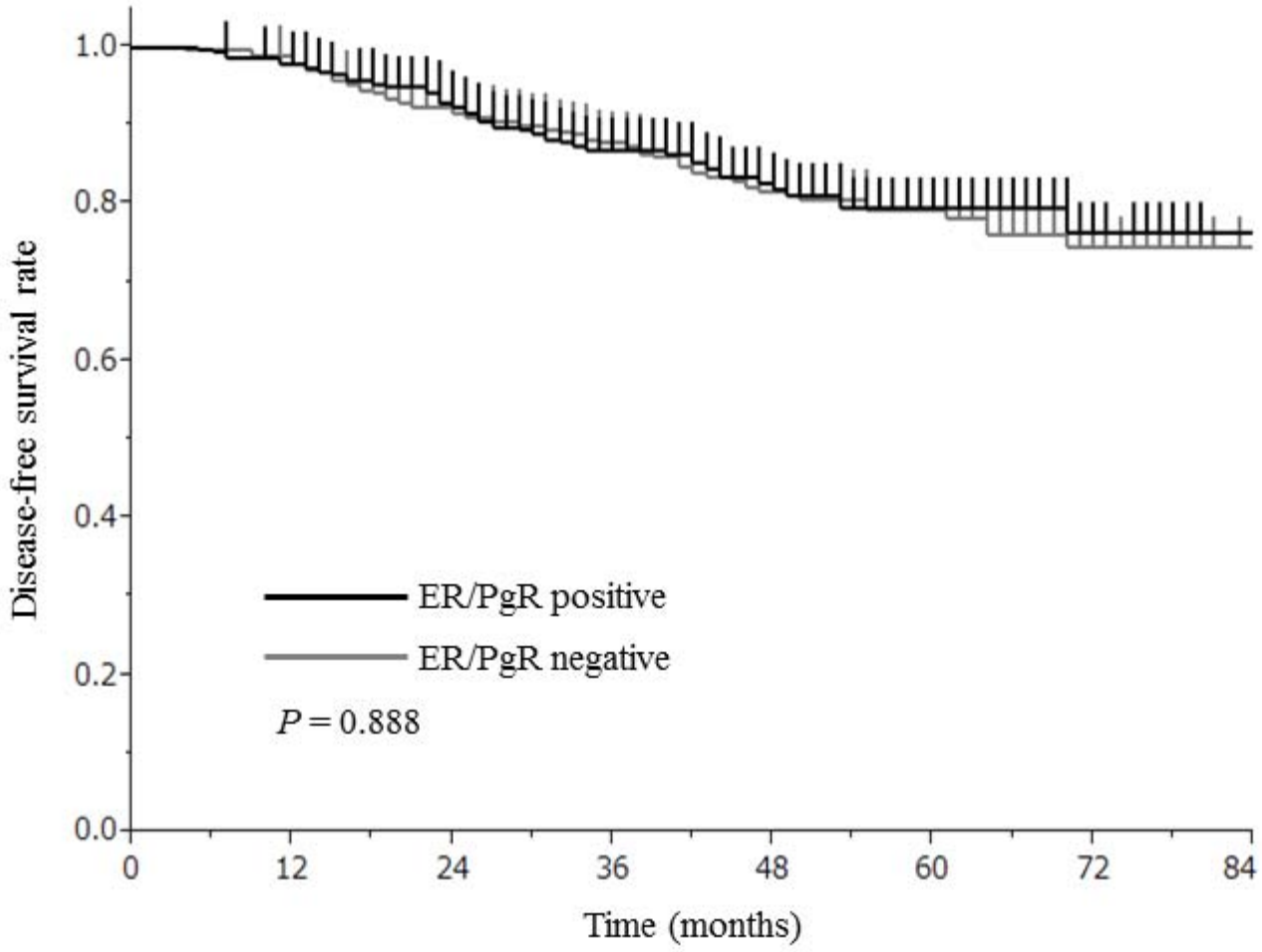
Figure 3. DFS curves of patients with pCR (ypT0/is + ypN0) versus non-pCR in the (A) whole dataset, (C) ER/PgR-positive dataset, and (E) ER/PgR-negative dataset. DFS curves of patients with spCR (ypT0 + ypN0) versus non-spCR in the (B) whole dataset, (D) ER/PgR-positive dataset, and (F) ER/PgR-negative dataset.

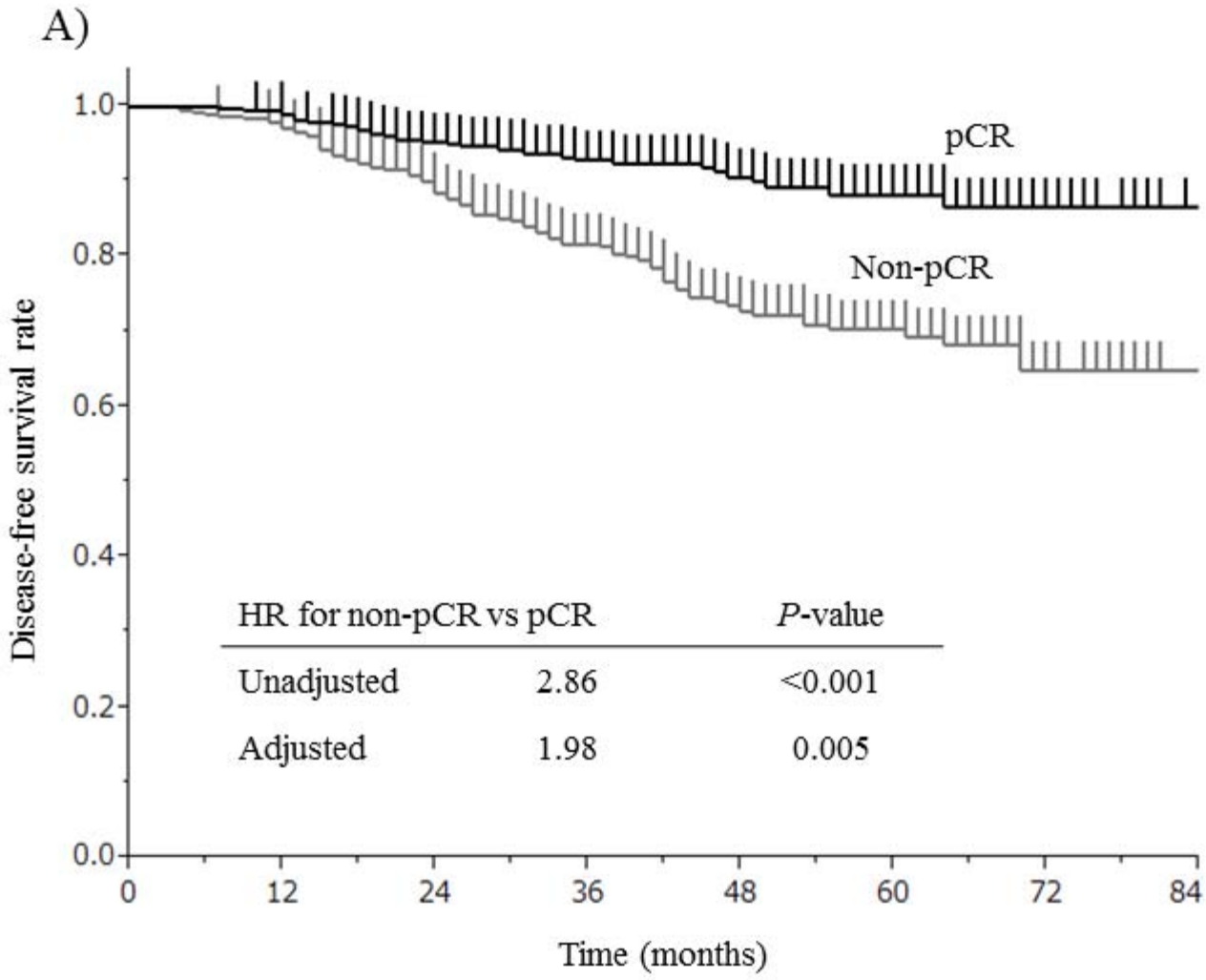

Collected
(N = 829)
Exclusion criterion (N = 53)
cM1 (N = 1)
Age > 70 (N = 15)
HER2 unknown (N = 8)
Out side the period (N = 29)
Whole dataset
(N = 776)
ER/PgR unknown
(N = 3)
ER/PgR positive dataset
(N = 334)
ER/PgR negative dataset
(N = 439)

A)

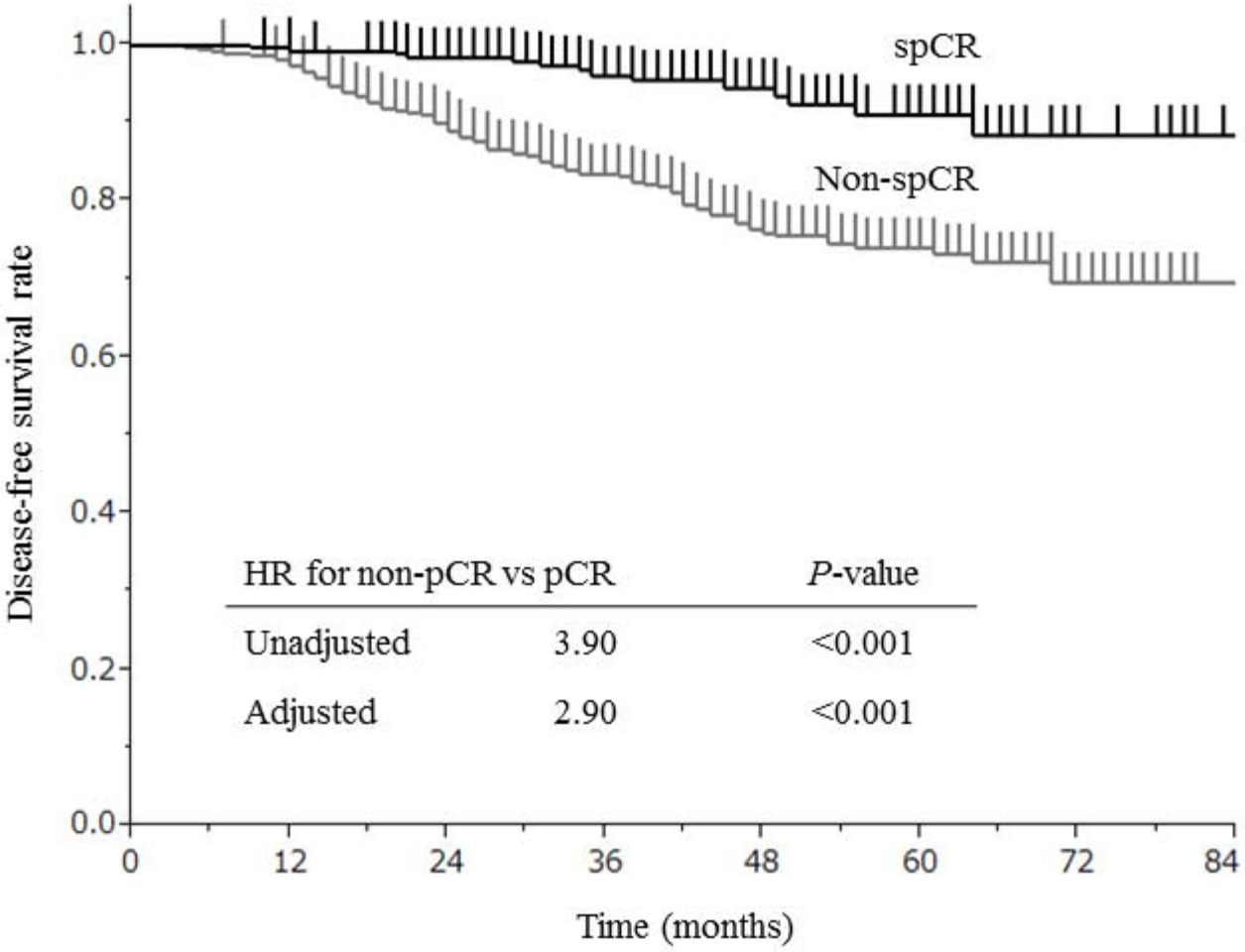

1.0
0.8
0.6
0.4
0.2
0.0
Disease-free survival rate
0
12
24
36
48
60
72
84
Time (months)

B)

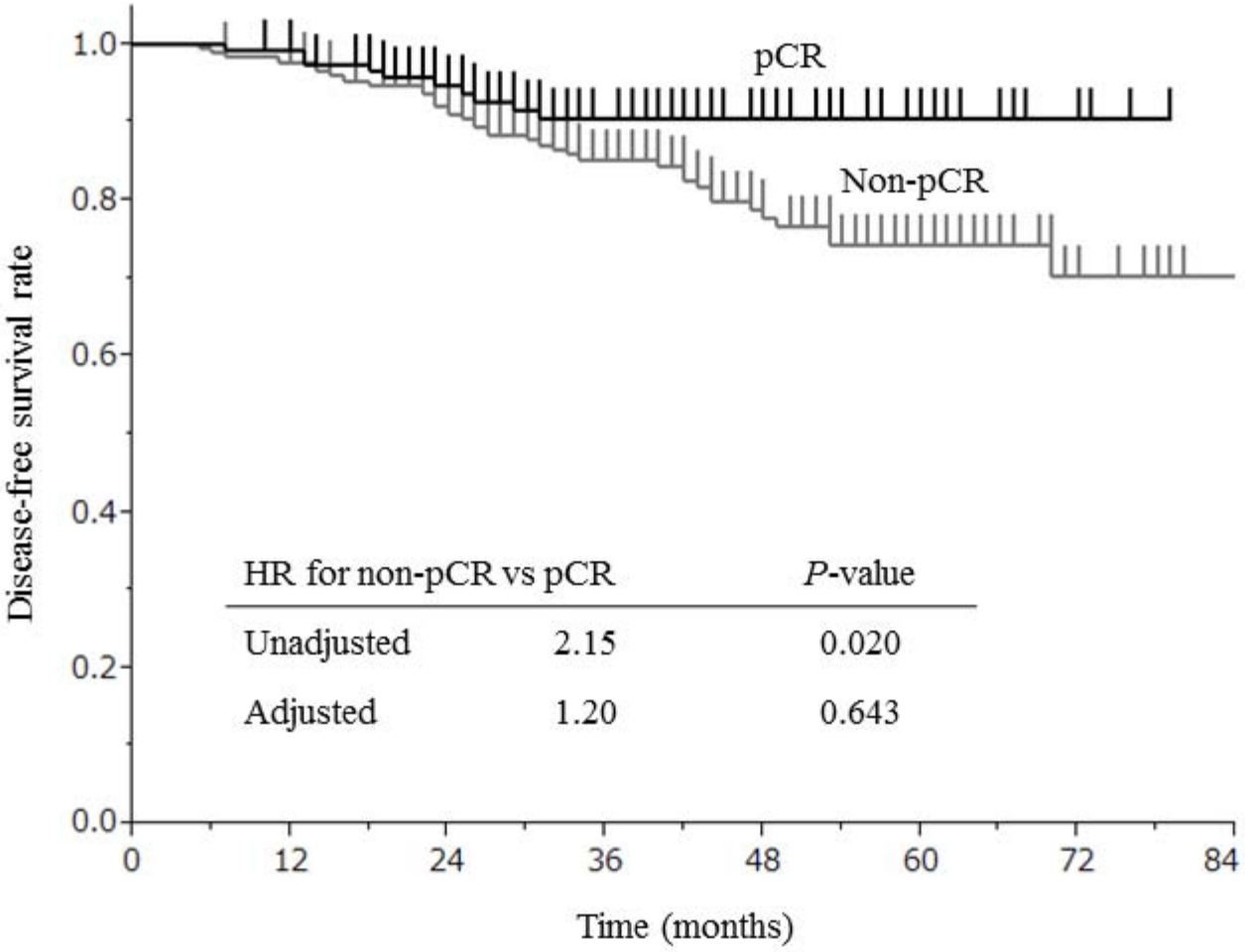

1.0
0.8
0.6
0.4
0.2
0.0
Disease-free survival rate
ER/PgR positive
ER/PgR negative
P = 0.888
0
12
24
36
48
60
72
84
Time (months)


A)
1.0
0.8
0.6
0.4
0.2
0.0
Disease-free survival rate
pCR
Non-pCR
HR for non-pCR vs pCR
P-value
Unadjusted
2.86
<0.001
Adjusted
1.98
0.005
0
12
24
36
48
60
72
84
Time (months)

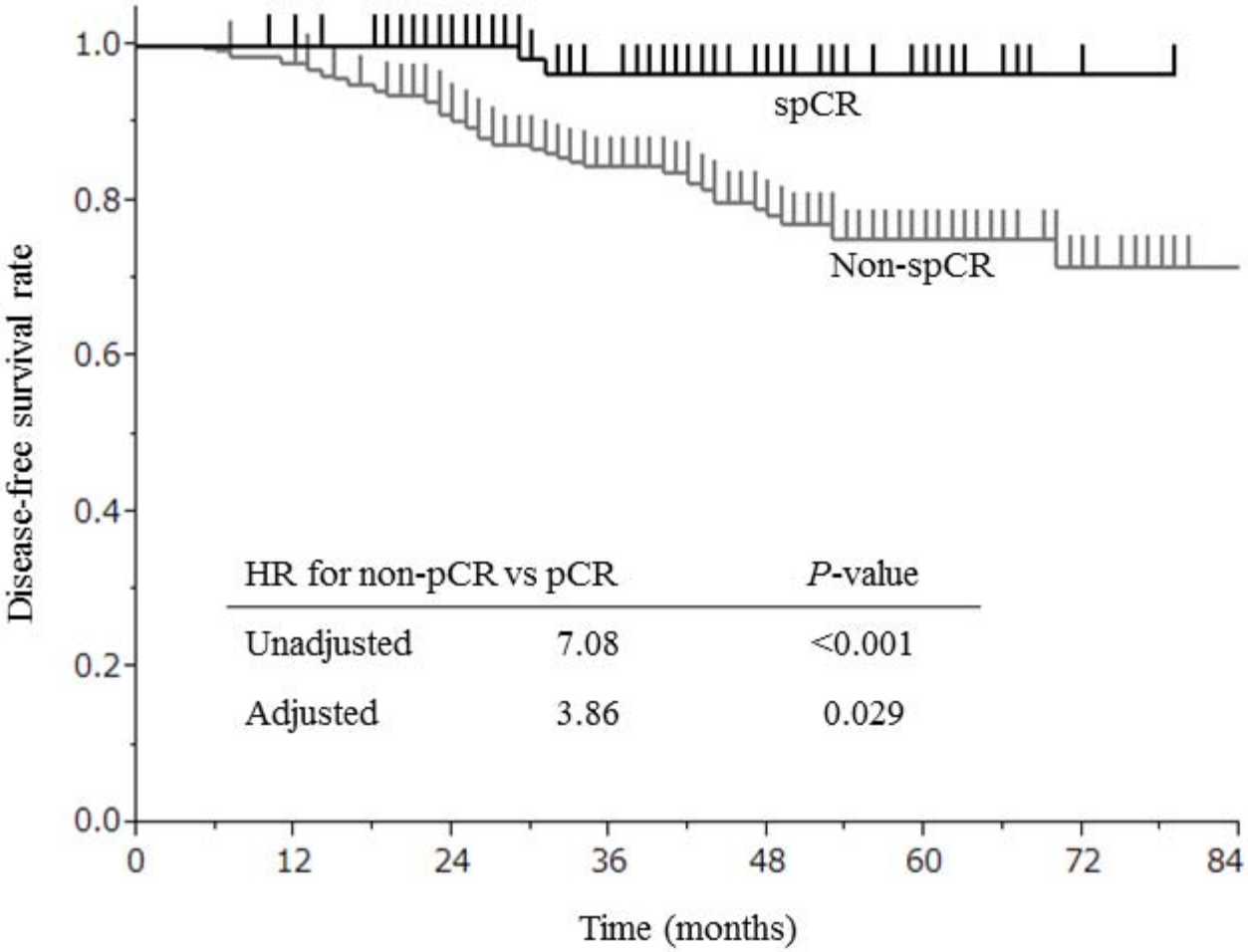
B)


spCR
Non-spCR
Disease-free survival rate
1.0
0.8
0.6
0.4
0.2
0.0
0
12
24
36
48
60
72
84
Time (months)
HR for non-pCR vs pCR
P-value
Unadjusted
3.90
<0.001
Adjusted
2.90
<0.001

C)

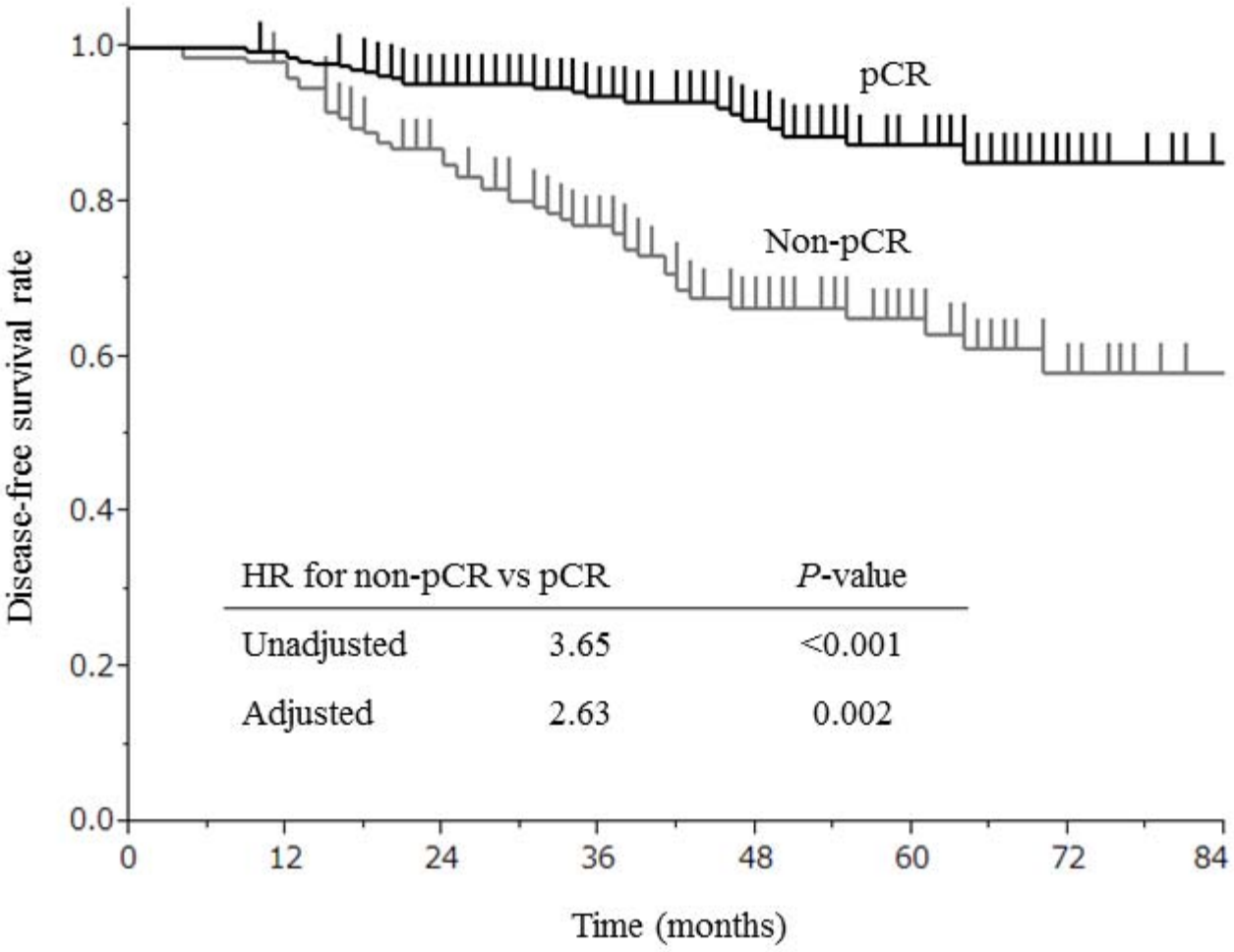

pCR
Non-pCR
Disease-free survival rate
1.0
0.8
0.6
0.4
0.2
0.0
0
12
24
36
48
60
72
84
Time (months)
HR for non-pCR vs pCR
P-value
Unadjusted 2.15 0.020
Adjusted 1.20 0.643

D)



HR for non-pCR vs pCR		*P*-value
Unadjusted	7.08	<0.001
Adjusted	3.86	0.029

E)



HR for non-pCR vs pCR		*P*-value
Unadjusted	3.65	<0.001
Adjusted	2.63	0.002

F)

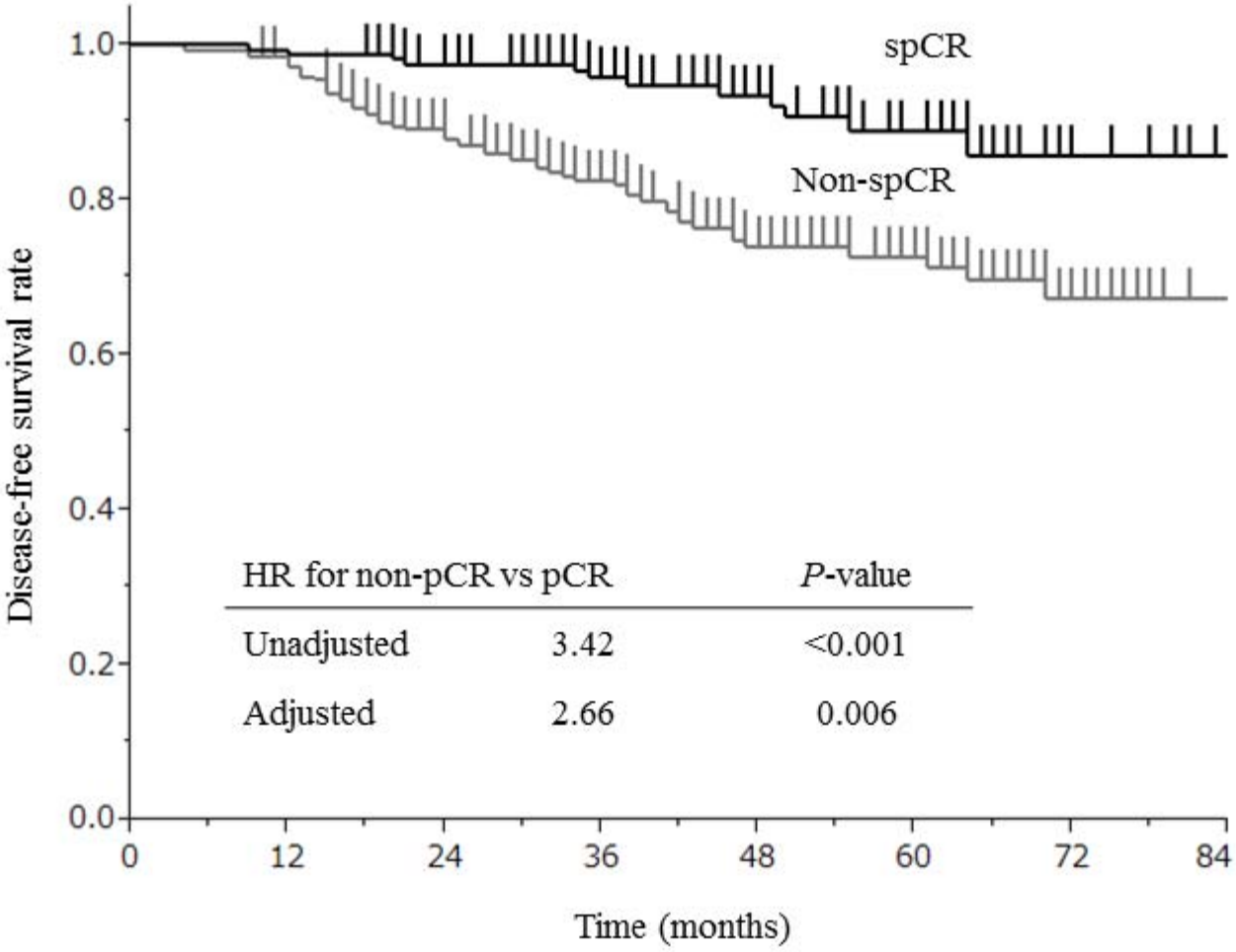

spCR
Non-spCR
Disease-free survival rate
1.0
0.8
0.6
0.4
0.2
0.0
0
12
24
36
48
60
72
84
Time (months)
HR for non-pCR vs pCR
P-value
Unadjusted
3.42
<0.001
Adjusted
2.66
0.006

Table S1. Summary of *P*-values of clinicopathological factors by the multivariate Cox regression for survival outcomes

	DFS	OS	DRFS
Factor	*P*	*P*	*P*
Age (years)			
≤40 vs >40	0.074	0.112	0.027
BMI			
25≤ vs <22	0.351	0.149	0.465
22≤, <25 vs <22	0.891	0.793	0.672
Clinical tumor size			
T3-4 vs T1-2	0.093	0.591	0.098
Clinical nodal status			
N2-3 vs N0	0.004	0.003	0.042
N1 vs N0	0.100	0.006	0.128
ER/PgR			
Negative vs Positive	0.933	0.137	0.450
Histological/Nuclear grade			

3 vs 1&2	0.011	0.032	0.018
pCR			
non-pCR vs pCR	0.005	0.246	0.002
Age (years)			
≤40 vs >40	0.088	0.156	0.026
BMI			
25≤ vs <22	0.348	0.159	0.502
22≤, <25 vs <22	0.993	0.857	0.681
Clinical tumor size			
T3-4 vs T1-2	0.160	0.725	0.147
Clinical nodal status			
N2-3 vs N0	0.004	0.002	0.048
N1 vs N0	0.070	0.004	0.101
ER/PgR			
Negative vs Positive	0.842	0.148	0.380
Histological/Nuclear grade			
3 vs 1&2	0.014	0.044	0.025
spCR			

non-pCR vs pCR	<0.001	0.048	0.001

BMI, body mass index; DFS, disease-free survival; DRFS, distant recurrence-free survival; ER/PgR, estrogen receptor/progesterone receptor; OS, overall survival; pCR, pathologic complete response; spCR, strict pathologic complete response.