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CLINICAL TRIAL

Prognostic value of p53 expression in hormone receptor-positive and human epidermal growth factor receptor 2-negative breast cancer patients receiving neoadjuvant chemotherapy

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Abstract

Purpose The aim of this study was to determine whether the outcome to neoadjuvant chemotherapy (NAC) can be predicted by analyzing p53 expression in hormone receptor (HR)-positive and human epidermal growth factor receptor 2 (HER2)-negative breast cancer patients.

Methods We retrospectively reviewed 594 patients diagnosed with stage I–III HR-positive, HER2-negative breast cancer, and treated with NAC at the Asan Medical Center between 2008 and 2014. Expression of p53 was assessed, and overall survival (OS) and breast cancer-specific survival (BCSS) were investigated and compared between groups.

Results At a median follow-up period of 69.8 months, OS and BCSS were higher in the p53-negative (p53(−)) group than in the p53-positive (p53(+)) group. Five-year OS was 95.4% in the p53(−) and 92.1% in the p53(+) group ($p=0.005$). BCSS was 96.2% in the p53(−) group and 93% in the p53(+) group ($p=0.008$).

Conclusion High expression of immunohistochemically detected p53 was strongly and significantly associated with decreased OS and BCSS than low p53 expression, suggesting that p53 may be a powerful prognostic factor in HR-positive, HER2-negative breast cancer patients receiving NAC.

Keywords Immunohistochemistry · Neoadjuvant therapy · Prognosis · Breast neoplasms · Tumor suppressor protein p53

Introduction

Breast cancer (BC) is the second leading cause of death and the most common malignancy among women in developed countries [1]. BC is a heterogeneous disease, which presents in different clinical and histological forms, resulting in substantial variation regarding prognoses and outcomes. The three predominant biomarkers of this cancer include the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) expression. Most studies assign BC to four major molecular subtypes: luminal A, luminal B, HER2-enriched, and basal-like BC. Almost 75% of all BCs express ER and/or PR, while up to 20% of BCs show overexpression or amplification of HER2 [2]. Hormone receptor-positive BC is associated with less aggressive clinicopathological characteristics and with better prognosis due to the benefits of endocrine therapy [3]. Neoadjuvant chemotherapy (NAC) is important for the treatment of BC as it can reduce the size of primary tumors, control loco-regional recurrence rates, eradicate the disease in regional lymph nodes, and convert node-positive disease to node-negative forms [4]. The pathologic complete response (pCR) following NAC is used as a surrogate marker for estimating disease-free survival (DFS) and overall survival (OS) [5, 6]. It is known that the pCR rate is higher in cases with triple-negative (TN) tumors and HER 2-positive tumors than in those with luminal types. TP53 is the most frequently mutated gene in BC; however, its potential role in the management of BC remains unclear [7]. Several studies have investigated the role of TP53 mutation for predicting the survival, but several crucial aspects of this relationship remain

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unclear. Also, there are many studies showing that the p53 mutation is associated with breast cancer-specific deaths, but most previous studies have not considered the potential confounding effects of estrogen/progesterone receptor (ER/PR) status, which affects BC survival [8]. The aim of this study was to determine whether the outcome of BC in hormone receptor (HR)-positive, HER2-negative patients receiving NAC can be predicted using p53 expression.

Methods

Patients and clinical data

We reviewed records of 594 patients diagnosed with stage I–III HR-positive and HER2-negative BC and treated with NAC at the Asan Medical Center between 2008 and 2014. Patients with distant metastases observed during the initial examination were excluded. Patient information and tumor characteristics were retrieved from a prospectively compiled database, which comprised information regarding the patients' age, clinical manifestations, clinical and pathological data, surgical methods, and follow-up period (Table 1). This study was approved by the Institutional Review Board of the Asan Medical Center, Seoul, South Korea (approval number 20171341). Informed consent was waived as this study was based on retrospective clinical data.

NAC was performed using standard chemotherapy regimens and was administered per the local guidelines. Pretreatment classification using cTNM and post-treatment classification using ypTNM classification were based on the definitions of the 7th edition of the American Joint Committee on Cancer staging system.

Pathological data

Pathological data including ER, PR, HER2, and p53 status were evaluated at the Department of Pathology of the Asan Medical Center. Expression of ER and PR were categorized by assigning proportion and intensity scores according to Allred's procedure. Proportions and intensity scores were add to produce a total score ranging from 0 to 8. Tumors with ≥ 1% positive cells were considered "HR-positive." HER2 status was assessed using a BenchMark XT autostainer (Ventana Medical Systems, Tucson, AZ, USA) and an OptiView DAB Detection Kit (Ventana Medical Systems) for HER2 (cat. no. 800-4422; clone 4B5; dilution 1:8; Ventana Medical Systems). The results were categorized based on the extent of cancer cell membrane staining (0: < 10% positive tumor cells; 1 +: partial membrane staining in > 10% of the tumor cells; 2 +: moderate staining of the entire cell membrane > 10% of the tumor cells; and 3 +: entire cell membranes strongly stained in > 30% of the tumor cells).

Table 1 Clinicopathological characteristics of patients

Parameter	*N* (%)
No. of patients	594
Age	
Age < 40	154 (25.9)
Age ≥ 40	440 (74.1)
Histology	
IDC	563 (94.8)
ILC	25 (4.2)
Others	1 (0.2)
Histologic grade	
G1	15 (2.5)
G2	461 (77.6)
G3	118 (19.9)
cT stage	
cT1	55 (9.3)
cT2	355 (59.8)
cT3	156 (26.3)
cT4	28 (4.7)
cN stage	
cN0	198 (33.3)
cN1	282 (47.5)
cN2	28 (4.7)
cN3	89 (14.5)
cStage	
cStage 1	14 (2.4)
cStage 2	380 (64.0)
cStage 3	200 (33.6)
Breast surgery	
BCS	287 (48.3)
TM	307 (51.7)
Axillary surgery	
SNB only	260 (43.8)
ALND	336 (56.2)
pCR	
No	552 (92.9)
Yes	42 (7.1)
Chemotherapy agent	
Adriamycin based only	177 (29.8)
Adriamycin + taxane	357 (60.1)
Taxane based only	35 (5.9)
Others	25 (4.2)
Endocrine therapy agent	
Aromatase inhibitor	125 (21.0)
SERM	459 (77.3)
None	10 (1.7)

BCS breast-conserving surgery, *TM* total mastectomy, *IDC* invasive ductal carcinoma, *ILC* invasive lobular carcinoma, *SNB* sentinel node biopsy, *ALND* axillary lymph node dissection, *pCR* pathologic complete response, *SERM* selective estrogen receptor modulator, *cT* clinical T stage, *cN* clinical N stage, *cStage* clinical stage

'HER2-negative' receptors were defined by immunohistochemistry (IHC) scores of 0, 1+, or 2+ or by a HER2/CEP17 ratio < 2.0 determined using fluorescence in situ hybridization or silver-enhanced in situ hybridization.

IHC evaluation of p53 was performed using a mouse monoclonal anti-human p53 (clone: DO-7) antibody (MA5-12557; DAKO Glostrup, Hovedstaden, Denmark). Staining was performed using an autoimmunostainer (Bond Polymer Refine Detection kit/Leica Bond-Max staining system, Leica Biosystems, Richmond, IL, USA) according to the manufacturer's instructions. Nuclear staining at > 10% was categorized as "p53-positive" and staining ≤ 10% was considered "p53-negative."

Statistical analyses

Chi-square test and *t*-tests were used to determine the trends of each parameter. OS was defined as the time from initial surgery to the time of death, and BC-specific survival (BCSS) was defined as the time from surgery to the time of BC-specific death, based on the Korean registry cause-of-death code. Survival curves were produced using the Kaplan–Meier method and survival differences between groups and factors were tested by performing a log-rank test. Multivariate analyses of the prognostic value of p53 were assessed using a stratified Cox proportional hazard regression model. All reported *p*-values originated from two-sided tests and statistical significance is reported at $p < 0.05$. Data analyses were performed using the Statistical Package for the Social Sciences version 20.0 (IBM Corp., SPSS Inc, Armonk, NY, USA).

Results

Characteristics

Patient characteristics are listed in Table 1. Overall mean age at initial surgery ($n = 594$) was 45.8 ± 9.5 years. When analyzed based on 40 years old, which is the standard of young age, which is commonly used, 154 (25.9%) patients were under 40 years old. The numbers of patients with initial T stages 1, 2, 3, and 4 were 55 (9.3%), 355 (59.8%), 156 (26.3%), and 28(4.7%), respectively. No lymph node involvement was observed in 33.3% of the patients ($n = 198$). The study cohort comprised 287 (48.3%) patients who had undergone breast-conserving surgery and 307 (51.7%) total mastectomy patients. In addition, 42 (7.1%) patients had postoperative pCR (Table 1).

Clinical pathological factors were compared according to p53 expression (Table 2). In total, 279 (47%) patients were initially p53-negative (p53(−)) and 315 (53%) patients were p53-positive (p53(+)). In the p53(−) group, pCR occurred

Table 2 Correlation between clinicopathological characteristics and p53 expression

Parameter	p53(−) *N* (%)	p53(+) *N* (%)	*p*-value
No. of patients	279 (47.0)	315 (53.0)	
Age			0.492
Age < 40	76 (27.2)	78 (24.8)	
Age ≥ 40	203 (72.8)	237 (75.2)	
Histology			0.128
IDC	261 (93.9)	302 (97.1)	
ILC	16 (5.8)	9 (2.9)	
Others	1 (0.4)	0	
Histologic grade			0.881
G1	8 (2.9)	7 (2.2%)	
G2	216 (77.4)	245 (77.8%)	
G3	55 (19.7)	63 (20.0%)	
cT stage			0.088
cT1	18 (6.5)	37 (11.7)	
cT2	165 (59.1)	190 (60.3)	
cT3	81 (29.0)	75 (23.8)	
cT4	15 (5.4)	13 (4.1)	
cN stage			0.179
cN0	100 (35.8)	98 (31.1)	
cN1	127 (45.5)	155 (49.2)	
cN2	17 (6.1)	11 (3.5)	
cN3	35 (12.5)	51 (16.2)	
cStage			0.385
cStage 1	8 (2.9)	6 (1.9)	
cStage 2	171 (61.3)	209 (66.3)	
cStage 3	100 (35.8)	100 (31.8)	
Breast surgery			0.429
BCS	130 (46.6)	157 (49.8)	
TM	149 (53.4)	158 (50.2)	
Axillary surgery			0.093
SNB only	112 (40.1)	148 (47.0)	
ALND	167 (59.9)	167 (53.0)	
pCR			0.816
No	260 (93.2)	292 (92.7)	
Yes	19 (6.8)	23 (7.3)	
Chemotherapy agent			0.663
Adriamycin based only	85 (30.5)	92 (29.2)	
Adriamycin + taxane	170 (60.9)	187 (59.4)	
Taxane based only	13 (4.7)	22 (7.0)	
Others	11 (3.9)	14 (4.4)	
Endocrine therapy agent			0.026
Aromatase inhibitor	49 (17.6)	76 (24.1)	
SERM	228 (81.7)	231 (73.3)	
None	2 (0.7)	8 (2.5)	

BCS breast-conserving surgery, *TM* total mastectomy, *IDC* invasive ductal carcinoma, *ILC* invasive lobular carcinoma, *SNB* sentinel node biopsy, *ALND* axillary lymph node dissection, *pCR* pathologic complete response, *SERM* selective estrogen receptor modulator, *cT* clinical T stage, *cN* clinical N stage, *cStage* clinical stage

in 19 (6.8%) patients and in 23 (7.3%) patients of the p53(+) group, which was not a significant difference ($p=0.816$), and no significant differences were found between the two groups regarding other clinical pathologic factors (Table 2).

Changes in p53 expression after chemotherapy

From the study cohort of 594 patients, 336 were selected to assess p53 expression before and after chemotherapy. Out of 197 p53(−) and 139 p53(+) patients, 124 (62.9%) and 71 (51.1%), respectively, showed no alteration in p53 expression after chemotherapy (Table 3).

Survival outcomes

The overall median follow-up period was 69.8 months (3.0–121.9 months). Based on pre-chemotherapy p53 expression, the p53(−) group showed higher OS ($p=0.005$) and BCSS ($p=0.008$) than the p53(+) group (Fig. 1). Five-year OS was 95.4% in the p53(−) group and 92.1% in the p53(+) group; BCSS was 96.2% in the p53(−) group and 93% in the p53(+) group.

We analyzed survival according to clinical responses to chemotherapy. In patients who did not achieve pCR after chemotherapy, OS and BCSS were higher in the p53(−) group than in the p53(+) group ($p=0.008$ and 0.004, respectively; Fig. 2). Five-year OS was 95.1% in the p53(−) group and 92.8% in the p53(+) group; BCSS was 96% in the p53(−) group and 92.2% in the p53(+) group. However, no significant difference in OS and BCSS between groups was observed in patients who achieved pCR after chemotherapy ($p=0.353$), as pCR occurs only in a minority of HR-positive, HER2-negative patients.

Outcomes are shown in Fig. 3, with four groups according to pre-chemotherapy and post-chemotherapy p53 status. Regardless of p53 expression after chemotherapy, the p53(−) group showed better OS and BCSS before chemotherapy than the p53(+) group ($p=0.020$ and $p=0.038$, respectively).

We performed univariate Cox proportional hazards regression analyses to identify the factors influencing OS and BCSS (Table 4). The results demonstrated that p53 expression was significantly associated with OS and BCSS ($p=0.009$ and $p=0.006$, respectively). We also found that clinical T and N stages were associated with OS. Furthermore, clinical N stage and histologic grade were significantly associated with BCSS. Multivariate analyses showed that high p53 expression was significantly and independently associated with lower OS and BCSS, compared to low p53, suggesting that p53 overexpression in HR-positive and HER2-negative BC patients may be a promising negative prognostic factor (OS: HR 2.06, 95% CI 1.15–3.69, $p=0.016$; BCSS: HR 1.95, 95% CI 1.25–4.70, $p=0.009$) (Table 5).

Table 3 p53 expression before and after chemotherapy

	Post-chemotherapy		Total
	p53(−)	p53(+)	
Pre-chemotherapy			
p53(−)	124	73	197
pre_p53%	62.9%	37.1%	100.0%
p53(+)	71	68	139
pre_p53%	51.1%	48.9%	100.0%
Total	195	141	336
	58.0%	42.0%	100.0%

Discussion

The role of TP53 as a prognostic factor for the BC treatment remains unclear [9, 10]. Recent studies have demonstrated that a mutation in the TP53 gene is one of the most common mutations in BC and can be used as prognostic indicator in this group of patients [11]. TP53 mutations are known indicators of poor prognosis in BC [12]. In recent years, the associations of p53 alterations and BC prognosis

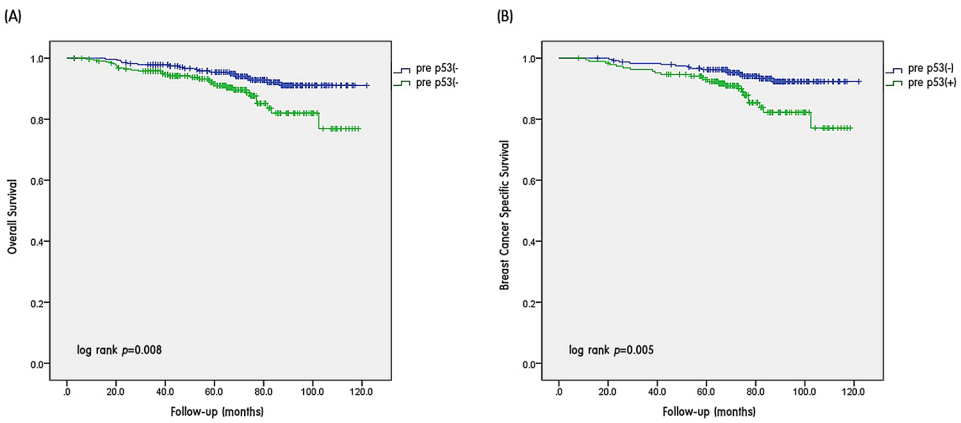

Fig. 1 Survival according to p53 expression: **a** overall survival (OS) by pre-chemotherapy p53 status, and **b** breast cancer-specific survival (BCSS) by pre-chemotherapy p53 status

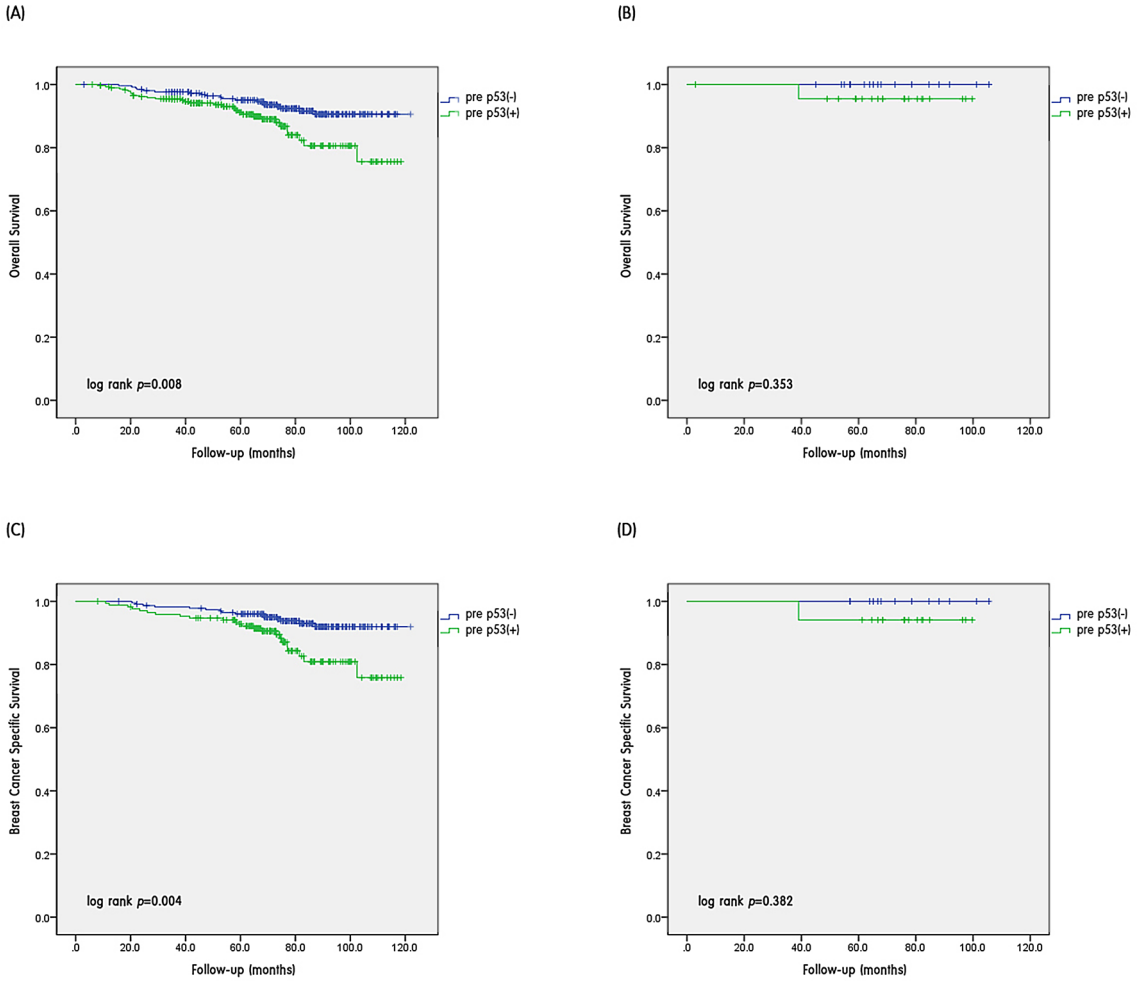

Fig. 2 Overall survival (OS) and breast cancer-specific survival (BCSS) plotted by chemotherapy response in p53(−) and p53(+) patients: **a** OS in patients with pathologic complete response (pCR); **b** OS in patients with non-pCR; **c** BCSS in patients with pCR; **d** BCSS in patients with pCR

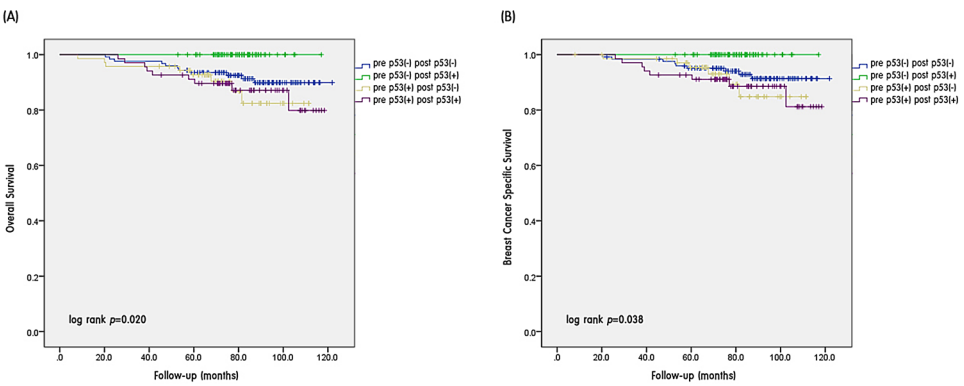

Fig. 3 Overall survival (OS) and breast cancer-specific survival (BCSS) plotted according to pre-chemotherapy and post-chemotherapy p53 expression: **a** OS, **b** BCSS

have been investigated in several studies; however, contradictory conclusions have been reported. Most studies did not consider potential effects of the ER/PR status even though it is an important molecular marker of BC with prognostic and predictive value [13, 14]. In the present study, we evaluated the prognostic value of p53 in a relatively large cohort of HR-positive, HER2-negative BC patients. We observed that after receiving adjuvant chemotherapy, p53(−) expression was a significant predictor of prognosis (OS, $p = 0.005$; BCSS, $p = 0.008$). Univariate

Table 4 Univariate analysis of overall survival (OS) and breast cancer-specific survival (BCSS)

Factors	OS			BCSS		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age at diagnosis (years)			0.804			0.995
< 40	1			1		
≥ 40	0.93	0.51–1.70	0.804	0.99	0.48–2.01	0.995
Surgery method			0.058			0.208
BCS	1			1		
Mastectomy	1.74	0.98–3.10	0.058	1.51	0.79–2.89	0.208
cT stage			0.040			0.432
cT1	1			1		
cT2	1.12	0.34–3.72	0.857	1.36	0.32–5.83	0.676
cT3	2.17	0.64–7.30	0.211	2.26	0.52–9.90	0.278
cT4	3.39	0.81–14.18	0.095	1.85	0.26–13.11	0.540
cN stage			< 0.001			< 0.001
cN0	1			1		
cN1	6.80	2.06–22.49	0.002	5.96	1.78–19.94	0.004
cN2	6.74	1.36–33.40	0.019	2.24	0.23–21.52	0.485
cN3	17.93	5.30–60.64	< 0.001	12.86	3.66–45.15	< 0.001
cStage			0.001			0.017
cStage1	1			1		
cStage2	0.80	0.107–5.95		0.80	0.11–6.00	
cStage3	2.36	0.32–17.27		1.90	0.26–14.05	
Histologic grade			0.051			0.046
G1/G2	1			1		
G3	1.81	0.99–3.26	0.051	1.97	1.01–3.83	0.046
pCR			0.182			0.323
No	1			1		
Yes	0.26	0.04–1.88	0.182	0.37	0.05–2.68	0.323
p53*			0.009			0.006
Negative	1			1		
Positive	2.14	1.21–3.80	0.009	2.48	1.30–4.73	0.006

BCS breast-conserving surgery, *pCR* pathologic complete response, *cT* clinical T stage, *cN* clinical N stage, *cStage* clinical stage

**p53* pre-chemotherapy p53

and multivariate analyses showed that p53(+)expression negatively affected OS and BCSS (Tables 4 and 5).

TP53 mutations are less frequent in luminal (A and B) tumors than basal-like tumors [15]. Breast tumors immunopositive for p53 are more frequently ER- and PR-negative [16]. In the current study, we investigated the role of p53 expression in HR+/HER2− patients after chemotherapy. pCR in the p53(−) group occurred at 6.8% and at 7.3% in the p53(+) group. There was significant difference in OS and BCSS between p53(−) and p53(+) in only pCR-negative patients because pCR occurs only in a minority of HR-positive, HER2-negative patients, and adjuvant endocrine therapy is the mainstay of systemic therapy [5].

The findings of the present study are in line with those of a meta-analysis of 37 studies on p53 expression and clinical outcome in over 9,800 patients; however, the BC-prognostic value of high p53 expression determined by IHC was lower than expected [17]. Mirza et al. [18] reviewed 16 studies that had assessed the prognostic value of p53 gene mutation/protein accumulation regarding decreased survival in node-negative BC patients. Using univariate analysis, eight studies showed that p53 was a significant prognostic factor for OS and DFS. Six studies used multivariate analysis and found that p53 was a significant prognostic factor. In contrast to our study, Bae et al.[19] investigated p53 expression in TN BC cases and found that patients with p53(+) showed better OS than p53(−) patients who underwent NAC. This shows that the role of p53 as a prognostic factor may differ depending on the subtype.

Our study has some limitations despite the fact it is one of the largest studies on p53 in HR+/HER2− BC patients. First, this study was retrospective and was conducted on

Table 5 Multivariate analysis of overall survival (OS) and breast cancer-specific survival (BCSS)

Factor	OS			BCSS		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age at diagnosis (years)			0.941			0.915
< 40	1			1		
≥ 40	0.98	0.53–1.81	0.941	1.04	0.51–2.14	0.915
Surgery method			0.599			0.518
BCS	1			1		
mastectomy	1.20	0.61–2.39	0.599	1.30	0.60–2.86	0.518
cT stage			0.530			0.461
cT1	1			1		
cT2	1.53	0.46–5.14	0.492	2.01	0.47–8.72	0.349
cT3	2.28	0.64–8.06	0.202	2.67	0.57–12.42	0.211
cT4	2.13	0.48–9.52	0.323	1.11	0.14–8.52	0.923
cN stage			< 0.001			0.002
cN0	1			1		
cN1	5.90	1.78–19.65	0.004	5.33	1.58–18.02	0.007
cN2	5.98	1.18–30.21	0.031	2.27	0.23–22.30	0.483
cN3	13.60	3.96–46.79	< 0.001	10.85	3.03–38.82	< 0.001
Histologic grade			0.084			0.060
G1/G2	1			1		
G3	1.72	0.93–3.17	0.084	1.72	0.93–3.17	0.060
pCR			0.176			0.222
No	1			1		
Yes	0.25	0.03–1.86	0.176	0.28	0.04–2.15	0.222
p53*			0.016			0.009
Negative	1			1		
Positive	2.06	1.15–3.69	0.016	1.95	1.25–4.70	0.009

BCS breast-conserving surgery, *pCR* pathologic complete response

*p53 pre-chemotherapy p53

data collected at only one institution. However, there is no available randomized controlled trial with this particular focus. Second, p53 was absent in many patients after NAC.

We investigated whether there was a difference in survival depending on p53 expression following chemotherapy, which is not reliable because pCR occurs only in a small proportion of patients. However, this is the first study on the prognostic value of p53 in HR+/HER2− patients after NAC, and thus, our results offer important insights for future research. Moreover, we integrated a comparably long follow-up period (median 69.8 months). Further studies targeting mutant p53 may help develop efficient immunotherapeutic agents.

In conclusion, we demonstrated that high p53 expression may be a potential prognostic factor in HR-positive, HER2-negative BC patients receiving NAC and that high p53 expression significantly correlates with lower OS and BCSS. However, further research is needed to unravel the role of p53 during BC treatment.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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