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Body mass index and progesterone receptor in postmenopausal ER-positive/HER2-negative breast cancer: A nation-wide study in Korean breast cancer society and the multi-institutional cohort

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A B S T R A C T

Background: Obesity is a risk factor for breast cancer and associated with increased estrogen levels that stimulate the progesterone receptor (PgR). Understanding interplay between obesity, PgR, and prognosis in estrogen receptor (ER)-positive/human epidermal growth factor receptor 2 (HER2)-negative breast cancer (ER+/HER2-) is crucial. This study aimed to investigate the association between body mass index (BMI) and the prognostic value of PgR.

Methods: Study included 10,125 postmenopausal patients with ER+/HER2-breast cancer between January 1991 to December 2019. Patients were categorized according to BMI (cutoff: 25 kg/m^2) and PgR (positive/negative). The primary outcomes were the 6-year overall survival (OS) in the Korean Breast Cancer Registry (KBCR) cohort and 6-year recurrence-free survival (RFS) in the multi-institutional cohort.

Results: In both cohorts, a greater proportion of patients with high BMI were PgR-positive, and the mean BMI was higher in the PgR-positive group. PgR-negativity was associated with worse 6-year OS in the KBCR cohort among patients with BMI ≥25 kg/m^2 (hazard ratio [HR], 1.45; 95 % confidence intervals [CI], 1.06–1.97; P = .02), but not in those with BMI <25 kg/m^2. Similarly, in the multi-institutional cohort, PgR-negativity was associated with worse 6-year RFS only in patients with BMI ≥25 kg/m^2 (HR, 2.93; 95 % CI, 1.29–6.69; P = .01). The mean 21-gene recurrence score was higher in the PgR-negative group, regardless of the BMI.

Conclusions: In postmenopausal patients with ER+/HER2-breast cancer, the prognostic impact of PgR is modified by BMI. PgR-negativity is a strong predictor of poor outcomes in obese patients but not in non-obese patients.

1. Introduction

The association between breast cancer development and persistently elevated estrogen levels in postmenopausal women is well-established [1–3]. Modern endocrine therapy is based on the principle that suppressing the action of estrogen in patients with breast cancer improves prognosis [4]. The mechanism by which estrogen influences the development and progression of breast cancer is complex. Current evidence suggests that genotoxic estrogen metabolites and estrogen receptor (ER)-mediated signaling play a role in promoting cellular proliferation [5–8].

Estrogen biosynthesis occurs via aromatase [9]. Unlike premenopausal women, in whom most estrogen is produced by the ovaries, postmenopausal women primarily produce estrogen through

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aromatization in peripheral tissues such as adipocytes [10,11]. Previous studies have reported increased aromatase levels and elevated circulating estrone and estradiol levels in obese postmenopausal women [12–16]. The body mass index (BMI) is the most widely used measure of obesity [17].

The progesterone receptor (PgR) is synthesized by tumor cells following stimulation by estrogen through interactions with ER, and its presence has been suggested as a biomarker for functional ER [18,19]. Paradoxically, PgR alters the chromatin-binding sites of the ER, subsequently regulating genes associated with cell cycle arrest, apoptosis, and differentiation [20,21]. In ER-positive/human epidermal growth factor receptor 2 (HER2)-negative (ER+/HER2-) breast cancer, PgR status is not only recognized as a prognostic factor [22,23] but also as a biomarker distinguishing endocrine sensitivity from endocrine resistance [24].

This study aimed to analyze the association between BMI, as an indicator of obesity, and PgR expression in postmenopausal patients with ER+/HER2-breast cancer, and to evaluate differences in the prognostic effect of PgR, across BMI stratified groups.

2. Methods

2.1. Study population

The Korean Breast Cancer Registry (KBCR) is a web-based system established by the Korean Breast Cancer Society in which information on newly diagnosed breast cancer patients is voluntarily registered each year by 102 institutions across Korea [25,26]. The registry contains data on clinicopathological characteristics and treatment [27]. Patient mortality status is updated annually using data from the Ministry of Health and Welfare, Korea; however, information on recurrence is not provided [28]. We collected data from the KBCR on patients diagnosed with ER+/HER2-primary breast cancer from January 1991 to December 2019. Because menopausal status was not collected in this registry, we included only women with age ≥60. Patients with stage 0 and IV disease were excluded from the analysis, as were those with insufficient information or mortality status.

For the multi-institutional cohort, we retrospectively collected data from patients diagnosed with ER+/HER2-primary invasive breast cancer who received treatment between January 2009 and December 2018 at three hospitals: Dongtan Sacred Heart Hospital, Gangnam Severance Hospital, and Hallym University Sacred Heart Hospital. We selected postmenopausal women with age ≥50 at diagnosis. Patients with missing information on clinicopathological factors, including BMI, and those with de novo Stage IV disease were excluded from the study.

This study was conducted in accordance with Good Clinical Practice guidelines and the tenets of the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board of the Dongtan Sacred Heart Hospital (approval number: 2024-02-004-001), which waived the requirement for written informed consent because of the retrospective design of the study.

2.2. Clinicopathologic characteristics

For patients in the KBCR cohort, the clinicopathological information and treatment entered the web-based system were directly applied to the analysis. ER, PgR, HER2, histologic grade (HG), and lympho-vascular invasion status were sourced from individual institution input data and assessed using the institution's own assay methods.

The clinicopathological information of the patients in the multi-institutional cohort was obtained through a comprehensive review of medical records. For stage classification, we used the pathological stage for patients who underwent upfront surgery, whereas for those who received neoadjuvant systemic therapy (NST), the clinical stage assessed by pretreatment evaluation was applied. The pathological factors were confirmed in the laboratories of each hospital. Surgical specimens were used for patients in the adjuvant setting, whereas biopsy samples were used for patients with NST. ER, PgR, and HER2 status were evaluated using immunohistochemistry, and their expression was reported as either positive or negative. ER and PgR were classified as positive when the Allred score was 3 or higher [29], and HER2 was classified as negative if the score was 0, 1+, or 2+ with negative in situ hybridization results [30]. A subset of patients underwent a 21-gene recurrence score (RS) assay (Genomic Health) at a central laboratory using surgical specimens from patients undergoing upfront surgery. The 21-gene RS has been used to estimate the risk of recurrence [31] and guide decisions regarding the use of adjuvant chemotherapy in addition to endocrine therapy [32,33].

2.3. BMI

BMI was calculated as body weight in kilograms divided by height in meters squared, as defined by the World Health Organization (WHO) [17]. According to the WHO-Asia-Pacific classification, individuals of Asian descent, including Koreans, are defined as obese if their BMI ≥25 kg/m^2 [34]. Based on this, we divided the patients according to a BMI cut-off of 25 kg/m^2. In the KBCR cohort, baseline measurements of body weight and height were recommended to be inserted before the initiation of treatment. For the multi-institutional cohort, the initial values were applied to the analysis by reviewing the medical charts.

2.4. Statistical analysis

The Student's t-test with a two-tailed *P* value was used to compare BMI as a continuous variable according to PgR expression. Differences among groups were evaluated using the chi-square test for categorical variables and one-way analysis of variance (ANOVA) for continuous variables, following verification with Levene's test.

The primary objective of this study was to compare oncologic outcomes according to PgR expression between groups classified using a BMI cutoff of 25 kg/m^2. The primary survival endpoints were the 6-year overall survival (OS) for the KBCR cohort and 6-year recurrence-free survival (RFS) for the multi-institutional cohort. OS was defined as the time from the date of breast cancer diagnosis to death from any cause. RFS was defined as the time from the date of diagnosis to the first documented recurrence, including locoregional recurrence, distant metastasis, or death from any cause, whichever occurred first. Distant disease-free survival (DDFS) was used as a secondary endpoint to provide further clinical relevance in a multi-institutional cohort. DDFS was defined as the time from diagnosis to the first occurrence of distant metastasis or death from any cause. For the endpoints, patients were censored at the last follow-up if no events had occurred. The 6-year timepoint was selected to capture events occurring during or within one year after the completion of endocrine therapy, which is clinically considered endocrine resistance. Kaplan–Meier survival estimates were used to analyze the prognosis, and differences between survival curves were assessed using the log-rank test. Multivariable analysis of factors affecting OS and RFS was performed using the Cox proportional hazards model to evaluate time-to-event data. All statistical tests were two-sided, and $P < .05$ was considered to be statistically significant. Statistical analyses were conducted using SPSS version 25.0 (IBM Inc., Armonk, NY, USA) and GraphPad Prism Version 9 (GraphPad Software).

3. Results

3.1. KBCR cohort

A total of 82,366 patients with ER+/HER2-primary breast cancer were in the KBCR registry. Of these, 15,904 patients with age ≥60 were selected (Fig. 1A). Patients with insufficient information on BMI, PgR, and survival outcomes were excluded, resulting in a final cohort of 8800 patients. Patients in the PgR-negative group had a higher pT stage and

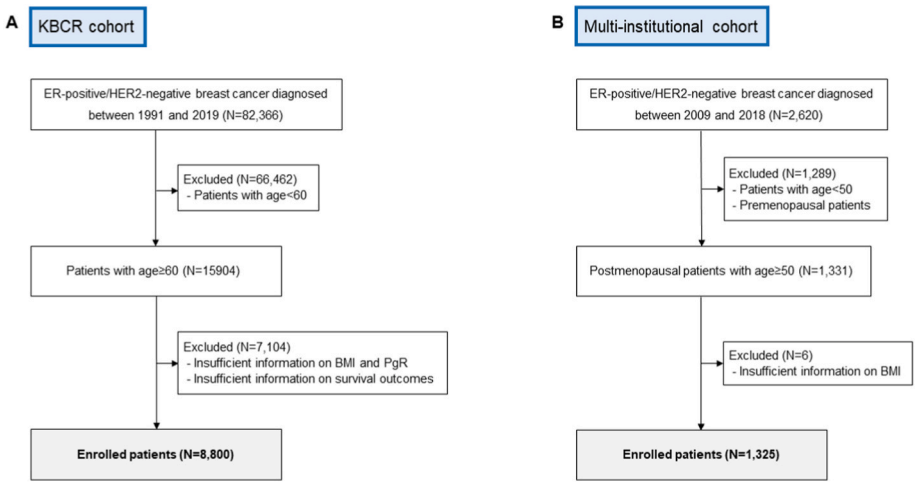

Fig. 1. Consort diagram of enrolled patients. (A) KBCR cohort. (B) Multi-institutional cohort
KBCR, Korean Breast Cancer Registry; ER, estrogen receptor; BMI, body mass index; PgR, progesterone receptor.

HG and received more chemotherapy than those in the PgR-positive group, regardless of BMI (Table 1).

A higher proportion of patients with high BMI (≥25 kg/m^2) were PgR-positive compared to patients with low BMI (<25 kg/m^2) (78.6 % vs. 73.1 %; $P < .001$; Fig. 2A). Mean BMI was also significantly higher in PgR-positive patients (25.4 kg/m^2 vs. 24.7 kg/m^2; $P < .001$; 95 % CI, −.83–.50; Fig. 1A).

During a median follow-up period of 52 months, the 6-year OS rate for all patients was 93.9 %, with a survival rate of 94.3 % for patients with BMI <25 kg/m^2 and 93.6 % for those with a BMI ≥25 kg/m^2 (Table 2). In the Kaplan–Meier survival analysis, PgR negativity was associated with a worse 6-year OS ($P = .04$; Fig. 3A). However, no significant difference was observed in survival according to PgR status in patients with BMI <25 kg/m^2 ($P = .46$; Fig. 3B), whereas significant difference was observed in patients with BMI ≥25 kg/m^2 ($P = .02$; Fig. 3C). In the multivariable analysis, PgR-negative was associated with reduced survival only in patients with BMI ≥25 kg/m^2, but not in those with BMI <25 kg/m^2 (BMI <25 kg/m^2: hazard ratio [HR], 1.15; 95 % CI, .85–1.56; $P = .37$; BMI ≥25 kg/m^2: HR, 1.45; 95 % CI, 1.06–1.97; $P = .02$; Table 2).

3.2. Multi-institutional cohort

We retrospectively identified 2620 patients with ER+/HER2-primary breast cancer from three institutions and selected 1331 postmenopausal patients with age ≥50 (Fig. 1B). After excluding six patients without BMI information, 1325 patients were included in the study. Baseline characteristics according to BMI and PgR status are summarized in Table 1. The group with BMI ≥25 kg/m^2 was older, had more LN metastasis, and a higher proportion received chemotherapy than the group with BMI <25 kg/m^2. Additionally, the group with BMI ≥25 kg/m^2 had a larger tumor size; however, a greater number of patients underwent breast-conserving surgery. In PgR-negative patients, HG was higher regardless of BMI, and PgR-negative patients were older in the group with BMI <25 kg/m^2.

Similar to the KBCR cohort, the multi-institutional cohort also had

Table 1
Baseline characteristics of enrolled patients in the KBCR cohort according to BMI and PgR status.

	BMI<25 kg/m^2 (N = 4453), (%)			BMI≥25 kg/m^2 (N = 4347), (%)			*P* (BMI<25 kg/m^2 Vs ≥ 25 kg/m^2)
	PgR-positive (N = 3255)	PgR-negative (N = 1198)	*P*	PgR-positive (N = 3417)	PgR-negative (N = 930)	*P*	
Age (range)	67.1 (60–100)	66.8 (60–92)	.15	67.4 (60–99)	66.8 (60–89)	.001	.047
pT stage			.02			<.001	<.001
I	2173 (66.8)	751 (62.7)		2125 (62.2)	510 (54.8)		
II	981 (30.1)	396 (33.1)		1188 (34.8)	386 (41.5)		
III or IV	101 (3.1)	51 (4.3)		104 (3.0)	34 (3.7)		
LN metastasis			.37			.34	.07
Negative	2217 (68.1)	799 (66.7)		2265 (66.3)	601 (64.6)		
Positive	1038 (31.9)	399 (33.3)		1152 (33.7)	329 (35.4)		
HG			<.001			.002	.30
I or II	2474 (76.0)	824 (68.8)		2619 (76.6)	662 (71.2)		
III	478 (14.7)	271 (22.6)		506 (14.8)	179 (19.2)		
Unknown	303 (9.3)	103 (8.6)		292 (8.5)	89 (9.6)		
LVI			.08			.07	.90
Negative	2146 (65.9)	756 (63.1)		2222 (65.0)	591 (63.5)		
Positive	820 (25.2)	312 (26.0)		890 (26.0)	233 (25.1)		
Unknown	289 (8.9)	130 (10.9)		305 (8.9)	106 (11.4)		
CTx			.03			<.001	.60
Not performed	1605 (49.3)	537 (44.8)		1660 (48.6)	385 (41.4)		
Performed	1406 (43.2)	567 (47.3)		1490 (43.6)	480 (51.6)		
Unknown	244 (7.5)	94 (7.8)		267 (7.8)	65 (7.0)		

KBCR, Korean Breast Cancer Registry; BMI, body mass index; PgR, progesterone receptor; LN, lymph node; HG, histologic grade; LVI, lympho-vascular invasion; CTx, chemotherapy.

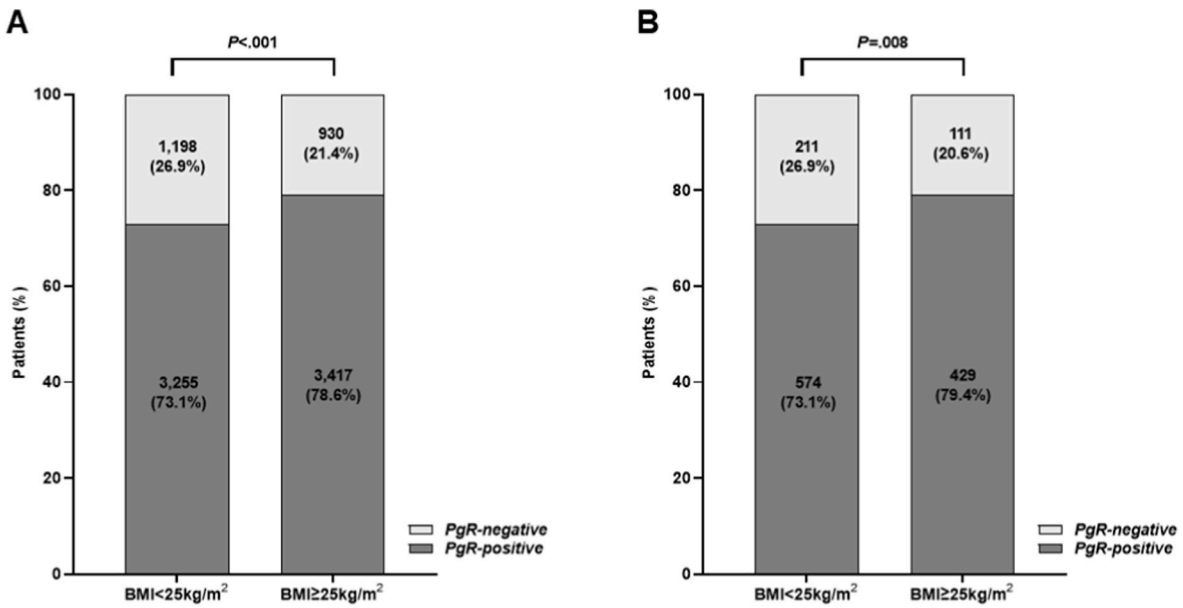

Fig. 2. Proportion of patients with PgR-positive/negative according to BMI. (A) KBCR cohort. (B) Multi-institutional cohort.
BMI, body mass index; PgR, progesterone receptor; KBCR, Korean Breast Cancer Registry.

Table 2
Multivariable analysis using Cox regression model for 6-year OS according to PgR in each BMI group in the KBCR cohort.

BMI	PgR	6-year OS rate	Adjusted HR (95 % CI)[b]	*P*[a]
All patients	Positive	94.3 %	Ref[c].	
	Negative	92.6 %	1.29 (1.04–1.60)	.02
BMI<25 kg/m^2	Positive	94.4 %	Ref.	
	Negative	93.5 %	1.15 (.85–1.56)	.37
BMI≥25 kg/m^2	Positive	94.1 %	Ref.	
	Negative	91.5 %	1.45 (1.06–1.97)	.02

OS, overall survival, PgR, progesterone receptor; BMI, body mass index; KBCR, Korean Breast Cancer Registry; HR, hazard ratio; CI, confidence intervals; LN, lymph node; HG, histologic grade; LVI, lympho-vascular invasion.

[a] Interaction $P = .003$.

[b] Covariates for multivariable models were pT stage (I vs II vs III or IV), LN metastasis (negative vs positive), HG (I/II vs III), LVI (negative vs positive), and chemotherapy (not performed vs performed).

[c] Reference value.

more PgR-positive patients in the higher BMI group (79.4 % vs. 73.1 %; $P = .008$; Fig. 2B), and mean BMI was slightly, but significantly higher in PgR-positive patients ($P = .02$; 95 % CI, −.01 to −.08; Fig. 1B).

During median follow-up period of 62 months, the 6-year RFS rate for all patients enrolled in our study was 94.8 %, with a recurrence rate of 94.4 % for patients with BMI <25 kg/m^2 and 95.4 % for those with a BMI ≥25 kg/m^2. In Kaplan–Meier survival analysis, PgR negativity was a risk factor for recurrence ($P = .006$; Fig. 2A). In the group with BMI ≥25 kg/m^2, PgR-negative patients showed poor 6-year RFS ($P = .001$; Fig. 2C). However, no significant difference was observed in the 6-year RFS according to PgR status in patients with BMI <25 kg/m^2 ($P = .27$; Fig. 2B). In the multivariable analysis, PgR-negative status was a poor prognostic factor for 6-year RFS in the overall patients (HR, 1.99; 95 % CI, 1.21–3.26; $P = .007$) and in patients with BMI ≥25 kg/m^2 (HR, 2.93; 95 % CI, 1.29–6.69; $P = .01$), but not in those with a BMI <25 kg/m^2 (HR, 1.52; 95 % CI, .81–2.86; $P = .19$; Table 3). The other significant prognostic factors are shown in Table 3. DDFS analysis showed results consistent with RFS, with the definitive negative prognostic impact of PgR-negativity observed only in patients with BMI ≥25 kg/m^2 (Table 2).

Among the subset of patients with RS data, the mean RS was significantly higher in the PgR-negative group than in the PgR-positive group (Fig. 4A), which was consistent across both BMI groups (Fig. 4B and C).

4. Discussion

Our large-scale retrospective cohort study confirmed the association between BMI and PgR expression in postmenopausal ER+/HER2-patients. Furthermore, we demonstrated that the prognostic influence of PgR status was modified by obesity, as measured by BMI. Specifically, no negative effect of PgR absence was observed in non-obese patients. Analysis of the subset with RS data showed that the aggressive biology of PgR-negative tumors was conserved in non-obese patients, similar to that in the general population. These results suggest that BMI as a host factor should be considered when interpreting PgR status as a tumor factor in ER+/HER2-breast cancer.

Previous meta-analyses have reported that obesity is associated with poor prognosis in patients with breast cancer, although the biological mechanisms remain incompletely understood [35,36]. The proposed contributors include hormonal alterations, adipocytokines, and inflammatory cytokines [37,38]. Based on these observations, we hypothesized that these adipocyte-mediated changes might influence PgR expression in postmenopausal patients with ER+/HER2-breast cancer.

Firstly, we aimed to determine whether PgR expression was more prevalent in obese postmenopausal women. In both large cohorts, we consistently found that PgR-positive breast cancer was more prevalent in patients with BMI ≥25 kg/m^2, and that patients with PgR-positive breast cancer had higher mean BMI compared to those with PgR-negative breast cancer. Previous studies reported a higher proportion of PgR-positive breast cancers in postmenopausal obese patients [39,40]. However, breast cancer subtypes do not differ according to BMI in premenopausal women [39,41]. This is thought to be because PgR is regulated by ER and estrogen. Estrogen production in postmenopausal women is primarily driven by adipocyte-driven aromatization, whereas estrogen is predominantly produced by the ovaries of premenopausal women [42,43].

Our second aim was to determine whether the prognostic impact of the PgR status differed according to BMI. In patients with higher BMI and a relatively estrogen-rich environment, PgR is highly expressed. However, in patients who did not express PgR in this environment, survival outcomes were worse, as expected. Nevertheless, the biological

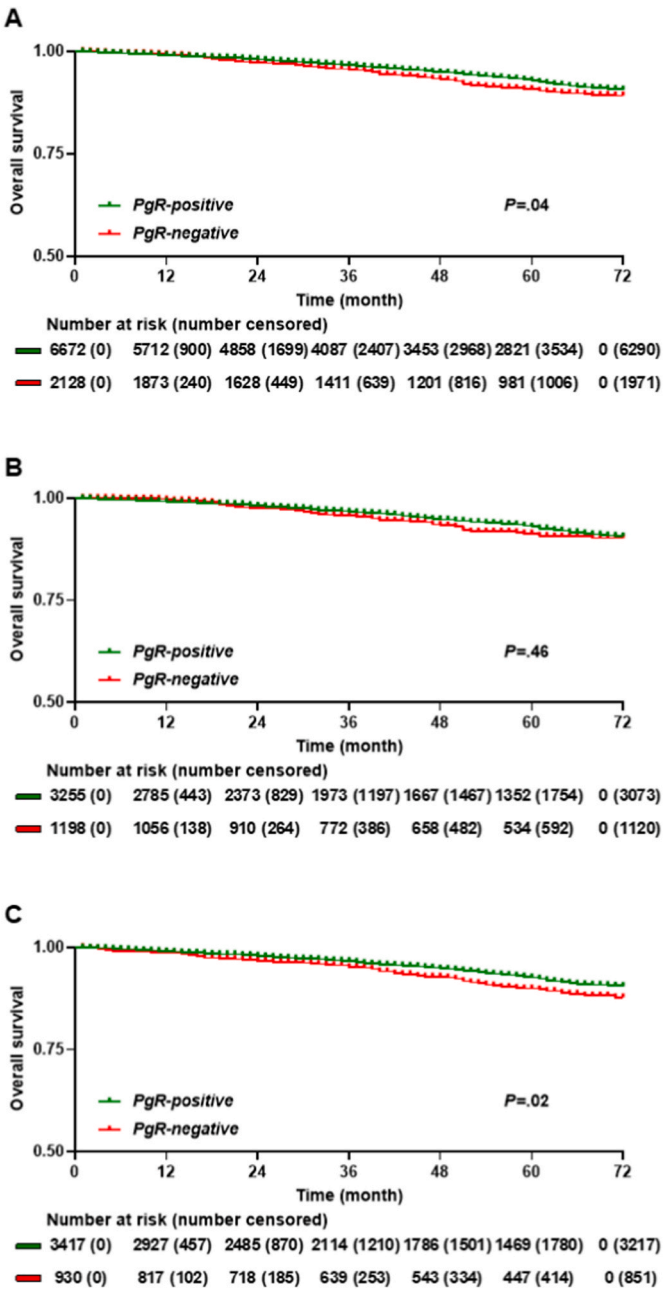

Fig. 3. Kalan-Meier survival curve for 6-year OS according to PgR status in each BMI group in KBCR cohort. (A) All patients. (B) Patients with BMI<25 kg/m^2. (C) Patients with BMI≥25kg/m^2
PgR; progesterone receptor; OS, overall survival; BMI, body mass index; KBCR, Korean Breast Cancer Registry.

mechanisms underlying the differential effects of PgR on endocrine resistance and prognosis according to BMI have not yet been fully elucidated.

Obesity is often associated with the development of insulin resistance, which increases the bioavailability of growth factors such as insulin-like growth factor-I (IGF-I) [44–46]. Previous studies have reported that IGF-I downregulates estradiol-induced PgR levels independent of ER through the PI3K/Akt/mTOR pathway, ultimately regulating ER activity [47]. This may help explain the mechanism in patients who did not express PgR despite being in an estrogen-rich environment via obesity, which typically supports PgR expression. It also suggests that growth factors derived from adipocytes may contribute to endocrine resistance, and that PgR could serve as a potential biomarker for activated growth factor signaling.

Surprisingly, we found that the negative effect of the absence of PgR on prognosis was diminished in non-obese postmenopausal women. When we compared RS according to PgR status to explore tumor-intrinsic factors, we found that PgR-negative tumors had aggressive tumor biology in non-obese patients as well as in obese patients. This suggests that host factors associated with lower BMI, which is indicative of a lower estrogen environment, may play a role in counteracting the negative prognosis associated with PgR negativity. Our findings support the hypothesis that weight control to reduce endogenous estrogen produced by adipose tissue is beneficial in postmenopausal women with ER-positive breast cancer. Further studies on these mechanisms are required.

To the best of our knowledge, our study is the first to demonstrate, using a large-scale cohort, that the effect of PgR on prognosis can differ according to BMI. Ohara et al. classified patients into four groups based on BMI and PgR using data from a small cohort of 184 patients and found that patients with a high BMI and PgR-negative status had poor oncological outcomes with a higher recurrence rate [48]. Oudanonh et al. also conducted an analysis combining BMI and PgR in 3747 patients with ER-positive primary breast cancer [49]. However, in contrast to our study, their research analyzed breast-cancer-specific survival and overall survival according to BMI within patient groups classified by PgR status and included premenopausal women in the cohort. These methodological differences make it difficult to directly compare their results with ours and suggest that it is difficult to determine the impact of PgR on endocrine resistance based on BMI using their approach.

A limitation of our study is that as a retrospective and observational cohort study, it may be subject to selection bias and does not allow the establishment of a causal relationship between BMI and PgR expression. Nevertheless, we established and analyzed a very large patient cohort, which would have been challenging to collect prospectively, and meticulously cleaned the clinicopathological information of the patients. Additionally, our study did not include variables related to comorbidities, such as diabetes. Furthermore, while we clinically identified the changes in the prognostic effect of PgR according to BMI, we were unable to directly demonstrate the changes in estrogen or IGF-I levels, which we hypothesized to be the underlying mechanism in obese patients. Finally, the attenuation of the negative effect of PgR negativity in normal-BMI patients should be validated in another cohort, ideally including Western patients. However, as our study is the first to focus on the interaction between obesity and the effects of PgR, we believe that future research will elucidate the underlying mechanisms in greater detail.

In conclusion, we confirmed that postmenopausal patients with ER+/HER2-breast cancer with BMI ≥25 kg/m^2 had a higher proportion of PgR-positive tumors compared to those with BMI <25 kg/m^2. Furthermore, we found that BMI modifies the prognostic significance of PgR status, with PgR-negativity associated with worse outcomes predominantly in patients with BMI ≥25 kg/m2. These findings highlight the complex interplay between host metabolic factors and tumor biology in the clinical outcomes of patients with breast cancer. Nevertheless, these results require cautious interpretation, as they are hypothesis-generating and do not yet warrant the incorporation of BMI into clinical decision-making. Our findings highlight metabolic health as a potential modifier of established prognostic biomarkers in breast cancer, necessitating validation through prospective studies across diverse populations before clinical implementation. Future research should explore the molecular mechanisms underlying this BMI-PgR interaction to identify new therapeutic strategies for personalized treatment.

CRediT authorship contribution statement

Janghee Lee: Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Soong June Bae:** Writing – original draft, Validation,

Table 3
Multivariable analysis using Cox regression model for 6-year RFS according to PgR in each BMI group in the multi-institutional cohort.

	Overall		BMI<25 kg/m^2		BMI≥25 kg/m^2	
	HR (95 % CI)	*P*	HR (95 % CI)	*P*	HR (95 % CI)	*P*
PgR						
Positive	Ref.[a]		Ref.		Ref.	
Negative	1.99 (1.21–3.26)	.007	1.52 (.81–2.86)	.19	2.93 (1.29–6.69)	.01
Tumor size						
<20 mm	Ref.		Ref.		Ref.	
≥20 mm	2.44 (1.41–4.20)	.001	3.40 (1.72–6.70)	<.001	1.38 (.57–3.34)	.48
LN metastasis						
Negative	Ref.		Ref.		Ref.	
Positive	1.81 (1.04–3.13)	.04	1.24 (.63–2.47)	.53	3.92 (1.36–11.25)	.01
HG						
I or II	Ref.		Ref.		Ref.	
III	1.78 (.99–3.19)	.06	1.66 (.76–3.63)	.20	1.91 (.77–4.76)	.16
CTx						
Not performed	Ref.		Ref.		Ref.	
Performed	1.30 (.65–2.60)	.46	1.20 (.53–2.69)	.67	2.06 (.44–9.73)	.36

RFS, recurrence-free survival; PgR, progesterone receptor; BMI, body mass index; HR, hazard ratio; LN, lymph node; HG, histologic grade; CTx, chemotherapy.
[a] Reference value.

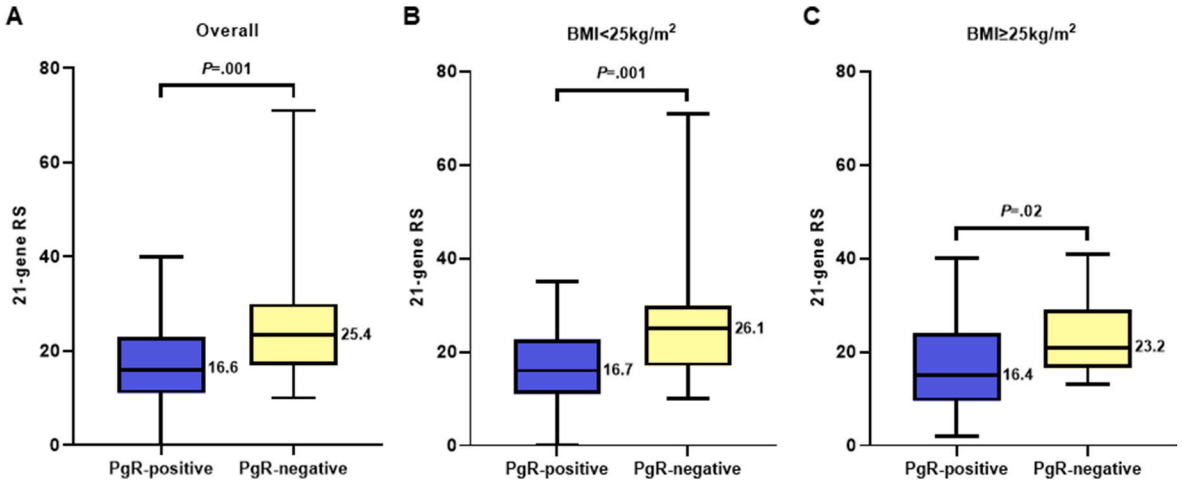

Fig. 4. Box plot of association between 21-gene RS and PgR in each BMI group in multi-institutional cohort. (A) All patients. (B) Patients with BMI<25 kg/m^2. (C) Patients with BMI≥25 kg/m^2.
BMI, body mass index; PgR, progesterone receptor; RS, recurrence score.

Methodology, Investigation, Formal analysis, Data curation. **Hong Kyu Kim:** Data curation. **Seok Jin Nam:** Data curation. **Hee Jeong Kim:** Data curation. **Soo Youn Bae:** Data curation. **Ho Yong Park:** Data curation. **Byung Kyun Ko:** Data curation. **Jung Ho Park:** Data curation. **Yeonjoo Kwon:** Data curation. **Youri Park:** Data curation. **Seung Ho Baek:** Data curation. **Yoowon Kook:** Data curation. **Sanghwa Kim:** Data curation. **Young Ah Lim:** Data curation. **Hee-Joon Kang:** Data curation. **Doyil Kim:** Data curation. **Joon Jeong:** Supervision, Methodology. **Sung Gwe Ahn:** Writing – review & editing, Validation, Methodology, Funding acquisition, Conceptualization.

Data availability statements

The datasets used and/or analyzed in the current study are available from the corresponding author upon reasonable request.

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Declaration of competing interest

The authors have no conflicts of interest to report.

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Appendix A. Supplementary data

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