The significance of body mass index and absolute lymphocyte count as a prognostic factor for disease-free survival in Korean breast cancer patients

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Directed by Professor Joon Jeong

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I would like to thank professor Joon Jeong for helping me choose the subject for my thesis and giving me guidance.
I would also like to thank my family for supporting me through my studies.
I will try my best to become a surgeon not just with skills but also with a heart, based on my 4 years in training as a resident and 3 years of graduate studies.

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ABSTRACT

The significance of body mass index and absolute lymphocyte count as a prognostic factor for disease-free survival in Korean breast cancer patients

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Background: Our study evaluated the association between body mass index (BMI) and absolute lymphocyte count (ALC) in healthy females and breast cancer patients. Additionally, we determined the prognostic value of these factors in breast cancer.

Methods: We retrospectively identified 1,225 primary invasive breast cancer patients and 35,991 healthy females registered at Gangnam Severance Hospital. BMI and complete blood count at the time of diagnosis were collected. Factors associated with disease-free survival (DFS) were assessed using a multivariable Cox proportional hazard model.

Results: BMI and ALC were positively correlated in breast cancer patients and healthy females (both $P<0.001$). In multivariable analysis, overweight or obese participants had worse DFS (hazards ratio [HR], 1.98; 95% confidence interval [CI], 1.34–2.92; $P=0.001$) than underweight or normal weight individuals, but patients with high ALC had better DFS than those with low ALC (HR, 0.43; 95% CI, 0.29–0.65; $P<0.001$). After risk stratification according to BMI/ALC, high-risk patients with high BMI/low ALC had worse DFS than others (HR, 2.48; 95% CI, 1.70–3.62; $P<0.001$). In subgroup analysis, human epidermal growth factor receptor 2-positive and early stage tumors were more affected by BMI/ALC than other tumor types.

Conclusions: BMI and ALC were positive correlated, but their effect on breast cancer prognosis was opposite. Patients with high BMI/low ALC had worse DFS than others. Underlying mechanisms for effect of BMI/ALC on breast cancer prognosis should be studied in the future.

Key words : body mass index, absolute lymphocyte count, breast cancer

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I. INTRODUCTION

The global prevalence of breast cancer has substantially increased over recent decades.[1] In South Korea, breast cancer is one of the most common malignancies among females, accounting for >2,000 deaths in 2016.[2] Since breast cancer is a heterogenic disease with several biological characteristics, various factors such as hormone receptors, human epidermal growth factor receptor 2 (HER2), grade, and Ki-67 labelling index (LI) as a cell proliferation marker affect disease prognosis.[3, 4] Currently, significant efforts are being made to develop methods for the accurate prediction of breast cancer prognosis.

Obesity is another major global health concern; in South Korea, >60% women aged >40 years are overweight or obese.[5] Obesity is an important risk factor for diabetes, cardiovascular disease, and kidney disease; it has also been recently recognized as a risk factor for breast cancer.[6] Although hormones, adipocytokines, and inflammatory cytokines have been identified as potential mediators, the biological mechanisms that explain the association between obesity and breast cancer survival have not been conclusively established.[7] Body mass index (BMI), calculated using body weight and height, is the most widely used measure for the degree of obesity.[8]

Inflammatory cells have an important role in cancer progression.[9] Several parameters such as tumor-infiltrating lymphocytes (TILs) and neutrophil-to-lymphocyte ratio (NLR) can be used to assess immune response. Among them, peripheral blood cell count has been widely used as it is easy and cost-effective. Lymphocytes, including natural killer cells, T

cells, and B cells, are types of white blood cells (WBCs) that are found in the vertebrate immune system.[10] T lymphocytes, involved in adaptive immunity, play a key role in tumor-specific immune response.[11]

Several researchers have suggested that BMI and immune response are closely related.[12] However, the clinical significance of this relationship has not been assessed in breast cancer patients. Therefore, our study aimed to identify the association between BMI and peripheral inflammatory cells in healthy females and breast cancer patients. We focused on the absolute lymphocyte count (ALC) and determined the effect of ALC and BMI on the prognosis of breast cancer patients.

II. MATERIALS AND METHODS

Study population

We retrospectively identified 1,225 primary invasive breast cancer patients from the Gangnam Severance Hospital breast cancer registry registered between January 2009 and December 2015. Patients' clinicopathologic information was extracted from their medical records. All patients were South Korean; patients from western countries were excluded owing to different BMI criteria, and Asian patients with non-Korean parentage were not included in the registry. Patients underwent breast cancer surgery as curative treatment and received adjuvant therapy if needed. Patients who had received neoadjuvant chemotherapy were excluded as accurate evaluation of surgical pathology and disease stage was difficult in these patients. Patients with de novo stage IV cancer were also excluded.

Further, 35,991 healthy women were included from the Gangnam Severance Health Promotion Center registry between January 2007 and July 2020 to reconfirm the association between BMI and ALC. Data on body weight, height, and CBC were collected. All women were South Korean and had never been diagnosed with or treated for malignant disease. Patients and healthy females excluded from the study were summarized in Supplementary Figure S1.

Our study was approved by the institutional review board of Gangnam Severance Hospital (approval number: 3-2020-0207), which waived the requirement for written informed consent owing to the retrospective study design.

Body mass index

Body weight and height of breast cancer patients were obtained on their first visit. If these were not measured at the first visit, measurements taken after admission for operation were used. The body weight and height of all healthy females were measured at their routine health examination. BMI was calculated as body weight in kilograms divided by the square of height in meters, defined by the World Health Organization (WHO) [8]. Participants were categorized using BMI cutoffs given in the WHO-Asia-Pacific classification [33]. According to the Asian standards, people with BMI <18.5 kg/m^2 are considered underweight, and those with BMI ≥23.0 kg/m^2 are considered overweight or obese.

Complete blood count

Peripheral venous blood samples were collected from all breast cancer patients for preoperative evaluation. For healthy females, same samples were obtained at their health checkup to evaluate hemoglobin levels and white blood cell counts. Venous blood was collected using 15 ml polypropylene tubes containing 10% ethylenediaminetetraacetic acid as an anticoagulant. All blood cell counts including WBC count, ANC, ALC, platelet count and monocyte count were assessed at the same institutional laboratory. NLR was calculated by dividing the absolute number of neutrophils by the absolute number of lymphocytes. Patients with WBC count≥$20.0\times10^3/\mu L$ were excluded from study due to the possibility of abnormal conditions including infectious disease at the time of examination. For risk stratification according to ALC, patients were divided into low and high groups based on the median value of ALC in the breast cancer cohort.

Statistical analysis

The primary endpoint was disease-free survival (DFS), and additional analysis was performed for estimating overall survival (OS) as the secondary endpoint. DFS was defined as the period between breast cancer surgery and tumor recurrence, secondary malignancy, or any cause of death. Contralateral breast cancer was classified as a secondary malignancy and not metastasis. OS was defined as the period from breast cancer surgery to death due to any reason. Statistical analyses were performed using SPSS version 25.0 (IBM Inc., Armonk, NY, USA). Difference between the groups was evaluated by the chi-square test for categorical

data and one-way ANOVA for continuous variables, after confirmation by Levene's test for equality of variances. Kaplan–Meier survival estimates were used to compare DFS, and the group differences in the survival curves were analyzed using the log-rank test. Univariable and multivariable Cox proportional hazard models were used to identify variables associated with DFS and OS and perform subgroup analysis with HR and corresponding 95% CI. All statistical tests were two sided, and a *P*-value <0.050 was considered statistically significant.

III. RESULTS

Association between BMI and ALC

In the breast cancer cohort, absolute lymphocyte count (ALC) was positive correlated with BMI. The average ALC was $1.81\times10^3/\mu L$; ALC was the lowest in underweight patients and the highest in overweight or obese patients (*P*<0.001; Figure 1A). Although not all observations were statistically significant, WBC, platelet count and monocyte count tended to increase with BMI (WBC, *P*<0.001; platelet, *P*<0.001; monocyte, *P*=0.001; Supplementary Figure S2). However, Absolute neutrophil count (ANC) was not correlated with BMI (*P*=0.073). NLR was significantly lower in overweight or obese patients than in underweight patients (*P*=0.025), but there was no significant difference compared with the NLR of normal-weight patients (*P*=0.641).

Next, we analyzed complete blood count (CBC) according to BMI in healthy females to compare results with those of breast cancer patients. The average age of healthy females was 46.7 years, and >50% had a normal body weight. 38.2% women were overweight or obese. In the healthy female cohort, BMI and ALC were also positively correlated. ALC was significantly higher in overweight or obese women than in underweight and normal-weight women (*P*<0.001; Figure 1B). The average ALC for healthy females was $1.89\times10^3/\mu L$. Other blood cell counts such as WBC, platelet count, monocyte count and ANC also had a positive correlation with BMI (all *P*<0.001; Supplementary Figure S3). NLR was lower in overweight or obese women than in normal-weight or underweight women (*P*<0.001). In addition, healthy females had significantly higher ALC than breast cancer patients (Supplementary Table S1). In contrast, WBC and ANC were higher in breast cancer patients than healthy females. There was no statistically difference in platelet and monocyte between the two groups.

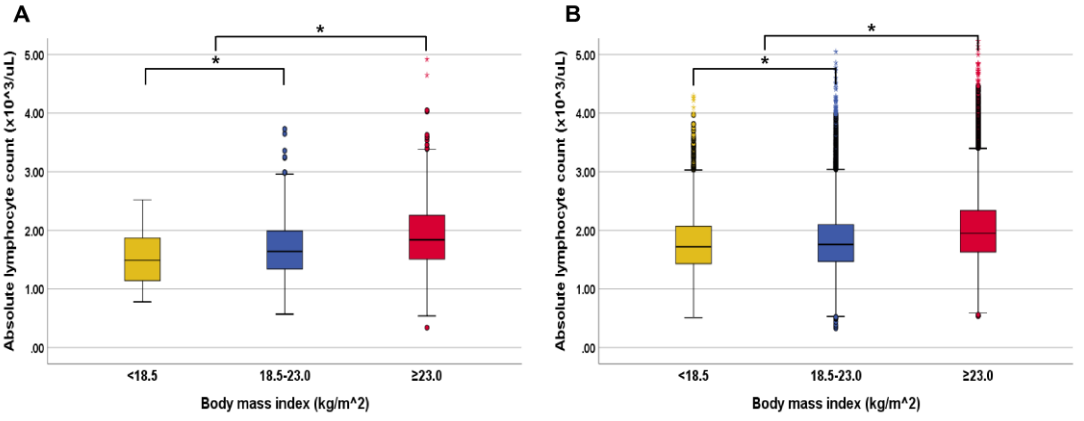

Figure 1. Box plot comparing ALC according to BMI:

(A) Breast cancer patients, (B) Healthy females

ALC, absolute lymphocyte count; BMI, body mass index

*P<0.050

Table 1. Clinicopathologic features of breast cancer patients

	Body mass index, kg/m^2 (%)				P-value
	All patients	<18.5	18.5–23.0	≥23.0	
Total	1,225 (100)	49 (4.0)	546 (44.6)	630 (51.4)	
Age, average (range), years	51.4 (24–87)	43.9 (26–67)	48.5 (24–87)	54.6 (28–87)	<0.001
Histologic grade					0.157
Low	250 (20.7)	11 (22.4)	125 (22.9)	114 (18.1)	
Intermediate	609 (50.4)	20 (40.8)	260 (47.6)	329 (52.2)	
High	350 (28.5)	18 (36.7)	155 (28.4)	177 (28.1)	
Unknown	16 (1.3)	0 (0.0)	6 (1.1)	10 (1.6)	
Nuclear grade					0.263
Low	122 (10.0)	8 (16.3)	61 (11.2)	53 (8.4)	
Intermediate	621 (50.7)	24 (49.0)	267 (48.9)	330 (52.4)	
High	467 (38.1)	17 (34.7)	212 (38.8)	238 (37.8)	
Unknown	15 (1.2)	0 (0.0)	6 (1.1)	9 (1.4)	

Estrogen receptor					0.778
Negative	355 (29.0)	12 (24.5)	159 (29.1)	184 (29.2)	
Positive	870 (71.0)	37 (75.5)	387 (70.7)	446 (70.8)	
Progesterone receptor					0.726
Negative	473 (38.6)	18 (36.7)	205 (37.5)	250 (39.7)	
Positive	752 (61.3)	31 (63.3)	341 (62.5)	380 (60.3)	
HER2					0.921
Negative	873 (71.2)	34 (69.4)	391 (71.5)	448 (71.1)	
Positive	306 (25.0)	12 (24.5)	133 (24.5)	161 (25.6)	
Unknown	46 (3.8)	3 (6.1)	22 (4.0)	21 (3.3)	
Ki-67 LI, %					0.370
<14	671 (54.8)	27 (54.0)	287 (52.5)	357 (56.7)	
≥14	554 (45.2)	22 (44.9)	259 (47.4)	273 (43.3)	
Tumor size, mm					0.001
≤20	801 (65.4)	36 (73.5)	385 (70.5)	380 (60.3)	
>20	424 (34.6)	13 (26.5)	161 (29.5)	250 (39.7)	
Positive lymph node, count					0.216
0	842 (68.7)	40 (81.6)	373 (68.3)	429 (68.1)	
1–3	296 (24.2)	6 (12.2)	139 (25.5)	151 (24.0)	
≥4	87 (7.1)	3 (6.1)	34 (6.2)	50 (7.9)	

HER2, human epidermal growth factor receptor 2; LI, labelling index

Baseline characteristics of breast cancer patients

Table 1 summarizes the clinicopathologic characteristics of patients according to BMI. There were 51.4% overweight or obese patients and 4% underweight patients. The average patient age was 51.4 years; the average age of patients tended to increase with the increasing BMI. Additionally, a high proportion of patients had tumors measuring >20 mm. Other features including grade, estrogen receptor (ER)/progesterone receptor (PR)/HER2 status, Ki-67 LI, and the number of positive axillary lymph nodes did not differ with BMI. Type of breast and axillary surgery and

adjuvant therapy also did not differ with BMI (Supplementary Table S2).

Table 2. Univariable and multivariable Cox regression analysis for DFS

	Univariable analysis		Multivariable analysis	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age, years*	1.00 (0.99–1.02)	0.775		
BMI, kg/m^2				
18.5–23.0	Ref.**		Ref.	
<18.5	0.76 (0.24–2.45)	0.644	0.50 (0.12–2.06)	0.334
≥23.0	1.57 (1.09–2.26)	0.016	1.98 (1.34–2.92)	0.001
WBC count, ×10^3/uL*	0.99 (0.89–1.09)	0.764		
ALC, ×10^3/uL*	0.52 (0.37–0.74)	<0.001	0.43 (0.29–0.65)	<0.001
ANC, ×10^3/uL*	1.06 (0.96–1.17)	0.270		
NLR, ×10^3/uL*	1.09 (1.04–1.14)	0.001	1.01 (0.94–1.07)	0.881
Platelet count, ×10^3/uL*	1.00 (0.99-1.00)	0.785		
Monocyte count, ×10^3/uL*	1.72 (0.38-7.80)	0.484		
Histologic grade				
Low	Ref.		Ref.	
Intermediate	1.51 (0.89–2.55)	0.128	0.94 (0.54–1.65)	0.831
High	2.03 (1.18–3.50)	0.011	0.85 (0.44–1.65)	0.625
Nuclear grade				
Low	Ref.			
Intermediate	1.29 (0.64–2.60)	0.486		
High	1.94 (0.96–3.91)	0.065		
Estrogen receptor				
Negative	Ref.		Ref.	
Positive	0.54 (0.38–0.78)	0.001	0.82 (0.46–1.49)	0.516
Progesterone receptor				
Negative	Ref.		Ref.	
Positive	0.54 (0.38–0.76)	<0.001	0.89 (0.50–1.56)	0.678

HER2				
Negative	Ref.		Ref.	
Positive	1.59 (1.10–2.31)	0.015	1.19 (0.80–1.79)	0.388
Ki-67 LI, %				
<14	Ref.		Ref.	
≥14	2.40 (1.67–3.45)	<0.001	1.94 (1.22–3.07)	0.005
Tumor size, mm				
≤20	Ref.		Ref.	
>20	2.12 (1.50–3.01)	<0.001	1.47 (1.00–2.18)	0.050
Positive lymph node, count				
0	Ref.		Ref.	
1–3	1.16 (0.77–1.76)	0.471	1.00 (0.65–1.55)	0.992
≥4	2.17 (1.27–3.73)	0.005	1.30 (0.72–2.34)	0.385

*Continuous variable

**Reference value

ALC, absolute lymphocyte count; ANC, absolute neutrophil count; BMI, body mass index; CI, confidence interval; DFS, disease-free survival; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; LI, labelling index; NLR, neutrophil-to-lymphocyte ratio; WBC, white blood cell

BMI and ALC as prognostic factors for DFS

The 5-year disease-free survival (DFS) for all patients was 91.9%. The 5-year distant recurrence and locoregional recurrence rates were 3.7% and 2.0%, respectively. The median follow-up period was 70 months. There were 152 events in 126 patients during follow-up. Six patients developed contralateral breast cancer and 14 patients died during follow-up. Details of disease events have been summarized in Supplementary Table S3. For the analysis, BMI was divided into three groups—underweight (<18.5 kg/m^2), normal weight (18.5–23.0 kg/m^2), and overweight or obese (≥23.0 kg/m^2), and continuous variables were used for blood cell counts. In univariable analysis, overweight or obesity, but not underweight, was a risk factor for DFS (hazards ratio [HR], 1.57; 95% confidence interval [CI], 1.09–2.26;

P=0.016; Table 2). Among blood cell counts, patients with high ALC had significantly better DFS than those with low ALC (HR, 0.52; 95% CI, 0.37–0.74; *P*<0.001). NLR was also statistically significant (*P* = 0.001), but the associated HR was 1.08, suggesting minimal impact on prognosis. Other known prognostic factors including histologic grade, ER/PR/HER2 status, Ki-67 LI, tumor size, and the number of positive lymph nodes (≥4) were also significant in univariable analysis. In multivariable analysis, high BMI was associated with worse DFS (HR, 1.98; 95% CI, 1.34–2.92; *P*=0.001) and high ALC was a good prognostic factor (HR, 0.43; 95% CI, 0.29–0.65; *P*<0.001). However, excluding large tumor size (>20 mm; HR, 1.47; 95% CI, 1.00–2.18; *P*=0.050) and high Ki-67 LI (HR, 1.94; 95% CI, 1.22–3.07; *P*=0.005), other factors were not significant in multivariable analysis. The Kaplan–Meier survival curves also revealed that the high BMI group had worse DFS than the normal and underweight groups (log-rank *P*=0.025; Figure 2A). Based on the median ALC of 1.74×10^3/uL in the breast cancer cohort, we divided patients into the low ALC group (*N*=615) and the high ALC group (*N*=610). Patients with high ALC had better DFS than those with low ALC according to the Kaplan–Meier survival analysis (log-rank *P*=0.018; Figure 2B). However, BMI and ALC were not risk factors for overall survival (OS) (Supplementary Table S4). Ki-67 LI and tumor size were the only prognostic factors associated with OS in multivariable analysis.

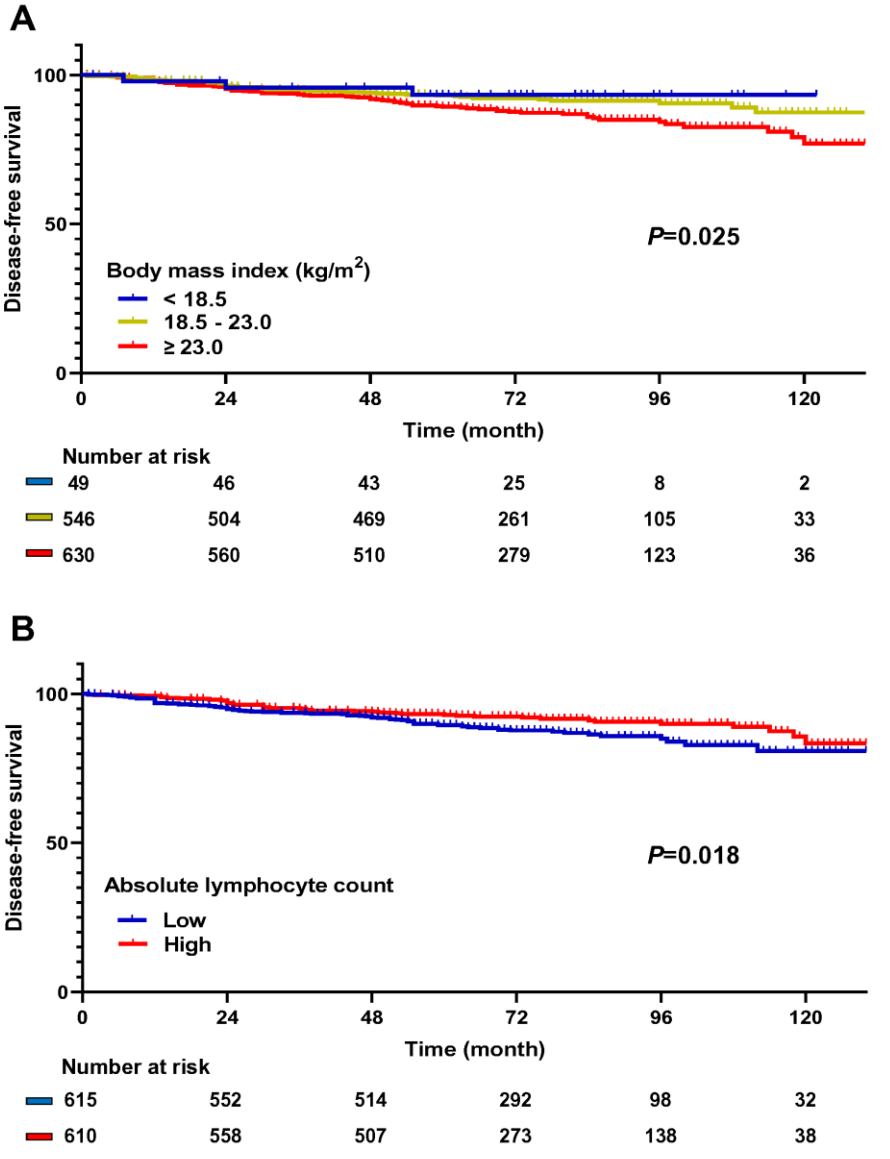

Figure 2. Kaplan–Meier survival curve for DFS according to BMI and ALC:
(A) BMI (log-rank *P*=0.025), (B) ALC (log-rank *P*=0.018)
ALC, absolute lymphocyte count; BMI, body mass index; DFS, disease-free survival

Risk stratification according to BMI/ALC

We scored patients according to BMI/ALC and divided them into two risk stratification groups (low and high). If patients were overweight or obese and had low ALC, they were classified into the high-risk group (*N*=258). Conversely, if patients were normal or underweight or had high ALC, they were classified into the low-risk group (*N*=967). The Kaplan–Meier survival curves showed that the high-risk group had poorer prognosis than the low-risk group (log-rank *P*<0.001; Figure 3). The high-risk group also had worse DFS than the low-risk group according to the multivariable Cox regression hazard model (HR, 2.48; 95% CI, 1.70–3.62; *P*<0.001; Table 3). However, OS did not differ between the risk stratification groups (log-rank *P*=0.528; Supplementary Figure S4).

In the subgroup analysis, BMI/ALC was a significant risk factor in both premenopausal (≤50yrs) and postmenopausal women (>50yrs) (premenopausal: HR, 0.38; 95% CI, 0.22-0.63; *P*<0.001; postmenopausal: HR, 0.47; 95% CI, 0.29-0.78; *P*=0.003; Figure 4). In addition, the low-risk group had significantly better DFS for HER2-positive tumor than the high-risk group (HR, 0.31; 95% CI, 0.17–0.58; *P*<0.001). There was also a difference in DFS for ER-positive/HER2-negative breast cancer between groups (HR, 0.39; 95% CI, 0.23–0.69; *P*=0.001). However, DFS for triple-negative breast cancer did not significantly differ between groups (*P*=0.244), although the HRs were different. Furthermore, the BMI/ALC risk groups were better validated for early breast cancer than for advanced breast cancer (stage I: HR, 0.44; 95% CI, 0.23–0.84; *P*=0.012; stage II: HR, 0.38; 95% CI, 0.24–0.63; *P*<0.001).

Table 3. Multivariable Cox regression analysis for DFS using the BMI/ALC risk stratification group

	HR (95% CI)	*P*-value
BMI/ALC risk group		
Low	Ref.**	
High	2.48 (1.70–3.62)	<0.001
NLR, $\times 10^3$/uL*	1.04 (0.98–1.10)	0.161

Histologic grade		
Low	Ref.	
Intermediate	0.98 (0.56–1.71)	0.940
High	0.86 (0.44–1.67)	0.654
Estrogen receptor		
Negative	Ref.	
Positive	0.79 (0.43–1.43)	0.428
Progesterone receptor		
Negative	Ref.	
Positive	0.95 (0.53–1.68)	0.855
HER2		
Negative	Ref.	
Positive	1.17 (0.78–1.76)	0.450
Ki-67 LI, %		
<14	Ref.	
≥14	1.94 (1.22–3.07)	0.005
Tumor size, mm		
≤20	Ref.	
>20	1.46 (0.98–2.15)	0.060
Positive lymph node, count		
0	Ref.	
1–3	0.98 (0.63–1.53)	0.943
≥4	1.35 (0.75–2.43)	0.321

*Continuous variable

**Reference value

ALC, absolute lymphocyte count; BMI, body mass index; CI, confidence interval; DFS, disease-free survival; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; NLR, neutrophil-to-lymphocyte ratio; LI, labelling index

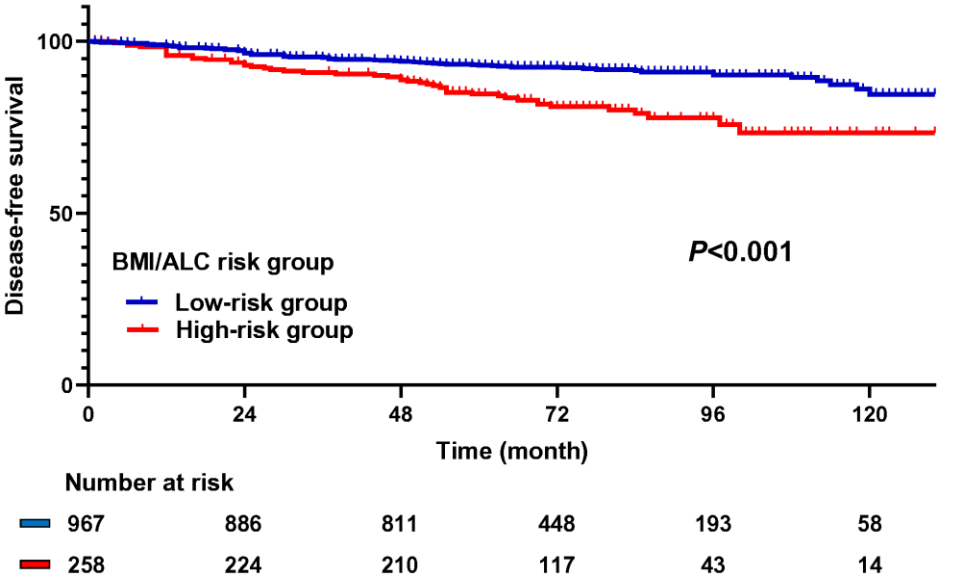

Figure 3. Kaplan–Meier survival curve for DFS according to the BMI/ALC risk stratification groups (log-rank *P*<0.001)

ALC, absolute lymphocyte count; BMI, body mass index; DFS, disease-free survival

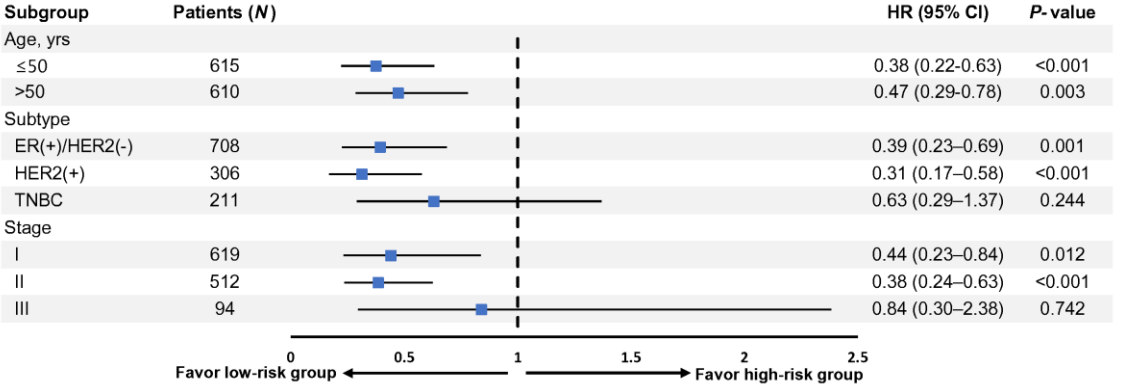

Figure 4. Subgroup analysis of DFS according to the BMI/ALC risk stratification groups

ALC, absolute lymphocyte count; BMI, body mass index; CI, confidence interval; DFS, disease-free survival; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; TNBC, triple-negative breast cancer

IV. DISCUSSION

Our study found that BMI and ALC were positive correlated not only in breast cancer patients but also in healthy females, but their effect on breast cancer prognosis was opposite. Being overweight or obese adversely affected DFS, but patients with high ALC had better DFS than those with low ALC. After BMI/ALC risk stratification, high-risk patients with high BMI/low ALC had significantly worse DFS than low-risk patients.

Recent reports have suggested that obesity is a risk factor for various metabolic diseases; it is also associated with the risk of breast cancer. The Predicting Risk of Cancer at Screening (PROCAS) study in United Kingdom found that weight gain in adults is a risk factor for breast cancer, especially for those with BMI <23.4 kg/m^2 at 20 years of age [13]. Of the 47,042 non-breast cancer patients followed up for a median of 5.6 years, 1,142 were diagnosed with breast cancer. Therefore, weight management is important for preventing breast cancer and metabolic diseases such as diabetes and cardiovascular disease.

Body weight is also an important prognostic factor in breast cancer patients. Chan et al. argued that obesity is associated with poor OS and breast cancer-specific survival (BCSS) in breast cancer patients in their systemic literature review of 82 follow-up studies [14]. In this meta-analysis, the relative risk (RR) of total mortality in obese women was 1.75 and 1.34 for premenopausal and postmenopausal breast cancer, respectively. Our study findings were also similar to those of previous studies. In our results, DFS of breast cancer patients is worse if BMI is high.

Unlike overweight or obese patients, prognosis of underweight patients did not differ from normal weight patients. Previous studies in South Korea have reported that underweight women may have risk factors for breast cancer such as early menarche and nulliparity, leading to worse OS and BCSS [15,16]. However, in our study, underweight was not a risk factor for DFS and OS. Additional investigations including more numbers of underweight patients than our study are needed since the proportion of underweight patients in our cohort was very small.

The importance of immune responses in breast cancer is gradually being recognized. Several studies have found that breast tumors with high TILs have better prognosis than those with low TILs. In addition, peripheral lymphocytes and neutrophils can migrate toward a tumor site and infiltrate the tumor microenvironment [17-20]. Thus, research on

immunologic markers in peripheral blood such as NLR, platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio is being actively conducted [21,22]. However, there is a lack of data on ALC as a prognostic marker in breast cancer. Although the reported findings were discordant, previous studies have argued that ALC can predict DFS and mortality [23,24]. In addition, some researchers have suggested that ALC is superior to NLR and PLR for predicting progression-free survival in breast cancer [25]. In our study, ALC was a good predictor of DFS in breast cancer patients. Furthermore, we demonstrated that ALC is more strongly associated with prognosis than other blood parameters including NLR.

We divided the patients into two groups using the median ALC (1.74×10^3/uL), which was consistent with the ALC reported in previous studies ($1.5–1.8\times10^3$/uL).[23,25] However, lymphopenia is defined as ALC $<1.0\times10^3$/uL, a much lower level; hence, low ALC in breast cancer patients and lymphopenia have different implications. Therefore, further research on new cutoff values that can be used to demarcate low and high ALC for oncology studies is needed. In addition, lymphocytes occasionally have opposing functions. CD8+ cytotoxic T lymphocytes increase antitumor immunity, and CD4+ helper T cells play critical roles in adaptive immune response along with B lymphocytes and CD8+ cytotoxic T cells [26-28]. However, exhausted CD8+ T lymphocytes and regulatory T cells (T_{reg}; subset of CD4+ T lymphocyte) suppress antitumor immunity [29,30]. Therefore, the immune response to breast tumor could vary depending on the composition of lymphocytes, which ultimately affects prognosis. Further investigation of the association between peripheral lymphocyte composition and survival is needed.

To our knowledge, this is the first study to simultaneously analyze BMI and ALC in breast cancer patients. Previous experimental studies have suggested that obesity results in hypertrophy of adipose tissue. The release of adiopocytokines leads to excessive immune cell recruitment with lymphocyte predominance [12,31]. Hypertrophic adipocytes increase the expression of pro-inflammatory cytokines and activate CD8+ cytotoxic T lymphocytes and CD4+ helper T cells, but not T_{reg} lymphocytes [32]. Our study demonstrated that these experimental results were consistent with clinical observations in breast cancer patients. In addition, the positive correlation between BMI and ALC was reconfirmed in a large healthy population. Therefore, we concluded that BMI and ALC are closely relevant. Particularly, the results regarding obesity and lymphocyte for healthy women may be relevant to other fields

of research. They may also be used to determine the effect of BMI/ALC on breast cancer development in further studies. Validation of the correlation between breast cancer occurrence and BMI/ALC in normal population might provide more specific information on the risk of breast cancer.

Our results suggest that increased BMI and ALC were not only independent prognostic factors, but their effect on breast cancer prognosis was opposite. ALC increased with the increasing BMI, but patients with high BMI/low ALC had worse DFS than those who did not. However, additional studies are necessary as the association between obesity and immune response and mechanisms underlying the effect of BMI/ALC on breast cancer prognosis are not fully understood.

Our study has some limitations. There was scope for selection bias owing to its retrospective design. Since patients with advanced breast cancer were usually treated with neoadjuvant chemotherapy in our institution, most participants in our cohort were early breast cancer patients. However, our finding that BMI and ALC are risk factors for DFS even in early breast cancer with a comparatively low recurrence rate may be meaningful. It was difficult to accurately analyze the effect of underweight on breast cancer prognosis owing to the small proportion of underweight patients in our cohort. Peripheral inflammatory cells can be affected by past history of patients including chronic disease, alcohol consumption and smoking habit. Our study did not take these variables into account. Analyzing them together in a future study could provide a clearer evidence for the prevention of breast cancer. Furthermore, measuring obesity using various techniques such as body fat measurement in addition to BMI may helpful in evaluating the association between breast cancer and obesity. Because body weight and CBC data were recorded only at the time of diagnosis, serial changes in these parameters could not be analyzed. Thus, we cannot ascertain if weight management after diagnosis is related to breast cancer prognosis.

V. CONCLUSION

In conclusion, patients with high BMI/low ALC had worse DFS than other groups. Therefore, these high-risk patients may require more careful observation and aggressive treatment. Additional studies are needed to delineate the underlying mechanisms by which BMI/ALC affect breast cancer prognosis.

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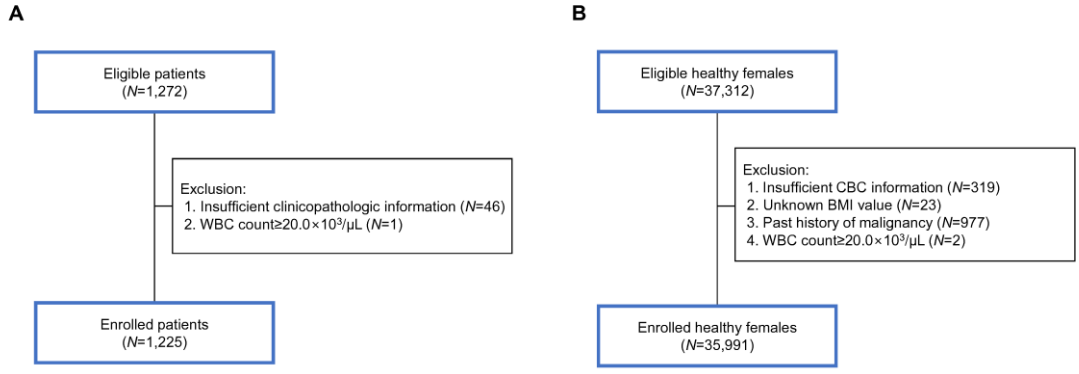
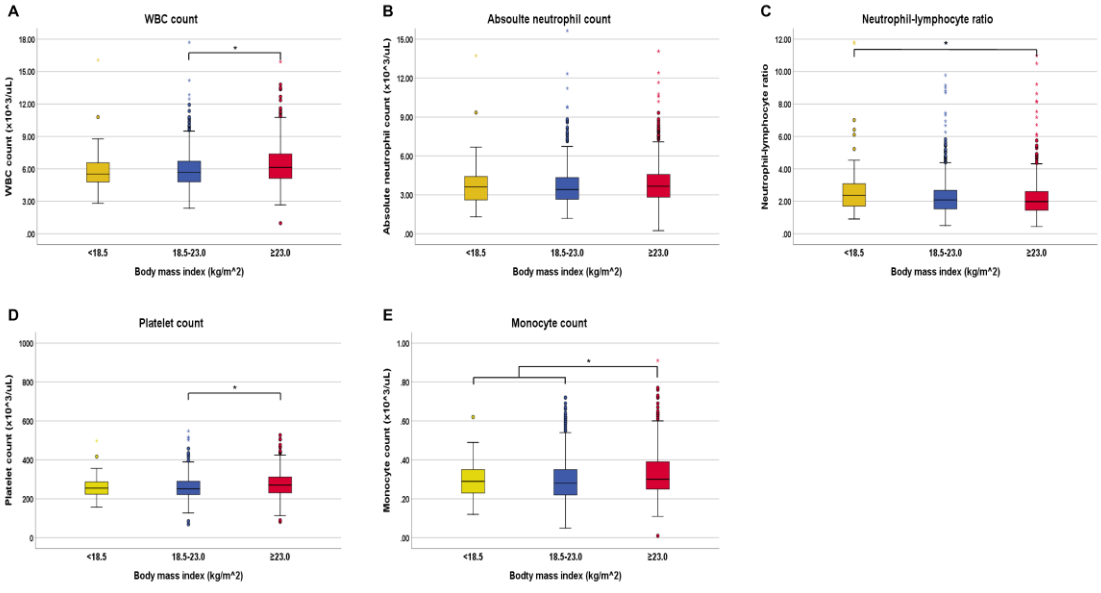
APPENDICES



Supplementary Figure S1. Flowchart of enrolled breast cancer patients and healthy females: (A) Breast cancer patients, (B) Healthy females

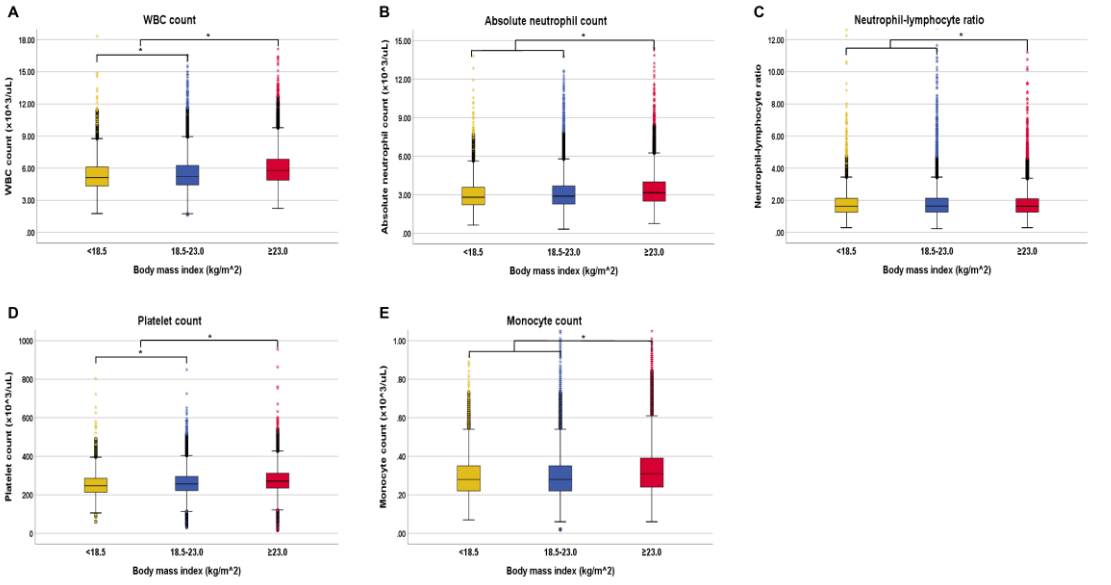
WBC, white blood cell; CBC, complete blood count; BMI, body mass index



Supplementary Figure S2. Box plot comparing CBC results according to BMI in breast cancer patients: (A) WBC count, (B) ANC, (C) NLR, (D) Platelet count, (E) Monocyte count

ANC, absolute neutrophil count; BMI, body mass index; CBC, complete blood count; NLR, neutrophil-to-lymphocyte ratio; WBC, white blood cell

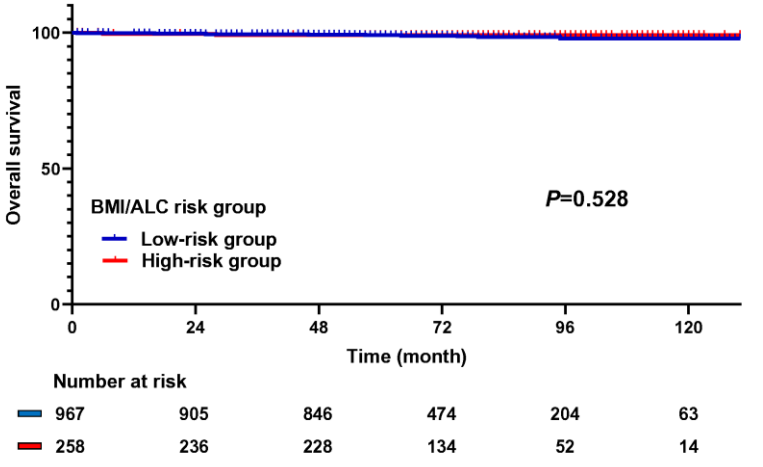
*P<0.050



Supplementary Figure S3. Box plot comparing CBC results according to BMI in healthy females: (A) WBC count, (B) ANC, (C) NLR, (D) Platelet count, (E) Monocyte count

ANC, absolute neutrophil count; BMI, body mass index; CBC, complete blood count; NLR, neutrophil-to-lymphocyte ratio; WBC, white blood cell

*P<0.050



Supplementary Figure S4. Kapan–Meier survival curve for OS according to the BMI/ALC risk stratification groups (log-rank P=0.529)

ALC, absolute lymphocyte count; BMI, body mass index; OS, overall survival

Supplementary Table S1. CBC results of breast cancer patients and healthy females

	All patients			Body mass index, kg/m^2 (%)								
				<18.5			18.5-23.0			≥23.0		
	Patients	Healthy female	*P*-value	Patients	Healthy female	*P*-value	Patients	Healthy female	*P*-value	Patients	Healthy female	*P*-value
Total	1,225	35,991		49	2,964		546	19,271		630	13,756	
(%)	(100)	(100)		(4.0)	(8.2)		(44.6)	(53.5)		(51.4)	(38.2)	
WBC*	6.16	5.66	<0.001	5.92	5.37	0.014	5.90	5.46	<0.001	6.41	6.00	<0.001
(range)	(0.98-17.70)	(1.69-19.75)		(2.81-16.06)	(1.76-19.75)		(2.36-17.70)	(1.69-19.26)		(0.98-15.90)	(2.26-17.13)	
ALC*	1.81	1.89	<0.001	1.51	1.79	<0.001	1.70	1.82	<0.001	1.92	2.02	<0.001
(range)	(0.34-4.92)	(0.33-7.18)		(0.78-2.52)	(0.51-4.30)		(0.57-3.73)	(0.33-7.18)		(0.34-4.92)	(0.54-5.67)	
ANC*	3.82	3.21	<0.001	3.92	3.05	<0.001	3.68	3.11	<0.001	3.93	3.39	<0.001
(range)	(0.24-15.64)	(0.24-15.64)		(1.32-13.72)	(0.64-17.61)		(1.20-15.64)	(0.33-17.61)		(0.24-14.06)	(0.76-14.40)	
NLR	2.34	1.80	<0.001	2.97	1.83	<0.001	2.37	1.82	<0.001	2.27	1.78	<0.001
(range)	(0.44-36.47)	(0.24-23.98)		(0.91-11.82)	(0.30-15.51)		(0.51-15.02)	(0.24-20.72)		(0.44-36.47)	(0.30-23.98)	
Monocyte*	0.32	0.31	0.413	0.30	0.29	0.947	0.30	0.30	0.702	0.32	0.33	0.360
(range)	(0.01-1.18)	(0.02-1.61)		(0.12-0.62)	(0.07-1.37)		(0.05-0.72)	(0.02-1.22)		(0.01-1.18)	(0.06-1.61)	
Platelet*	266.6	266.6	0.990	261.2	253.4	0.370	258.2	261.5	0.186	274.4	276.5	0.392
(range)	(69.0-548.0)	(17.0-955.0)		(158.0-498.0)	(61.0-803.0)		(69.0-548.0)	(32.0-849.0)		(82.0-527.0)	(17.0-955.0)	

*$\times 10^3$/uL

ALC, absolute lymphocyte count; ANC, absolute neutrophil count; CBC, complete blood count; NLR, neutrophil-to-lymphocyte ratio; WBC, white blood cell

Supplementary Table S2. Surgery and adjuvant treatment for breast cancer patients

	Body mass index, kg/m^2 (%)				*P*-value
	All patients	<18.5	18.5–23.0	≥23.0	
Breast surgery					0.587
Total mastectomy	556 (45.4)	25 (51.0)	252 (46.2)	279 (44.3)	
Breast conserving surgery	669 (54.6)	24 (49.0)	294 (53.8)	351 (55.7)	
Axillary surgery					0.465
SLNB	1007 (82.2)	43 (87.8)	452 (82.8)	512 (81.3)	
ALND	218 (17.8)	6 (12.2)	94 (17.2)	118 (18.7)	
Endocrine therapy					0.293
Not performed	379 (30.9)	14 (28.6)	172 (31.5)	193 (30.6)	
Performed	841 (68.7)	35 (71.4)	374 (68.5)	432 (68.6)	
Unknown	5 (0.4)	0 (0.0)	0 (0.0)	5 (0.8)	
Chemotherapy					0.583
Not performed	485 (39.6)	24 (49.0)	221 (40.5)	240 (38.1)	
Performed	737 (60.2)	25 (51.0)	324 (59.3)	388 (61.6)	
Unknown	3 (0.2)	0 (0.0)	1 (0.2)	2 (0.3)	
Radiotherapy					0.841
Not performed	492 (40.2)	22 (44.9)	214 (39.2)	256 (40.6)	
Performed	727 (59.3)	27 (55.1)	330 (60.4)	370 (58.7)	
Unknown	6 (0.5)	0 (0.0)	2 (0.4)	4 (0.6)	
Anti-HER2 therapy					0.257
Not performed	983 (80.2)	43 (87.8)	442 (81.0)	498 (79.0)	
Performed	235 (19.2)	6 (12.2)	103 (18.9)	126 (20.0)	
Unknown	7 (0.6)	0 (0.0)	1 (0.2)	6 (1.0)	

ALND, axillary lymph node dissection; HER2, human epidermal growth factor receptor 2; SLNB, sentinel lymph node biopsy

Supplementary Table S3. Distribution of disease events in breast cancer patients

	All patients	Body mass index, kg/m^2 (%)			Absolute lymphocyte count, ×10^3/uL (%)	
		<18.5	18.5–23.0	≥23.0	Low	High
Total event	152	5 (3.6)	48 (34.8)	85 (61.6)	88 (63.8)	50 (36.2)
Recurrence	87	5 (5.7)	31 (35.6)	51 (58.6)	56 (64.4)	31 (35.6)
Locoregional	32	2 (6.3)	12 (37.5)	18 (56.3)	24 (75.0)	8 (25.0)
Distant	55	3 (5.5)	19 (34.5)	33 (60.0)	32 (58.2)	23 (41.8)
Secondary malignancy	51	0 (0.0)	17 (33.3)	34 (66.6)	32 (62.7)	19 (37.3)
Contralateral breast cancer	6	0 (0.0)	1 (16.7)	5 (83.3)	2 (33.3)	4 (66.6)
Thyroid cancer	19	0 (0.0)	9 (47.4)	10 (52.6)	14 (73.7)	5 (26.3)
Lung cancer	14	0 (0.0)	3 (21.4)	11 (78.6)	9 (64.3)	5 (35.7)
Stomach cancer	4	0 (0.0)	2 (50.0)	2 (50.0)	2 (50.0)	2 (50.0)
Colorectal cancer	1	0 (0.0)	1 (100.0)	0 (0.0)	1 (100.0)	0 (0.0)
Other cancer	7	0 (0.0)	1 (14.3)	6 (85.7)	4 (57.1)	3 (42.9)
Death	14	1 (7.1)	8 (57.1)	5 (35.7)	10 (71.4)	4 (28.6)

Supplementary Table S4. Univariate and multivariable Cox regression analysis of OS

	Univariate analysis		Multivariable analysis	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age*	1.00 (0.94–1.04)	.686		
Body mass index				
18.5–23.0	Ref.**			
<18.5	1.40 (0.17–11.10)	0.757		
≥23.0	0.55 (0.18–1.68)	0.294		
WBC count*	1.07 (0.82–1.38)	0.629		
ALC*	0.41 (0.14–1.25)	0.116		
ANC*	1.14 (0.90–1.45)	0.264		
NLR*	1.08 (0.95–1.22)	0.249		
Histologic grade				
Low	Ref.			
Intermediate	2.69 (0.32–22.37)	0.360		
High	5.63 (0.69–45.79)	0.106		
Nuclear grade				
Low	Ref.			
Intermediate	NE	NE		
High	NE	NE		
Estrogen receptor				
Negative	Ref.			
Positive	0.54 (0.19–1.55)	0.252		
Progesterone receptor				
Negative	Ref.			
Positive	0.58 (0.20–1.64)	0.301		
HER2				
Negative	Ref.			
Positive	2.49 (0.84–7.40)	0.102		
Ki-67 LI, %				

<14	Ref.		Ref.	
≥14	8.06 (1.80–36.04)	0.006	4.64 (1.01–21.27)	0.048
Tumor size, mm				
≤20	Ref.		Ref.	
>20	11.63 (2.60–51.98)	0.001	7.77 (1.66–36.50)	0.009
Positive lymph node, count				
0	Ref.		Ref.	
1–3	0.70 (0.15–3.13)	0.657	0.50 (0.10–2.32)	0.366
≥4	5.19 (1.56–17.25)	0.007	2.09 (0.61–7.12)	0.239

*Continuous variable

**Reference value

ALC, absolute lymphocyte count; ANC, absolute neutrophil count; CI, confidence interval; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; LI, labelling index; NE, not estimated; NLR, neutrophil-to-lymphocyte ratio; Ref, reference; OS, overall survival; WBC, white blood cell

ABSTRACT(IN KOREAN)

한국인 유방암 환자의 무병 생존 기간 예측 인자로서 체질량지수 및 절대 림프구 수의 중요성

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서론 : 본 연구는 한국인 유방암 환자와 정상 여성간 체질량지수 및 절대 림프구 수 사이의 연관성을 평가했다. 또한 유방암 환자에 있어서 예후 예측 인자로서 체질량지수 및 절대 림프구 수의 활용 가치에 대해 평가했다.

연구 방법 : 강남세브란스병원 유방암센터에 등록된 1,225명의 한국인 여성 유방암 환자와 건강검진상 등록된 5,991명의 정상 여성을 대상으로 후향적 연구를 진행하였다. 진단 당시의 체질량지수 및 전체 혈구 계산 결과를 반영하였다. 무병 생존 기간과 관련된 요인은 Cox 비례 위험 모델을 사용하여 평가하였다.

결과 : 체질량지수와 절대 림프구 수는 유방암 환자 및 정상 여성 모두에서 양의 상관관계를 보였다. 다변량분석에서 과체중 혹은 비만 그룹에 속하는 유방암 환자의 경우, 저체중 혹은 정상체중 그룹보다 무병 생존 기간이 더 짧았다. 절대 림프구 수가 높은 환자군의 경우, 절대 림프구 수가 낮은 환자군에 비해 무병 생존 기간이 더 길었다. 절대 림프구 수/체질량 지수에 대한 예후 판정시, 고위험 환자군 중 높은 체질량지수 및 낮은 절대 림프구 수를 가진 경우 다른 환자들에 비해 짧은 무병 생존 기간을 가졌다. 하위 집단 분석에서 사람 표피 증식 인자 수용체-2(HER-2) 및 초기 종양군은 다른 그룹에 비해 체질량지수/절대 림프구 수의 영향을 많이 받았다.

결론 : 체질량지수와 절대 림프구 수는 양의 상관관계가 있었지만, 유방암의 예후에 미치는 영향은 정반대였다. 높은 체질량지수와 동시에 낮은 절대 림프구 수를 가진 환자들은 다른 환자들에 비해 더 짧은 무병 생존 기간 결과를 보였다. 향후 체질량지수/절대 림프구 수가 유방암의 예후에 영향을 미치는 기전에 대한 추가적인 연구가 필요하다.

핵심되는 말 : 체질량지수, 절대 림프구 수, 유방암