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Hyperglycemia during Adjuvant Chemotherapy as a Prognostic Factor in Breast Cancer Patients without Diabetes

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Conflict of Interest
The authors declare that they have no competing interests.

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ABSTRACT

Purpose: Breast cancer treatments, including chemotherapy, administered in combination with glucocorticoids can induce hyperglycemia. This study aimed to investigate the effect of hyperglycemia during adjuvant chemotherapy on the prognosis of breast cancer patients without a known history of diabetes.
Methods: In this study, 936 patients who underwent breast cancer surgery from 2010 to 2015 were initially selected as participants. Chemotherapy-related hyperglycemia was defined as fasting plasma glucose levels ≥ 100 mg/dL or random blood glucose levels ≥ 140 mg/dL during 2 or more cycles of adjuvant chemotherapy. After dividing the patients into the euglycemia and hyperglycemia groups, univariate and multivariate analyses were performed, and survival outcomes were analyzed by propensity score matching.
Results: The mean age of the patients was 47.4 ± 7.7 years, and the median follow-up period was 70.1 months. Eighty-two patients (19.4%) were diagnosed as having hyperglycemia. There were significant differences between the euglycemia and hyperglycemia groups with respect to age, hypertension, body mass index, axillary surgery extents, nodal stage, and total steroid dosage. T stage, vascular invasion, and hyperglycemia were identified as prognostic factors of relapse-free survival (RFS). The 5-year RFS rates were 92.0% and 82.3% in the euglycemia and hyperglycemia groups, respectively, and there was a statistically significant difference between the 2 groups ($p = 0.011$). The 5-year overall survival rates were 94.6% and 92.0% in the euglycemia and hyperglycemia groups, respectively, showing no statistically significant difference between the 2 groups ($p = 0.113$).
Conclusion: These data suggest that hyperglycemia during adjuvant chemotherapy is a prognostic factor for RFS in breast cancer patients without diabetes.

Keywords: Breast neoplasms; Chemotherapy, adjuvant; Hyperglycemia; Prognosis; Survival

INTRODUCTION

Various factors, such as nutritional imbalances, decreased physical activity, old age, obesity, stress, and infection, contribute to the development of hyperglycemia in cancer patients [1,2]. In addition, chemotherapeutic agents themselves and glucocorticoids used to prevent side effects of chemotherapy can cause treatment-induced hyperglycemia [3].

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Recent studies have indicated that hyperglycemia affects poor outcomes in cancer patients [1]. In particular, in patients with pancreatic, colorectal, and bladder cancer, hyperglycemia has been reported to increase short and long-term mortality and prevalence [4,5]. Hyperglycemic events during chemotherapy occur in 4%–18% of cancer patients with diabetes [4]. In cancer patients with diabetes, chemotherapy-related hyperglycemia reduces the efficacy of chemotherapeutic agents and increases the risk of chemotherapy-induced toxicities such as neutropenia and neuropathy [5,6]. The incidence of chemotherapy-related hyperglycemia in early breast cancer patients without diabetes has been reported to be 9.8% [7]; however, no study has investigated the effect of chemotherapy-related hyperglycemia on survival in breast cancer patients without diabetes. Therefore, this study aimed to investigate the effect of hyperglycemia during chemotherapy on survival in breast cancer patients without diabetes.

METHODS

Patient selection

We retrospectively analyzed 936 patients who underwent breast cancer surgery from January 1, 2010 to December 31, 2015. Of 936 patients, 423 were finally included in the analysis by excluding patients diagnosed with diabetes before surgery, those who did not undergo adjuvant chemotherapy, or those who received adjuvant chemotherapy that did not include glucocorticoids (**Figure 1**). Except for patients who died during follow-up, all patients were followed up for at least 1 year after surgery, and the median follow-up time was 70.1 months (range, 11.4–115.2 months).

Data collection

Patients' medical records were retrospectively reviewed to investigate clinicopathological data, such as gender, age at diagnosis, tumor location, operation methods, pathologic

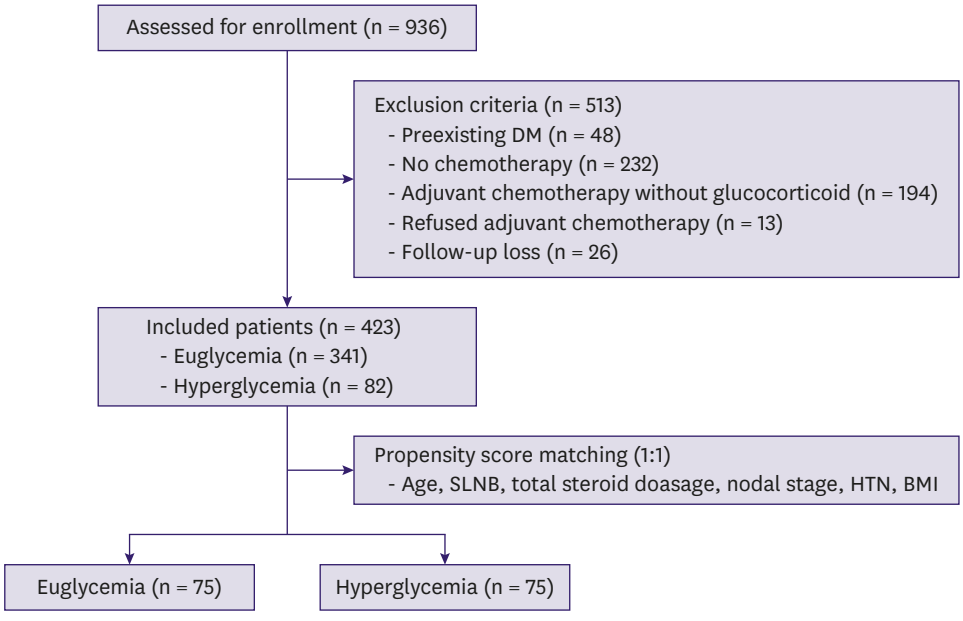

Figure 1. Flow chart of patients who met the inclusion/exclusion criteria for the study.
DM = diabetes mellitus; SLNB = sentinel lymph node biopsy; HTN = hypertension; BMI = body mass index.

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subtype, T stage, N stage, estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor-2 (HER-2) status, p53, Ki-67, radiotherapy, hormone therapy, target therapy, recurrence, and death. In addition, the total amount of glucocorticoids used for each chemotherapy regimen was examined. Moreover, hyperlipidemia, hypertension (HTN), and body mass index (BMI), which are among the signs of metabolic syndrome (MS), were investigated. ER, PR, and HER-2 levels were evaluated using standard avidin-biotin complex immunohistochemical staining methods. The ER and PR statuses were assessed based on the Allred score, which was expressed as the sum of the proportion score and the intensity score of positively stained tumor cells. Tumors with an Allred score of at least 3 were regarded as positive. The intensity of HER-2 staining was scored as 0, 1+, 2+, or 3+. Tumors with a 3+ score were classified as HER-2 positive, and tumors with a 0 or 1+ score were classified as HER-2-negative. For tumors with a 2+ score, gene amplification using silver *in situ* hybridization was performed to identify HER-2 status.

Adjuvant treatment methods

Adjuvant chemotherapy administered to patients enrolled in this study included anthracycline, cyclophosphamide, and taxane. In the anthracycline + cyclophosphamide regimen, 12 mg of IV dexamethasone was administered for each cycle. In the paclitaxel regimen, 20 mg of IV dexamethasone was administered for each cycle. In docetaxel-containing regimens, 48 mg of oral dexamethasone was administered for each cycle. Four or eight cycles of adjuvant chemotherapy were performed at 3-week intervals considering the patients' general condition and pathological stage. Intravenous glucocorticoids were administered as the pre-chemotherapy medication. Oral antiestrogen hormone medications were administered to patients with hormone receptor-positive breast cancer. For patients with HER-2-positive breast cancer, trastuzumab was intravenously administered for 1 year. In addition, among patients who underwent breast-conserving surgery or a modified radical mastectomy, radiotherapy was administered to those at a high risk for local relapse.

Definition of chemotherapy-related hyperglycemia

In all patients receiving 4 or 8 cycles of adjuvant chemotherapy, including glucocorticoids, the fasting plasma glucose level or random glucose level was measured before each cycle of chemotherapy was initiated. In this study, chemotherapy-related hyperglycemia was defined as fasting plasma glucose levels ≥ 100 mg/dL or random blood glucose levels ≥ 140 mg/dL during 2 or more cycles of adjuvant chemotherapy with reference to the criteria of impaired glucose tolerance (prediabetes) defined according to the criteria of the American Diabetes Association [8]. The patients were divided into the euglycemia and hyperglycemia groups according to blood glucose values.

Outcomes

Relapse-free survival (RFS) was defined as the duration from the date of breast cancer surgery to the recurrence at a local or regional site, occurrence of metastasis at a distant site, or a recently developed cancer at the contralateral breast. Overall survival (OS) was defined as the duration from the date of breast cancer surgery to death irrespective of the cause of death.

Statistical analysis

The χ^2 test or Fisher's exact test was conducted for categorical variables and the independent *t*-test for continuous variables. The Kaplan-Meier method and log-rank test were used for univariate survival analysis. The Cox proportional hazards model was used in univariate and multivariate analyses. Propensity score matching (PSM) of the euglycemia and hyperglycemia

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groups was performed according to age, sentinel lymph node biopsy (SLNB), total steroid dosage, N stage, HTN, and BMI. The euglycemia and hyperglycemia groups were matched at a 1:1 ratio using the nearest-neighbor method. Multivariate analysis was conducted if the *p*-value was < 0.200 in the univariate analysis. A *p*-value < 0.05 was considered statistically significant. All statistical analyses were conducted using R version 3.2.5 (Vienna, Austria; http://www.R-project.org).

Ethical approval

This study was conducted after obtaining the approval of the Institutional Review Board of Jeonbuk National University Hospital (No. 2020-02-010). The requirement for obtaining patient's informed consent was waived because this was a retrospective analysis related to the follow-up of patients with breast cancer.

RESULTS

Patient characteristics

All 423 enrolled patients were female. A summary of the clinicopathological characteristics of the patients is presented in **Table 1**. The mean age of the patients was 47.4 ± 7.7 years. Of 423 patients, 46 (10.8%) had HTN and 38 (9.0%) had hyperlipidemia. There were 266 patients (62.9%) with a BMI of 23 or higher. There were 391 patients (92.4%) diagnosed with invasive ductal carcinoma. In terms of the pathological stage, 206 patients (48.7%) were T1 cases and 194 patients (45.9%) were N0 cases. In total, 319 patients (75.4%) were ER positive and 300 (70.9%) were PR positive. Moreover, 152 patients (35.9%) were diagnosed with HER-2-positive breast cancer. Radiotherapy was administered to 363 patients (85.8%), hormone therapy to 322 patients (76.1%), and target therapy to 146 patients (34.5%). The mean amount of corticosteroids administered during chemotherapy was 12 mg in 177 patients who received 4 cycles of anthracycline + cyclophosphamide, 16 mg in 204 patients treated with 4 cycles of anthracycline + cyclophosphamide followed by 4 cycles of paclitaxel, 48 mg in 23 patients treated with 4 cycles of docetaxel + cyclophosphamide, and 30 mg in 19 patients treated with 4 cycles of anthracycline + cyclophosphamide followed by 4 cycles of docetaxel. In short, a total of 50–149 mg of glucocorticoids was administered during chemotherapy to 204 patients (48.2%).

Table 1. Patient characteristics

Characteristics	Values
Age (yr)	47.4 ± 7.7
< 50	282 (66.7)
≥ 50	141 (33.3)
Hypertension	
Yes	46 (10.8)
No	377 (89.1)
Hyperlipidemia	
Yes	38 (9.0)
No	385 (91.0)
BMI (kg/m^2)	24.4 ± 3.5
< 23	157 (37.1)
≥ 23	266 (62.9)
Tumor location	
Right	210 (49.6)
Left	213 (50.4)

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Table 1. (Continued) Patient characteristics

Characteristics	Values
Breast conserving surgery	
Yes	308 (72.8)
No	115 (27.2)
Sentinel lymph node biopsy	
Yes	215 (50.8)
No	208 (49.2)
Pathologic subtype	
Invasive ductal carcinoma	391 (92.4)
Invasive lobular carcinoma	13 (3.1)
Medullary carcinoma	5 (1.2)
Others	14 (3.3)
T stage	
T1	206 (48.7)
T2	202 (47.8)
T3	14 (3.3)
T4	1 (0.2)
N stage	
N0	194 (45.9)
N1	147 (34.8)
N2	50 (11.8)
N3	32 (7.6)
Estrogen receptor	
Positive	319 (75.4)
Negative	104 (24.6)
Progesterone receptor	
Positive	300 (70.9)
Negative	123 (29.1)
HER-2	
Positive	152 (35.9)
Negative	271 (64.1)
Vascular invasion	
Present	15 (3.5)
Absent	408 (96.5)
Lymphatic invasion	
Present	46 (10.9)
Absent	377 (89.1)
p53	
Positive	178 (42.1)
Negative	245 (57.9)
Ki67 (%)	
< 14	152 (35.9)
≥ 14	271 (64.1)
Radiotherapy	
Yes	363 (85.8)
No	60 (14.2)
Hormone therapy	
Yes	322 (76.1)
No	101 (23.9)
Target therapy	
Yes	146 (34.5)
No	277 (65.5)
Total steroid dosage (mg)	
< 50	177 (41.8)
50–149	204 (48.2)
150–249	42 (9.9)
Hyperglycemia	
No	341 (80.6)
Yes	82 (19.4)

Values are presented as mean ± standard deviation or number (%).
BMI = body mass index; HER-2 = human epidermal growth factor receptor-2.

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Differences in patient characteristics between the euglycemia and hyperglycemia groups

Hyperglycemia occurred in 82 (19.4%) out of 423 patients. There were more patients aged over 50 years ($p = 0.002$), without SLNB ($p = 0.012$), lymph node metastasis ($p = 0.025$), HTN ($p = 0.039$), and high BMI ($p = 0.001$) in the hyperglycemic group. Furthermore, there were more steroids used in the hyperglycemic group ($p < 0.001$) (**Table 2**). PSM was conducted for the euglycemia and hyperglycemia groups. After matching, the euglycemia and hyperglycemia groups had the same number of patients, with 75 patients in each group, and it was confirmed that there were no statistically significant differences in patient characteristics between the 2 groups (**Table 2**).

Table 2. The patients' characteristics before and after PSM

Characteristics	Before PSM			After PSM		
	Euglycemia (n = 341)	Hyperglycemia (n = 82)	*p*-value*	Euglycemia (n = 75)	Hyperglycemia (n = 75)	*p*-value*
Age (yr)			0.002			0.743
< 50	240 (70.4)	42 (51.2)		43 (57.3)	40 (53.3)	
≥ 50	101 (29.6)	40 (48.8)		32 (42.7)	35 (46.7)	
Hypertension			0.039			0.158
Yes	31 (9.1)	15 (18.3)		7 (9.3)	14 (18.7)	
No	310 (90.9)	67 (81.7)		68 (90.7)	61 (81.3)	
Hyperlipidemia			0.178			0.586
Yes	27 (7.9)	11 (13.4)		6 (8.0)	9 (12.0)	
No	314 (92.1)	71 (86.6)		69 (92.0)	66 (88.0)	
BMI (kg/m^2)			0.001			0.052
< 23	140 (41.1)	17 (20.7)		29 (38.7)	17 (22.7)	
≥ 23	201 (58.9)	65 (79.3)		46 (61.3)	58 (77.3)	
Tumor location			0.587			0.189
Right	172 (50.4)	38 (46.3)		46 (61.3)	37 (49.3)	
Left	169 (49.6)	44 (53.7)		29 (38.7)	38 (50.7)	
BCS			0.150			0.481
Yes	254 (74.5)	54 (65.9)		54 (72.0)	49 (65.3)	
No	87 (25.5)	28 (34.1)		21 (28.0)	26 (34.7)	
SLNB			0.012			1.000
Yes	184 (54.0)	31 (37.8)		31 (41.3)	30 (40.0)	
No	157 (46.0)	51 (62.2)		44 (58.7)	45 (60.0)	
Pathologic subtype			0.546			0.562
IDC	317 (93.0)	74 (90.2)		70 (93.3)	67 (89.3)	
Others	24 (7.0)	8 (9.8)		5 (6.7)	8 (10.7)	
T stage			0.275			1.000
T1	171 (50.1)	35 (42.7)		33 (44.0)	32 (42.7)	
≤ T2	170 (49.9)	47 (57.3)		42 (56.0)	43 (57.3)	
N stage			0.025			0.291
N0	166 (48.7)	28 (34.1)		20 (26.7)	27 (36.0)	
≤ N1	175 (51.3)	54 (65.9)		55 (73.3)	48 (64.0)	
Estrogen receptor			0.923			1.000
Positive	258 (75.7)	61 (74.4)		53 (70.7)	54 (72.0)	
Negative	83 (24.3)	21 (25.6)		22 (29.3)	21 (28.0)	
Progesterone receptor			0.654			0.600
Positive	244 (71.6)	56 (68.3)		53 (70.7)	49 (65.3)	
Negative	97 (28.4)	26 (31.7)		22 (29.3)	26 (34.7)	
HER-2			1.000			0.866
Positive	123 (36.1)	29 (35.4)		29 (38.7)	27 (36.0)	
Negative	218 (63.9)	53 (64.6)		46 (61.3)	48 (64.0)	
Vascular invasion			0.786			1.000
Present	13 (3.8)	2 (2.4)		1 (1.3)	2 (2.7)	
Absent	328 (96.2)	80 (97.6)		74 (98.7)	73 (97.3)	

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Table 2. (Continued) The patients' characteristics before and after PSM

Characteristics	Before PSM			After PSM		
	Euglycemia (n = 341)	Hyperglycemia (n = 82)	*p*-value*	Euglycemia (n = 75)	Hyperglycemia (n = 75)	*p*-value*
Lymphatic invasion			0.308			0.810
Present	34 (10.0)	12 (14.6)		9 (12.0)	11 (14.7)	
Absent	307 (90.0)	70 (85.4)		66 (88.0)	64 (85.3)	
p53			1.000			1.000
Positive	143 (41.9)	35 (42.7)		32 (42.7)	32 (42.7)	
Negative	198 (58.1)	47 (57.3)		43 (57.3)	43 (57.3)	
Ki67 (%)			0.602			0.305
< 14	120 (35.2)	32 (39.0)		23 (30.7)	30 (40.0)	
≥ 14	221 (64.8)	50 (61.0)		52 (69.3)	45 (60.0)	
Radiotherapy			0.312			0.829
Yes	296 (86.8)	67 (81.7)		63 (84.0)	61 (81.3)	
No	45 (13.2)	15 (18.3)		12 (16.0)	14 (18.7)	
Hormone therapy			1.000			0.705
Yes	260 (76.2)	62 (75.6)		58 (77.3)	55 (73.3)	
No	81 (23.8)	20 (24.4)		17 (22.7)	20 (26.7)	
Target therapy			1.000			0.865
Yes	118 (34.6)	28 (34.1)		28 (37.3)	26 (34.7)	
No	223 (65.4)	54 (65.9)		47 (62.7)	49 (65.3)	
Total steroid dosage (mg)			< 0.001			1.000
< 50	164 (48.1)	13 (15.9)		13 (17.3)	13 (17.3)	
50–149	156 (45.7)	48 (58.5)		46 (61.3)	46 (61.3)	
150–249	21 (6.2)	21 (25.6)		16 (21.3)	16 (21.3)	

PSM = propensity score matching; BMI = body mass index; BCS = breast conserving surgery; SLNB = sentinel lymph node biopsy; IDC = invasive ductal carcinoma; HER-2 = human epidermal growth factor receptor 2.
*Pearson's χ^2 test.

Univariate and multivariate analyses after PSM

A univariate analysis was conducted to identify prognostic factors for RFS, and it was found that there were statistically significant differences in T stage and hyperglycemia between the 2 groups. In multivariate analysis, hyperglycemia (hazard ratio [HR], 3.504; 95% confidence interval [CI], 1.390–8.836; $p = 0.008$), T stage (HR, 3.649; 95% CI, 1.216–10.947; $p = 0.021$), and presence of vascular invasion (HR, 5.088; 95% CI, 1.037–24.954; $p = 0.045$) were identified as independent prognostic factors (**Table 3**). The univariate analysis for OS revealed that there were statistically significant differences in BCS and T stage, but multivariate analysis did not show any significant factors (**Table 4**).

Survival analysis after PSM

Cancer recurrence occurred in 7 and 17 patients of the euglycemia and hyperglycemia groups, respectively, and the 5-year RFS rates in the euglycemia and hyperglycemia groups were 92.0% and 82.3%, respectively ($p = 0.011$, **Figure 2**). Four and 9 patients in the euglycemia and hyperglycemia groups, respectively, died, resulting in 5-year OS rates of 94.6% and 92.0%, respectively ($p = 0.113$, **Figure 3**).

DISCUSSION

Breast cancer is a very common cancer; it has the second highest incidence rate worldwide among all types of cancers and is ranked as the fifth leading cause of cancer-related mortality [9]. Among several treatment modalities for breast cancer, adjuvant chemotherapy is known to improve RFS and OS in breast cancer patients [10]. Several systemic reviews reported that preexisting diabetes increases all-cause mortality in breast cancer patients and is an independent factor of poor RFS and OS [11,12]. Hyperglycemia may develop because of chemotherapeutic agents or

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Table 3. Univariate and multivariate analyses of the RFS

Characteristics	RFS			
	Univariate		Multivariate	
	HR (95% CI)	*p*-value*	HR (95% CI)	*p*-value†
Age (≥ 50 vs. < 50 yr)	0.880 (0.390–1.990)	0.761	-	-
Hypertension (yes vs. no)	0.790 (0.240–2.650)	0.703	-	-
Hyperlipidemia (yes vs. no)	0.440 (0.060–3.310)	0.429	-	-
BMI (≥ 23 vs. < 23 kg/m^2)	0.500 (0.220–1.120)	0.090	0.477 (0.199–1.145)	0.098
Tumor location (left vs. right)	1.240 (0.560–2.760)	0.598	-	-
BCS (no vs. yes)	2.230 (1.000–4.960)	0.050	1.075 (0.433–2.665)	0.876
SLNB (no vs. yes)	1.920 (0.760–4.840)	0.168	1.569 (0.589–4.179)	0.367
Pathologic subtype (others vs. IDC)	1.160 (0.270–4.980)	0.844	-	-
T stage (≥ T2 vs. T1)	4.430 (1.510–13.010)	0.007	3.649 (1.216–10.947)	0.021
N stage (≥ N1 vs. N0)	1.440 (0.530–3.890)	0.469	-	-
Estrogen receptor (positive vs. negative)	0.600 (0.260–1.370)	0.224	-	-
Progesterone receptor (positive vs. negative)	0.700 (0.310–1.600)	0.397	-	-
HER-2 (positive vs. negative)	1.010 (0.440–2.310)	0.990	-	-
Vascular invasion (present vs. absent)	4.230 (0.980–18.250)	0.053	5.088 (1.037–24.954)	0.045
Lymphatic invasion (present vs. absent)	0.620 (0.150–2.640)	0.518	-	-
p53 (positive vs. negative)	1.030 (0.460–2.320)	0.949	-	-
Ki67 (positive vs. negative)	2.080 (0.780–5.570)	0.146	1.742 (0.623–4.875)	0.290
Radiotherapy (yes vs. no)	1.090 (0.370–3.200)	0.872	-	-
Hormone therapy (yes vs. no)	0.640 (0.280–1.510)	0.309	-	-
Target therapy (yes vs. no)	1.100 (0.480–2.530)	0.819	-	-
Hyperglycemia (yes vs. no)	2.970 (1.220–7.220)	0.016	3.504 (1.390–8.836)	0.008

RFS = relapse-free survival; HR = hazard ratio; CI = confidence interval; BMI = body mass index; BCS = breast conserving surgery; SLNB = sentinel lymph node biopsy; IDC = invasive ductal carcinoma; HER-2 = human epidermal growth factor receptor 2.
*Kaplan-Meier survival estimates compared by log-rank test; †Cox proportional hazards model.

Table 4. Univariate and multivariate analyses of the OS

Characteristics	OS			
	Univariate		Multivariate	
	HR (95% CI)	*p*-value*	HR (95% CI)	*p*-value†
Age (≥ 50 vs. < 50 yr)	0.580 (0.180–1.900)	0.372	-	-
Hypertension (yes vs. no)	0.980 (0.750–2.130)	0.129	-	-
Hyperlipidemia (yes vs. no)	0.920 (0.120–7.140)	0.936	-	-
BMI (≥ 23 vs. < 23 kg/m^2)	0.710 (0.230–2.180)	0.553	-	-
Tumor location (left vs. right)	1.080 (0.360–3.210)	0.893	-	-
BCS (no vs. yes)	3.320 (1.080–10.180)	0.035	1.764 (0.544–5.715)	0.344
SLNB (no vs. yes)	2.020 (0.550–7.390)	0.286	-	-
Pathologic subtype (others vs. IDC)	2.230 (0.490–2.510)	0.298	-	-
T stage (≥ T2 vs. T1)	10.220 (1.330–78.770)	0.026	7.781 (0.998–60.690)	0.050
N stage (≥ N1 vs. N0)	4.530 (0.590–35.010)	0.148	4.363 (0.520–36.572)	0.175
Estrogen receptor (positive vs. negative)	0.460 (0.150–1.410)	0.128	-	-
Progesterone receptor (positive vs. negative)	0.680 (0.220–2.070)	0.493	-	-
HER-2 (positive vs. negative)	0.770 (0.240–2.510)	0.666	-	-
Vascular invasion (present vs. absent)	3.400 (0.440–26.240)	0.241	-	-
Lymphatic invasion (present vs. absent)	0.640 (0.080–4.900)	0.664	-	-
p53 (positive vs. negative)	1.240 (0.420–3.700)	0.700	-	-
Ki67 (positive vs. negative)	1.180 (0.360–3.830)	0.785	-	-
Radiotherapy (yes vs. no)	0.730 (0.200–2.670)	0.638	-	-
Hormone therapy (yes vs. no)	0.510 (0.170–1.560)	0.237	0.460 (0.150–1.407)	0.173
Target therapy (yes vs. no)	0.840 (0.260–2.730)	0.773	-	-
Hyperglycemia (yes vs. no)	2.510 (0.770–8.160)	0.126	2.775 (0.828–9.308)	0.098

OS = overall survival; HR = hazard ratio; CI = confidence interval; BMI = body mass index; BCS = breast conserving surgery; SLNB = sentinel lymph node biopsy; IDC = ninvasive ductal carcinoma; HER-2 = human epidermal growth factor receptor 2.
*Kaplan-Meier survival estimates compared by log-rank test; †Cox proportional hazards model.

glucocorticoids used to prevent side effects. Fifteen percent of breast cancer patients treated with regimens including docetaxel experienced hyperglycemic events, and 9% of patients receiving chemotherapy with doxorubicin plus cyclophosphamide developed hyperglycemia [13].

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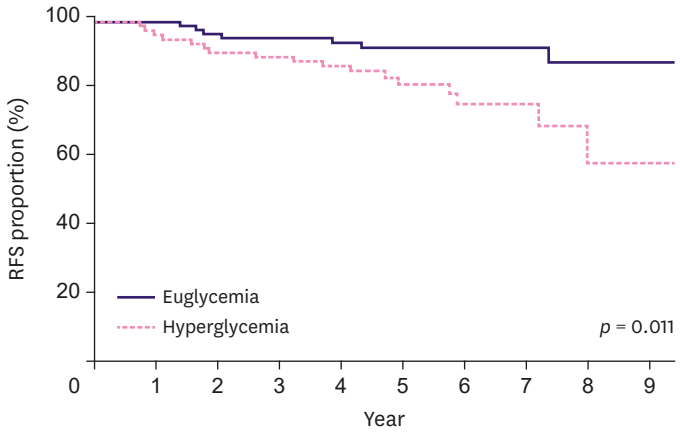

Figure 2. RFS in the euglycemia and hyperglycemia groups.
RFS = relapse-free survival.

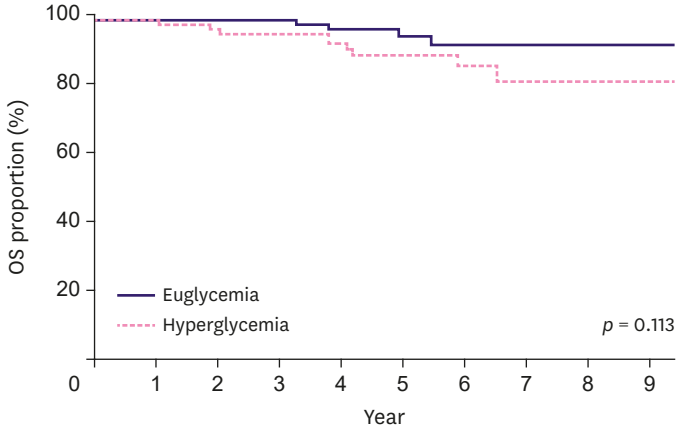

Figure 3. OS in the euglycemia and hyperglycemia groups.
OS = overall survival.

Chemotherapeutic agents cause direct toxic effects of reducing the production and release of insulin by pancreatic β-cells [1]. This functional decline in pancreatic β-cells persists even after chemotherapy is completed [14]. A previous study reported that of 24,976 postmenopausal breast cancer survivors, 9.7% were newly diagnosed with type 2 diabetes mellitus (T2DM). The study also found that patients were most often diagnosed with T2DM within 2 years of cancer treatment, and adjuvant chemotherapy was a risk factor for T2DM [15]. In this study, 10 patients (12.2%) in the hyperglycemic group had newly diagnosed T2DM after chemotherapy. Glucocorticoids used to reduce chemotherapy-induced toxicity also cause insulin resistance and hyperglycemia in the body. All patients enrolled in this study were treated with chemotherapy regimens including glucocorticoids, and the incidence of hyperglycemic events was 19.4% (82 patients). In previous studies, the incidence of hyperglycemic events in patients who received the docetaxel regimen including glucocorticoids was reported to be 13.7%–43% [13,16]. Glucocorticoid use leads to the decrease of glucose intake and increase of glucose production in muscle and adipose tissue. In addition, long-term glucocorticoid therapy has a proapoptotic effect on pancreatic β-cells, which leads to the reduction of insulin secretion. It has also been reported that when glucocorticoids are used in patients without diabetes, hyperglycemic events occur in more than 50% of patients, and after treatment using glucocorticoids, the odds ratio for diabetes is

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increased to 1.36–2.31. The hyperglycemic effects of glucocorticoids have been reported to be the greatest within 6–8 hours after glucocorticoid injection [17].

This study analyzed the association between hyperglycemia and survival during adjuvant chemotherapy in breast cancer patients without diabetes. In this study, hyperglycemia occurred in 19.4% of enrolled patients, and there were significant differences in age, HTN, BMI, SLNB, N stage, and total steroid dosage between the euglycemia and hyperglycemia groups. The 5-year RFS rates were 92.0% and 82.3% in the euglycemia and hyperglycemia groups, respectively, with the hyperglycemia group showing a statistically significantly lower rate. The 5-year OS rates were 94.6% and 92.0% in the euglycemia and hyperglycemia groups, respectively, so the 5-year OS rate was lower in the hyperglycemia group than in the euglycemia group, although there was no statistically significant difference between the 2 groups. In this regard, a retrospective cohort study of cervical cancer patients without diabetes also reported that hyperglycemia during neoadjuvant chemotherapy acted as a negative prognostic factor that reduces recurrence-free survival and cancer-specific survival [18]. Hyperglycemia was also found to be a poor prognostic factor for 5-year OS and RFS in acute lymphocytic leukemia patients without diabetes [19].

With respect to biological mechanisms based on which hyperglycemia leads to poor cancer outcomes, the following mechanisms have been reported to be involved in the association between hyperglycemia and cancer outcomes. First, in the hyperglycemic condition, the production of pro-inflammatory factors, such as interleukin-6, tumor necrosis factor-α, and cyclooxygenase-2, is increased. These factors stimulate oncogene expression, cell cycle regulation, and breast tumor cell proliferation [20]. Second, hyperglycemia increases tumor cell invasion and metastasis. In human lung epithelial cells, the expression of heme oxigenase-1 (HO-1) in cells is increased by high glucose concentrations [21]. HO-1 increases the expression of cluster of differentiation 147 and matrix metalloproteinase-9 protein, which are involved in tumor cell invasion, thereby indicting tumor cell invasion [22]. Third, hyperglycemia increases hydrogen peroxide levels *in vivo* and *in vitro*, thereby promoting the migration of cancer cells [23]. Fourth, hyperglycemia inhibits p53 apoptotic activity, thus inducing cell apoptotic resistance [24].

MS is characterized by central adiposity, insulin resistance, low serum high-density lipoprotein cholesterol, high serum triglyceride and high blood pressure, and high blood glucose levels. Several studies have reported that MS is an independent risk factor for outcomes in postmenopausal female breast cancer patients [25,26]. In this study, the proportion of patients with HTN and high BMI was statistically significantly higher in the hyperglycemia group than in the euglycemia group. These results can be attributed to the fact that risk factors for hyperglycemia, such as nutritional imbalances, obesity, stress, and infection, overlap with the characteristics or causes of MS in cancer patients. In this study, univariate and multivariate analyses performed to identify prognostic factors for RFS revealed that hyperglycemia, high N stage, and presence of vascular invasion were statistically significant prognostic factors. Except for hyperglycemia, hyperlipidemia, HTN, and high BMI, which are among the signs of MS, were not identified as prognostic factors.

This study had several limitations. First, because this study is a single-institution retrospective study, there are limitations in generalizing the results. Second, patients enrolled in this study underwent a blood glucose test to measure the serum fasting glucose level or the random glucose level once in the morning on the day when they were admitted to the hospital for

chemotherapy. Therefore, in the participants of this study, serial measurements of blood glucose levels were not performed as in normal patients with diabetes. Third, although intensive hyperglycemia control in patients with nondiabetic leukemia has been reported to improve survival outcomes of patients [27], we did not investigate whether appropriate interventions had been provided to patients with chemotherapy-related hyperglycemia included in this study. However, despite the aforementioned limitations, this study had the following major strengths. First, although many studies have been conducted on poor prognosis of hyperglycemia in breast cancer patients with diabetes, this study is the first research to investigate the prognostic role of hyperglycemia during chemotherapy in breast cancer patients without diabetes. Second, all patients enrolled in this study were treated with a uniform chemotherapy regimen. Third, the PSM method was applied to adjust for factors, such as age, N stage, and the total amount of steroids used during chemotherapy, which could affect the analysis. In the future, a well-designed multicenter prospective study should be conducted to investigate whether an active intervention in patients with chemotherapy-related hyperglycemia will contribute to the improvement of the survival rate of breast cancer patients.

In conclusion, hyperglycemia occurring during adjuvant chemotherapy in breast cancer patients without diabetes was found to be associated with poor RFS. Because hyperglycemia is a prognostic factor that can be controlled, a follow-up study should be conducted to explore methods for adequate glucose monitoring and control in patients with chemotherapy-related hyperglycemia.

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