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Patient reporting pain intensity immediately after surgery can be associated with underlying depression in women with breast cancer

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Abstract

***Objective*: The aims of this study were to determine the prevalence of severe, definite depression symptoms, as measured using the Center for Epidemiological Studies Depression Scale (CES-D), and the association between high CES-D scores (i.e., ≥25) and sociodemographic and perioperative factors during perioperative period.**

***Methods*: Among 1690 consecutive breast cancer patients who were admitted for definitive breast surgery during the study period, 1499 patients were included in this study. Patients with a past medical history of psychiatric medication or support, a plan for elective surgery due to locoregional recurrence, or any metastatic disease were excluded. The CES-D score was checked 1 day before definitive surgeries. The sociodemographic data and perioperative data were analyzed.**

***Results*: The mean CES-D score was 18.5, with 24.1% (362/1499) and 56.7% (850/1499) having high CES-D scores of ≥25 and ≥16, respectively. Multivariate analysis revealed that the number of family members with any malignancy (≥2 vs. 0), sedative medication (yes vs. no), and postoperative numeric rating scale scores (persistent, severe pain vs. stably mild pain) were significantly associated factors for severe, definite depression symptoms [CES-D score of ≥25: adjusted odds ratio (OR) = 1.56, 95% confidence interval (CI) = 1.10–2.21, $p = 0.013$; adjusted OR = 1.65, 95% CI = 1.00–2.71, $p = 0.048$; and adjusted OR = 2.14, 95% CI = 1.15–3.95, $p = 0.016$, respectively].**

***Conclusion*: Depression may increase the intensity of postoperative acute pain. Self-reporting of persistent postoperative pain intensity is potentially useful in detecting hidden depression symptoms in breast cancer patients during the perioperative period.**

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Introduction

Depression is common in breast cancer patients [1]. Although the prevalence rates of depression in cancer settings are widely debated [1,2], it is universally accepted that depression in breast cancer patients is associated with deleterious effects on the health-related quality of life [3,4] and even survival [5,6]. However, despite its importance, the ability of oncology professionals to reliably detect depression is poor [7,8]. Compared with noncancer settings, appropriate evaluation of depression in breast cancer patients can be much more difficult because of a wide range and complicated combination of symptoms: sadness, induced when faced with a diagnosis of breast cancer; pain or fatigue, induced by surgery, radiotherapy, or chemotherapy; and anxiety, which accompanies repeated threats to life [1].

Depression can occur at any time throughout the cancer course, but its occurrence during the initial period of treatment is especially important. Failure to identify depressed patients who may benefit from referral to specialist psychological services during this period can result in reduced adherence to subsequent essential but troublesome adjuvant treatments [9,10], which may be the main reason for the survival rate being worse in patients with untreated depression [11]. Although various screening tools have been developed and validated for this purpose, full screening is less likely to be adopted in busy oncology clinics dealing with this cancer population because of the associated burdens on both patients and staff, and its low cost-effectiveness. In particular, during the initial period when women are faced with a recent diagnosis of breast cancer and are awaiting breast surgery, they are understandably prone to feeling frail and unwell.

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The Center for Epidemiological Studies Depression Scale (CES-D) is a 20-item self-report scale measuring the presence and degree of depressive symptoms over the past week. Each item ranges from 0 (seldom or never) to 3 (almost always), with the total scores from 0 to 60 [12]. Although the CES-D is well established and is a valid and reliable measure of depressive symptoms in the cancer setting [13,14] and among Koreans [15–19], the 20-item version is associated with higher cost and greater staff resources and is thus not routinely used in real oncology settings. Therefore, simpler and more practicable predictors than burdensome questionnaires could be developed to guide oncology professionals so that they do not overlook or underestimate the possibility of depression, despite obstacles including a lack of clinician time, poor patient cooperation, and lack of familiarity with screening methods [20]. However, there have been few efforts to determine predictors of high-risk groups for positive screening results regarding depression immediately before or after definitive surgery for patients with breast cancer.

The aim of this study was to determine the prevalence of severe, definite depression symptoms screened using the CES-D (cutoff score, ≥25) and the associated sociodemographic factors of high CES-D scores (≥25) in women with a recent diagnosis of breast cancer who are awaiting definitive surgery. We also aimed to test the hypothesis that the pain intensity reported by patients in the immediate postoperative period is associated with underlying depression status as indicated by a previous study [21].

Methods

During the study period between November 2012 and October 2013, 1690 consecutive patients with breast cancer were admitted to the Breast Cancer Center, Asan Medical Center, Seoul, Korea. Among these, 182 patients with a past medical history of psychiatric medication or support for any diagnosis ($n=54$), a plan of elective surgery due to locoregional recurrence ($n=117$), or any metastatic disease at the time of diagnosis ($n=11$) were excluded; thus, 1508 patients were ultimately recruited into this prospective study. Among the 1508 patients initially recruited for participation, those who did not respond to at least one item in the CES-D ($n=9$) were excluded from the analysis. The final analysis included a total of 1499 patients. Neoadjuvant systemic therapy (NST) had already been administered to 271 of these patients (20.1%) at admission. Among the remainder, 148 (11.0%) had received a preoperative diagnosis of *in situ* carcinoma and 1080 (79.9%) of invasive carcinoma. Written informed consent to participate was obtained from all patients prior to surgery because of further follow-up plans for extended studies, and the study protocol (including use of the database) was approved by the Institutional Review Board of Asan Medical Center (no. 2013-1031).

The Korean language version of the CES-D, which is a 20-item self-reporting scale that had been validated for a Korean population [15–18], was employed in this study. The CES-D was administered when the patients were admitted to a ward, 1 day before they received definitive surgery. For 271 patients who had received NST, the time of administration of the CES-D was calculated as being within 6 weeks after completion of recent neoadjuvant chemotherapy. Cronbach's α for the scale was 0.87 in this study. The CES-D cutoff score of ≥25 used in the present study was found to best correspond to major depression and is regarded as indicating severe, definite depression symptoms; the need for a higher cutoff score in Asian ethnic groups due to their different response styles to positive-affect items was considered [15–18,22].

All of the patients' sociodemographic data were retrieved from our prospectively collected database. Clinical data that were generated before definitive surgeries involved planned surgery types shared preoperatively by both a patient and an operator, and presence of sedative medication (zolpidem in this study cohort) administered at each patient's request on the night before surgery. Based on the patients' perception of disease severity, we used three practical categories as a surrogate for disease extent, rather than the conventional cancer staging: carcinoma *in situ*, invasive carcinoma already receiving NST, and invasive carcinoma receiving surgery without NST. We also collected data from the patients' self-reporting on the 11-point numeric rating scale (NRS) regarding pain intensity at 1 h after operation on the surgery day [NRS on postoperative day (POD)0] and at 8 AM on the day after surgery (NRS on POD1). The NRS is based on the degree of interference with postoperative patients' function, and the collected NRS values were dichotomized according to a cutoff of 4, as follows: 0–3, no or mild pain versus 4–10, moderate or severe pain [23,24]. There was no postoperative patient-controlled analgesia; instead, postoperative pain was controlled by intravenous injection of ketorolac upon patients' requests.

Correlations between higher CES-D scores (≥25) and the variables were evaluated using the chi-square test, and the means of continuous variables such as age and CES-D scores among different groups were compared using analysis of variance. Logistic regression was used to evaluate odds ratios for each variable and to determine independent predictors for higher CES-D scores (≥25). Unless stated otherwise, the data are presented as mean ± standard deviation values, and the cutoff for statistical significance was set at $p<0.05$.

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All statistical analyses were performed using SPSS version 21.0 (SPSS, Chicago, IL, USA).

Results

Prevalence of severe, definite depression symptoms (CES-D score ≥25) and their associated factors

The age of the entire cohort ($n=1499$) was 50.3 ± 10.3 years (range, 23–85 years), and the numbers of patients with carcinoma *in situ*, invasive carcinoma already receiving NST, and invasive carcinoma planning to receive surgery without NST were 148 (9.9%), 271 (18.1%), and 1080 (72.0%), respectively. Breast-conserving surgery (BCS) was planned and performed in 1184 patients (79.0%), and total mastectomy (TM) was performed in 315 patients (21.0%). Axillary lymph node dissection (ALND) and sentinel lymph node biopsy (SLNB) were performed in 386 (25.8%) and 1036 (69.1%) patients, respectively. A sedative-hypnotic drug was administered to 77 patients (5.1%) who had never taken such drugs routinely but wanted to take such a drug to relieve their anxiety or insomnia on the night before the surgery. The pain ratings on the surgery day and the 1st day after surgery were 5.8 ± 1.7 and 2.2 ± 1.2, respectively. The number of patients with a pain rating of 4 points or more was 1338 (91.2%) on the surgery day and 201 (13.4%) on the first day after surgery. The number of patients administered with ketorolac for postoperative pain control was 1342 (89.5%). The details of the patient sociodemographic factors are summarized in Table 1.

The overall CES-D score and the proportion of patients with CES-D scores of ≥25 were 18.5 ± 9.7 (range, 0–57) and 24.1% (362/1499), respectively. Differences in mean values were statistically significant in subgroups categorized according to age at diagnosis, educational attainment, presence of current employment, current status of smoking, family history of any malignancy, and menopausal status (Table 1). The CES-D score was higher in the 45–59 years age subgroup than in those aged <45 years, and higher in patients with two or more cancer patients in their family than in those with no family history of any malignancy. Patients with higher educational levels tended to have lower CES-D scores, and a statistically significant difference in this parameter was found between the subgroup with less than high-school education and that with college education or higher. Additional subgroups with significantly higher mean CES-D scores were those with no current job, current smoking, and hysterectomy. Patients with a preoperative diagnosis of *in situ* carcinoma had significantly lower CES-D scores compared with those with invasive carcinoma, regardless of their NST experience. However, none of the aforementioned factors were significantly associated with the subgroup of patients with a CES-D score of ≥25 (Table 1).

Significantly associated factors in terms of both mean CES-D scores and proportion of patients with a CES-D score of ≥25 included surgery types, sedative medication, pain ratings on the first day after surgery, and the use of postoperative intravenous pain control (Table 1). Patients who received TM or ALND exhibited higher CES-D scores, and a higher proportion exhibited CES-D scores of ≥25. Although mean CES-D scores were higher in the ALND subgroup than in the SLNB subgroup, the difference disappeared after being stratified according to the surgery type of breast.

Higher scores and prevalence of depression were also found among patients who wanted to take sedative medication, and with a pain rating of 4 or more on the first day after surgery. In addition, patients who were administered postoperative intravenous pain control showed higher CES-D score and higher proportion in CES-D scores of ≥25.

Multivariate analysis of associated factors for CES-D scores of 25 or more

As mentioned earlier, pain ratings of ≥4 on both the surgery day and the first day after surgery were positively associated with severe, definite depression symptoms (CES-D score ≥25). Because the pain ratings on the surgery day were significantly correlated with those on the first day after surgery, we created a new variable, that of postoperative NRS score (Table 1), which comprised four subgroups: 1, stably mild pain (pain ratings of <4 on the surgery day and on the first day after surgery); 2, relieved pain (pain ratings of ≥4 on the surgery day and <4 on the first day after surgery); 3, aggravated pain (pain ratings of <4 on the surgery day and of ≥4 on the first day after surgery); and 4, persistent, severe pain (pain ratings of ≥4 on the surgery day and on the first day after surgery).

The following 10 variables were considered in the multivariate logistic regression analysis: age at diagnosis, smoking, educational level, number of family members with any malignancy, sedative medication, breast surgery type, axillary surgery type, disease extent, administration of ketorolac, and postoperative NRS score. Seven of these variables had a significant odds ratio in the univariate analysis, three of which persisted in the multivariate analysis (Table 2): postoperative NRS score, number of family members with any malignancy, and sedative medication.

Discussion

The findings of the present study suggest that the number of family members with any malignancy (≥2 vs. 0) along with sedative medication (yes versus no) preoperatively

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Table 1. Mean CES-D scores and proportions of higher CES-D score with the two cutoffs according to patients' characteristics

Variables	Number of patients (%)	CES-D score			CES-D score ≥ 25		CES-D score ≥ 16	
		Mean	SD	p^a	*N* (%)	p^b	*N* (%)	p^b
Total patients	1499 (100)	18.5	9.7		362 (24.1)		850 (56.7)	
Sociodemographic								
Age (years)				0.016		0.107		0.084
≤44	439 (29.3)	17.4[c]	9.1		96 (21.9)		230 (52.4)	
45–59	789 (52.6)	19.0[d]	10.0		208 (26.4)		465 (58.9)	
≥60	271 (18.1)	18.6[c,d]	9.7		58 (21.4)		155 (57.2)	
Marital status				NS		NS		NS
Single	113 (7.6)	18.1	9.5		30 (26.5)		55 (48.7)	
Married	1330 (88.7)	18.4	9.7		316 (23.8)		764 (57.4)	
Divorced or widowed	56 (3.7)	19.5	11.4		16 (28.6)		31 (55.4)	
Education level				0.002		0.190		0.194
Less than high school	307 (20.5)	19.8[e]	10.4		85 (27.7)		184 (59.9)	
High school	587 (39.2)	18.8[e,f]	9.5		142 (24.2)		339 (57.8)	
College or more	603 (40.3)	17.5[f]	9.5		134 (22.2)		326 (54.1)	
Unknown	2							
Religiosity				NS		NS		NS
No	518 (34.6)	18.7	9.8		123 (23.7)		299 (57.7)	
Yes	980 (65.4)	18.3	9.7		238 (24.3)		550 (56.1)	
Unknown	1							
Current job				0.013		0.202		0.122
No	918 (61.2)	18.9	9.9		232 (25.3)		535 (58.3)	
Yes	581 (38.8)	17.7	9.4		130 (22.4)		315 (54.2)	
Current smoker				0.027		0.058		0.009
No	1445 (96.6)	18.3	9.7		343 (23.7)		810 (56.1)	
Yes	51 (3.4)	21.4	9.1		18 (35.3)		38 (74.5)	
Unknown	3							
Current alcohol user				NS		NS		NS
No	1190 (79.5)	18.6	9.7		285 (23.9)		667 (56.1)	
Yes	307 (20.5)	19.3	9.8		77 (25.1)		182 (59.3)	
Unknown	2							
Personal history of any malignancy				NS		NS		NS
No	1432 (95.5)	18.4	9.8		342 (23.9)		811 (56.6)	
Yes	67 (4.5)	18.9	8.8		20 (29.8)		39 (58.2)	
No. of family members with any malignancy				0.036		0.128		0.037
0	749 (50.0)	17.9[g]	10.0		169 (22.6)		402 (53.7)	
1	531 (35.4)	18.8[g]	9.3		129 (24.3)		311 (58.6)	
≥2	219 (14.6)	19.6[h]	9.8		64 (29.2)		137 (62.6)	
BMI (kg/m^2)				NS		NS		NS
<18.5	49 (3.3)	19.1	10.0		15 (30.6)		29 (59.2)	
18.5–22.9	682 (45.5)	18.2	9.8		155 (22.7)		382 (56.0)	
23–24.9	329 (21.9)	18.5	9.4		80 (24.3)		190 (57.8)	
25–29.9	369 (24.6)	18.9	10.0		96 (26.0)		210 (56.9)	
≥30	70 (4.7)	18.0	8.9		16 (22.9)		39 (55.7)	
Menopausal status				0.049		0.457		0.126
Premenopausal	897 (59.8)	18.1[i]	9.6		217 (24.2)		500 (55.7)	
Postmenopausal	477 (31.8)	18.5[i]	10.1		109 (22.9)		268 (56.2)	
Hysterectomy	124 (8.4)	20.4[j]	8.8		35 (28.2)		81 (65.3)	
Perioperative								
Type of surgery, breast				<0.001		0.039		0.001
Breast-conserving surgery	1184 (79.0)	18.0	9.6		272 (23.0)		646 (54.6)	
Mastectomy	315 (21.0)	20.2	9.9		90 (28.6)		204 (64.8)	
Type of surgery, axilla				0.011		0.022		0.010
Axillary lymph node dissection	386 (25.8)	19.7[k]	9.7		111 (28.8)		243 (63.0)	
Sentinel lymph node biopsy	1036 (69.1)	18.0[l]	9.5		229 (22.1)		569 (54.9)	
No axillary operation	77 (5.1)	18.0[k,l]	9.9		22 (28.6)		38 (49.4)	
Disease extent				0.005		0.491		0.003

Continues

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Table 1. *Continued*

Variables	Number of patients (%)	CES-D score			CES-D score ≥ 25		CES-D score ≥ 16	
		Mean	SD	p^a	*N* (%)	p^b	*N* (%)	p^b
In situ	148 (9.9)	16.1[m]	9.5		32 (21.6)		66 (44.6)	
Invasive with NST	271 (18.1)	19.2[n]	10.1		72 (26.6)		168 (62.0)	
Invasive without NST	1080 (72.0)	18.6[n]	9.6		258 (23.9)		616 (57.0)	
Sedative medication				<0.001		0.022		<0.001
No	1422 (94.9)	18.2	9.7		50 (3.5)		790 (55.6)	
Yes	77 (5.1)	22.5	9.9		27 (35.1)		60 (77.9)	
NRS POD0				0.025		0.051		0.017
<4	129 (8.8)	16.6	9.1		22 (17.1)		60 (46.5)	
≥4	1338 (91.2)	18.6	9.8		331 (24.7)		768 (57.4)	
Unknown	32							
NRS POD1				<0.001		<0.001		0.015
<4	1297 (86.6)	18.1	9.4		291 (22.4)		720 (55.5)	
≥4	201 (13.4)	21.1	11.3		71 (35.3)		130 (64.7)	
Unknown	1							
Postoperative NRS score				<0.001		<0.001		0.006
Subgroup 1: POD0 < 4 and POD1 < 4	127 (8.7)	16.7[o]	9.2		22 (17.3)		60 (47.2)	
Subgroup 2: POD0 ≥ 4 and POD1 < 4	1144 (78.0)	18.1[o]	9.4		262 (22.9)		642 (56.1)	
Subgroup 3: POD0 < 4 and POD1 ≥ 4	1 (0.1)	14.0	NA		0 (0.0)		0 (0.0)	
Subgroup 4: POD0 ≥ 4 and POD1 ≥ 4	194 (13.2)	21.1[p]	11.4		69 (35.6)		126 (64.9)	
Unknown	33							
Postoperative intravenous pain control				0.005		0.031		0.004
No	157 (10.5)	16.4	8.7		27 (17.2)		72 (45.9)	
Yes	1342 (89.5)	18.7	9.8		335 (25.0)		778 (58.0)	

CES-D, Center for Epidemiological Studies Depression Scale; SD, standard deviation; NS, not significant (NS means that *p*-value is more than 0.1); NST, neoadjuvant systemic therapy; NRS, numeric rating scale; POD, postoperative day; POD0, the day when surgery was performed; POD1, the next day after surgery.

[a]Calculated by the *t*-test or analysis of variance.

[b]Calculated by the chi-square test.

[c–p]Means with different letters are significantly different by Tukey HSD post-hoc test.

Table 2. Multivariate analysis of associated factors for higher CES-D scores

Variables	Severe, definite depression symptoms (CES-D ≥ 25)						Probable depression symptoms (CES-D ≥ 16)					
	Univariate			Multivariate			Univariate			Multivariate		
	OR	95% CI	*p*	Adjusted OR	95% CI	*p*	OR	95% CI	*p*	Adjusted OR	95% CI	*p*
Age at diagnosis (45–59 years vs. the others)	1.29	1.01–1.64	0.035	1.28	1.00–1.64	0.055	1.21	0.99–1.49	0.066	1.19	0.96–1.48	0.111
Current smoker (yes vs. no)	1.75	0.97–3.15	0.061	1.61	0.88–2.94	0.124	2.29	1.21–4.34	0.011	2.05	1.07–3.94	0.031
Education level (less than high school vs. college or more)	1.34	0.98–1.84	0.069	1.34	0.97–1.87	0.080	1.27	0.96–1.68	0.092	1.19	0.88–1.59	0.256
Numbers of family members with any malignancy (≥2 vs. no)	1.42	1.01–1.99	0.043	1.56	1.10–2.21	0.013	1.44	1.06–1.96	0.020	1.60	1.16–2.21	0.004
Sedative medication (yes vs. no)	1.75	1.08–2.84	0.023	1.65	1.00–2.71	0.048	2.82	1.63–4.89	<0.001	2.69	1.54–4.70	<0.001
Type of surgery, breast (mastectomy vs. breast-conserving surgery)	1.34	1.01–1.77	0.040	1.14	0.84–1.57	0.401	1.53	1.18–1.98	0.001	1.35	1.01–1.80	0.044
Type of surgery, axilla (axillary lymph node dissection vs. sentinel lymph node biopsy)	1.42	1.09–1.85	0.009	1.25	0.93–1.67	0.137	1.40	1.10–1.77	0.007	1.20	0.92–1.56	0.018
Disease extent (invasive vs. *in situ*)	1.17	0.78–1.77	0.450	1.37	0.79–2.35	0.262	1.72	1.22–2.42	0.002	1.71	1.11–2.64	0.016
Administration of ketorolac (yes vs. no)	1.60	1.04–2.47	0.033	1.30	0.79–2.15	0.300	1.63	1.17–2.27	0.004	1.38	0.93–2.05	0.108
Postoperative NRS score (persistent, severe pain vs. stably mild pain)	2.64	1.53–4.55	0.001	2.14	1.15–3.95	0.016	2.07	1.31–3.27	0.002	1.48	0.88–2.48	0.142

CES-D, Center for Epidemiological Studies Depression Scale; OR, odds ratio; CI, confidence interval; NRS, numeric rating scale.

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and the patient-reported pain intensity (persistent, severe pain versus stably mild pain) postoperatively can be associated factors for severe, definite depression symptoms (CES-D score of ≥25) in breast cancer patients awaiting definitive surgery.

In the present study population, the mean CES-D score was 18.5, and the proportions of patients with CES-D scores of ≥25 and ≥16 were 24.1% (362/1499) and 56.7% (850/1499), respectively. The reported prevalence rates of depression among breast cancer patients vary. However, while the most frequently cited estimates based on structured interviews are 5–15%, a generally higher and more variable range of 15–30% has been reported based on screening instruments [20]. Given that most of the previous studies using the CES-D implemented a cutoff for depression of ≥16, the prevalence at that cutoff was also calculated in the present study and was found to be 56.7% (850/1499; Table 1). This is 1.4–2.0 times higher than reported in the Korean general population: 27% of 2015 women aged 20–59 years with a CES-D score of ≥16 [16], and 41% of 2366 women of all ages [17]. It should be considered that the prevalence of depression in this study may be exaggerated because of the timing of CES-D, the day just before the definitive surgery, when patients can feel uneasiness attributed to upcoming surgeries. Therefore, the finding of high prevalence of depressive symptoms quantified using the CES-D in the present study is noteworthy, but the absolute values were cautiously interpreted given that they were derived during the 1-week period immediately before the definitive surgery. To the best of our knowledge, the study sample explored herein is the largest among those included in studies that have analyzed this specific period.

The aim of the present study was to determine the sociodemographic and perioperative data for predicting subgroups with high CES-D scores (≥25). Among the sociodemographic data, age at diagnosis and the number of family members with any malignancy were significant in the univariate analysis (Table 1). Depressive symptoms are reportedly more common in younger breast cancer patients than in their older counterparts [25,26]. In addition, studies that focused on younger breast cancer patients found that the prevalence of depressive symptoms was highest in the youngest age groups: 25–34 years at diagnosis in [27] and 45–49 years at the survey in [28]. However, the findings of the present study are inconsistent with these results given that the reported prevalence of depressive symptoms was the same in the youngest age group (<45 years) and the oldest age group (>60 years; Table 1). Adverse effects may be easily understood as the spillover effect of cancer history in the family on depressive symptoms experienced by relatives, but a full explanation requires further consideration of various interacting factors including bereavement [29], relationship types [30], and experienced burden levels of caregiving [31].

Among the perioperative data, presence of sedative medication, TM, ALND, presence of ketorolac administration, and postoperatively persistent, severe pain were significantly associated factors for high CES-D scores (≥25) in the univariate analysis (Table 1). Previous studies regarding the association between the surgery type and depressive symptoms are still inconclusive: no difference between TM and BCS [32], in relation to TM [33], or in relation to BCS [34]. TM resulting in impaired body image appears to cause more depression than BCS, and vice versa; patients receiving BCS would worry about the completeness of surgically removed tissue, presenting with traits of anxiety and/or neuroticism [34]. However, adjustment for other variables, as indicated in Table 1, removed the statistical significance for breast or axillary surgery types.

Patients who want to take sedatives may experience greater anxiety, which, as expected, was correlated with a higher prevalence of depressive symptoms than for those who do not. In addition to presence of sedative medication, the postoperative NRS score was found to be significantly associated factors for higher CES-D scores (≥25) in the multivariate analysis. The intensity of operation-related acute pain, as explored in the present study, can be influenced by the extent of surgery and previous preoperative chemotherapy. As expected, the mean pain ratings were significantly higher in the TM subgroup than in the BCS subgroup, irrespective of depressive symptoms, and persistent, severe pain was more prevalent in the TM and NST subgroups (data not shown). However, when stratified as depicted in Figure 1, subgroup 4 with a self-reporting persistent pain intensity had a tendency toward a higher mean CES-D score across all except the TM subgroup. This could be due to the smallness of the sample but requires further exploration in longitudinal studies. In addition, when these findings are interpreted, it needs to be considered that patients in the TM subgroup should be closely monitored for possible depression regardless of postoperative pain ratings. Possible effects of the axillary surgery type on postoperative pain rating were also considered by adding this variable in the multivariate analysis. Although the mean pain ratings were significantly higher in the ALND subgroup than in the SLNB subgroup, the difference was significant only in the BCS subgroup, not in the TM subgroup (data not shown).

This study was subject to some limitations. First, cross-sectional analysis does not inherently guarantee a causal association, but the time order of implementing CES-D and performing surgery was clear in this study. Another report supporting our finding is that, regardless of its source, presurgery emotional distress has been linked to postsurgery side effects subsequently experienced by patients, such as postsurgery pain, nausea, and fatigue [35]. Given that pain ratings measure pain intensity based on the degree of interference with patients' activities of daily

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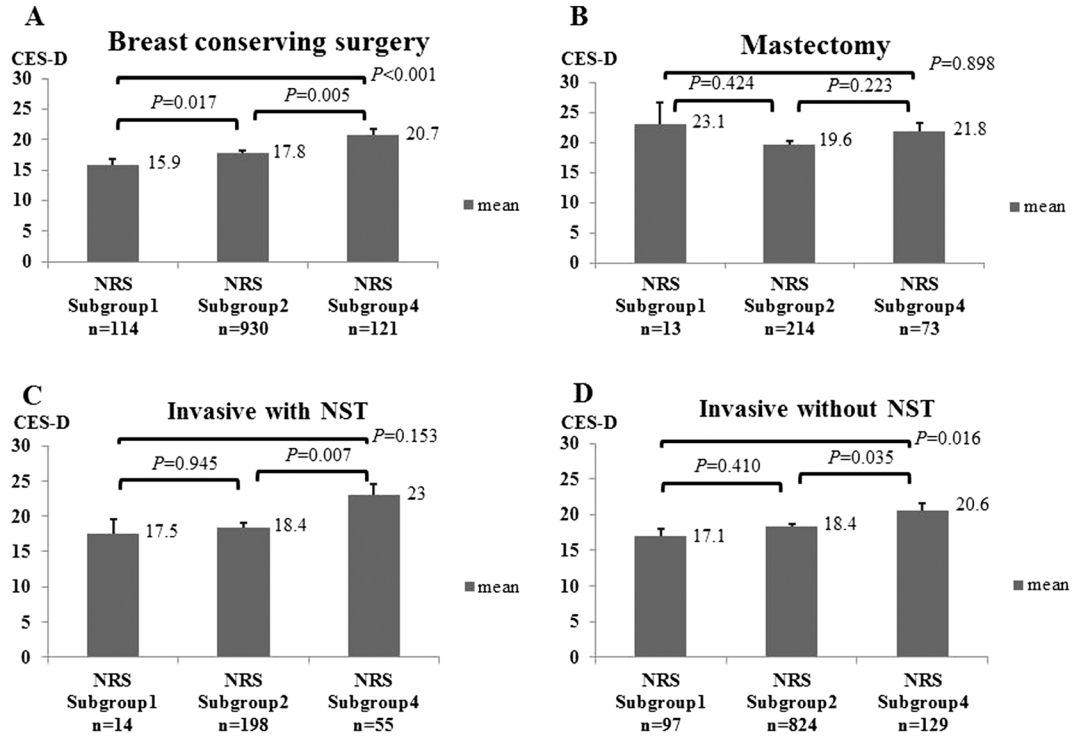

Figure 1. Comparison of mean Center for Epidemiological Studies Depression Scale (CES-D) scores among the numeric rating scale (NRS) groups. Stratification according to the surgery type (a, b) and the presence of neoadjuvant systemic therapy (NST) (c, d) revealed that NRS subgroup 4, with self-reporting persistent pain intensity, had a tendency toward higher mean CES-D scores across all except the total mastectomy subgroup. Data are mean and standard deviation values (subgroup 1, the day of surgery NRS <4 and the first day after surgery NRS <4; subgroup 2, the day of surgery NRS ≥ 4 and the first day after surgery NRS <4; subgroup 4, the day of surgery NRS ≥ 4 and the first day after surgery NRS ≥ 4)

living, we cautiously but reasonably concluded that depression increases the intensity of postoperative acute pain. Second, personality characteristics, which could potentially affect our results [36], were not considered in our study design. Third, the arbitrary dichotomization of pain ratings with a cutoff of 4 in the data analysis should also be considered. Although disputable in terms of the optimal cutoff value for higher pain ratings, this approach could be much more practicable and easier to apply in real clinical settings. Fourth, a single question such as 'Are you depressed?' may have been more appropriate for addressing the aim of this study [37], but this is not always the case with some populations given that depression can present differently, such as with low energy and concentration difficulty, and less like a depressed mood and with thoughts of death [38]. Finally, our results were obtained in breast cancer patients awaiting definitive surgery, and so, caution is necessary when attempting to generalize the results.

In conclusion, because the factors reported here are routinely measured and were focused on the earliest time point during the long cancer journey from diagnosis until definitive surgery, they could be practicably generalized and potentially useful in detecting hidden depression in breast cancer patients.

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Conflict of interest

The authors have declared no conflicts of interest.

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