



PRE-PHARMACOLOGICAL MANAGEMENT: BI-SCREENING FOR DEPRESSION AMONG BREAST CANCER PATIENTS

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Abstract – Objective: This study aimed to evaluate depression among Jordanian patients with breast cancer during the COVID-19 pandemic.

Patients and Methods: A cross-sectional study targeted female Jordanian patients with breast cancer who were receiving active treatment at King Abdullah University Hospital in Jordan. The severity of depression was assessed using the PHQ-9 scale, followed by analysis of the Brain-derived neurotrophic factor (BDNF) serum levels.

Results: A total of 300 patients participated in this study (mean age 45.3 years). Of the 300 participants, 41% (n = 123) were classified as depressed (PHQ-9 \geq 5), and 59% (n = 177) were classified as nondepressed (PHQ-9 < 5). The prevalence of depression was 41.6% according to the PHQ-9 scale. Of these, 20.8%, 66.6%, and 13.6% had mild, moderate, and severe depression, respectively. Multivariate logistic regression showed that the likelihood of depression was higher with increased age, being married, and having a higher education ($p < 0.05$). Somatic presentation of depression, mainly sleep problems and loss of energy, were the most prevalent symptoms among patients. An inverse association was found between PHQ-9 scores and BDNF levels. ROC curve analysis for BDNF serum, predicting depression, yielded the following indices: AUC = 0.737 (95% CI 0.645-0.830), with 90.1% sensitivity and 82.5% (1-specificity). Patients with mild depression had a significantly higher level of BDNF serum than those with moderate or severe depression.

Conclusions: A substantial number of Jordanian patients with breast cancer have been suffering from depression during the COVID-19 pandemic. The adoption of multiple screening approaches allows for the initiation of early management of depression.

KEYWORDS: Breast cancer, Depression, COVID-19, BDNF, PHQ-9 test, Pharmacovigilance, Jordan



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INTRODUCTION

In Jordan, the Ministry of Health announced the first COVID-19 case on March 2, 2020. Since then, and similar to other countries, the pandemic has had a profound impact on Jordanian livelihoods¹. The fear of being infected, in addition to the economic burden due to job losses, may initiate negative mental health sequelae. Patients with malignant tumors may be more vulnerable and less adaptive to restrictions and have limited access to health care services². For patients with breast cancer, there are unique consequences, such as body image changes and fertility problems related to breast cancer, even among survivors³⁻⁵. Previous studies have reported a variety of perceived psychological needs among breast cancer patients' perceived psychological needs, which are affected by patients' sociodemographics, including age at diagnosis and marital status⁶⁻⁸, and clinical characteristics, including stage of cancer and exposure to chemotherapy^{9,10}.

Despite numerous reports of its high prevalence among breast cancer patients, depression remains an underdiagnosed comorbidity in patients, with major implications for patient suffering, mortality, and healthcare expenditure^{11,12}. Reasons for underdiagnosis and undertreatment may include social stigma, poor understanding of its implications, and lack of familiarity with antidepressants^{13,14}. The implementation of a screening protocol is an inevitable starting point to tackle this health problem. The Patient Health Questionnaire (PHQ-9) has been validated in several clinical studies for screening for depression, including studies among patients with breast cancer^{15,16}. It includes items related to somatic symptoms, such as loss of energy, sleep problems, and loss of appetite, and symptoms of emotional distress, such as self-blame, loss of pleasure, and feeling hopeless¹⁷. Additionally, the PHQ-9 scale makes it possible to stratify the tested population into groups according to the severity of the depression, recommending measures that range from initiating close monitoring to offering immediate pharmacotherapy or psychotherapy¹⁸. In parallel, implementing biomarker testing can be useful. Brain-derived neurotrophic factor (BDNF) is the most abundant neurotrophin in the brain and periphery and is the most documented single predictor of depression¹⁸⁻²⁰. Several clinical studies have revealed decreased BDNF serum levels in depressed patients, which have been correlated with the severity of symptoms found in patients with suicidal ideation^{21,22}. In this study, we conducted a PHQ-9 screening test to determine the prevalence and predictors of depression, followed by an analysis of BDNF serum protein levels in Jordanian breast cancer patients during the COVID-19 pandemic.

PATIENTS AND METHODS

Study participants and setting

This cross-sectional study included 300 patients with breast cancer who were receiving active treatment at King Abdullah University Hospital in Irbid (Jordan) between January and March 2021. This hospital provides radiotherapy and chemotherapy services and accepts referrals from all over the country. Data on patients' demographics and clinical characteristics were collected. Written informed consent was obtained from all participants. The study protocol was approved by the Institutional Review Board (IRB) (Ref. No. 2281-1-13).

Assessment of depression

Depression was assessed using the PHQ-9 questionnaire (*Supplementary Table 1*). The response categories were based on the frequency of the PHQ-9 items over a 2-week period. Scores of 0, 1, 2, and 3 were assigned to the response categories of "not at all," "several days," "more than half the days," and "nearly every day," respectively. The severity of depression was assessed by the PHQ-9 scale, with scores of ≥ 5 , ≥ 10 and ≥ 15 representing mild, moderate, and severe levels of depression, respectively. The principal investigator monitored the data quality and supervised the data collection process. Although the PHQ-9 was originally written in English, a published translated Arabic version of the test is available (MMHRC). It was revised to assure clarity prior to use in the current study.

Analysis of BDNF serum levels

Based on PHQ-9 scores, participants were classified into nondepressed and depressed patients. This was followed by a sub-classification of depressed patients according to severity level (mild, moderate, and severe). Serum samples were collected into serum separator tubes from an equal number of patients in each group and processed within two hours of collection. Following clot formation, samples were centrifuged at 1200 g for 10 minutes at room temperature and the serum transferred to a 15 mL polypropylene tube. Serum samples underwent further centrifugation at 1800 g for 10 minutes at room temperature and were then stored in aliquots at -80°C until analysis by Sandwich Elisa immunoassay ultrasensitive kit (Cat#:DB01-SK00752-02), according to the manufacturer's instructions (Aiscera Bioscience Inc., Santa Clara, CA, USA).

Statistical analysis

The data obtained was entered in Microsoft Excel 2016 (Microsoft Corporation, Albuquerque, NM, USA) and analyzed using the statistical package SPSS (Version 21.0, Armonk, NY, USA). Analytical methods included univariate descriptive statistics for all participants. To compare depressed and non-depressed patients, we used the 2-sample *t*-test for continuous variables and Pearson's chi-square test for categorical variables. Multivariate stepwise logistic regression was used to determine the predictors of depression. Mann-Whitney tests were used to determine any differences in BDNF serum concentrations between nondepressed and depressed breast cancer patients. The Kruskal-Wallis with Dunn's multiple comparison test were used to determine any difference between depressed breast cancer patients' BDNF serum concentrations stratified by the severity of depression (PHQ-9) test. The receiver operating characteristic (ROC) curve was generated to de-

termine the performance of BDNF as a diagnostic marker for depression. The statistical significance was defined at $p < 0.05$.

RESULTS

Prevalence of depression among breast cancer patients

A total of 300 females participated in this study (mean age 45.3 years; $S.D = 7.4$). The majority of participants were married (91%), living in a city (75%), and nearly 85% were unemployed. More than half of participants (57%) had a higher education. Furthermore, 31.0%, 51.6%, and 17.3% had been diagnosed with stage I, II, and III, respectively. Almost 79% received chemotherapy treatment (**Table 1**).

Of the 300 participants, 41% ($n = 123$) were classified as depressed (PHQ-9 ≥ 5), and 59% ($n = 177$) were classified as nondepressed (PHQ-9

TABLE 1. Sociodemographic/Clinical characteristics and prevalence of depression.

	All Patients ($n=300$) N (%)	Non-depressed ($n=177$) N (%)	Depressed ($n=123$) N (%)	p-value
Age group				
30-39	103 (34.3)	79 (44.6)	24 (19.5)	0.001
40-49	105 (35.0)	27 (15.2)	78 (63.4)	
50-59	53 (17.6)	36 (20.3)	17 (13.8)	
≥ 60	39 (13.0)	35 (19.7)	4 (3.2)	
Marital Status				
Single	18 (6.0)	3 (1.6)	15 (12.1)	0.036
Married	273 (91.0)	72 (4.2)	101 (82.1)	
Divorced/Widowed	9 (3.0)	2 (1.1)	7 (5.6)	
Education level				
Illiterate	13 (4.3)	11 (6.2)	2 (1.6)	0.171
Elementary	52 (17.3)	25 (14.1)	27 (21.9)	
Secondary	63 (21.0)	27 (15.2)	36 (29.2)	
University	172 (57.3)	114 (64.4)	58 (47.1)	
Employment status				
Unemployed	257 (85.7)	166 (93.7)	91 (73.9)	0.241
Employed	43 (14.3)	11 (6.2)	32 (26.0)	
Place of residence				
City	225 (75.0)	173 (97.7)	82 (66.6)	0.381
Village	75 (25.0)	34 (19.2)	41 (33.3)	
Stage at diagnosis				
Stage 1	93 (31.0)	72 (40.6)	21 (17.0)	0.032
Stage 2	155 (51.6)	89 (50.2)	66 (53.6)	
Stage 3	52 (17.3)	16 (9.0)	36 (29.2)	
Chemotherapy				
Yes	238 (79.3)	152 (85.8)	86 (69.9)	0.001
No	62 (20.3)	25 (14.1)	37 (30.0)	

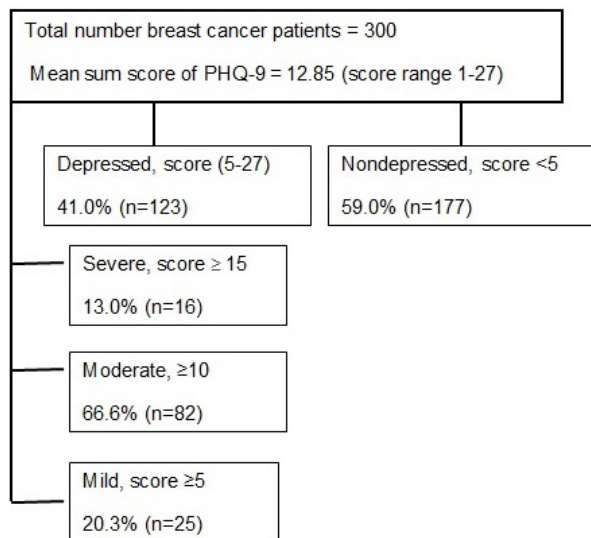


Fig. 1. Depression status among breast cancer patients

< 5). Depression was more common among patients who were married, had higher education, and were unemployed. Furthermore, depression was more common among patients who had received chemotherapy (Table 1). The majority of the depressed patients had it in a moderate severity (66.6%), followed by patients with mild (20.3%) and severe (13.0%) depression (Figure 1).

Predictors of depression among breast cancer patients

The multivariate logistic regression showed that the likelihood of depression was higher with increased age, being married, and receiving higher education. Patients who had been diagnosed at stage II or stage III were three to four times more likely to suffer from depression compared with patients who had been diagnosed at stage I. Similarly, chemotherapy treatment significantly increased the risk of depression. Occupational status and place of residence did not contribute significantly to the prediction of depression in breast cancer patients (Table 2).

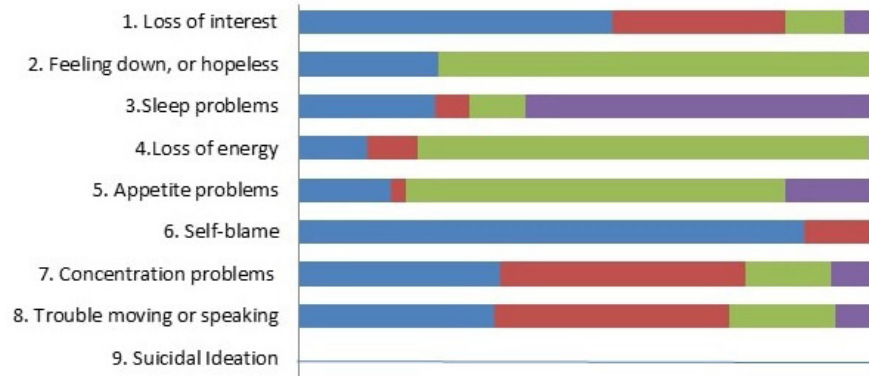
Depressive symptoms among breast cancer patients

The prevalence of depressive symptoms was based on the PHQ-9 items, which contributed to emotional or functional distress. The highest prevalence for depressive symptoms was found for items 3 (sleep problems), 4 (loss of energy), and 2 (feeling down or hopeless). Participants did not respond to item 9 (suicidal ideation) (Figure 2).

TABLE 2. Predictors of depression among breast cancer patients.

Variable	Odds ratio	95% confidence interval of adjusted OR	p-value
Marital Status			
Single	1	Ref	
Married	3.68	(1.25-5.72)	0.05
Divorced/Widowed	0.703	(0.42-1.16)	0.162
Education			
Illiterate	1	Ref	
Elementary	1.73	(0.75-3.02)	0.915
Secondary	2.62	(1.08-4.43)	0.223
University	3.87	(1.42-6.47)	0.042
Employment Status			
Unemployed	1	Ref	
Employed	0.967	(0.94-3.98)	0.241
Place of Residence			
City	1	Ref	
Village	1.7	(1.43-55)	0.321
Stage at diagnosis			
Stage1	1	Ref	
Stage 2	3.52	(2.73-7.21)	0.021
Stage3	4.631	(0.24-9.19)	0.05
Increased age	2.58	(1.32-4.47)	0.001
Received Chemotherapy	3.51	(0.95-4.56)	0.001

OR, odds ratio; 95% CI, 95% confidence interval *p<0.05.



	1. n (%)	2. n (%)	3. n (%)	4. n (%)	5. n (%)	6. n (%)	7. n (%)	8. n (%)	9. n (%)
■ Not at all	163 (54.3)	73 (24.3)	71 (23.6)	36 (12.0)	48 (16.0)	263 (87.6)	105 (35.0)	102 (34.0)	0 (0.0)
■ Several days	90 (30.0)	227 (75.6)	18 (6.0)	26 (8.6)	8 (2.6)	37 (12.3)	128 (42.6)	122(40.6)	0 (0.0)
■ More than half of the days	31 (10.3)	0 (0.0)	29 (9.6)	236 (78.6)	197 (65.6)	0 (0.0)	44(14.6)	55 (18.3)	0 (0.0)
■ Nearly everyday	16 (5.3)	0 (0.0)	182 (60.6)	3 (1.0)	47 (15.6)	0 (0.0)	23(7.6)	21 (7.0)	0 (0.0)

Fig. 2. Depressive symptoms among breast cancer patients.

Correlation of BDNF serum with PHQ-9 scores among breast cancer patients

The BDNF serum in the breast cancer patients was analyzed. A significant inverse correlation was found between PHQ-9 scores and BDNF serum (Figure 3A). A ROC curve was generated to determine the performance of BDNF as a diagnostic marker for depression. At a 95% significance level, BDNF concentrations 53.59 ng/ml identified depressed patients with 90.1% sensitivity and 82.5% (1-specificity) and the area under the curve (AUC) = 0.737 (95% CI 0.645–0.830), indicating that BDNF can be used to identify patients with depression (Figure 3B). Depressed breast cancer patients had significantly lower BDNF serum levels compared with non-depressed patients. Patients with mild depression had a significantly higher level of BDNF serum than those with moderate or severe depression. However, the level of BDNF serum in the moderately depressed group was not significantly different from that of the severely depressed group (Figure 3C).

DISCUSSION

There is a particular complexity in managing depression among cancer patients due to the nature of cancer compared with other nonneoplastic dis-

eases^{23,24}. Screening can generally succeed to a certain degree, as it identifies patients whose condition is otherwise unrecognized and untreated²⁵. To our knowledge, this is one of the first studies evaluating depression in a specific patient group during the COVID-19 pandemic in Jordan. The prevalence of depression among breast cancer patients was found to be 41%, showing an increase compared with a previous study (pre-COVID-19 pandemic), which reported a rate of 30.2%²⁶. During the time of the pandemic, a high prevalence of depression was also described among cancer patients in China (63.3%)²⁷. In the US and Hong Kong, lower rates were reported: 26.4%²⁸ and 15.2%²⁹, respectively. Differences in reported prevalence across populations can be expected due to patient-related factors, differences in the healthcare systems, and methods of depression assessment^{30,31}. In this study, over half of the patients with depression had moderate severity (66.6%). Being married, being diagnosed at an advanced stage, and receiving chemotherapy raised the risk of depression among the study population. Married patients have the advantage of the presence of a partner and presumably receive more social support through the extended family network^{32,33}. However, studies have shown that husbands of women with breast cancer reported higher scores of depression, and a poor use of problem-focused coping. In addition, the psychological adjustment

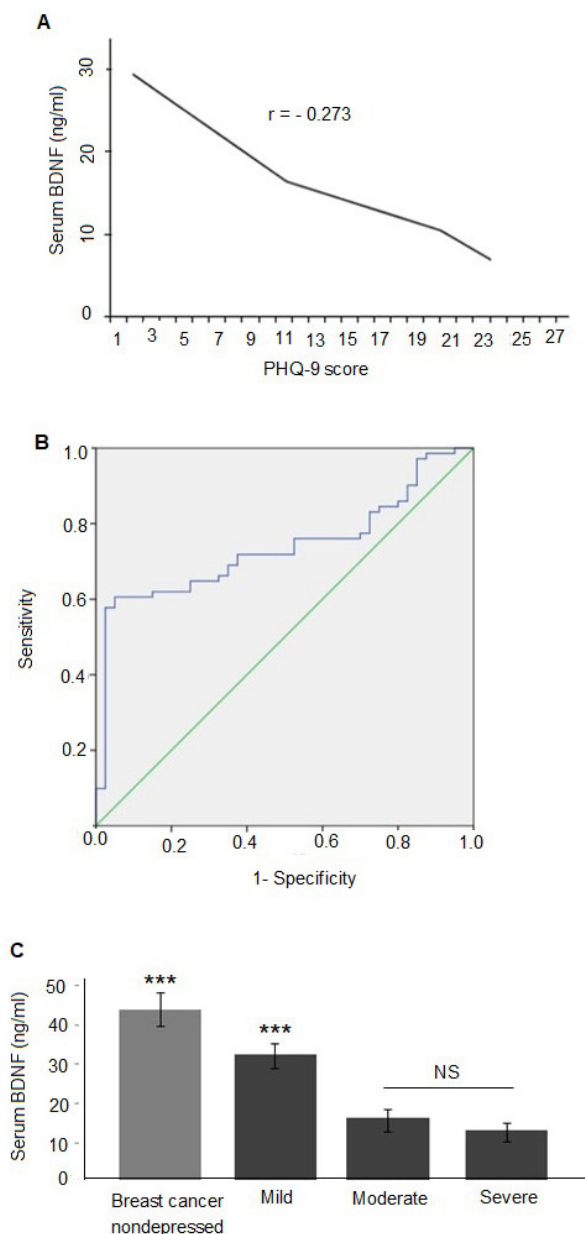


Fig. 3. A, Inverse correlation between PHQ-9 scores and BDNF serum in breast cancer patients ($r = -0.273$, $p < 0.001$). B, ROC curve for BDNF serum AUC = 0.737 (95% CI 0.645–0.830). C, Breast cancer patients with depression (mild; $n = 15$, moderate; $n = 15$, severe; $n = 15$) had lower BDNF serum compared with non-depressed patients ($n = 15$) ($p < 0.0001$). Patients with mild depression had a higher level of BDNF serum (38.532 ± 4.256 ng/ml) compared with patients with moderate (27.612 ± 4.978 ng/ml, $p < 0.0001$) and severe depression (11.742 ± 3.143 ng/ml, $p < 0.001$). The BDNF serum was not significantly different between moderate and severe depression ($p > 0.05$).

for those in distressed marriages is generally poor, especially for those with troubled relationships prior to the women's diagnoses^{34,35}.

With regards to projecting depression as the desire for death, the participants did not respond

to the PHQ-9 test item about "suicidal ideation". One possible explanation could be related to religious beliefs, which place a heavy weight on one's intentions and actions³⁶. Moreover, defining the responses to stressors in the time of the COVID-19 pandemic is a gross product of cultural beliefs regarding mental health. Access to mental health services was described as below the actual requirements with an insufficient share of total health expenditure in Jordan and other Arab countries³⁷. The implications of depression in breast cancer patients may begin at diagnosis and continue to negatively affect patients' treatment planning and outcomes³⁸. In one cohort study, only 51% of breast cancer patients with depression agreed to start chemotherapy, compared to 92% of the control group (breast cancer patients without depression)³⁹. Abu-Helalah et al⁴⁰ reported a high rate of delay in diagnosis and treatment-seeking among Jordanian women with breast cancer. The authors related such a delay, one that exceeds 12 months for some patients, to several factors, including a sense of denial and passive acknowledgement of the condition. Issues related to delay in diagnosis and treatment planning may further deepen during the time of the pandemic, due to restrictions and limited access to health care services.

In this study, depressed breast cancer patients had lower BDNF serum levels compared with nondepressed patients. Patients with mild depression had a significantly higher level of BDNF serum than those with moderate or severe depression. This supports the utility of using BDNF for identifying depressed patients who are mostly in need of psychotherapy or antidepressants. The use of a biomarker analysis may help the patient understand his or her mental condition and form a motivation to seek mental health help services. The use of BDNF serum analysis as an approach with translational potential may positively influence clinical judgments^{41,42}. Our findings showed that somatic presentation of depression, manifesting mainly in sleep problems and loss of energy, was the most prevalent symptom among patients. Patients can be reluctant to inform their providers about these symptoms, and they can be dismissed by clinicians. Previous studies have shown strong associations between depression, chronic pain, and somatic symptoms (43,44). In addition to serving as a predictor of depression, low BDNF levels may also be a mediator of depressive symptoms. Decreased BDNF has been linked to depression pathogenesis, mainly by increased pro-inflammatory cytokine levels^{45,46}. It has since been linked to a subset of depressive symptoms. Decreased BDNF concentration

is accompanied by metabolic changes, including a decrease in insulin sensitivity and glucose uptake by muscle cells; such alterations in the body-energy hemostasis can lead to tiredness and inability to perform physical activities as usual^{47,48}. Similar changes in hypothalamus-pituitary-adrenal (HPA) axis regulation were reported to explain sleep problems among depressed patients⁴⁹. Targeting BDNF has been proposed as a novel strategy in the treatment of depression. Preclinical findings provide strong evidence that BDNF mediates antidepressant pharmacological actions^{50,51}.

One of the limitations of this study is related to the fact that patients attending only one hospital were included; a multicenter collaboration can be associated with higher rates of patient enrolment. Moreover, cancer patients with severe mental health problems may stop attending hospital for cancer treatment during the period of a pandemic. Therefore, it is possible that in this study, the prevalence of depression was underestimated. The strengths of the current study include the use of a hybrid approach for depression screening. Moreover, the uniformity of the assessment allows comparison of the findings of this study with other studies.

CONCLUSIONS

This study revealed that during the COVID-19 pandemic, a substantial number of Jordanian breast cancer patients have been suffering from depression. The interrelation of the PHQ-9 and BDNF serum in the assessment of depression among breast cancer patients supports the integration of these approaches in standard cancer care.

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ETHICAL COMMITTEE:

The study was conducted according to the Institutional requirements and Helsinki Declaration.

INFORMED CONSENT:

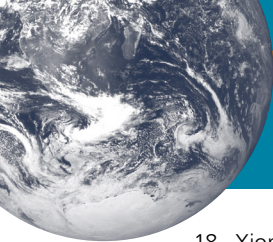
All participants in this study signed the informed consent.

CONFLICT OF INTEREST:

The Authors declare no conflict of interest

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