

Cognitive Impairment and Depression Among Breast Cancer Patients Undergoing Chemotherapy in a Tertiary Hospital

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ABSTRACT

Background

Breast cancer is the leading cause of cancer death among women worldwide. Studies showed conflicting results regarding presence of cancer, cancer treatment, and its association with dementia. Likewise, depression is often associated with cognitive problems.

Objectives

This study aims to determine the prevalence and association of cognitive impairment and depression among breast cancer patients

Methods

This is a prospective cross-sectional study utilizing Montreal Cognitive Assessment – Philippines (MOCA-P) and Patient Health Questionnaire (PHQ-9) Filipino version questionnaires through face-to-face interview. In analyzing the presence of cognitive impairment and depression, Chi-square was performed; all significant factors from this test underwent binary logistic regression to ascertain the statistical effect size for the presence of cognitive impairment and depression.

Results

Results showed that 80.8% (97 out of 120 patients) have cognitive impairment while 27.5% of the patients have depression. Among the patients with cognitive impairment, 24.2% of them had depression. Results also showed significant association between the level of education and MOCA-P score suggesting that the higher the level of education, the better the MOCA-P score. This study showed no significant association between presence of cognitive impairment and depression.

Conclusion

In analyzing and managing patients with cognitive impairment, the level of educational attainment should be put into consideration since it is correlated significantly with MOCA-P results. As such, concomitant depression should be addressed accordingly since it may affect the patients' overall health status.

Introduction

Breast cancer is the leading cause of cancer death among women worldwide.¹ Cancer and treatment-related symptoms are major stressors in patients with breast cancer undergoing treatment for the disease. Advances in cancer treatments, such as chemotherapy, have resulted in significantly

improved survival rates leading to a large and growing cohort of chemotherapy-exposed older adults. Although most cancer diagnoses originate outside the central nervous system, cancer and its treatments have been associated with significant cognitive decline. Cognitive impairment is a significant side effect of cancer and its treatments that can persist for decades or more beyond treatment cessation.² The possible mechanisms for

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chemotherapy-induced cognitive changes, include direct neurotoxic effects, DNA damage and telomere length, inflammation and cytokine deregulation, and estrogen or testosterone reduction, as well as genetic polymorphisms that may render individuals more susceptible to these effects.³ However, a population-based studies found an inverse link between cancer and dementia, that is patients with dementia having a lower risk of subsequently developing cancer, and cancer patients being less often diagnosed with dementia.⁴

Studies revealed that the depression among breast cancer patients was up to 32.2%.⁵ Depression is often associated with cognitive problems as well and is defined as sudden in onset, rapid progression, intact insight, inconsistent behavior, and depressed mood.⁶ Since this study will be looking on the presence of cognitive impairment among breast cancer patients undergoing chemotherapy, it is imperative to know its association with depression.

Review of Related Literature

It has been previously suggested that cancer and neurodegenerative disease have an inverse relationship.⁷ Ahles et al. showed that older patients tend to have poorer cognitive outcome after chemotherapy.⁸ Koppelmans et al. demonstrated that gray-matter atrophy after chemotherapy is analogous to approximately 4 years of aging on the brain.⁹ Sanoff et al. showed that elevated expression of age-related molecular markers after chemotherapy corresponds to approximately 15 years of chronological aging.¹⁰

In a study by Bender et.al., breast cancer patients who received adjuvant chemotherapy plus tamoxifen exhibited deterioration on measures of visual memory and verbal working memory and reported more memory complaints and women who received chemotherapy alone also exhibited deteriorations in verbal working memory. However, cognitive function scores were better in women who received no therapy. The study concluded that adjuvant chemotherapy

in women with breast cancer can be associated with deteriorations in memory and this may persist over time and the addition of tamoxifen may lead to more widespread memory deficits.¹¹

Chemotherapy reduces blood flow, negatively affecting brain glucose is highly toxic to neural cells especially the glial progenitor cells responsible for white matter integrity.¹² Doxorubicin commonly used in breast cancer has shown to increase peripheral ROS production thereby develop brain mitochondrial dysfunction, structural deformity and cognitive impairment in both clinical and preclinical settings.¹³ Patients underwent a chemotherapeutic regimen of doxorubicin/docetaxel along with cyclophosphamide that elevated plasma IL-1 β and IL-6 had increased cognitive abnormalities.¹⁴ Cyclophosphamide was associated with microglia induced inflammation and behavioral defects.¹⁵ Platinum-based agents (cisplatin, oxaliplatin, carboplatin etc.) disrupt protein synthesis by cross-linking the vulnerable mitochondrial DNA to irreversible mutation than nuclear DNA. These agents are neurotoxic to neuronal progenitor cell and oligodendrocytes through excitotoxic alterations and apoptotic pathway.¹⁶ Oxaliplatin upregulates glial fibrillary acidic protein (GFAP) immunodensity, TNF- α , IL-1 β , Monocyte Chemoattractant Protein- 1 (MCP-1) and Macrophage Inflammatory Protein-1 α (MIP-1 α) expression.¹⁷ Taxanes (Paclitaxel, docetaxel) cause a structural compromise in vital areas of the cerebral cortex and peripheral neurons. Mitochondria is prone to taxanes-induced damage as established in a neuropathic rodent model.¹⁸ 5-fluorouracil impairs cognition by decreasing neuronal progenitor cell proliferation in subventricular zone of the dentate gyrus.¹⁹ Cognitive impairment is an adverse reaction of cancer chemotherapy and is likely to affect up to 75% of patients during the treatment and 35% of patients experience it for several months after the chemotherapy. These patients manifest symptoms like altered working ability, awareness, concentration,

visual-verbal memory, attention, executive functions, processing speed, fatigue and behavioral dysfunctions.²⁰

A population-based study showed that patients with breast cancer were found to have a significantly lower risk of developing dementia compared with patients without breast cancer.⁷ Receipt of chemotherapy and endocrine therapy among breast cancer patients did not influence the incidence of dementia. The findings strongly suggest an inverse relationship between cancer and neurodegeneration, regardless of the adverse effects of cancer treatment on cognitive function. However, the effect of methodological biases including surveillance or survival bias has not been completely ruled out, calling into question the inverse direction of the association between cancer and dementia. In fact, emerging evidence suggests that cancer and dementia might share a positive association. Moreover, different strategies and further research are needed to be done to reduce the impact of potential biases on the association between cancer and dementia.⁷

Rationale/ Significance of the Study

This study aims to determine the prevalence of cognitive impairment and depression among breast cancer patients undergoing chemotherapy in a tertiary hospital. While there's a recent published systematic review and meta-analysis on the prevalence of cognitive impairment following chemotherapy using the use of self-report and neuropsychological tests, none of these reviewed studies uses MOCA-P (Montreal Cognitive Assessment-Philippines) which is a Filipino version of the questionnaire and no published local data regarding the presence of cognitive impairment of Filipino breast cancer patients using MOCA-P.²¹ Cancer and chemotherapy already have a significant negative impact on the patient's quality of life as well as to their family. The results of this study will not only provide pertinent data regarding the varying literature results on breast cancer and its association with cognitive impairment, but also provide

information on the healthcare provider of the prevalence of this condition thus ensuring adequate plans and timely management for the patient.

Operational Definition of Terms

1. **Cognitive Impairment.** Using the standardized **MOCA-P** (Montreal Cognitive Assessment – Philippines) questionnaire Filipino version by Dr. Dominguez et.al., breast cancer patients undergoing chemotherapy were assessed. A MOCA-P score of 21 or below is considered as cognitively impaired. Two points were added to the MoCA-P score for those breast cancer patients with ≤ 7 years of education.²⁴
2. **Depression** was assessed using Patient Health Questionnaire (**PHQ-9**) Filipino version by Dr. Garabiles et. al. A cut-off score of 6 and above indicates the presence of depression.²⁵
3. **Breast Cancer Stage.** In this study, staging was defined using TNM (Tumor, Node, Metastasis) staging. Stage 0 for non-invasive carcinoma in situ, and stages I through IV, which are used for invasive breast cancer, as documented on the patients' files at the tumor clinic.
4. **Radiation exposure.** Patients who underwent radiation targeted for breast cancer.
5. **Timing of Chemotherapy.** Patients who had at least one cycle of chemotherapy either neoadjuvant (chemotherapy prior surgery), adjuvant (chemotherapy after surgery), or palliative chemotherapy were included in this study.
6. **Age group.** In this study, young or early adulthood includes ages 20–39 years old, middle adulthood would be 40–59 years old, and old age includes ages 60 or above by M.E. Lachman.²³

Objectives

A. General Objective

To determine the prevalence and association of cognitive impairment and

depression among breast cancer patients in a tertiary hospital.

B. Specific Objectives

1. To determine the prevalence of cognitive impairment among breast cancer patients using the Filipino version of Montreal Cognitive Assessment (MoCA-P).
2. To determine if there is significant association between the patients' age, marital status, level of education, cancer stage, timing of chemotherapy (adjuvant, neoadjuvant or palliative), breast surgery, exposure to radiation, and the presence of cognitive impairment.
3. To determine the prevalence of depression among these breast cancer patients using Patient Health Questionnaire (PHQ-9) Filipino version.
4. To determine if there is significant association between the patients' age, marital status, level of education, cancer stage, timing of chemotherapy (adjuvant, neoadjuvant or palliative), breast surgery, exposure to radiation, and the presence of depression.
5. To determine if there is an association between cognitive impairment and depression among the breast cancer patients undergoing chemotherapy.

Methodology

A. Research Design

Prospective Cross-Sectional Study

B. Sample Size Computation

In a study done by Ng, T. et., al. a total of 166 breast cancer patients were recruited.²¹ For this study, a sample size of 117 or more patients are needed to have a confidence level of 95% that the real value is within $\pm 5\%$ of the measured value. Purposive sampling was utilized. The final number of patients included in the analysis of this study was 120.

C. Procedure

MOCA-P and PHQ-9 Filipino version questionnaires was used for the face-to-face interview of the patients which lasted for approximately 20-30 minutes per patient during the patient's regular follow up consult at the tumor clinic. All patients included in this study have completed booster doses of covid-19 vaccine. The primary authors of MOCA-P and PHQ-9 Filipino version were emailed and were asked for their permission. Demographic profile, stage of cancer, timing of chemotherapy and radiation therapy were obtained from the interview of the patients and by reviewing their medical records and charts.

D. Statistical Analysis

The data collected were encoded in Microsoft Excel version 2019. All Statistical computations were carried out using the SPSS IBM version 22 software made available last April 16, 2020. Qualitative data (marital status, educational attainment, employment status, etc. were presented as frequencies and simple percentage. Continuous data were expressed as means and standard deviations.

In determining the extent of relationship between the categorical variables, that is, the demographic profile (e.g., age, marital status, employment status, educational status) of the patients, presence of cognitive impairment and depression, a Chi-square test was performed. Likewise, all significant factors from this test (p -value < 0.05) underwent binary logistic regression (normal, not normal) to ascertain the statistical effect size for the presence of cognitive impairment and depression.

Participants

Inclusion Criteria:

1. Patients age 19 and above
2. Diagnosed with Breast Cancer regardless of stage at the tumor clinic
3. Had at least one session of any chemotherapy regimen and/or hormonal therapy
4. With or without radiation therapy exposure (except brain radiation)

Exclusion Criteria:

1. History of stroke
2. Patients with aphasia
3. Brain metastases with or without brain radiation therapy
4. Diagnosed case of anxiety disorder or those who feel anxious prior the interview

Data collection process

Letters for approval were submitted and approved by the TRB and Institutional Ethics and Review Board (IERB). After approval, patients with breast cancer currently undergoing chemotherapy at the Tumor Clinic who meet the inclusion criteria were included in the study. Consent forms were given and signed by the patients. Patients who do not consent for the study or choose to withdraw from their participation were excluded. Results and data were handled with confidentiality, collated and analyzed.

Ethical Considerations

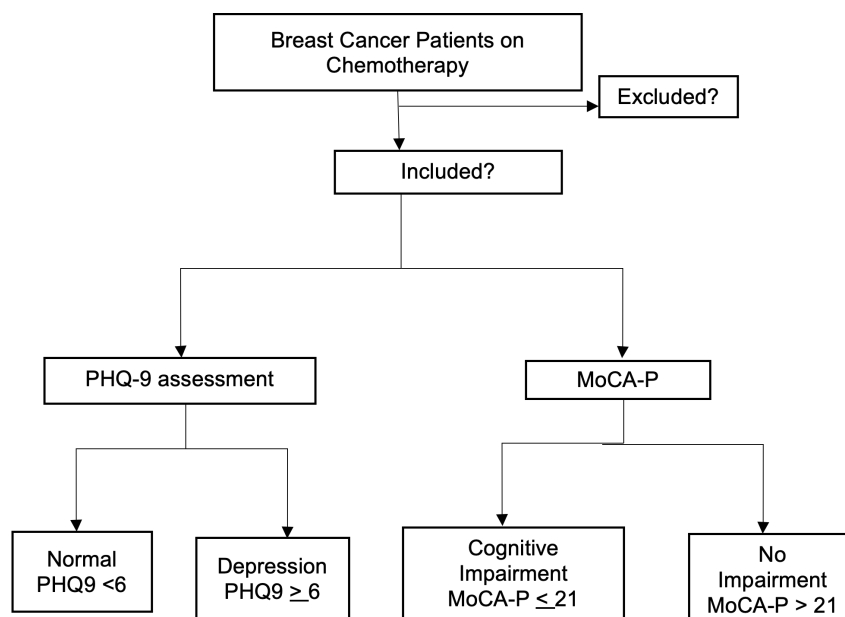
This study commenced after obtaining approval from the TRB and IERB. There is no conflict of interest in this study. Written informed consent were obtained from the patients. Physicians who handle breast

cancer patients would benefit from the results of this study and use this research as their reference. For breast cancer patients, their relatives and guardians, the results of this study would provide awareness with regards to the prevalence of cognitive impairment and depression of breast cancer patients undergoing chemotherapy and the availability of psychiatric and psychological help in the hospital. Patients with depression were advised and given referral to psychologist at the OPD for counselling. This research is presented in the research committee of the adult neurology training program and submitted for publication.

Results and Discussions

All participants in this study were female breast cancer patients undergoing chemotherapy at the tumor clinic. The prevalence rate of breast cancer patients with cognitive impairment was 80.8% (97/120 patients), signifying approximately 81 out of 100 patients had cognitive impairment. The mean age was 51.5 years old, with the youngest breast cancer patient's age of 25 and oldest age of 78 years old. A total of ninety-seven patients had cognitive impairment, and of these patients with cognitive impairment,

Figure 1. Flow Diagram of study population



majority or 52.5% were in the middle age group. Majority (60.8%, n= 73) of the patients were married. Twenty-four (20%) of the patients were single, 11 (9.2%) were widows, and 7 (5.8%) were separated. There was no significant association between MOCA-P results and marital status among breast cancer patients. Most of the patients were high school graduates (35%, n=42) and college graduates (33.3%, n=40). Sixteen (13.3%) were college level as well as elementary graduates, five (4.17%) patients were high school level. There was significant association between the level of educational attainment and MOCA-P results at p-value of 0.004. Most of the breast cancer patients were also unemployed (80.8%, n=97) where in 62.5% of them had cognitive impairment compared to 18.1% of unemployed patients without cognitive impairment. However, in this study there was no significant association between employment status and cognitive impairment. Most of the patients were on the stage 2 of their disease (51.67%, n=62). In this study, for stage 4 cancer, the usual sites of metastasis were lungs, bones, and liver. Most of the patients already underwent breast surgery (55%, n=66). Most of the patients also did not have exposure to radiation (80%, n=96) compared to those who had radiation exposure (20%, n=24). There was no significant association among patients who underwent breast surgery and/or radiation therapy with regards to presence of absence of cognitive impairment (see table 1).

In this study, since educational attainment is significantly associated with cognitive impairment, the odds that the cancer patient will have a cognitive impairment if the patient's highest educational attainment is elementary is 12.778 times than the patient that is college graduate. This signifies that elementary graduate patients are more likely than college graduate to have a cognitive impairment. Further, the odds that the cancer patient will have a cognitive impairment if the patient's highest educational attainment is high school level is 9.5 times than the patient that is a college graduate signifying that high school

level patients are more likely than college graduate to have a cognitive impairment. The likelihood that the cancer patient will have a cognitive impairment if the patient's highest educational attainment is high school graduate is 6.742 times than the patient that is college graduate suggesting that high school graduate patients are more likely than college graduate to have a cognitive impairment. Also, the likelihood that the cancer patient will have a cognitive impairment if the patient's highest educational attainment is college level is 1.267 times than the patient that is college graduate suggesting that college level patients are more likely than college graduate to have a cognitive impairment. These results show that lower educational attainment is associated with lower MOCA-P score. Further, the results suggest that the higher the level of education, the better the MOCA-P score (see table 2).

In terms of depression, 87 (72.5%) patients have no depression; the prevalence rate of depression of these breast cancer patients was 27.5% (33 patients). Some of these patients reported being hopeless, had lost interest in doing things, had trouble staying or falling sleep, and felt bad about themselves. Many of these patients felt they were a burden to their family especially that many of them had to stop working while ongoing treatment. They also expressed concern regarding the stability of their financial status and the future of their children. All patients with depression were advised referral to psychologist for counseling and given written referral forms. All of these patients were informed and appraised of the availability of the psychologist at the outpatient department who offers free counseling.

In this study, there was significant association between cancer stage and depression at p-value of 0.012. There was no significant association between age, marital status, educational attainment, employment status, timing of chemotherapy, history of breast surgery or exposure to radiation and the presence of depression. A prevalence rate of 27.5% breast cancer patients with

Table 1.Demographics and Presence or Absence of Cognitive Impairment

	No Cognitive Impairment	With Cognitive Impairment	P-VALUE
Age (n, %)			
Young Adult	1 (0.8)	13 (10.8)	0.383
Middle Age	15 (12.5)	63 (52.5)	
Old Age	7 (5.8)	21 (17.5)	
Total	23 (19.2)	97 (80.8)	
Marital Status			
Living In	0 (0)	5 (4.2)	0.395
Married	12 (10)	61 (50.8)	
Separated	2 (1.7)	5 (4.2)	
Single	5 (4.2)	19 (15.8)	
Widow	4 (3.3)	7 (5.8)	
Educational Attainment (n, %)			
Elementary Graduate	7 (5.8)	9 (7.5)	0.004*
High School Level	2 (1.7)	3 (3.3)	
High School Grad	11 (9.2)	31 (25.8)	
College Level	1 (0.8)	15 (12.5)	
College Grad	2 (1.7)	38 (31.7)	
Employment Status			
Employed	1 (0.8)	12 (10)	0.236
Retired	0 (0)	8 (6.7)	
Self Employed	0 (0)	2 (1.7)	
Unemployed	22 (18.3)	75 (62.5)	
Stage of Cancer (n, %)			
Stage 2	9 (7.5)	22 (18.3)	0.206
Stage 3	11 (9.2)	51 (42.5)	
Stage 4	3 (2.5)	24 (20.0)	
Timing of chemotherapy			
Adjuvant	8 (6.7)	38 (31.7)	0.473
Neoadjuvant	9 (7.5)	32 (26.7)	
Both Neoadjuvant and Adjuvant	4 (3.3)	9 (7.5)	
Palliative	2 (1.7)	18 (15.0)	
Breast surgery			
Yes	13 (10.8)	53 (44.2)	0.870
No	10 (8.3)	44 (36.7)	
Radiation			
Yes	5 (4.2)	19 (15.8)	0.817
No	18 (15.0)	78 (65.0)	

* Significant at p value <0.05

Table 2. Odds Ratio and Confidence Interval Results

Educational Attainment	No Cognitive Impairment	With Cognitive Impairment	Odds (CI)
Elementary Graduate	7 (5.8)	9 (7.5)	14.778 (2.616-83.465)
High School Level	2 (1.7)	3 (3.3)	9.5 (1.038-86.968)
High School Grad	11 (9.2)	31 (25.8)	6.742 (1.389-32.717)
College Level	1 (0.8)	15 (12.5)	1.267 (0.107-15.031)
College Grad	*	*	*

*Reference group

depression signify approximately 28 out of 100 breast cancer patients had depression (see table 3).

These results are comparable to the results of the study by Balouchi et. Al., which showed to be up to 32.2%⁵ and in the recent study by Que et. al., in the Philippines which showed 22% of cancer patients have depression.²⁶ Additionally, in this study, out of the 97 (80.8%) patients with cognitive impairment, 29 (24.2%) of these cognitively impaired patients had depression. Although there is no significant association between cognitive impairment and depression, the results of this study provide insights and provide additional data for us healthcare providers to prioritize, screen and address the mental health issues especially that the presence of depression among these cancer patients is quite high (see table 4).

In this study, since cancer stage is significantly associated with depression, the odds that the cancer patient will develop depression if the patient has a stage 2 stage cancer is 0.688 times than the patient with stage 4 cancer. For patients with stage 2 cancer (compared to stage 4 cancer patient), the odds of developing depression would be expected to decrease by a factor of 0.688 given the other variables in the model are held constant. Patients with stage 2 cancer are less likely than patient with stage 4 cancer to develop depression (see table 5). The likelihood that the cancer patient will develop depression if the patient has a stage 3 cancer is 0.24 times than the patient with stage 4 stage cancer. This signify that the likelihood

for patients with stage 3 cancer relative to stage 4 breast cancer patient to develop depression would be expected to decrease by a factor of 0.24, implying that patients with stage 3 cancer are less likely than patients with stage 4 cancer to develop depression (see table 5). These findings suggest that the higher the cancer stage, the more vulnerable to develop depression compared to earlier stages of breast cancer.

Conclusion

This study showed that there is a high prevalence of cognitive impairment among breast cancer patients undergoing chemotherapy with an overall rate of 80.8%. Results showed that majority of the patients were in the middle age group, married, and mostly finished high school or college, and majority had stage 3 breast cancer. There was no significant correlation between the timing of chemotherapy given with regards to the presence of cognitive impairment. This study supports Oh J, Lee study results which showed that receipt of chemotherapy and endocrine therapy among breast cancer patients did not influence the incidence of dementia. This study further suggests that regardless of cancer stage and/or chemotherapy given, and even for an advanced cancer stage undergoing multiple cycles of chemotherapy, these patients may still have within normal MOCA-P results. The results showed significant association between the level of education and MOCA-P score suggesting that the higher the level of education, the better the MOCA-P score. In

Table 3. Demographics and Depression

	Without Depression	With Depression	P-VALUE
Age (n, %)			
Young Adult	9 (7.5)	5 (4.2)	0.380
Middle Age	55(45.8)	23 (19.2)	
Old Age	23 (19.2)	5 (4.2)	
Total	87 (72.5)	33 (27.5)	
Marital Status			
Living In	4 (3.3)	1 (0.8)	0.812
Married	52 (43.3)	21 (17.5)	
Separated	4 (3.3)	3 (2.5)	
Single	18 (15.0)	6 (5.0)	
Widow	9 (7.5)	2 (1.7)	
Educational Attainment (n, %)			
Elementary Graduate	12 (10)	4 (3.3)	0.76
High School Level	5 (4.2)	1 (0.8)	
High School Grad	32 (26.7)	10 (8.3)	
College Level	12 (10)	4 (3.3)	
College Grad	26 (21.7)	14 (11.7)	
Employment Status			
Employed	9 (7.5)	4 (3.3)	0.686
Retired	7 (5.8)	1 (0.8)	
Self Employed	1 (0.8)	1 (0.8)	
Unemployed	70 (58.3)	27 (22.5)	
Stage of Cancer (n, %)			
Stage 2	20(16.7)	11(9.2)	0.012*
Stage 3	52(43.3)	10(8.3)	
Stage 4	15(12.5)	10(27.5)	
Timing of chemotherapy			
Adjuvant	32 (26.7)	14 (11.7)	0.677
Neoadjuvant	32 (26.7)	9 (7.5)	
Both Neoadjuvant and Adjuvant	10 (8.3)	3 (2.5)	
Palliative	13 (10.8)	7 (5.8)	
Breast surgery			
Yes	47 (39.2)	19 (15.8)	0.727
No	40 (33.3)	14 (11.7)	
Radiation			
Yes	16 (13.3)	8 (6.7)	0.474
No	71 (59.2)	25 (20.8)	

* Significant at *p* value <0.05

Table 4. Association of Cognitive Impairment and Depression

MOCA P (n, %)	PHQ9 Score		P-VALUE
	Without Depression	With Depression	
Without cognitive impairment	19 (15.8)	4 (3.3)	0.227
With cognitive impairment	68 (56.7)	29 (24.2)	

Table 5. Odds Ratio and Confidence Interval Results

Stage of Cancer (n, %)	Without Depression	With Depression	Odds (CI)
2	20(16.7)	11(9.2)	0.688 (0.239 - 1.979)
3	52(43.3)	10(8.3)	0.24 (0.087 - 0.665)
4	*	*	*

conclusion, in analyzing and managing patients with cognitive impairment, the level of educational attainment should be put into consideration since it is correlated significantly with their MOCA-P results. In this study, results showed a 27.5% prevalence rate of breast cancer patients with depression. Results also showed that the higher the cancer stage, the higher the likelihood of developing depression, further implying that patients on advanced stage of breast cancer may be more vulnerable to develop depression compared to patient with earlier stages of breast cancer. This may imply that concomitant depression and possibly other mental issues of the patient should be addressed and managed accordingly since it can affect the patients' overall health status and their response to treatment as well as recovery from the illness.

Recommendations

Future studies may utilize or compare baseline MOCA-P prior and after chemotherapy. Other types of cancer may also be explored in terms of cognitive impairment and depression. Future researchers may explore on the presence of anxiety, depression and correlate with the presence of cognitive impairment of the patient.

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