



Executive function in breast cancer survivors and the influencing factors[☆]



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Received 13 November 2018; accepted 17 April 2019

Available online 26 June 2019

KEYWORDS

Breast cancer survivor;
Chemotherapy;
Executive function

Abstract

Objective: The objective of this study was to analyze executive function (EF) in postchemotherapy breast cancer survivors and factors that influence it.

Method: This cross-sectional study was conducted in 2 hospitals in Jakarta and Bandung, Indonesia. Respondents consisted of 82 breast cancer survivors who had completed 6 cycles of chemotherapy, 81 nonchemotherapy breast cancer survivors, and 80 noncancer female patients, who were determined by consecutive sampling. Data collection tools included patient care documentation, Trail Making Test B, Pittsburgh Sleep Quality Index, Perceived Stress Scale, and Piper Fatigue Scale. Data analysis was done using multiple logistic regression.

Results: The mean age of the respondents was 43.06 ± 8.18 years, the mean score of stress was 13.12 ± 5.55 , 81.1% of respondents had <12 years of education, 81.1% were not using hormonal therapy, 51.4% were in menopause, 62.6% did not have anemia, 51% had poor sleep quality, and 47.32% experienced mild fatigue. Furthermore, 86.6% of postchemotherapy breast cancer survivors had experienced EF impairment. Variables that had significant relationships with EF impairment were age, stress, length of education, classification of respondents, type of chemotherapy, hormonal therapy usage, menopausal status, hemoglobin level, and sleep quality.

Conclusions: It was concluded that most influencing variables that disrupt EF are chemotherapy type, age, and stress (OR 18.089, 1.138, and 1.104, respectively).

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[☆] Peer-review under responsibility of the scientific committee of the Second International Nursing Scholar Congress (INSC 2018) of Faculty of Nursing, Universitas Indonesia. Full-text and the content of it is under responsibility of authors of the article.

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Introduction

Decreased cognitive function is a phenomenon commonly found in breast cancer survivors who have received chemotherapy.¹ Study of cognitive impairment is increasing in this population,² and it is a significant research focus by health care providers.³ This phenomenon is popularly called *chemobrain* or *chemofog*.^{4,5} This problem is experienced by approximately 16–75% of breast cancer survivors after chemotherapy,⁶ but it depends on individual characteristics.⁷

One of the most complained-of cognitive problems by post-chemotherapy breast cancer survivors is the impairment of executive function (EF).⁸ EF includes three capabilities that interact with each other, including inhibitory control, working memory, and cognitive flexibility. The functions are then developed into skills such as reasoning, problem-solving, and planning capabilities.^{9,10} The advanced impact of this impairment can be in the form of rigid thinking patterns, difficulty in understanding alternative views or ideas, multitasking disturbances, difficulty in expressing ideas, reasoning disturbance, and repetitive errors. In addition, impaired language, social, cognitive, and memory skills also can be found.¹¹

The etiology of cognitive impairment due to chemotherapy is most likely caused by many factors that interact with each other, both directly and indirectly.¹² Because of contrasting information, the etiology of chemobrain has not yet been elucidated.⁴ Some of the mentioned conditions related to the decline in post chemotherapy cognitive function are the effects of chemotherapy on the central nervous system, peripheral neuropathy, anemia, fatigue, psychosocial stress, sleep disturbances, hormone changes, and other factors.^{13–15}

Indonesia has many hospitals that provide chemotherapy services. However, data on EF impairment in breast cancer survivors and its influencing factors have never been published, so discussion about this is scarce. The objective of this study was to identify EF impairment in post-chemotherapy survivors of breast cancer and its influencing factors.

Method

Design, population and setting of study

This study used a cross-sectional design. There were 243 respondents in this study, consisting of 82 post-chemotherapy breast cancer survivors, 81 non-chemotherapy breast cancer survivors, and 80 non-cancer female patients. The research was located in Fatmawati hospital, in Jakarta Special Capital Region, and Hasan Sadikin hospital in Bandung, West Java. Respondents were taken using consecutive sampling. Subjects should have completed 6 cycles of chemotherapy as an inclusion criterion to be considered post-chemotherapy breast cancer survivors. Non-chemotherapy breast cancer survivors should have received no chemotherapy. All respondents were 20–50 years old, able to read and write, and had no history of psychiatric disorders or neurological diseases.

Variables and data collection

All field investigators received training in specific neuropsychology tests, interviewing, and data recording before conducting the study. The data on the respondents' characteristic was obtained through patient care documentation. EF data was collected through a neuropsychological test, the Trail Making Test B (TMT B). The TMT is a widely used instrument in neuropsychological studies as a rapid indicator of cognitive processes and EFs.¹⁶ TMT is an adequate measurement, available independent of language, and instructions have been translated into several languages.¹⁷ TMT consisted of TMT A and B. TMT B is adequate to evaluate mental flexibility,^{18,19} and is sensitive to EFs since the test requires multiple abilities to complete.²⁰

Sleep quality data was collected through the Indonesian version of the Pittsburgh Sleep Quality Index (PSQI). Alim has tested the validity and reliability of its Indonesian version in Jakarta, resulting in a Cronbach's Alpha internal consistency result of 0.79 and a content validity score of 0.89.³¹ Construction validity showed a component correlation with a good PSQI global score. It also showed significant group validity ($p < 0.001$), with a sensitivity value of 1, specificity of 0.81, and a point of intersection of 5.³¹

Fatigue data was collected through the Piper Fatigue Scale 12 (PFS-12), which consists of 12 questions and yields a maximum score of 10. A score of 0 indicates that a subject is not tired, 1–3 indicates mild fatigue, 4–6 indicates moderate fatigue, and 7–10 indicates severe fatigue. Stress data was collected through the Perceived Stress Scale (PSS), which consists of 10 questions. Higher stress scores indicate heavier stress. Researchers have translated the instruments of stress and fatigue into Indonesian, then re-translated them into English and consulted with nursing experts. Cronbach's alpha for each of these questionnaires were 0.81 and 0.84, respectively.

Data analysis

Data analysis was performed using statistical software. The Pearson Chi Square and Fisher Exact Test were applied for comparisons of categorical variables. A *T*-test was used for two-group comparisons of continuous variables. Multiple logistic regression analysis was applied to estimate odd ratios as well as their 95% confidential intervals for variables associated with EF impairment. A *p* value of <0.05 was applied as statistically significant.

Ethical aspects

All research activities were carried out after obtaining ethical clearance from the Research Ethics Committee of the Faculty of Nursing, Universitas Indonesia, and the hospitals used as research locations. All respondents received study explanations and gave approval by signing the informed consent before data collection began.

Results

Characteristics of respondents

The amount of post-chemotherapy breast cancer survivors who experienced mild-to-serious EF impairment was approximately 71 (86.6%), and the total number of respondents with mild-to-serious EF impairment was approximately 142 (58.5%). Significant variables associated with EF were age, length of education, survivor category, chemotherapy category, hormonal therapy usage, menopausal status, hemoglobin level, sleep quality, and stress. Fatigue was not significantly related (see Table 1).

Factors affecting EF

The logistic regression equation of EF (mild-to-serious impairment) is as follows:

$$-6.202 - 1.486 * \text{education} + 1.855 * \text{types of chemotherapy (1)} + 2.133 * \text{types of chemotherapy (2)} + 2.895 * \text{types of chemotherapy (3)} - 0.664 * \text{Hb} + 0.129 * \text{Age} + 0.099 * \text{stress}.$$

The most dominant factor associated with EF is the type of chemotherapy (line 3) with an OR value of 18.089. This further explains that survivors who got chemotherapy line 3 have an 18.089-times greater risk to experience mild-to-serious EF impairment. Only 49.3% of EFs could be

Table 1 Respondent characteristics (n = 243).

	Total	Executive function		p value
		Mild-to-serious impairment	Normal	
Age, years [mean ± SD]	43.06 ± 8.18	46.01 ± 6.55	38.91 ± 8.49	0.000
Stress [mean ± SD]	13.12 ± 5.55	14.05 ± 5.44	10.42 ± 4.95	0.000
Duration of education [n (%)]				
<12 yrs	197 (81.1)	122 (61.9)	75 (38.1)	0.034
≥12 yrs	46 (18.9)	20 (43.5)	26 (56.5)	
Survivor categories [n (%)]				
Postchemotherapy	82 (33.7)	71 (86.6)	11 (13.4)	0.000
Nonchemotherapy	81 (33.3)	43 (53.1)	38 (46.9)	
Noncancer	80 (32.9)	28 (35.0)	52 (65.0)	
Chemotherapy categories [n (%)]				
First line	47 (19.3)	40 (85.1)	7 (14.9)	0.000
Second line	27 (11.1)	24 (88.9)	3 (11.0)	
Third line	8 (3.3)	7 (87.5)	1 (12.5)	
Nonchemotherapy	161 (66.3)	71 (44.1)	90 (55.9)	
Hormone therapy usage [n (%)]				
Yes	46 (18.9)	34 (73.9)	12 (26.1)	0.028
None	197 (81.1)	108 (54.8)	89 (45.2)	
Menopausal status [n (%)]				
Yes	125 (51.4)	95 (76.0)	30 (24.0)	0.000
None	118 (48.6)	47 (39.8)	71 (60.2)	
Hemoglobin level [n (%)]				
Anemia	91 (37.4)	62 (68.1)	29 (31.9)	0.025
Non-anemia	152 (62.6)	80 (52.6)	72 (47.4)	
Quality of sleep [n (%)]				
Poor	124 (51.0)	85 (68.5)	39 (31.5)	0.002
Good	119 (49.0)	57 (47.9)	62 (52.1)	
Fatigue [n (%)]				
None	10 (4.12)	3 (30.0)	7 (70.0)	0.317
Mild	115 (47.32)	68 (59.1)	47 (40.9)	
Moderate	111 (45.68)	67 (60.4)	44 (39.6)	
Severe	7 (2.88)	4 (57.1)	3 (42.9)	
Executive function	243 (100)	142 (58.5)	101 (41.5)	

Table 2 Logistic regression analysis of factors affecting executive function ($n = 243$).

Variable	<i>B</i>	<i>p</i> value	OR	95% CI	<i>R</i> square
Education	-1.486	0.001	0.226	0.093–0.553	0.493
Type of chemo (1)	1.855	0.000	6.394	2.282–17.917	
Type of chemo (2)	2.133	0.003	8.439	2.115–33.668	
Type of chemo (3)	2.895	0.016	18.089	1.709–191.460	
Hb level	-0.664	0.064	0.515	0.255–1.040	
Age	0.129	0.000	1.138	1.086–1.192	
Stress	0.099	0.003	1.104	1.033–1.179	
Constant	-6.202				

explained by length of education, type of chemotherapy, age, hemoglobin levels, and stress variables (see Table 2).

Discussion

A total of 71 (86.6%) of postchemotherapy breast cancer survivors had mild-to-serious EF impairment. EF impairment is one of the disorders that is often complained of by postchemotherapy breast cancer survivors, often manifested as difficulty in finding the right words when communicating, multitasking disorders, and inability to think clearly when solving problems.²¹ In line with research results by Mihuta et al., breast cancer survivors had worse EF than healthy control groups, or women without cancer (TMT B score 56.9 ± 17.6 vs. 48.1 ± 11.2).⁸ Kesler et al. found significant differences in EF using the Behavioral Rating Inventory of Executive Function (BRIEF) in women who received chemotherapy, those who did not receive chemotherapy, and healthy women with the following results: 64 ± 13 , 52 ± 12 , and 51 ± 9 , respectively.²² Research in children showed that those with acute lymphoblastic leukemia and being treated with chemotherapy experienced a decrease in EF compared to the healthy control group.²³

Chemotherapy can cause cognitive dysfunction as one of many direct effects of neurotoxicity on brain tissue.^{12,24,25} Inflammation processes induced by chemotherapy contribute to hippocampal volume changes that underlie this impairment.²⁶ Assessments using magnetic resonance imaging (MRI) in post-chemotherapy breast cancer survivors after one month of receiving chemotherapy show that survivors experience a decrease in gray matter volume. After one year of treatment, partial improvements can be observed in the persisting disorders in the frontal and temporal areas.²⁷ Women who underwent chemotherapy showed significantly worse outcomes, including additional reduction in left caudal lateral prefrontal function and decreased EF compared to women who did not undergo chemotherapy and healthy women.²²

The type of chemotherapy used was the most dominant factor associated with the impairment of EF in post-chemotherapy breast cancer survivors. Many chemotherapy agents are able to penetrate the brain blood barrier, such as 5-fluorouracil. Agents like this can cause neurotoxic damage to the central nervous system through injury to microglia, oligodendrocyte, and axon neurons; damage to myelin formation; and changes to fluid contents

and neurotransmitters.¹² Studies of the neurotoxicity of 5-fluorouracil revealed that it has reduced levels of brain-derived neurotrophic factor (BDNF) and doublecortin, a protein-regulating neuronal migration in the brain, leading to the development of chemobrain.²⁸ Patients who received cyclophosphamide, methotrexate, 5-fluorouracil, bleomycin, etoposide, cisplatin, or taxane had increased risks of developing severe cognitive impairments due to chemotherapy.¹² In addition, the usage of multimodal treatments and the application of multiple chemotherapeutic regimens significantly increased the risk of neurotoxicity incidence.²⁴

Age was the second most dominant factor associated with EF impairment in breast cancer survivors (OR 1.138; 95% CI 1.086–1.192). This is in line with Kesler's study, which states that older age is associated with an increase in EF impairment in chemotherapy patients.²⁶ Pok Ja Oh's study also shows that, among predictors of objective cognitive function, age and cycle of chemotherapy are the most dominant factors. These variables predicted approximately 34.8% of the variation in objective cognitive function in this study. Approximately 83.4% of respondents of Pok Ja Oh's study were >50 years old, so it is possible that the decline of cognitive function was accelerated by aging.²⁹

The third most dominant factor in EF impairment was stress (OR 1.104; 95% CI 1.033–1.179). Stress has long been believed to be a contributor to cognitive decline.² It stimulates the production of glucocorticoids that damage the hippocampus, as evidenced by the smaller hippocampi seen in stressed individuals and cancer patients examined via MRI.¹⁵ On the other hand, breast cancer patients perceive their cognitive appearance negatively if they have poor emotional functioning.³⁰

Implications for nursing practice

Assessment of cognitive function, including EF, is important for post-chemotherapy breast cancer survivors. Comprehensive assessments of cognitive function, including influencing factors, are needed to develop nursing care plans that suit the needs of this population. The ultimate goal is to provide high-quality nursing services and improve survivors' quality of life. Continuous training and education can help nurses to study quality cognitive functions.

Study limitations

This study only identifies the factors of age, stress, type of chemotherapy, menopausal status, hemoglobin level, quality of sleep, and fatigue. Several other factors that might affect the incidence of cognitive impairment in post-chemotherapy breast cancer survivors that were not identified in this study include diet, daily activities, exercise, social support, and genetic factors. For further study, it is necessary to identify more comprehensive factors.

Post-chemotherapy breast cancer survivors who experience mild-to-serious EF impairment totaled approximately 71 (86.6%) of the sample, and total respondents with mild-to-serious EF impairment comprised approximately 142 (58.5%) respondents. The most dominant factor associated with EF impairment was the type of chemotherapy used. Around 49.3% of EF impairment could be explained by length of education, type of chemotherapy, age, hemoglobin levels, and stress variables. It is recommended that nurses conduct comprehensive assessments of cognitive function in post-chemotherapy breast cancer survivors and consider the influencing factors as a way to develop excellent nursing care plans to optimize survivors' quality of life.

Conflict of interests

The authors declare no conflict of interest.

Acknowledgements

This work is supported by Hibah TADOK 2018 funded by DRPM Universitas Indonesia No. 1252/UN.R3.1/HKP.05.00/2018.

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