

The correlation between interleukin-6 levels and quality of life in late-stage breast cancer patients with anxiety syndrome at Haji Adam Malik General Hospital, Medan

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ABSTRACT

Aim Breast cancer is the most common cancer among women worldwide, including Indonesia. Breast cancer patients are prone to have anxiety and it affects their quality of life. Interleukin-6 (IL-6) is one of the pro-tumorigenic cytokines that increases in breast cancer, and is associated with worse prognosis and cancer metastasis. Several studies demonstrated the correlation between inflammatory cytokines and anxiety disorders. Therefore, this study aimed to determine the correlation between IL-6 and quality of life with anxiety syndrome in patients with late-stage breast cancer.

Methods This cross-sectional study involved women with late-stage breast cancer (Stage III and IV). IL-6 level was assessed using Sandwich enzyme-linked immunosorbent assay (Sandwich-ELISA). The quality of life and anxiety syndromes were assessed using the European Organization for Research and Treatment of Cancer 30-Item Quality of Life Questionnaire (EORTC QLQ-C30) and Hospital Anxiety and Depression Scale (HADS)-A questionnaire, respectively. Kruskal-Wallis test was used to determine the correlation between variables. A $p < 0.05$ was considered statistically significant.

Results Fifty-nine women met the inclusion criteria. Higher IL-6 level ($p < 0.001$) and poor QoL ($p < 0.001$) were related to severe anxiety disorders in late-stage breast cancer patients.

Conclusion IL-6 level and quality of life can be potentially used for the risk stratification and early detection of anxiety syndrome in late-stage breast cancer patients.

Keywords: anxiety, breast neoplasm, cytokine, quality of life

INTRODUCTION

Breast cancer is the most common cancer in women globally, surpassing lung cancer. Global Cancer Incidence, Mortality, and Prevalence (GLOBOCAN) 2020 reported an estimated 2.3 million new cases of breast cancer worldwide in 2020, with 684,996 deaths. Breast cancer accounts for 1 in 4 of all cancer cases and for 1 in 6 of all cancer deaths among women, ranking first in incidence in the vast majority of countries (1). The estimated breast cancer prevalence in Indonesia was 0.5%, and it ranked as the second most common cancer type following cervical cancer (2). The mortality rate of breast cancer has decreased in most Western countries due to modern therapy and early detection strategies, but developing countries have higher mortality rates of breast cancer than developed countries (15.0 per 100,000 vs 12.8 per 100,000) (1-3).

Various therapeutic methods have been developed based on the molecular characteristics of breast cancer. The treatment methods determined by the breast cancer stage, ranging from loco-regional therapies (surgery and radiotherapy), systemic, neoadjuvant therapy, and targeted drugs or immune checkpoint inhibitors (3).

Breast cancer is a multifactorial disease that involves genetic and environmental factors that play a role in its development, including inflammatory diseases (4). Interleukin-6 (IL-6) is one of the pro-tumorigenic cytokines. IL-6 dysregulation will trigger the pathogenesis of various diseases, such as cancer. There were increased IL-6 levels in breast cancer, and it was associated with a bad prognosis and metastasis (4). The survival rate of breast cancer reaches 85% and sequelae are common in breast cancer survivors, such as body image, psychological, and family problems (5). Breast cancer has negative psychological effects such as anxiety, stress, fear, and depression that are associated with quality of life in which these symptoms do not only affect breast cancer patients but also affect breast cancer survivors (5-7).

Anxiety is one of the most common psychological problems among breast cancer patients (8). The potent role of inflam-

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mation in mental disorders pathogenesis has attracted much attention for several past years, and some studies have proved the correlation between those variables (9,10). Breast cancer symptoms may lead to lower quality of life (5).

The aim of this study was to determine the correlation between IL-6 level and quality of life with anxiety syndrome in late-stage breast cancer patients in Haji Adam Malik General Hospital, Medan, Indonesia.

PATIENTS AND METHODS

Patients and study design

This cross-sectional study was conducted in the Oncology Surgery polyclinic of Haji Adam Malik General Hospital, Medan, Indonesia, from February 2024 to May 2024.

It used consecutive sampling method. The inclusion criteria were: women diagnosed with late-stage breast cancer (stage IIIA, IIB, IIC, and IV) based on histopathological examination, aged 30 – 65 years, on chemotherapy and having completed at least three cycles of chemotherapy, and signed informed consent voluntarily. The exclusion criteria were: the participants had communication difficulties, comorbidities such as diabetes, cardiac disease, epilepsy, infection, and autoimmune disorders, a history of psychiatric illness, pregnant women, lactating mothers, patients who were consuming autoimmune medication or hydroxychloroquine, had surgeries or infection for the last one week before data collection. The association between IL-6 levels and quality of life with the severity of anxiety syndrome was analysed.

Ethical clearance and permission were obtained prior to data collection. We gave a brief explanation about this research, and the patients were asked to give informed consent before the data collection process was started. All data were kept confidential.

Methods

After the informed consent was signed voluntarily, participants were asked to fill in demographic data and a Hospital Anxiety and Depression Scale-A questionnaire (HADS-A) to assess their anxiety levels (5). The hospital Anxiety and Depression Scale consists of 7 anxiety questions that have scores of 0 – 3, respectively, and a total score of 0 - 21. The results were categorized into no anxiety (score of 0), mild (score of 1 – 10), moderate (score of 11 – 15), and severe (score of 16 – 21) anxiety.

Participants had venous blood samples (± 5 mL) collected for IL-6 level measurement using a sandwich enzyme-linked immunosorbent assay (Sandwich ELISA) in the hospital laboratory. After the venous blood sampling, participants were asked to fill out the European Organization for Research and Treatment of Cancer 30-Item Quality of Life Questionnaire (EORTC QLQ-C30) for quality of life assessment (11). This questionnaire consists of five domains, including physical, emotional, social, role, and cognitive. The results were grouped into good, moderate, and poor quality of life. We provided an explanation about each questionnaire beforehand to avoid misunderstanding.

Statistical analysis

Descriptive analysis was conducted for all data. The numeric data were presented in mean \pm standard deviation (mean \pm SD) or median (min-max) for normally and abnormally distributed data, respectively. The data normality was assessed using the

Kolmogorov-Smirnov test. The categorical data were presented in frequency (percentage). The correlations were determined using one-way ANOVA for normally distributed data or the Kruskal-Wallis test for abnormally distributed data. A $p < 0.05$ was considered statistically significant.

RESULTS

This study included 59 selected women based on inclusion and exclusion criteria. The mean age was 51.14 \pm 7.26 years. Most women were unemployed (86.4%) and high school graduates, 54 (91.5%). They had been diagnosed with breast cancer for 1 to 6 years. Based on the disease stage, most women had stage IV breast cancer, 29 (49.2%). The mean of IL-6 level was 3.37 \pm 2.72 μ g/dL. Based on the HADS-A and EORTC QLQ-30 scores, most women had mild anxiety, 29 (49.2%) and good quality of life, 37 (62.7%) (Table 1).

Table 1. Characteristics of the women with breast cancer

Characteristics	No (%) of women
Mean \pm SD age (years)	51.14 \pm 7.26
Occupation	
Employed	8 (13.6)
Unemployed	51 (86.4)
Education	
High school	54 (91.5)
Diploma or bachelor	5 (8.5)
Stage	
IIIA	5 (8.5)
IIB	10 (16.9)
IIC	15 (25.4)
IV	29 (49.2)
HADS-A	
Mild anxiety	29 (49.2)
Moderate anxiety	20 (33.9)
Severe anxiety	10 (16.9)
EORTC QLQ C-30	
Good	37 (62.7)
Moderate	6 (10.2)
Bad	15 (27.1)
Median duration of breast cancer (min – max) (years)	3 (1 – 6)
Mean\pmSD IL-6 (μg/dL)	3.37 \pm 2.72

HADS-A, Hospital Anxiety and Depression Scale-A questionnaire; EORTC QLQ C 30, European Organization for Research and Treatment of Cancer 30-Item Quality of Life Questionnaire

The correlations between variables were determined using the Kruskal-Wallis test. The analysis revealed a significant difference in the severity of anxiety syndrome based on the QoL level, which implies that there was a correlation between IL-6 and anxiety, with poor QoL associated with severe anxiety syn-

Table 2. The association between IL-6 level and quality of life with the severity of anxiety syndrome

Variable	N (%) of participants	p
IL-6 with the severity of anxiety syndrome	59 (100)	<0.001
Quality of life with the severity of anxiety syndrome	59 (100)	<0.001

drome ($p < 0.001$). Furthermore, there was also a significant difference in the severity of anxiety syndrome based on the QoL level which implies that there was a correlation between QoL and anxiety, with poor QoL associated with severe anxiety syndrome ($p < 0.001$) (Table 2).

DISCUSSION

The mean age of women in this study was 51.14 years, similarly to a study where the mean age of breast cancer patients was around 50 years of age (58.6 ± 9.4). The breast cancer risk increases with age starting from the 40s (12). Age is one of the breast cancer risk factors. The most common age of breast cancer patients is between 50 and 69 years (13). Most women were unemployed and high school graduates. Poverty, low educational status, and the absence of health insurance were associated with low breast cancer survival rates (14).

Based on the mean quality of life score, patients who had been diagnosed with breast cancer for more than one year have a better quality of life, particularly in the general health status and functional status, compared to those with less than one year of diagnosis. Anxiety increases at the time of cancer diagnosis but tends to diminish over time as patients adapt to their illness. (15). Most women in this study were stage IV breast cancer patients, which is in accordance with a study in which 55% of participants had stage IV breast cancer (16). The advanced stage of breast cancer was associated with the lower education levels, living in rural areas, limited access to advanced screening technology, and inequitable healthcare (17,18).

The mean of IL-6 level of our patients was 3.37. IL-6 plays an important role in the process of the normal mammary epithelial cells transformation through NF-kB activation. It is also associated with TNM staging, breast cancer metastasis and recurrence since high IL-6 levels are strongly associated with aggressive tumours (19). Based on HADS-A and EORTC QLQ-30 scores, most women had mild anxiety and good quality of life, respectively. Similarly, Hajj et al. demonstrated that most breast cancer patients who received chemotherapy experienced anxiety. It is estimated that 42.4% of breast cancer patients had at least mild anxiety (8,20). Social support had a positive role in reducing anxiety symptoms including support from family members, hospitals and nursing professionals (8).

Our study demonstrated a correlation between IL-6 levels and anxiety syndrome, consistent with other studies, suggesting that the immune-inflammatory system may play a role in anxiety (21,22). However, another study stated that IL-6 levels had less consistent association with anxiety (23). Age is another factor associated with anxiety syndrome. Older age is associated with lower anxiety, including in cancer patients. On the other hand, younger cancer patients are more prone to anxiety syndrome. It may be due to the higher impact of cancer on their life plans, and older patients had more life experience (24). Additionally, we found that quality of life and anxiety syndrome

were also correlated; higher quality of life was associated with milder anxiety syndrome, similar to the other studies (20,24). Studies demonstrated that anxiety and depression during cancer diagnosis and therapy would increase physical and psychological symptoms that adversely impact the quality of life and decrease adaptation during therapy. Longer duration of breast cancer is associated with higher anxiety and depression which leads to decreased quality of life (25).

This was the first study in Indonesia to determine the correlation between IL-6 levels and quality of life with anxiety syndrome in late-stage breast cancer patients. Therefore, this study can be a guide for future studies.

Our study has several limitations: we only examined one pro-inflammatory cytokine level, and IL-6 without any adjusted or multivariate analysis. Furthermore, this was a single-centre study and was time-consuming due to the need for precise and timely blood sampling and sample storage.

In conclusion, the correlation between IL-6 levels and breast cancer stage and anxiety syndrome in late-stage breast cancer has been demonstrated in this study. Quality of life was correlated with anxiety syndrome in late-stage breast cancer. It implies that IL-6 level and quality of life have the potential to be applied for anxiety syndrome risk stratification or early detection in late-stage breast cancer patients, although further studies are required. Longitudinal, multicentre studies are needed to explore the causal relationship between these variables and to increase the generalizability of the study findings.

AUTHORS CONTRIBUTION

Conceptualization, E.Y.D, M.M.A, E.E, V.C, and K.B.S; Methodology, E.Y.D, M.M.A, and E.E; Software, E.Y.D; Validation E.Y.D; Formal Analysis, E.Y.D and M.M.A; Investigation E.Y.D; Resources, E.Y.D and M.M.A; Data Curation, E.Y.D, M.M.A, and E.E; Writing (original draft), E.Y.D and M.M.A, Writing (Review & Editing), E.Y.D, M.M.A, E.E, V.C, and K.B.S; Visualization, E.Y.D, M.M.A, and E.E; Supervision E.Y.D, M.M.A, E.E, V.C, and K.B.S; Project Administration, E.Y.D..

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TRANSPARENCY DECLARATION

Conflicts of interest: None to declare.

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