

ORIGINAL RESEARCH

TYPE 2 DIABETES MELLITUS, ANEMIA, AND HYPERTENSION AS THE RISK FACTORS FOR METASTATIC BREAST CANCER

Diabetes Mellitus Tipe 2, Anemia dan Hipertensi sebagai Faktor Risiko Metastasis Kanker Payudara

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ABSTRACT

Background: Breast cancer is one of the most common gynecologic malignancies in women and the main cause of death in 25% of all cases. The main cause of death from breast cancer is metastases, and it is estimated that 5-10% of breast cancers have metastasized at the time of early diagnosis with an advanced stage.

Purpose: To analyze the risk factors that influence the incidence of metastases in patients with advanced breast cancer. **Methods:** This study is an analytic observational study with a cross-sectional design. The number of samples in the study was 120 patients. The inclusion criteria of the study sample were breast cancer patients with advanced stages III and IV in the last five years. The exclusion criteria were incomplete patient medical records. The sampling technique in this study was consecutive sampling. This research was conducted at Ibnu Sina Hospital, Makassar City. The variables analyzed in this study were type 2 diabetes mellitus, anemia, and hypertension, tested with the chi-square test. **Results:** The results of this study showed that diabetes mellitus type 2 ($p=0.01$; Prevalence Rate [PR] = 1.79; 95% CI=1.32-2.42) and anemia ($p=0.03$; Prevalence Rate [PR] = 1.82; 95% CI = 1.61-2.86) is a risk factor that affects the incidence of metastases in patients with advanced breast cancer. While the risk factor that has no effect is hypertension. **Conclusion:** Type 2 diabetes mellitus and anemia are risk factors that influence the incidence of metastases in breast cancer patients.

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ABSTRAK

Latar Belakang: Kanker payudara merupakan salah satu penyakit keganasan ginekologi yang paling umum terjadi pada wanita dan penyebab kematian utama sebanyak 25% dari semua kejadian. Penyebab kematian akibat kanker payudara adalah metastasis, diperkirakan 5-10% kanker payudara sudah bermetastasis pada saat didiagnosis dini dengan stadium lanjut. **Tujuan:** Menganalisis faktor risiko yang mempengaruhi kejadian metastasis pada pasien kanker payudara stadium lanjut. **Metode:** Penelitian ini merupakan penelitian observasional analitik dengan desain cross-sectional, jumlah sampel dalam penelitian adalah 120 pasien. Kriteria inklusi sampel penelitian adalah pasien kanker payudara dengan stadium lanjut III dan IV dalam lima tahun terakhir. Kriteria eksklusi adalah rekam medis pasien yang tidak lengkap. Teknik pengambilan sampel dalam penelitian ini dengan consecutive sampling. Penelitian ini dilakukan di Rumah Sakit Ibnu Sina Kota Makassar. Variabel yang dianalisis dalam penelitian ini adalah diabetes melitus tipe 2, anemia, dan hipertensi yang diuji dengan uji chi-square. **Hasil:** Hasil penelitian ini menunjukkan bahwa diabetes melitus tipe 2 ($p=0,01$; Prevalence Rate [PR]=1,79; CI 95%=1,32-2,42) dan anemia ($p=0,03$; Prevalence Rate [PR]=1,82; CI 95%=1,61-2,86) merupakan faktor risiko yang mempengaruhi kejadian metastasis pada pasien kanker payudara stadium lanjut. Sedangkan faktor risiko yang tidak berpengaruh adalah hipertensi. **Kesimpulan:** Diabetes melitus tipe 2 dan anemia merupakan faktor risiko yang mempengaruhi kejadian metastasis pada pasien kanker payudara.

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INTRODUCTION

Breast Cancer is the most common illness characterized by uncontrolled cell growth and spread (Shumway et al., 2016). As much as 7% of women with breast cancer present with metastatic breast cancer at initial diagnosis, while 20-80% of women diagnosed with early-stage breast cancer can adapt treatment strategies. They can also develop distant metastases within five years (Wu et al., 2017).

Data from the American Cancer Society in 2019 estimated 268,600 new breast cancer cases, and about 41,760 women and 500 men are estimated deaths resulting from breast cancer. In 2010, they mentioned that cancer ranks second as the leading cause of death, under cardiovascular disease (Shumway, Sabolch, & Jagsi, 2016). Breast cancer in Indonesia ranks first with 3.90% of new cases. Data from Indonesia's basic health

research (Riskesdas) in 2013 and 2018 showed an increase in the prevalence of cancer in Indonesia from 1.40% to 1.49% (Ministry of Health RI, 2018). According to Pathological Based Registration, more than 80% of cases were found to be in advanced stages III and IV, while the rest were diagnosed at the early stage of breast cancer. The cancer stage will greatly determine the prognosis of the patient's recovery and life expectancy (Ministry of Health RI, 2019).

A recent study found that women with metastatic breast cancer are among the leading breast cancer deaths. It estimated that 5-10% of breast cancers have metastasized when diagnosed at an early stage with an advanced stage. Distant metastases may occur with or without local recurrence in the breast. Metastases are widely known to have a poorer prognosis than non-metastatic breast cancer. There are different studies also published that the pattern of metastasis

may be mutually exclusive among the various biologic types of breast cancer and distant metastases. Bones, liver, and lungs are common sites of metastasis (Seneviratne et al., 2016; Wang et al., 2019).

The timing of metastasis is difficult to predict. Still, several factors may affect the risk of metastasis based on surveillance epidemiology, such as age, tumor size, lymph node involvement, hormonal status, HER2 status, lymphovascular invasion, histopathological degree, genetic profile, and comorbid factors (Malmgren et al., 2018, 2020).

Research conducted by Lim (2018) related to comorbidity. He stated that comorbidity conditions could be substantial in breast cancer patients. Comorbidity usually commonly includes various disorders, for example, diabetes and hypertension, and there can also be psychological disorders.

Diabetes can increase the aggressiveness of breast cancer. The incidence of diabetes with breast cancer is 20-23% higher than breast cancer without diabetes (Kang et al., 2018). Diabetes triggers angiopathy, which can trigger massive damage to blood vessel constriction, both micro and macro. Several biological mechanisms and metabolic pathways in the blood utilize high glucose in producing reactive oxygen species as a means of metastasis (McCall et al., 2018).

Anemia and thrombocytopenia in cancer patients focus on two main etiologies, namely the presence of metastases and systemic microvascular and TMA (thrombotic microangiopathy). Anemia often manifests in cancer patients due to nutrient deficiency, effects of chemotherapy and radiation therapy (Morton & George, 2016). Another comorbidity is that hypertension is a common chronic disease that is a significant risk factor for vascular disease and is also implicated as a risk factor for breast cancer. Hypertension has a 15% chance of increasing the risk of breast cancer (Han et al., 2017).

Studies on metastases have previously been conducted, but studies related to comorbidities in breast cancer patients are still rare. The study is expected to represent breast cancer patients related to the comorbidities experienced. This study analyzed the risk factors associated with the incidence of metastatic breast cancer at Ibnu Sina Hospital Makassar.

METHODS

This research was conducted as an observational analytic study with a *cross-sectional*

design. The population in this study was all female breast cancer patients registered as patients at the Surgery Polyclinic of the Ibnu Sina Hospital in 2015-2020, amount 573 patients. This study uses the minimum sampling formula by Lemeshow, Ogston, Hosmer, Klar, & Lwanga (1991) to obtain a sample of 120 patients with inclusion criteria, namely patients with advanced-stage III and IV breast cancer. Meanwhile, the exclusion criteria were incomplete patient medical records. Sampling is non-random (non-probability), and the sampling technique used is purposive sampling.

The dependent variable in this study was metastases obtained from the patient's medical record status. The independent variables were age, menopausal status, histopathological grade, tumor size, lymph nodes, type 2 diabetes mellitus, anemia and hypertension. The variables were categorized, namely age 50 years and <50 years, menopausal status was categorized as postmenopausal and premenopausal, histopathological grades were grade I, II and grade III, tumor size was T0-T2 (tumor 2cm or more but not more than 5cm in greatest dimension) and T3-T4 (tumor <5cm in largest dimension or any dimension with direct extension to chest/skin), while the lymph nodes were categorized as N. positive and N negative. Type 2 diabetes mellitus, anemia and hypertension are classified with "yes" and "no".

The data collected was then analyzed univariate and bivariate. The univariate analysis in frequency distribution and bivariate analysis using the chi-square test with a P value of 0.05 was considered statistically significant. The Prevalence Ratio (PR) calculation was applied to calculate the magnitude of the risk of disease problem. Processing and analyzing data using SPSS 2.4.

This study was conducted at Ibnu Sina hospital, Makassar, Indonesia. In this study, researchers used secondary data for the previous five years of medical records. Data retrieval was done in November-December 2020. This study obtained the approval of the ethics and the health research ethics commission of the Muslim University of Indonesia with the number 125/A.1/KEPK-UMI/XII/2020.

RESULTS

Based on the results of research at the Ibnu Sina Hospital in Makassar, it was found that there were 120 respondents with advanced-stage breast cancer. In this study, most of the patients in the 50 years age group with menopausal status experienced post-menopause. The highest

histopathological grade in the patient was grade III, tumor size T3-T4, and lymph nodes were negative.

Based on the characteristics of the patients in this study (Table 1), most of the respondents were in the 50-58 year age group—menopausal status of most menopausal respondents (64.16%). The degree of histopathology in respondents with a proportion of grade III (57.50%) and TN status (tumor size, nodules/lymph nodes) were the most respondents with tumor size status T3-T4 (67.50%), in gland status, namely N is negative (52.50%).

Table 1
Frequency Distribution of Respondents

Variables	n	%
Age		
(Average±SB)	50,68 ±9,700	
≥ 50 years	77	64.16
< 50 years	43	35.84
Menopausal Status		
Postmenopausal	77	64.16
Premenopausal	43	35.84
Histopathological Grade		
Grade I and Grade II	51	42.50
Grade III	69	57.50
Tumor Size		
T0-T2	39	32.50
T3-T4	81	67.50
Lymph Nodes		
N positive	57	47.50
N negative	63	52.50
Total	120	100.00

Relationship between Type 2 Diabetes Mellitus and Breast Cancer Metastasis

Table 2 shows that in breast cancer patients with type 2 diabetes mellitus comorbidities with metastasis, 80% with the chi-square analysis test obtained a p-value value of 0.00 ($p < 0.05$). There is a significant correlation between type 2 diabetes mellitus and metastatic incidence in breast cancer patients at Ibnu Sina Hospital Makassar. Type 2 diabetes mellitus increases the risk of a 1.79 times more chance of metastatic events in breast cancer patients (PR 1.79; 95% CI 1.32-2.42).

Relationship between Anemia and Breast Cancer Metastasis

Table 2 shows that breast cancer patients with comorbidities anemia who have metastases were 69.80% with chi-square test analysis obtained a p-value of 0.03 ($p < 0.05$), which means there is a significant correlation between anemia and metastatic event at Ibnu Sina Hospital Makassar. Anemia increases the risk of a 1.82 times more risk of metastatic events in breast cancer patients (PR 1.82; 95% CI 1.16-2.86).

Relationship between Hypertension and Breast Cancer Metastasis

Table 2 showed that in breast cancer patients with hypertension comorbidities, 55.90% with chi-square test analysis obtained a p-value of 0.48 ($p > 0.05$), which means there was no significant correlation to metastatic at Ibnu Sina Hospital Makassar.

DISCUSSION

Characteristics of Respondents

The majority of breast cancer patients who had metastases in the age group of ≤ 50 years and with the status of menopause were already menopausal. That suggested that the average age of those experiencing metastases was in the already menopausal group. The same thing was also shown in research by Putra, 2019, which stated that the percentage of 46-54-year-olds are more metastatic (Putra et al., 2019). Research from Gogia et al. (2019) with a study comparing the age of breast cancer patients with metastases in western countries and India. In western countries, the average age of breast cancer patients with metastases is 60-70 years. On the other hand, the average age reported in India is 48 years (range 22-80 years), still being treated with advanced and metastatic stages.

The status of menopause data from the American Cancer Society, 2019, stated that women who menopause at 55 years or more have a 12% higher risk than the average population of menopause age of 50-54 years. It involves more prolonged exposure to reproductive hormones, i.e., exposure to high estrogen and progesterone (Shumway, Sabolch, & Jagsi, 2016).

Table 2

Chi-Square Statistical Test Results for the Relationship between Diabetes, Anemia, and Hypertension with Metastasis Breast Cancer

Variable	Metastasis				Total		P Value	PR (95%CI)
	Yes		No		n	%		
	n	%	n	%				
Type 2 diabetes mellitus								
Yes	44	80.00	11	20.00	55	100.00	0.01	1.79 (1.32-2.42)
No	29	40.60	36	55.40	65	100.00		
Anemia								
Yes	60	69.80	26	30.20	86	100.00	0.03	1.82 (1.16-2.86)
No	13	38.20	21	61.80	34	100.00		
Hypertension								
Yes	19	55.90	15	44.10	34	100.00	0.48	0.89 (0.633-1.25)
No	54	62.80	32	37.20	86	100.00		
Total	73	60.80	47	39.20	120	100.00		

A degree in histopathology assesses the morphology of cells suspected to be part of tumor tissue. The recommended histopathological gradation system was according to The Nottingham Combined Histologic Grade (according to Elston-Ellis, which was a modification of Bloom-Richardson). The benefit of determining the degree of differentiation was choosing the type of therapy to be given (Lodi et al., 2017). The degree of histopathology can determine cancer's aggressiveness, namely the more aggressive cancer, the more likely it is to metastasize. The histopathological assessment provides useful prognostic information on breast cancer. The degree system can be used prognostic factor for breast cancer. Grade II tumors are the most common tumors found in moderate-grade malignancies. Then, there are grade I and grade III tumors. (Lodi et al., 2017; Sejati et al., 2019).

Breast cancer in patients with histopathological grades who had the most metastasis was in grade III and considered one of the factors for metastasis with poor prognosis indicators. It is the same thing with Ehinger et al. (2017) that most studies related to the histopathological examination in breast cancer patients were grade III, with a percentage of 35% developing distant metastases during the follow-up period, grade III had a poor prognosis.

Tumor, nodule/KGB, and metastases (TNM) status size are directly related to the percentage of axillary lymph node involvement. Tumor size showed that the size of T3-T4 with metastases and lymph nodes mainly was Nodule Positive. These results were based on the examination of the patient's pathology. Clinically, the larger the size

of the tumor and the extension to the surrounding tissue increased the percentage of metastatic events. The tumor size was directly proportional to the formation of blood vessels (angiogenesis), which continued in metastasis (Castañeda-Gill & Vishwanatha, 2016; Madu et al., 2020). The axillary lymph nodes are the initial area of the spread of cancer cells from the lymph nodes of cancer cells spread throughout the body to metastasis (Castañeda-Gill & Vishwanatha, 2016). The same research by Jamnasi et al. (2016) that showed T3-T4 tumor size status was a significant risk factor for breast cancer in the metastatic group compared to the metastatic free group. Moreover, there is research from Niasari & Hoesin (2016) stated that related VEGF (Vascular Endothelial Growth Factor) expression in invasive carcinoma NST grade III with metastases in axillary lymph nodes is higher in the positive N (nodules) group (N1, N2, N3) than in the negative N (N0).

Relationship between Type 2 Diabetes Mellitus and Breast Cancer Metastasis

In this study, breast cancer with type 2 diabetes mellitus had 1.79 times more risk of metastasis with a value ($p = 0.01$; $PR = 1.79$; $95\%CI = 1.32-2.42$) compared to patients who did not have type 2 diabetes mellitus. The same thing was also shown in research by Raza, Asif, Rehman, & Sheikh (2018). Breast cancer patients with lymph node metastases showed significant blood sugar levels. Nineteen per cent of the 13 patients in the stage III group of metastatic, compared to breast cancer patients without metastases, can occur because diabetes mellitus type 2 refers to a metabolic disorder that displays

high blood glucose. High glucose levels contribute to the metastatic behavior of breast cancer through cell migration and invasion capacity (Sun et al., 2019).

Type 2 diabetes mellitus and the risk of mammary carcinoma on insulin growth factor (IGF-1) is one of the developments of mammary carcinoma and can act as a mitogen to increase tumorigenesis. Type 2 diabetes mellitus leads to metastases of breast cancer and requires the process of angiogenesis. Angiogenesis is the normal physiological process involving proliferation, migration, and morphogenesis from existing vessels into new blood vessels. Still, uncontrolled angiogenesis can also cause cancer, rheumatoid arthritis, and blindness in people with diabetes mellitus. Tumor growth and metastases largely depend on angiogenesis. Several studies have confirmed that angiogenic activators play an essential role in tumor development (Madu, Wang, Madu, & Lu, 2020). Other studies have stated that patients diagnosed with breast cancer with high glucose or type 2 DM are at increased long-term risk and enhancement in mortality (Sun, Sun, Rong, & Bai, 2019).

Relationship between Anemia and Breast Cancer Metastasis

Anemia is a reduction in the volume of hemoglobin. Anemia is a multifactorial complication in patients with malignancies. The frequency of anemia often occurs in cancer patients, is about 40% (Kenar et al., 2020; Pourali et al., 2017). The results showed that breast cancer patients with anemia were 4.50 times more at risk for metastatic values ($p = 0.03$; $PR = 1.82$; $CI = 1.16-2.86$) than patients without anemia. The same thing was also shown the research by Kenar, Köksoy, Urun, & Utkan (2020), which showed that anemia often occurred in patients with advanced-stage cancer with metastases (59%) compared to patients with advanced-stage non-metastatic cancer (55%).

Chemotherapeutic agents cause anemia directly by disrupting hematopoiesis. It includes synthesizing red blood cell precursors in the bone marrow. Previous studies have shown that anemia increases to 90% with cancer after chemotherapy during follow-up. That occurs in older cancer patients with low intake and a history of bleeding (Beaudoin-Maitre & Vallée, 2019).

Relationship between Hypertension and Breast Cancer Metastasis

Hypertension is one prevalent comorbidity and is more common in older patients. This study shows that breast cancer patients with hypertension did not have a risk associated with metastasis. A meta-analysis study reported that hypertension had a 15% increased risk of breast cancer considering the effect on postmenopausal women with involvement of estrogen metabolism. Still, this study found that hypertension in Asia is not associated with an increased risk of breast cancer, with a relatively low incidence of breast cancer in developing countries (Han et al., 2017).

A different study by Anwar et al., (2021) stated that hypertension increased by 74% in breast cancer patients. The risk of distant metastases increases with the number of comorbidities, 37% occurring at age >65 years. There is no hypertension associated with the risk of breast cancer metastases [OR 2.30, 95% CI: 1.07–4.95, $p = 0.03$]. Based on the theory of increased angiotensin II in hypertension, it believes to cause an increase in reactive oxygen species (ROS), which will later cause damage to blood vessels and lead to oxidative stress. In addition, oxidative stress also plays a vital role in tumor cell metastases through angiogenesis, leading to metastasis (Whelton et al., 2018).

Research Limitations

This research has limitations. This study uses a non-probability method where the level of generalization of research results is low and only involves a sample so that the results of this study cannot be generalized to this hospital or other hospitals.

CONCLUSION

The majority of breast cancer patients in this study were 50 years of age and had experienced menopause. This study shows that breast cancer patients with comorbidities type 2 diabetes mellitus and anemia are risk factors for metastases. The occurrence of breast cancer metastases in patients cannot be separated from prognostic factors, tumor size, histopathological grade and nodules (lymph nodes) in patients, so the patient should be monitored more precisely and followed up regularly.

CONFLICT OF INTEREST

There is no conflict of interest in this study.

AUTHOR CONTRIBUTION

EE: Writing, Original draft preparation, Conceptualization Editing, SB and AS: Research Supervisor, Methodology, and Reviewing. All authors participated actively and approved the final submission.

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