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Relationship between comorbidity and mortality of stage IV breast cancer: A literature review

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Abstract

Breast cancer is a major health concern on a global scale because breast cancer is the cancer with the highest prevalence and the 5th highest mortality in women worldwide (The Global Cancer Observatory, 2020). Based on data from the World Health Organization (WHO) in 2020, the prevalence of breast cancer worldwide reached 7,790,717 cases with the 5th highest mortality rate worldwide. In 2020, breast cancer in Indonesia had the highest prevalence with the 2nd highest mortality rate, namely 22,430 people (The Global Cancer Observatory, 2020). Mortality in breast cancer patients is influenced by various factors, including age, gender, genetics, family history, tumor pathology, clinical parameters (tumor size and location, nodule status, presence of metastatic disease, clinical stage, and histological grade), presence of comorbidities, and type of treatment. Worse survival rates from breast cancer have been found overall in breast cancer patients with comorbidities compared to those without. Literature reviews on breast cancer mortality in patients with and without comorbidities, based on CCI scores, are still very limited. Therefore, researchers are interested in conducting research on the relationship between comorbidities and mortality of breast cancer patients. This review is expected to be useful for enriching knowledge about the relationship between comorbidities and mortality in stage IV breast cancer patients. However, further research is needed with more comprehensive variables to determine the risk factors for breast cancer, the relationship between comorbidities and mortality in breast cancer patients, and survival in breast cancer patients.

Keywords: Breast cancer; Comorbidity; Mortality; CCI Score

1 Introduction

Breast cancer is a major health concern on a global scale because breast cancer is the cancer with the highest prevalence and the 5th highest mortality in women worldwide (The Global Cancer Observatory, 2020). In Indonesia, breast cancer ranks first with the highest cancer prevalence in Indonesia, as well as one of the largest contributors to cancer deaths in Indonesia (Kemenkes RI, 2022). Based on data from The Global Cancer Observatory (Globocan) in 2020, breast cancer in Indonesia has the highest prevalence, namely 201,143 cases with the 2nd highest mortality rate, namely 22,430 people (The Global Cancer Observatory, 2020).

There are several factors that can worsen the prognosis of breast cancer and cause breast cancer mortality. Mortality in breast cancer patients is influenced by various factors, including socio-demographic variables (age, gender, genetics, and family history), tumor pathology, clinical parameters (tumor size and location, nodule status, presence of metastatic disease, clinical stage, and histological grade), presence of comorbidities, and type of treatment (Fujimoto et al., 2019). An individual who receives a diagnosis of breast cancer may have been diagnosed or treated for accompanying chronic

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diseases, commonly known as comorbidities (Fu et al., 2015). Many studies have reported that comorbidity is most often measured by a comorbidity index, namely the Charlson Comorbidity Index (CCI) (Nechuta et al., 2013). The Charlson Comorbidity Index (CCI) is a method for predicting mortality by classifying various comorbid conditions and has been widely used to measure disease burden (Suastika et al., 2016). Worse survival rates from breast cancer have been found overall in breast cancer patients with comorbidities compared to those without comorbidities (Søgaard et al., 2013).

Research conducted by Samuel, et al. in 2018 stated that women who have one or more comorbidities are associated with a significant increase in breast cancer mortality rates (Azubuike et al., 2018). This is because patients with comorbidities will be more susceptible to the toxicity of cancer treatment physiologically (Misganaw et al., 2023). In addition, comorbidities are also associated with differences in morphology, histology, differentiation, and proliferation status of cancer cells.

Literature reviews on breast cancer mortality in patients with and without comorbidities, are still very limited. Therefore, researchers are interested in conducting research on the relationship between comorbidities and mortality rates of stage IV breast cancer patients.

2 Review Content

2.1 Breast Cancer

2.1.1 Definition of Breast Cancer

Breast cancer is a disease in which abnormal breast cells experience uncontrolled growth and division, eventually forming a tumor. There are several types of breast cancer and the classification of breast cancer depends on which cells in the breast turn cancerous (Centers for Disease Control and Prevention, 2022). Breast cancer occurs in epithelial cells (85%) or lobules (15%) in the mammary glands (World Health Organization, 2020). Initially, cancer growth is limited to the ducts or lobules ("in situ") where it generally does not cause symptoms and has minimal metastatic potential. Over time, this in situ cancer can grow and invade the surrounding breast tissue, then spread to nearby lymph nodes (regional metastases) or to other organs in the body (distant metastases) (World Health Organization, 2020).

2.1.2 Patophysiology of Breast Cancer

Breast cancer occurs due to environmental exposure (external factors) with a genetically susceptible host. Breast cancer generally starts from ductal hyperproliferation, then develops into a benign tumor or even carcinoma that metastasizes to other organs after receiving constant stimulation from exposure to carcinogenic factors.

The pathophysiology of breast cancer occurs in multistages where each stage is associated with one or more specific mutations of minor or major regulatory genes. Clinically and histopathologically, there are various morphological stages on the way to malignancy. Initially, ductal hyperplasia occurs which is characterized by excessive and unevenly distributed polyclonal epithelial cell proliferation, where the chromatin pattern and nuclear shape overlap and the ductal lumen is irregular. This is an early sign of malignancy. These cells have relatively little cytoplasm with unclear cell boundaries and are cytologically benign. Clinically, breast cancer is characterized by changes in hyperplasia to atypical (clonal) hyperplasia with clearer and non-overlapping cytoplasm and cell nucleus characteristics and regular duct lumen (Sjamsuhidajat and Jong, 2017).

The process that occurs after atypical hyperplasia is the emergence of carcinoma in situ, both ductal and lobular carcinoma. Carcinoma in situ gives a cytological picture, namely cell proliferation that is in accordance with malignancy, but has not invaded the stroma and penetrated the basement membrane. Lobular carcinoma in situ generally spreads throughout the tissue of one breast or bilaterally and is generally not palpable or visible on examination. Meanwhile, ductal carcinoma in situ gives a diverse picture because it is a segmental duct lesion that can be classified. After tumor cells penetrate the basement membrane and invade the stroma, the tumor grows invasively and can spread hematogenously and lymphogenously, causing metastasis to other organs (Sjamsuhidajat and Jong, 2017).

2.1.3 Risk Factor of Breast Cancer

Breast cancer is caused by a variety of factors, but it is thought that breast cancer is caused by several factors (multifactorial). Breast cancer risk factors can be divided into modifiable and non-modifiable risk factors.

Modifiable Risk Factor

- Gender

Most cases of breast cancer occur in women and rarely occur in men. The number of male breast cancer sufferers is only less than 1% (Abdulkareem, 2013). This occurs mainly due to differences in hormonal stimulation. Men have insignificant estrogen levels, while women have breast cells that are very susceptible to hormones and their imbalances, especially the hormones estrogen and progesterone.

- Age

The risk of breast cancer increases with age. Currently, as many as 80% of breast cancer sufferers are individuals over the age of 50 years, where more than 40% of them are over the age of 65 years. Based on data from Surveillance, Epidemiology, and End Results (SEER), the risk of women suffering from breast cancer in the United States is a lifetime risk of 1 in 8, a risk from birth to age 39 of 1 in 202, a risk of 40-59 years of age of 1 in 26, and a risk of 60-69 years of age of 1 in 28.

- Genetics

The risk of breast cancer is increasing in relation to several genetic mutations. The two main genes that are characterized by high penetrance are BRCA1 (located on chromosome 17) and BRCA2 (located on chromosome 13) (Łukasiewicz et al., 2021). Both genes are mainly associated with increased breast carcinogenesis (Shiovitz and Korde, 2015). Mutations in these genes are mostly inherited in an autosomal dominant manner, but sporadic mutations are also frequently reported. Other breast cancer genes that have high penetrance are TP53, CDHI, Phosphatase and Tensin Homolog (PTEN), and Serine / Threonine Kinase-11 (STK11) (Shahbandi et al., 2020). Based on a recent study from Poland, mutations in the X-Ray Repair Cross Complementing 2 (XRCC2) gene also have the potential to increase the risk of breast cancer (Łukasiewicz et al., 2021).

- Family history

A meta-analysis study conducted by Russel, et al. in 2000 concluded that women with one or more first-degree relatives with breast cancer have a higher risk of developing breast cancer (Abdulkareem, 2013). Based on data from the Nurses' Health Study, women with a family history of breast cancer diagnosed before the age of 50 have a risk of 1.69 and women with a family history of breast cancer diagnosed at the age of over 50 have a risk of 1.37 compared to women without a family history of breast cancer (Cohen et al., 2023).

- Reproductive history

Women who start their menstrual period (menarche) under the age of 12 and start menopause over 55 will be exposed to hormones for longer, so they have a higher risk of developing breast cancer (Centers for Disease Control and Prevention, 2022). In the European Prospective Investigation into Cancer and Nutrition study, women who experienced early menarche (under the age of 13) showed a risk of breast cancer of almost twice as much (Hillers-Ziemer and Arendt, 2020). In addition, pregnancy, breastfeeding, and hormonal imbalance will affect the induction of carcinogens in the breast microenvironment (Husby et al., 2018).

- History of breast cancer

A history of breast cancer is associated with a greater risk of developing new cancerous lesions in the breast. In addition, several other non-cancerous breast diseases such as atypical hyperplasia or lobular carcinoma in situ are also associated with a higher risk of developing breast cancer (Centers for Disease Control and Prevention, 2022).

- History of radiation therapy

The risk of secondary malignancy after radiation therapy is an individual problem that depends on the characteristics of each patient. Women who have a history of radiation therapy to the chest or breast (eg, in the treatment of Hodgkin's lymphoma) at age 30 have a higher risk of developing breast cancer.

Non-Modifiable Risk Factor

- Physical activity

Women who are not physically active will have a higher risk of developing breast cancer. Physical activity can reduce the risk, recurrence, and mortality from breast cancer. This is because physical activity can induce changes in inflammatory and immune mediators that can contribute to the prevention of breast cancer (Xu and Rogers, 2020).

- Body Mass Index (BMI)

The risk of breast cancer increases in obese women, namely with a BMI of 30 kg/m2 or more. Research conducted by Kang Liu, et al. in 2018 showed that every 5 kg/m2 increase in BMI was associated with a 2% increase in the risk of breast cancer (Liu et al., 2018). This occurs because increased body fat can increase inflammation and affect the level of circulating hormones that facilitate pro-carcinogenic events.

- Alcohol consumption

Excessive alcohol consumption can increase the risk of breast cancer. According to the International Agency for Research on Cancer (IARC), in 2020 alcohol consumption was the cause of almost 400,000 new cases of breast cancer (World Health Organization, 2021). This is because excessive alcohol intake can increase estrogen levels and this hormonal imbalance influences the high risk of breast carcinogenesis (Zeinomar et al., 2019).

- Smoking history

Cigarette smoke contains chemicals in the form of carcinogens such as tobacco that can trigger cancer (Sreenivas, 2023). Carcinogens carried to breast tissue can increase the likelihood of mutations in oncogenes and proliferation suppressor genes (especially p53). Smoking is associated with an increased risk of breast cancer, especially in women who start smoking in adolescence or peri-menarche. A longer smoking history and smoking before the first pregnancy are also risk factors for breast cancer (Jones et al., 2017).

- History of hormonal contraceptive use

Based on research conducted by Nicole D. White in 2018, there was an increased risk of breast cancer of around 20% in women who were using or had recently used hormonal contraceptives (White, 2018). Research in Denmark showed that there was a significant relationship between the duration of use of contraceptive pills and breast incidence. Use of contraceptive pills for 13 years had the highest relative risk increase of 18% and use for 5 years had a relative risk increase of 5%. The overall risk of breast cancer increases with the use of any hormonal contraceptive (Daly et al., 2021).

- Diet

Diet plays a role in inducing or inhibiting cancer growth. The World Health Organization (WHO) classifies processed meat ingredients such as ham, bacon, salami, and frankfurts as group 1 carcinogens that can increase the risk of gastrointestinal malignancies to breast cancer (Wilson et al., 2018). Studies conducted in animal models have shown that a diet high in polyunsaturated fats may increase the risk of breast cancer (Ubago-Guisado et al., 2021). Conversely, a diet high in fiber such as vegetables, fruits, nuts, whole grains, and lean protein may decrease the risk of breast cancer (Dandamudi et al., 2018).

2.1.4 Management of Breast Cancer

Breast cancer management can be done through several types of therapy according to the pathophysiological conditions (stage and metastasis) of the patient's breast cancer. Based on the Centers for Disease Control and Prevention (CDC) 2022, there are several types of breast cancer therapy: surgery, chemotherapy, radiotherapy, and hormonal therapy.

Surgery

There are two main types of breast cancer surgery: breast-conserving surgery and mastectomy. Breast-conserving surgery involves removing the tumor in the breast, while mastectomy involves removing the entire breast (National Health Service, 2022). In some cases, both breast-conserving surgery and mastectomy are performed at the same time to recreate the breast.

Breast-conserving surgery ranges from lumpectomy or wide local excision, where the tumor and a small amount of surrounding breast tissue are removed, to partial mastectomy or quadrantectomy, where up to a quarter of the breast is removed. The amount of breast tissue removed depends on the type, size, and location of the breast cancer in the patient and the size of the patient's breasts.

Mastectomy is the removal of the entire breast tissue, including the nipple. There are several types of mastectomy therapy, namely simple mastectomy (total mastectomy), radical mastectomy, skin-sparing mastectomy, nipple-sparing mastectomy, and double mastectomy (bilateral mastectomy) (National Health Service, 2022).

- Simple mastectomy (total mastectomy)

A procedure to remove the entire breast, including the nipple, areola, fascia, pectoralis major muscle, and skin.

- Radical mastectomy

A procedure to remove the axillary lymph nodes and pectoralis muscle (the chest muscle under the breast).

- Skin-sparing mastectomy

In this procedure, only the breast tissue, nipple, and areola are removed, while most of the skin above the breast is left. The amount of breast tissue removed is the same as a simple mastectomy.

- Nipple-sparing mastectomy

A nipple-sparing mastectomy is similar to a skin-sparing mastectomy, in that only the breast tissue is removed, while the skin of the breast is kept. However, in this procedure, the nipple and areola are left in place. This procedure may be followed by breast reconstruction.

- Double mastectomy (bilateral mastectomy)

A procedure to remove both breasts and is performed as a risk-reducing or preventive surgery for women who are at high risk for breast cancer, such as those with BRCA gene mutations.

Chemotherapy

Chemotherapy uses anticancer (cytotoxic) drugs to kill cancer cells, which can be given intravenously or orally (American Cancer Society, 2023a). The drugs travel through the bloodstream to reach cancer cells throughout the body. Several different drugs are used in chemotherapy, often 2 to 3 drugs given at once. The choice of drugs and their combination depends on the type and metastasis of the breast cancer. Chemotherapy can be given after surgery (adjuvant chemotherapy) or before surgery (neoadjuvant chemotherapy).

Adjuvant chemotherapy is used to destroy cancer cells that have not been removed because they are left behind or have spread but cannot be seen. These cells are considered microscopic because they cannot be seen with the naked eye. If left to grow, these cells can form new tumors elsewhere in the body. Adjuvant chemotherapy can also reduce the risk of breast cancer recurrence (American Cancer Society, 2023a).

Neoadjuvant chemotherapy is given to shrink the size of the tumor before surgery, so that the tumor can be removed with less extensive surgery. Therefore, neoadjuvant chemotherapy is often used to treat cancers that are too large to be surgically removed when first diagnosed, have many lymph nodes involved with the cancer, or are inflammatory breast cancers (American Cancer Society, 2023a).

Adjuvant and neoadjuvant chemotherapy drugs given to breast cancer patients include anthracyclines (such as doxorubicin and epirubicin), taxanes (such as paclitaxel and docetaxel), 5-fluorouracil (5-FU) or capecitabine, cyclophosphamide (cytoxan), and carboplatin (paraplatin) (American Cancer Society, 2023a).

Chemotherapy can cause side effects, depending on the type, dose, and duration of the drug. Some side effects of chemotherapy include hair loss, mouth sores, loss of appetite, weight loss, nausea, vomiting, diarrhea, fatigue, vaginal

dryness due to chemotherapy-induced menopause, nerve damage, increased chance of infection, and easy bruising or bleeding (National Health Service, 2022). Chemotherapy side effects usually go away after treatment is complete. However, some side effects can be reduced or controlled with medications (American Cancer Society, 2023a).

Radiotheraphy

Radiotherapy (radiation therapy) is a treatment that uses high-energy rays or particles that can destroy cancer cells (American Cancer Society, 2023a). The target of this therapy is to destroy the DNA of cancer cells and eradicate them. Radiotherapy is usually done after surgery and chemotherapy to kill remaining cancer cells. Types of radiotherapy include breast, chest wall, breast enhancement, and lymph node radiotherapy.

- Breast radiotherapy

Performed after the patient has undergone breast-conserving surgery. Breast radiotherapy uses radiation applied to all remaining breast tissue.

- Chest wall radiotherapy

Performed after the patient has undergone mastectomy surgery. Chest wall radiotherapy uses radiation applied to the chest wall.

- Breast enhancement radiotherapy

High-dose radiotherapy to the area where the cancer was removed can affect the appearance of the patient's breasts, so breast enhancement radiotherapy is performed to strengthen and improve the appearance of the patient's breasts.

- Radiotherapy to the lymph nodes

Radiation therapy is performed on the axillary area and surrounding areas to kill cancer in the lymph nodes.

Radiotherapy can cause several side effects, including irritation and darkening of the breast skin, changes in the shape, size, and color of the breast, pain in the breast or chest area, breast swelling, hair loss in the axilla, sore throat, lymphedema, and fatigue (Cancer Research UK, 2021b).

Hormonal Therapy

Some types of breast cancer are affected by hormones, such as estrogen and progesterone. Breast cancer cells have receptors (proteins) that attach to estrogen and progesterone, helping them grow. Hormone therapy can stop these hormones from attaching to their receptors. Hormone therapy can reach cancer cells throughout the body, not just in the breast. It is recommended for patients who have tumors that are hormone receptor positive. However, it does not help patients who do not have hormone receptors (hormone receptor negative) (American Cancer Society, 2023a).

The type of hormone therapy depends on the stage and grade of the breast cancer, which hormones it is sensitive to, the patient's age, history of menopause, and history of therapy. Some types of hormone therapy include tamoxifen, aromatase inhibitors, and ovarian ablation or suppression (National Health Service, 2022).

- Tamoxifen

Tamoxifen stops estrogen from binding to estrogen receptor-positive cancer cells.

- Aromatase inhibitors

This type of drug will block aromatase, which is a substance that helps the body produce estrogen after menopause. Before menopause, estrogen is made by the ovaries. Three aromatase inhibitors are anastrozole, exemestane, and letrozole.

- Ovarian ablation or suppression

Ablation can be done with surgery or radiation therapy. In women who have not experienced menopause, estrogen is produced by the ovaries. Ablation aims to stop the ovaries from producing estrogen, so that the patient will experience menopause earlier. Ovarian suppression can use the drug goserelin, which is a luteinising hormone-releasing hormone agonist (LHRHa).

2.2 Comorbidity

2.2.1 Comorbidity of Breast Cancer

Comorbidity affects prognosis, therapy, outcomes, and is associated with decreased health outcomes. Based on research conducted by Misganaw et al. in 2023, comorbid conditions and advanced clinical stages have a higher risk of mortality (Misganaw et al., 2023). This is in line with research conducted by Samuel et al. in 2018 which stated that women who have one or more comorbidities are associated with a significant increase in breast cancer mortality (Azubuike et al., 2018). This is because patients with comorbidities will be more susceptible to the toxicity of cancer treatment physiologically (Misganaw et al., 2023). In addition, comorbidity is also associated with differences in morphology, histology, differentiation, and proliferation status of cancer cells (Søgaard et al., 2013). In her 2014 study, Jennifer stated that the risk of breast cancer mortality is high in breast cancer patients over 65 years of age who have comorbidities (Jordan et al., 2014).

Research conducted by Jennifer, et al. in 2011 stated that the comorbidities that most often cause breast cancer mortality are heart disease (coronary heart disease, congestive heart failure, myocardial infarction, and other heart diseases), diabetes mellitus, chronic obstructive pulmonary disease, and chronic kidney disease (Patnaik et al., 2011). In addition, research by Sarah, et al. in 2013 also stated that comorbidities such as hypertension, diabetes mellitus, asthma, coronary heart disease, and chronic gastritis can increase the risk of breast cancer mortality (Nechuta et al., 2013).

Several studies have explained that there is a relationship between breast cancer patients with comorbid hypertension, chronic lung disease, rheumatic disease, and diabetes mellitus with a ρ value <0.05. Similar results were also obtained in Hwa's study in 2021 which stated that comorbid chronic lung disease, ulcers, malignancies with metastasis, and diabetes had a ρ value <0.001 which means there is a relationship between chronic lung disease, ulcers, malignancies with metastasis, and diabetes with mortality in breast cancer patients.

2.2.2 Charlson Comorbidity Index (CCI) Score

Charlson Comorbidity Index (CCI) is a method for predicting mortality by classifying various comorbid conditions and has been widely used to measure disease burden (Suastika et al., 2016). CCI contains 19 diseases, including diabetes with diabetic complications, congestive heart failure, peripheral vascular disease, chronic lung disease, mild and severe liver disease, hemiplegia, kidney disease, leukemia, lymphoma, metastatic tumors, and AIDS, each of which is weighted according to its potential impact on mortality. Cardio-cerebrovascular disease (CVD) of comorbidities in CCI is defined as a history of cardiac arrhythmia, peripheral vascular disease, cerebral vasculopathy, ischemic heart disease, or chronic heart failure (Charlson et al., 1987). Since then, CCI has been adapted and verified as applicable and valid to predict outcomes and risk of death from many comorbid diseases (Huang et al., 2014).

CCI is calculated according to the scoring system established by Charlson, et al. in 1987, where the research sample was grouped into groups that had at least one or more comorbidities and groups that did not have comorbidities based on the categorization of comorbidities calculated by the Charlson Comorbidity Index (CCI) (Charlson et al., 1987). Then, assign a score for each condition that the patient has according to the CCI table. Example: chronic lung (1) and lymphoma (2) = total score (3).

The severity of comorbid diseases was recorded and scored according to the CCI. Patients were divided into four groups:

- No comorbidity, with a CCI score of 0,
- Mild comorbidity, with a CCI score of 1–2,
- Moderate comorbidity, with a CCI score of 3–4,
- Severe comorbidity, with a CCI score ≥ 5.

Tabel 1 Charlson Comorbidity Index (CCI)

Score	Comorbidity
1	Myocardial infarction
	Congestive heart failure
	Peripheral vascular disease
	Dementia
	Cerebrovascular disease
	Chronic pulmonary disease
	Connective tissue disease
	Ulcer
	Mild liver disease
	Diabetes without complication
2	Hemiplegia
	Moderate to severe renal disease
	Diabetes with complication
	Tumor
	Leukemia
	Lymphoma
3	Moderate to severe liver disease
6	Metastatic solid tumor
	Acquired immuno-deficiency syndrome (AIDS)

(Charlson *et al.*, 1987)

Breast cancer survivors with increased comorbidity, as assessed by Charlson Comorbidity Index (CCI) scores of 1, 2, and >3, have a higher risk of non-routine disposition, prolonged hospitalization, and inpatient mortality compared to breast cancer survivors with a CCI score of zero (Fu et al., 2015). Several previous studies have found that comorbidity is associated with survival and mortality. Breast cancer patients with comorbidity have a worse prognosis than patients without comorbidity. Thus, it can be stated that the more comorbidities a breast cancer patient has (the higher the CCI score), the higher the risk of breast cancer patient mortality. A limitation of the CCI, however, is that it does not capture all types of comorbidities that may prove relevant to health outcomes in the breast cancer patient population. For example, neither mental health comorbidities nor musculoskeletal comorbidities are captured in the CCI, even though disease entities such as depression and arthritis are frequently present in the breast cancer patient population, and appear to influence health outcomes and quality of life (Fu et al., 2015).

2.3 Prognosis

The World Health Organization (WHO) states that breast cancer is a malignant neoplasm that is the largest global burden for women (World Health Organization, 2018). Breast cancer is the most commonly diagnosed cancer in women worldwide with 2.26 million new cases in 2020. In addition to being the most common, breast cancer is also the leading cause of cancer death in women worldwide, reaching 684,996 deaths (Ferlay et al., 2020). In low- to middle-income countries, the incidence of breast cancer is expected to increase further due to westernized lifestyles (such as delayed pregnancy, reduced breastfeeding, low age at menarche, lack of physical activity, and poor diet (Łukasiewicz et al., 2021).

Breast cancer patient mortality is influenced by various factors, namely socio-demographic variables (age, sex, genetics, and family history), tumor pathology, clinical parameters (tumor size and location, nodule status, presence of metastatic disease, clinical stage, and histological grade), presence of comorbidities, and type of treatment (Fujimoto et al., 2019).

Tumor characteristics (high grade, high tumor size, nodule involvement) are associated with a higher risk of breast cancer mortality, as previously shown by Mauguen et al. (Mauguen et al., 2013). Conversely, the risk of mortality is lower for tumors with estrogen or progesterone receptor positive (Lafourcade et al., 2018). Research conducted by Caroline et al. in 2004 stated that postmenopausal women who had used menopausal hormone therapy (MHT) before breast cancer diagnosis had a lower risk of recurrence and mortality (Antoine et al., 2004). However, women who underwent MHT also underwent more routine monitoring through mammography so that they had an earlier cancer diagnosis. Therefore, the good prognosis in women who used MHT did not have a significant relationship (Lafourcade et al., 2018).

Exposure to smoking after breast cancer diagnosis can increase the risk of breast cancer recurrence, but not the risk of mortality. This can be explained by the fact that almost half of smokers quit smoking after being diagnosed with cancer (Lafourcade et al., 2018). Women with obesity have a higher risk of breast cancer recurrence and mortality (Contiero et al., 2013). Research conducted by Alexandre, et al. in 2018 did not confirm the relationship between alcohol consumption or education level with the risk of breast cancer mortality. The year of breast cancer diagnosis was used as a marker for breast cancer treatment, but no significant association was found between the year of cancer diagnosis and mortality risk.

3 Conclusion

In conclusion, this paper explores the relationship between comorbidity and mortality of breast cancer patients based on CCI score. There is a relationship between and mortality of breast cancer patients, where breast cancer patients with comorbidity have higher mortality rate than those without comorbidity. This paper highlights the relationship between comorbidity and mortality of breast cancer patients and emphasizes the need for a comprehensive strategy involving various sectors to implement therapeutic interventions for breast cancer patients with the aim of reducing breast cancer mortality rate. Therefore, further research is needed related to comorbidity and mortality of stage IV breast cancer patients by collecting more complete data on breast cancer risk factors, clinical pathology, molecular characteristics, and treatments or therapies used.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest to be disclosed.

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