

Factors Contributing to Bleeding in Breast Cancer Wounds: A Literature Review

Nurmila Sari¹, Haryanto^{2,*}, Lidia Hastuti³

¹Master of Nursing, Institut Teknologi dan Kesehatan Muhammadiyah Kalimantan Barat, Pontianak-Indonesia

²Wound Management and Medical Surgical Nursing Department, Institut Teknologi dan Kesehatan Muhammadiyah Kalimantan Barat, Pontianak-Indonesia

³Child and Maternity Nursing Department, Institut Teknologi dan Kesehatan Muhammadiyah Kalimantan Barat, Pontianak-Indonesia

*Corresponding authors: haryanto@stikmuhptk.ac.id

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Abstract

Aims: In Indonesia, breast cancer ranks first in the number of new cases; there is a significant increase in the number of cases every year. Complications of breast cancer include bleeding that affects quality of life, psychology, activity limitations, anemia, increased treatment time, economic burden, and the threat of death. Breast cancer is often found in advanced stages, increasing the risk of bleeding. The literature review analyzes research articles that discuss factors associated with breast cancer wound bleeding.

Methods: Inclusion criteria include articles discussing breast cancer bleeding, cancer in general, cancer wounds, themes relevant to research, research can be a quantitative, qualitative, mixed method, meta-analysis, in English and Indonesian, from 2013 to 2023, full text. Keywords in the database are "risk factors," bleeding, breast cancer, and malignant wound. Literature searches use journal databases, namely Pubmed and ScienceDirect. This research uses the author's literature review method to analyze, evaluate, and criticize published research results.

Results: Fifteen articles met the inclusion criteria, most of them retrospective, examining factors of anticoagulation therapy on breast cancer bleeding, articles examining bleeding factors in several types of cancer, and five articles examining factors of post-operative breast cancer bleeding.

Conclusion: Breast cancer wound bleeding factors are chemotherapy, radiation, comorbidities, malignant fungating wounds, BMI \geq 40, dressings, thrombocytopenia, reconstructive surgery, advanced stage, infection, and therapy (anticoagulants, anti-inflammatory pain relief, NSAIDs). Suggestions for further research are analyzing various bleeding factors, examining which factors are most related to bleeding, and looking at the pattern of relationships between several factors in bleeding.

Keywords: risk factors; bleeding; breast cancer

Introduction

Breast cancer is the most common malignancy in women worldwide and is a global problem. Based on data from the GLOBOCAN International Agency for Research on Cancer in 2020, there are five most significant cancer cases in the world in women and men: breast, lung, colorectum, prostate, and stomach. Cancer incidence in women globally also ranks breast cancer first, followed by colorectum, lung, cervical, and thyroid cancer. Breast cancer is the highest cancer incidence in women globally, with an incidence rate of 2,261,419 or 24.5% of the total cancer incidence (International Agency for Research on Cancer, 2020).

The top five countries worldwide with the highest breast cancer rates are China 416,371 (18.4%), USA 253,465 (11.2%), India 178,361 (7.9%), Japan 92,024 (4.1%), Brazil 88,492 (3.9%). Indonesia ranks eighth with 65,858 cases (2.9%). In Indonesia, there were 396,914 new cases of cancer, with details of new cases of breast cancer 65,858 (16.6%), cervical cancer 36,633 (9.2%), lung cancer 34,783 (8.8%), colorectum cancer 34,189 (8.6%) and liver cancer 21,392 (5.4%). This data shows that breast cancer ranks first in several cancers. Breast cancer is the world's fifth leading cause of death at 684,996 (6.9%). Breast cancer is the first cause of death in women in Indonesia, with a death rate of 22,430 (GLOBOCAN International Agency for Research on Cancer in 2020). Risk factors for breast cancer include female gender, age > 50 years, family and genetic history, previous history of breast disease, history of early menstruation (< 12 years), late menarche (>55 years), reproductive history (childless and non-breastfeeding), hormonal, obesity, alcohol consumption, history of chest wall radiation, environmental factors (Komite Nasional Penanggulangan Kanker, Kemenkes RI 2015 and Risnah, 2020).

Breast cancer also affects the quality of life, which becomes less suitable, namely in terms of physical health and social relationships (Agustiyaningsih et al., 2021). A complication that often arises in breast cancer is bleeding; if not treated properly, it will have an impact on further complications such as anemia (Loeffler & Hart, 2018), increased length of stay, and increased economic burden (Nwaogu et al., 2015), anxiety, activity limitations to the threat of death (Beer, 2019)

RSUD Dr. Soedarso Pontianak is the highest referral hospital in West Kalimantan Province. The existence of surgical oncology and hematology-oncology subspecialists has led to an increase in the number of cancer visits and cancer wound cases. Based on medical record data from RSUD Dr. Soedarso, in 2020, there were 234 cases; in 2021, there were 281 cases; there was an increase of almost 90% in 2022, namely 424 points. The author often finds cancer wounds in wet conditions, exudate, masses or nodules, necrotic tissue, slough, and bleeding. Various factors can influence the incidence of bleeding in cancer wounds. Increased risk of surgical complications in bleeding, hematoma, and necrosis in breast cancer after receiving bevacizumab chemotherapy or repeated surgery (Gerber B. et al., 2014). Another study showed an association between bleeding risk in cancer patients who received anticoagulant therapy (Zakai et al. 2018).

Breast cancer bleeding complications after mastectomy prolonged hospital stay by 1.3 days ($P < 0.0001$), increasing hospital costs by \$5495 per admission ($P < 0.0001$). Nationally, bleeding complications added 1254 hospital days at a cost exceeding \$5.3 million (Nwaogu et al. 2015). This study shows that breast cancer with bleeding prolongs

hospitalization days and burdens the economy. In line with this research, conditions in Indonesia show a swelling financial burden. From 2019 to 2020, cancer treatment costs BPJS 7.6 trillion rupiah (Kementerian Kesehatan Republik Indonesia, 2022). In Indonesia, more than 70% of cases are found at an advanced stage (Kementerian Kesehatan Republik Indonesia, 2022). In the advanced stage, bleeding often occurs, and the focus of treatment and care is on controlling bleeding symptoms, complaints, and problems with the lesion or wound (Agra, 2016; Johnstone & Rich, 2018). Bleeding is significantly higher in malignant fungating injuries treated with alginate or non-adherent. A tiny hemorrhage significantly increased the risk of severe bleeding—hemostatic dressings controlled bleeding in 70.6% of cases (Nicodème, 2021).

The novelty of this research is that it analyzes several factors related to specific bleeding in breast cancer wounds. According to the researchers, no literature review analyzes specific bleeding factors in breast cancer wounds. Several things differentiate this research based on a review of several previous studies. Several previous studies only discussed 1 factor as an independent variable for the occurrence of breast cancer. There is also an article that produces three risk factors for bleeding but is not specific to breast cancer but to several types of cancer (Nicodème, 2021). Five themes examining bleeding factors in breast cancer were investigated after surgery. This is what differentiates the author's research from previous research. The author discusses several factors for specific bleeding events in breast cancer that can occur before or after surgery in different places and objects. The author included the time criterion because, in the field, the author found several bleeding incidents that occurred before surgery, after mastectomy with open wounds, or the growth of new cancer tissue in the surgery area.

Through this research, it is hoped that the results can increase literacy and contribute to the development of nursing science, becoming a reference regarding the development of nursing science, especially breast cancer wound care and oncology nursing. The results of this research can be a reference in providing nursing care to breast cancer patients who are bleeding so that nurses can be more careful in preventing bleeding and preventing further complications by paying attention to the bleeding factors.

Based on the various problems above, the author feels it is necessary to conduct a literature review to determine the factors that cause bleeding in breast cancer wounds. Therefore, this literature review aims to determine what factors can trigger bleeding in breast cancer wounds.

Methods

This research uses the literature review method by analyzing, evaluating, and criticizing published research related to the objectives. Literature searches were conducted with database journals, namely Pubmed, ScienceDirect, and identification of other sources. The keywords used in the database are "risk factors," bleeding, breast cancer, and malignant wound. The identification process was done through the journal database, and 477 articles were found. Then, I screened and excluded five duplicated articles and scrutinized them to assess eligibility, where the selected articles met the predetermined inclusion criteria. At the eligibility stage, 457 articles were excluded, based on the selection of titles and abstracts, 131 articles were excluded, 298 articles were unsuitable for the research area, and 28 were full text. Finally, at the determination stage, the author determined 15 articles to be discussed in the research after going through a selection process based on the inclusion criteria. The selected articles are from research

on cancer or breast cancer that experiences bleeding. Researchers assess whether each article reviewed is appropriate or not based on the inclusion criteria.

The inclusion criteria of the selected articles were:

1. Articles that discussed bleeding in cancer in general, bleeding in breast cancer, and cancer wounds.
2. Articles with themes and content relevant to the research question.
3. Quantitative, qualitative, mixed method, and meta-analysis research articles.
4. Articles in English and Indonesian
5. Articles published from 2013 to 2023
6. Articles that are available in full text.

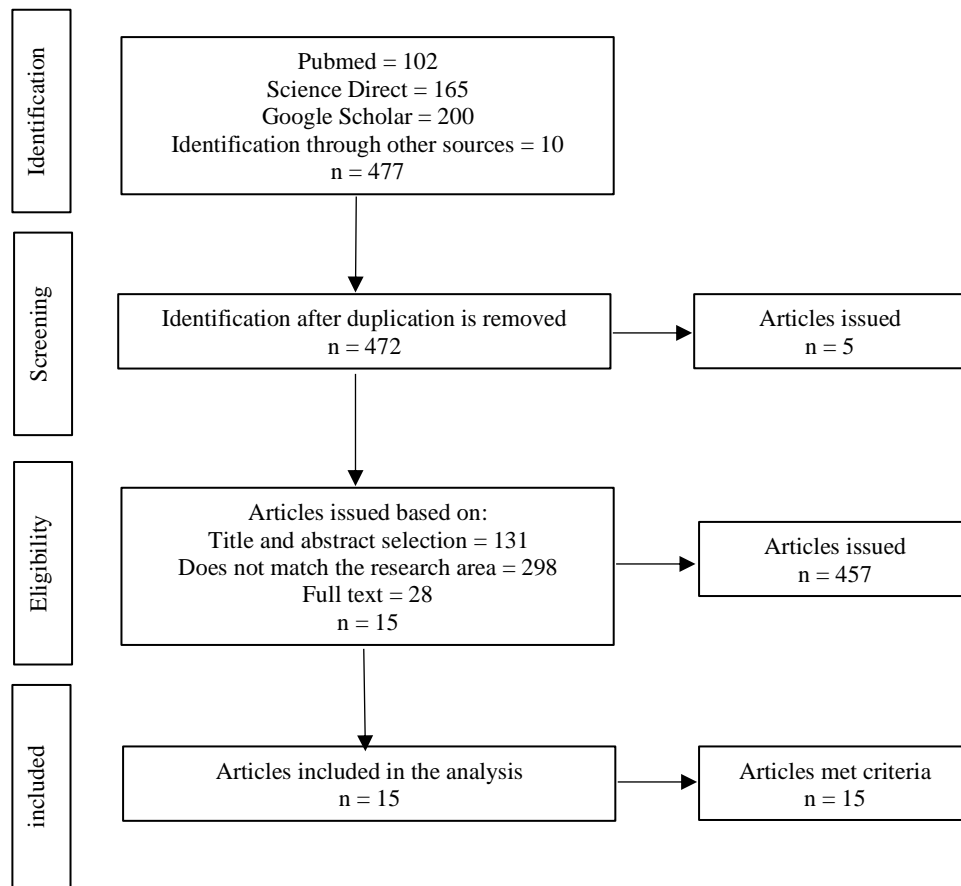


Figure 1. PRISMA Diagram

Result

The literature review results contained 15 articles (Figure 1). that were included with the distribution of articles per year from 2013 to 2023 (Figure 2).

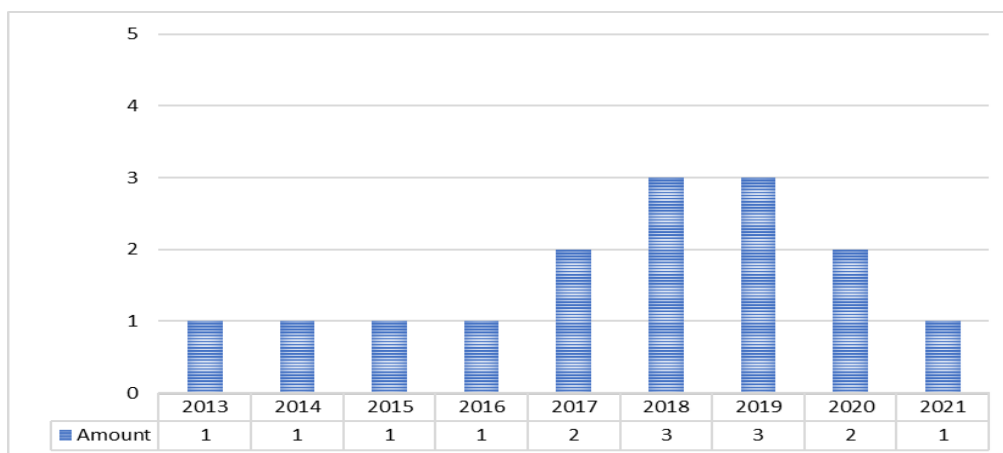


Figure 2. Distribution of Articles per Year

15 articles included which describing the research results, objectives, methodology, and other information. The results of the review were 15 articles that met the criteria. Most of the retrospective study articles examined only one factor of anticoagulation therapy on breast cancer bleeding. Of the articles that examined risk factors for bleeding in several types of cancer, five articles examined factors of breast cancer bleeding after surgery (Table 1).

Discussion

The results of the final search of this literature review obtained 15 articles that discuss factors related to the occurrence of bleeding in breast cancer. Research by Nwaogu et al. (2015) showed that breast cancer patients who have comorbid diseases with CHF are risk factors for bleeding. Research related to the effects of chemotherapy conducted by Gerber et al. (2014) states that there is an increased risk of surgical complications in the form of bleeding, hematoma, and necrosis in breast cancer patients who receive additional chemotherapy bevacizumab or after repeated surgery.

Most bleeding events were gastrointestinal (33%) and retroperitoneal (14%). In multivariable analysis, anemia was the reason for admission, GI cancer site, BMI \geq 40, and thrombocytopenia (Patell R. et al., 2017). Anticoagulants are associated with cancer patients' bleeding risk (Zakai et al., 2017). Bleeding often occurs in advanced stages due to cancer tissue, such as local tumor invasion, abnormal tumor vasculature, or tumor regression. Bleeding is also associated with radiation therapy and chemotherapy undergone. Bleeding conditions are exacerbated by immunotherapy, non-steroidal anti-inflammatory drugs (NSAIDs), anticoagulants, and anti-inflammatory pain relievers should be considered because anti-platelet properties can worsen bleeding (Johnstone et al., 2018).

Table 1. Article Review Table

No.	Title	Year	Research Methodology	Research Results Related to Bleeding Factors	Research Objectives	Number of Citations	Distribution by Country	Authors
1	Early Removal of Drains and The Incidence of Seroma After Breast Surgery	2013	Controlled clinical trial	Early drain removal (5th hr after surgery) or when drainage volume is less than 50 mL/24 hrs slightly increases seroma formation	Adult women > 25 years old	8	Japan	Okada, N. et al.
2	Surgical Outcome After Neoadjuvant Chemotherapy and Bevacizumab	2014	Prospective	Administration of bevacizumab chemotherapy increases the risk of surgical complications (bleeding, hematoma, necrosis, wound infection, abscess)	Adult women	10	Germany Switzer-land	Gerber, B. et al.
3	Economic Impact of Bleeding Complications After Mastectomy	2015	Quantitative	CHF was significantly associated with bleeding. It was bleeding prolonged hospital days by 1.3 days (P < 0.0001), increasing hospital costs by \$5495 per admission (P < 0.0001). Nationally, bleeding complications accounted for an additional 1254 days of hospitalization costs exceeding \$5.3 million.	Adult women	5	United States	Nwaogu, I. Y. et al.
4	Malignant Neoplastic Wounds: Clinical Management Performed by Nurses.	2016	Exploratory study, Qualitative	Nurses' knowledge about the clinical management of wounds in patients with cancer is weak	clinical nurses who provide care to advanced patients	8	Brazil	Agra, G. et al.
5	Identifying Predictors for Bleeding in Hospitalized Cancer Patients	2017	Retrospective cohort study	Most bleeding events were gastrointestinal (33%) and retroperitoneal (14%). In multivariable analysis, anemia as the reason for admission, GI cancer site, BMI ≥ 40, and thrombocytopenia.	Adult women and men	20	United States	Patell, R. et al.
6	Breast Cancer Recurrence After Reoperation for Surgical Bleeding	2017	Cohort Study	There is no evidence of the association between reoperation for bleeding and breast cancer recurrence.	Women	3	Denmark	Pedersen R.N. et al.
7	Impact Of Anticoagulant Choice on Hospitalized Bleeding Risk When Treating Cancer-Associated Venous thromboembolism	2018	Retrospective study	Anticoagulants are associated with bleeding risk similar to warfarin and LMWH in cancer patients.	Women and men aged ≥18 years	10	country of England	Zakai, N. A. et al.
8	Bleeding In Cancer Patients and Its Treatment	2018		Bleeding is caused by the cancer tissue, radiation therapy, and chemotherapy, exacerbated by immunotherapy, non-steroidal anti-inflammatory drugs/NSAIDs, anticoagulants, and anti-inflammatory pain relievers.	Adult women and men	21	United States	Johnstone, C. & Rich, S. E.

9	Bleeding After Free Flap-Based Breast Reconstruction	2018	Retrospective study	Reconstructive surgery is associated with a significantly increased risk of bleeding complications.	Adult women, post-mastectomy reconstructive breast surgery	6	United States	Orr, J. P. et al.
10	Assessment Of Bleeding Incidences Associated with Rivaroxaban Therapy in Adults with Solid Tumors	2019	Retrospective study	Sixty-four patients (44%) bleeding using anticoagulant rivaroxaban. Kidney cancer 40%, bleeding bladder cancer 54%, bleeding breast cancer 40%, bleeding melanoma 58%, bleeding pancreatic cancer 45%, and 56% bleeding renal cell carcinoma patients.	Female, male ≥18 years old	-	United States	Weddle, K. J., Kiel, P. J. & Patel, P. J.
11	Bleeding Incidence and Risk Factors Among Cancer Patients Treated with Anticoagulation	2019	Cohort	Cancer patients on anticoagulants experience more bleeding than non-cancer. Increased risk of bleeding with CKD stage III or more metastatic disease, thrombocytopenia, and BMI≥40 slightly increases the risk. Bleeding.	Female, male ≥18 years old	16	United States	Angelini, D.E. et al.
12	Description of the Development of Post Mastectomy Breast Cancer Wound Condition After Wound Care	2019	Descriptive research in the form of a case study	The results showed changes in the clinical appearance of the wound, exudate production, and bleeding. Wound care affects the development of post-mastectomy breast cancer wound conditions, significantly changes in clinical appearance and reducing exudate production and bleeding.	Women ≥ 18 years old with post-mastectomy cancer wound	2	Indonesia	Nadiva, D. H & Muafiro, A
13	Risk Factors for Major Bleeding During Anticoagulation Therapy in Cancer-Associated Venous Thromboembolism	2020	Retrospective	Major bleeding events occurred frequently during anticoagulant therapy in patients with cancer-related VTE. End-stage cancer, chronic kidney disease, and gastrointestinal cancer were independent risk factors for major bleeding.	Men and women with active cancer receiving anticoagulant therapy	7	Japan	Nishimoto, Y. et al.
14	Bleeding risk in breast cancer patients during concomitant administration of warfarin and tamoxifen	2020	Case-control study	Risk of bleeding in patients anticoagulated with warfarin who started tamoxifen within the previous 30 days. There is a potential association between tamoxifen use during warfarin and bleeding risk in patients with breast cancer.	Adult women with breast cancer	-	Sweden	Valachis, A. et al.
15	Frequency And Management of Hemorrhagic Malignant Wounds: A Retrospective Single-Centre, Observational Study.	2021	Retrospektif, single-center, observational study.	Bleeding was significantly higher in malignant fungating wounds (p < 0.01). She was treated with alginate or non-adherent. A tiny bleed significantly increased the risk of significant bleeding (p < 0.001). Hemostatic dressings controlled bleeding in 70.6% of cases.	Women and men > 18 years old	3	Paris, France	Nicodème, M.

Another study in 64 patients (44%) of bleeding used the anticoagulant rivaroxaban. Renal cancer bleeding 40%, bladder cancer bleeding 54%, breast cancer bleeding 40%, melanoma bleeding 58%, pancreatic cancer bleeding 45%, 56% of renal cell carcinoma patients bleeding. (Weddle et al., 2019). Major bleeding occurs during anticoagulation therapy in patients with cancer-related VTE, end-stage cancer, chronic kidney disease, and gastrointestinal cancer (Nishimoto, 2020). Cancer patients treated with anticoagulants experience more bleeding than non-cancer patients. Among anticoagulant-treated cancer patients with CKD factor stage III or more, metastatic disease, thrombocytopenia increased bleeding risk, and BMI \geq 40 slightly increased bleeding risk (Angelini et al., 2019).

Major bleeding events frequently occur during anticoagulant therapy in patients with cancer-related VTE. End-stage cancer, chronic kidney disease, and gastrointestinal cancer are independent risk factors for major bleeding (Nishimoto et al., 2020). Bleeding risk in patients anticoagulated with warfarin who started tamoxifen within the previous 30 days. There is a potential association between tamoxifen use during warfarin and bleeding risk in patients with breast cancer (Valachis et al., 2020).

Research related to early drain removal (5th hour after surgery) or when the drainage volume is less than 50 mL/24 hr slightly increases seroma formation (Okada et al., 2013). There is no evidence of an association between reoperation for bleeding and breast cancer recurrence (Pedersen et al., 2017). However, reconstructive surgery significantly increases the risk of bleeding complications (Orr et al., 2018).

The development of breast cancer wounds after surgery significantly changes clinical appearance, and the presence of exudate and bleeding is strongly influenced by how wound care is performed (Nadiva & Muafiro, 2019). There is more substantial bleeding in malignant fungating wounds. The risk of severe bleeding increases due to a single slight bleed. Hemostatic dressings controlled bleeding in 70.6% of cases (Nicodème, 2021)

Various factors that trigger bleeding from the above research studies need special attention, starting when conducting assessments, performing wound care interventions, and evaluating during treatment. If bleeding continues, it will adversely affect the patient's condition. Anxiety, fear, and physical weakness are also felt so that patients cannot and are afraid to move.

The high number of cases, mortality rates, and high costs have made the government prioritize breast cancer treatment in Indonesia. In this provision, the Indonesian National Strategy for Breast Cancer Management includes three pillars: health promotion, early detection, and case management. This study is in line with government programs prioritizing breast cancer treatment. It is hoped that the results of this study will become part of the message across the three pillars of breast cancer prevention.

Limitation of the Study

The limitation of this research is that the literature still needs to be expanded, and this research did not find research with randomized controlled trials. Therefore, further research is required.

Contribution to Global Nursing Practice

The results of this research are expected to provide insights into the risk factors for bleeding so that nurses can work harder to prevent bleeding by focusing on these factors. In the future, the results of this study could serve as a basis for developing guidelines or assessment tools and interventions related to factors encountered by cancer wound patients.

Conclusion

Based on the results of the review process carried out by the author, it can be concluded that various factors for the occurrence of bleeding in breast cancer wounds are chemotherapy factors, radiation, the presence of comorbidities such as CHF, CKD, the presence of fungating wounds (malignant fungal wounds), BMI \geq 40, the use of dressings, thrombocytopenia, reconstructive surgery, advanced stages and metastases, infectious factors, as well as the administration of therapy (anticoagulants, anti-inflammatory therapy pain relievers, non-steroidal anti-inflammatory drugs (NSAIDs)). Suggestions for further research are analyzing various bleeding factors, examining which factors are most related to bleeding, and looking at the pattern of relationships between several factors in bleeding.

Author Contribution

NS designed the method, searched online, and summarized the content. HY and LH summarized the content. NS, HY, and LH completed the manuscript.

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Conflict of Interest

The author declares no conflict of interest.

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