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Correlation Between Preoperative Serum Albumin Levels And Post-Operating Seroma Incidence Of Modified Radical Mastectomy In Breast Cancer Patients

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ABSTRACT

Background: Surgical therapy is still the mainstay of therapy for breast cancer, and modified radical mastectomy (MRM) is the most frequently performed procedure. Seroma formation after breast surgery is a complication that is often found due to the formation of dead space anatomically. A low albumin level indicates an ongoing systemic response and is a one of marker for a seroma. Aim To determine the postoperative complications of modified radical mastectomy in breast cancer patients, namely the incidence of postoperative seroma with preoperative serum albumin levels. ***Methods:*** An analytic observational study using a cross sectional study design conducted at the medical record of Prof. Dr. IGNG Ngoerah Denpasar Hospital in January 2019-December 2021. The research subjects were all patients with breast cancer underwent MRM. This study's data analysis consisted of univariate and bivariate analysis using IBM SPSS version 23. ***Results:*** 128 subjects divided into two groups, 30 subjects with seroma and 98 subjects without seroma. Low albumin levels <3.5 gr/dl in the seroma group were found in 18% case and in the group without seromas 39.1%, normal albumin levels > 3.5 gr/dl with seromas occurring in 5.5% respondents and normal albumin levels without seroma found 37.5% respondents. The RR value was 2.4 (CI 95% 1.14-5.34) with a p-value of 0.013. ***Conclusion:*** Pre-operative low albumin level < 3.5 gr/dl correlated to high seroma formation after modified radical mastectomy.

Keywords: Albumin; Breast Cancer; Modified radical mastectomy; Seroma

INTRODUCTION

Breast cancer is the most common malignancy suffered by women worldwide. Epidemiology globally shows that the burden of cancer care is increasing, especially in low- and middle-income countries, with more than 20 million new cancer cases each year.[1] Worldwide there were approximately 2.1 million cases of breast cancer diagnosed in women in 2018, accounting for nearly 1 in 4 of the most frequently diagnosed cancer cases in most countries. Breast cancer is the leading cause of cancer death in over 100 countries except for Australia/New Zealand, Northern Europe, North America and many countries in Sub-Saharan Africa.

Breast cancer deaths show less variability, with the highest mortality estimates in Melanesia, while Fiji has the most increased mortality worldwide.[2]

Breast cancer is the second most common cancer worldwide and the most common cancer among women. The risk of developing breast cancer for every woman in the United States is 12.4% or one in eight women.[3] In 2012, approximately 1.67 million new breast cancer cases were identified worldwide, accounting for 25% of all cancers.

The incidence rate is higher in developed countries and varies significantly according to race and ethnicity. Breast cancer incidence rates vary worldwide, ranging from 27 per 100,000 in Central Africa and East Asia to 92 per 100,000 in North America. The incidence of breast cancer is estimated to reach 3.2 million cases in 2050.[4]

Breast cancer is also a significant health problem in Indonesia; this cancer constitutes 30.5% of all existing cancer diagnoses and 21.5% of cancer-related deaths in women. Even worse, breast cancer in Indonesia is mainly diagnosed at an advanced stage with an increasingly high mortality rate.[5]

Surgical therapy is still the mainstay of therapy for breast cancer, and modified radical mastectomy (MRM) is the most frequently performed procedure.[6] There are various complications related to the development of tumor cells, such as residual disease or axillary recurrent, as well as non-oncological complications that arise after surgery, such as surgical wound infections, lymphedema, chronic pain, necrosis of the flap, hematoma including seroma formation.[7]

Seroma formation after breast surgery is defined as the accumulation of serous fluid containing blood plasma and/or lymph under a skin flap or in the axilla.[8] Seroma is the most frequently recurring postoperative problem in modified radical mastectomy (MRM) and axillary lymph node dissection (ALND) operations, with an incidence varying from 3% to 85%.[9] Seroma formation is a frequent complication due to the formation of dead space anatomically. Seroma not only causes discomfort to the patient but also requires multiple percutaneous aspirations and surgery. In addition, the formation of a seroma also carries the risk of infection and abscess formation.[10,11]

Seroma is considered to contain lymphatic fluid due to damage to the lymphatic channels, but the pathophysiology is not fully understood, and there are still various controversies. One study showed that there was no relationship between patient characteristics and seroma including albumin levels.[12] However, other studies have concluded that the concentration of serum albumin is a good predictor of postoperative outcome.[13]

Low albumin levels indicate an ongoing systemic response leading to protein loss. The advantage of using serum albumin level as a pre-therapy prognostic factor is that it is an inexpensive, reproducible and powerful predictor.[14] Study Yan-Ping et al (2011) found that total serum protein is a risk factor for seroma formation, which is one of the postoperative complications, so it is vital to predicting postoperative complications.[15]

Based on the controversy above, the authors are interested in the relationship between preoperative serum albumin levels and the incidence of postoperative MRM seromas in KPD patients at Prof. Dr. I.G.N.G Ngoerah General Hospital, Denpasar.

METHOD

This research is an analytic observational study with a cross-sectional study design. A cross-sectional study is a study that studies the distribution, prevalence, and relationship of exposure and disease (outcome) simultaneously. The study was conducted by identifying cases of patients who underwent modified radical mastectomy surgery. Furthermore, preoperative albumin levels were evaluated, such as age, BMI, comorbid diseases, type of surgery, length of operation and use of drains and staging. The research was conducted at the Prof. Dr. I.G.N.G Ngoerah Hospital Medical Record Installation and the Department of Surgery of the Faculty of Medicine UNUD/Prof. Dr. I.G.N.G Ngoerah General Hospital. This research was conducted from January 2022 to June 2022 with ethical clearance number 1204/UN14.2.2.VII.14/LT/2022.

The inclusion criteria in this study included (1) Age of patients listed in medical records with age < 60 years, (2) patients with breast cancer as evidenced by the results of anatomical pathology with stage I – stage II (stages IIA and IIB), (3) patients with stages T1-T3, N0-N1, M0 with tumor size < 5 cm, regional lymph node involvement ≤ 3 regional lymph nodes (4) Albumin sampling time ≤ 30 days before surgery, (5) Undergoing MRM surgery at Prof. Dr. I.G.N.G Ngoerah Hospital from January 2019 to December 2021 with the number of regional lymph nodes resected <20 glands. Exclusion criteria in this study included incomplete medical record data and breast cancer patients who were obese with a BMI > 30 Kg/m2. Data analysis in this study consisted of univariate analysis (descriptive statistics) and bivariate analysis with chi square test. Statistical significance was assessed using a 95%. The entire data analysis process above uses the statistical software SPSS 25.0.

RESULTS

This study involved 128 medical records of patients who underwent modified radical mastectomy surgery from 2019-2021. The characteristics of the respondents were described based on age, length of operation, albumin levels, BMI, comorbid diseases, use of heparin, type of drain, use of drain, and staging. Data is presented in table 1.

TABLE 1: Characteristics of Respondents.

Variable	Seroma		*p.s*
	Yes (n=30)	No (n=98)	
Age (mean, SD)	49±7.7	49.3±7.2	0.172*
Length of Operation (Mean, SD)	210.1±54	192.9 ± 49.4	0.863*
Albumin Levels (Mean, SD)	3.4 ±0.6	3.7±0.6	0.007*
BMI (n, %)			
Obesity (BMI > 25 kg/m2)	20 (15.6%)	27 (21.1%)	0.000**
Normal (BMI 18.5-25 kg/m2)	10 (7.8%)	71 (55.5%)	
Use of Heparins			
Yes	1(0.8%)	0 (0%)	0.070**
No	29 (22.7%)	98 (76.6%)	
Comorbid Diseases			
Yes	15 (11.7%)	27 (21.1%)	0.022**
No	15 (11.7%)	71 (55.5%)	

Variable	Seroma		p.s
	Yes (n=30)	No (n=98)	
Drain Type			
Vacuum	30 (23.4%)	98 (76.6%)	-
Non-Vacuum	0 (0%)	0 (0%)	
Use of Drains			
Yes	30 (23.4%)	98 (76.6%)	-
No	0 (0%)	0 (0%)	
Stagging			
Staging 1	3 (2.3%)	9 (7%)	
Staging 2	12 (9.4%)	36 (28.1%)	
Staging 3	15 (11.7%)	53 (54.1%)	0.926**
Staging 4	0 (0%)	0 (0%)	

** Mann Whitney U Test; ** Chi-Square*

The results of the data normality test on data in the numerical form obtained a p-value > 0.05 so that the data was declared not normally distributed so that bivariate analysis for numerical data was analyzed using the Mann-Whitney U Test while categorical data were analyzed using chi-square. The results of the analysis of the relationship between preoperative albumin levels and the occurrence of seromas are presented in Table 2.

TABLE 2: Relationship between Albumin Levels and the Occurrence of Postoperative Seroma Modified Radical Mastectomy.

Variable	Seroma		RR	CI 95%	p-value
	Yes	No			
Albumin (n, %)					
Low (< 3.5 gr/dl)	23 (18%)	50 (39.1%)	2,4	1.14-5.34	0.013
Normal > 3.5 gr/dl)	7 (5.5%)	48 (37.5%)			

DISCUSSION

The average age of patients who underwent Modified Radical Mastectomy surgery was found to be 49 years and there was no difference between the seroma group and the group without seroma. Age characteristics in this study are different from research Ridha (2017) with an average age of 45 and 47.3 years.[16] Breast cancer is rarely found in women under the age of 20, and the highest rates are found in those aged 45-66 years[17]. The average age of the research subjects is also different as in the research Kurnia (2014), with an average age of 48.5 years (range 33-69 years) and different Banerjee et al (2001) with a median age of 62.3 years (range 36-90 years).[18,19] This difference relates to the subjects of different populations. Banerjee investigated the subject in developed countries with high life expectancies compared to developing countries like Indonesia.

The results of the study showed that there was no difference in the duration of the operation between the seroma group and the group without seroma. The duration of surgery in the seroma group was found to be an average of 210.1 minutes longer than the non-seroma group with an average of 192.9 minutes. This shows that the shorter the duration of the operation, than making less seroma post-operative.[20] Study Pan (2015) found the mean operative time to be 128 minutes and multivariate logistic regression analysis showed that operative time was significantly associated with the incidence of postoperative seroma (P=0.0066, coefficient = 0.03, OR=1.03), with an increase in operative time by 10 minutes to be associated with a 30% higher risk of seroma formation.[21]

There is a significant relationship between BMI and seroma after modified radical mastectomy surgery. These results are in accordance with research Kurnia (2016) that obesity is a risk factor for breast cancer.[22] Study Chaudhary (2020) also found a higher incidence of seromas noted in obese patients increased serous exudation in tissues with a higher adipose cell content, and the associated comorbidities commonly found in obesity.[23,24] According to research Kurnia (2016) obesity as a risk factor for breast cancer. [22] Furthermore, obesity plays a role in the poor healing process and potential complications following a mastectomy procedure.[25–27] Study Banerjee et al., (2001) found a significant correlation between obesity and post-mastectomy complications (p = 0.015) and reported that the total drainage volume in those with obesity was higher than in those without obesity with BMI criteria >30kg/m2) significantly with a p value <0.05.[28]

BMI has a positive linear correlation with seroma formation, and it has been predicted that those with a high BMI produce more seroma than those with a lower BMI.[28,29] In research Kurnia et al., (2016) found a moderate positive correlation (correlation coefficient 0.581), statistically significant linear correlation (p < 0.01) between BMI and total seroma with a determinant coefficient (R2) of 0.338 and this indicated that BMI contributed to total seroma formation during hospitalization as much as 33.8%. It was found that as reported by Banerjee, there is a moderate positive linear correlation between drainage volume and BMI in subjects with breast cancer who underwent MRM with or without axillary dissection or wide excision.[22]

The results showed that there was no significant relationship between the use of heparin and the occurrence of postoperative seroma after modified radical mastectomy. Heparin is commonly used in clinical practice for the prevention and treatment of various thrombotic conditions. Their use can be associated with bleeding that can range from mild to life threatening. Non-traumatic causes of breast hematoma are very rare.[30] The incidence of seroma has been proven correlated with certain factors the use of some drugs such as tamoxifen and heparin.[31–33] All subjects in this study were installed with a drain type of drain with a vacuum drain as much as 23.4% seroma occurred. In research Chaudhary (2020) mentioned that the greater the release of drain production, the greater the risk of seroma occurring.[29]

There is a significant relationship between the presence of comorbidities and the occurrence of postoperative seroma after modified radical mastectomy.

In line with the findings Kabbash et al (2020) and Ouldamer et al., (2016) that the incidence of seromas has been proven correlated with obesity, age, breast size, hypertension, presence of malignancy nodes in the axilla, number of nodes dissected, baseline shoulder exercises, and the use of some medications. [34,35] Poor health condition (ASA score), and diabetes mellitus, support the occurrence of postoperative seroma.[36,37] Different research results were obtained in research Hembram et al. (2020) that hypertension and DM are not related to the occurrence of seroma but Douay et al. (2008)found that hypertension and DM were significantly associated with the occurrence of seroma after mastectomy surgery. Most of the research samples were found to be at stage 3 (54.1%) postoperative modified radical mastectomy.[38,39]

Postoperative breast seroma is defined as the accumulation of serous fluid containing blood plasma and/or lymph fluid under a skin flap or in the axilla.[11] Seroma is the most frequently recurring postoperative problem in modified radical mastectomy (MRM) and axillary lymph node dissection (ALND) operations with an incidence varying from 3% to 85%.[40] Seroma formation is a frequent complication, due to the formation of dead space anatomically. Seroma not only causes discomfort to the patient, but its resolution requires multiple percutaneous aspiration and surgery. In addition, the formation of a seroma also carries the risk of infection and abscess formation.[11,41]

The results showed that the low albumin level in the seroma group was found to be higher (18%) compared to the normal albumin level in the case of seroma (5.5%). There is a significant relationship between low albumin levels and seroma occurrence with an RR value of 2.4 and a p-value <0.05. The results of this study are in line with research Baderiya et al., (2019) concluded that the concentration of serum albumin is a good predictor of postoperative outcome.[42] Study Yan-Ping et al (2011) also found that total serum protein is a risk factor for seroma formation, which is one of the postoperative complications, so it is important to predict postoperative complications.[43]

The results of this study are different from the results of a study by Pan et al (2015) who found that serum albumin was not significantly related to the incidence of seromas in breast cancer patients with p=0.295. Albumin has been widely used in clinical practice because of its unique physiological and pharmacokinetic characteristics. [12] Studies assessing the appropriate use and safety of albumin in cancer patients are lacking. In a retrospective survey involving 53 patients receiving albumin infusion, only 5.7% of the indications were suitable for albumin administration. Sometimes appropriate and inappropriate indications are considered at 10% and 84.3% at a relatively high cost.[44] Research conducted involving 1,070 patients with active cancer found patients with albumin levels below 75%.[45]

Albumin leaves the intravascular space into the interstitium and then returns via the lymphatic system, with a circulating half-life of 16–18 hours. A state of equilibrium is maintained between the different compartments, influenced by a transcapillary discharge rate equal to 4–5% in healthy individuals and by lymphatic flow that is dependent on clearance from the interstitium.[44]Low albumin levels indicate an ongoing systemic response leading to protein loss. The advantage of using serum albumin level as a pre-therapy prognostic factor is that it is inexpensive, reproducible and very strong predictor.[46]

Low albumin levels are associated with inflammation. Inflammation increases capillary permeability and release of serum albumin and causes expansion of the interstitial spaces. In the interstitium, albumin acts as a major extracellular collector, antioxidant agent, and as a supplier of amino acids to cells and matrix. Albumin as a constitutive protein is needed in health and disease. Albumin levels may continue to decrease 3-7 days after surgery and may increase slowly during clinical recovery with normal levels attainable after 3-4 months, reflecting the anti-inflammatory phase of the wound, the process of healing and tissue rebuilding and remodeling. [47] Distribution of several solutes including serum albumin, as well as proteins and electrolytes into the interstitial space, plasma volume, and cell mass. Albumin can enter cells and cell organelles and in pharmacology albumin is considered as a potential carrier to prolong drug effects but in disease conditions albumin's half-life becomes short thus increasing intracellular damage.[48]

Increased vascular permeability to cells and plasma solutes is a universal reaction in trauma, chronic disease and cancer. This can be seen by the presence of edema in wound healing to maintain intravascular volume by trauma or postoperative patients. In postoperative wounds every type of immune cell appears, producing cytokines and growth factors that support the healing process.[49–51] This process is stimulated by proinflammatory and inflammatory cytokines, and wound edema occurs due to expansion of the interstitial space.[52,53] The role of albumin induces increased capillary permeability and angiogenesis, then increases the influx of cells and plasma solutes into the wound and growing tissue. Other sites (muscle and adipose tissue) release these solutes into the vascular compartment from where they enter the extracellular extravascular compartment (interstitium) at an increased rate, also facilitated by increased capillary permeability.[51,54]

The presence of dead space formed from tissue dissection is filled with serous fluid. This fluid changes composition over time postoperatively. At first it resembles lymph fluid with blood clots, indicating damage to the blood and lymph vessels resulting from tissue dissection. The later days tend to resemble exudate, which forms in response to surgical trauma and represents the acute phase of wound healing. [55,56]An exudate rich in protein and cellular elements that drains slowly from blood vessels due to inflammation. Impaired vascular permeability allows larger and denser molecules to pass through the membrane, which filters proteins and cellular elements and produces an aqueous solution. The transudation process increases the pressure on the veins and capillaries which forces fluid to pass through the cell walls. This process causes the formation of a seroma. Hypoalbuminemia reflects an inflammatory state that impairs response to events such as surgery or chemotherapy.[51]

CONCLUSION

The results of the research and discussion show that there is a significant relationship between low albumin levels and the occurrence of post modified radical mastectomy surgery seroma. Serum albumin is not only a window to see the patient's nutritional status but also an important factor in predicting the patient's prognosis. Low albumin levels indicate an ongoing systemic response that is protein loss. The advantage of using serum albumin level as a pre-therapy prognostic factor is that it is an inexpensive, reproducible and very strong predictor.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest related to the publication of this research article.

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ETHICS IN RESEARCH
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