

RISK FACTORS FOR SEROMA DEVELOPMENT FOLLOWING BREAST CANCER SURGERY

Ghazia Qasmi,¹ Muhammad Hassan,² Shahrukh Muneer,³ Syed Qasim Ammar,⁴ Hana Nasir,⁵ Aysha Zafar,⁶ Muaz Shafique-ur-Rehman⁷

ABSTRACT

Background and Objective: Seroma formation is a common complication after modified radical mastectomy and breast conservation surgery in breast cancer patients. This study investigates the factors influencing seroma development in women undergoing breast cancer surgery at a tertiary care hospital in Lahore, Pakistan.

Methods: A retrospective analysis was conducted at a tertiary care hospital in Lahore, including 159 female breast cancer patients aged 20 years and above from 01 august 2020 to 30 September 2022. Patients who underwent modified radical mastectomy (MRM) or breast conservation surgery were included, while those with uncontrolled diabetes, advanced liver disease, or prior axillary surgery were excluded. Data were collected using a semi-structured questionnaire, covering socio-demographic characteristics, known risk factors, and disease history and was analyzed using SPSS-26.

Results: Seroma formation was observed in 37(23.27%) patients out of 159 total patients. On bivariate analysis the findings revealed a higher incidence of seroma among patients from urban areas as compared to rural (29.9% vs 12.9%, $p=0.013$) and higher in lower socioeconomic backgrounds ($> 32\%$ Vs 19.2% , $p=0.042$). High body mass index ($p=0.015$) was also associated with increased seroma formation with more in higher BMI as compared to normal BMI (29% Vs 11.5% , $p=0.015$). Surgical factors, like the number of axillary lymph nodes involved ($p=0.032$) and postoperative wound infections ($p<0.001$) were also significantly associated with seroma formation. However, on multivariate analysis only body mass index with over weight patients (AOR= 4.89, 95% CI=1.29-8.79), axillary lymph nodes involvement (AOR=2.88, 95% CI=1.18-7.05) and post operative infection (AOR=6.23, 95% CI=2.54-15.28) showed significant association. However, factors such as age, education, neoadjuvant chemotherapy, diabetes, hypertension, and postoperative radiation showed no significant association with seroma formation.

Conclusion: Our study found a higher rate of seroma formation, with possible predictors including body mass index, extent of axillary nodal clearance and post operative infection. Mitigation of these factors can prevent seroma formation and better recovery of patient.

Key Words: Seroma, Mastectomy, Breast Conservation Surgery, Hypertension, Breast Neoplasms.

How to cite: Qasmi G, Hassan M, Muneer S, Ammar SQ, Nasir H, Zafar A, et.al. Risk factors for seroma development following breast cancer surgery: JAIMC. 2024; 22(3): 82-88

1. Department of Surgery, Sharif Medical City/Hijaz Hospital, Lahore.
2. Sharif Medical City, Lahore.
- 3-7. Hijaz Hospital, Lahore

Correspondence:

Ghazia Qasmi, Hijaz Hospital/Sharif Medical City Lahore.
Email: ghazia.qasmi@gmail.com

Submission Date: 27-07-2024
1st Revision Date: 30-08-2024
Acceptance Date: 28-09-2024

Seroma is a collection of serous fluid in a dead space of skin flaps, axilla or breast following mastectomy or breast conservation surgery.¹ Seroma formation is a common complication in breast cancer patients undergoing mastectomy. Its incidence ranges from 15% to 81%.² While, this condition is not life threatening; yet, it may be associated with considerable morbidity, such as wound dehiscence, flap necrosis, sepsis, overall delay in recovery and potential delay in adjuvant

therapy.³

Exact pathophysiology of seroma formation after mastectomy is unknown. It is formed by acute inflammatory exudates in response to surgical trauma and acute phase of wound healing.⁴ It has been proposed that extensive dissection in mastectomy and axillary lymphadenectomy damages several blood vessels and lymphatics and the subsequent oozing of blood and lymphatic fluid from a large surface area, compared with breast conserving surgery which leads to seroma formation.^{5,6}

Previous studies have identified age of the patient, hypertension, higher body mass index (BMI), operative technique and increased drain output during first 24 hours as the risk factors related to post-operative seroma formation.^{7,8} However, no causative association has been established with any of these factors. According to Oertli et al.⁹ fibrinolytic activity contributes to seroma formation, whereas Petrek et al.¹⁰ in a prospective randomized trial reported that the most significant influencing factors in the causation of seroma were the number and extent of axillary lymph node involvement. Nevertheless, other authors, Gonzalez et al.¹¹ and Hashemi et al.¹² showed that that modified radical mastectomy was more likely to be associated with seroma formation than local excision and axillary dissection. These studies did not report age, BMI, obesity and tumour size as risk factor for seroma formation.

Data on factors related to seroma formation after mastectomy are inconsistent in Pakistan. Few studies have reported incidence of seroma formation after mastectomy ranging from 24% to 27%;¹³ however, a comprehensive elaboration of associated factors has not been reported. Only BMI was identified as the factor affecting seroma formation; in addition to the use of flap fixation technique, which minimizes the risk of seroma formation.

The objective of this study was to describe factors affecting seroma formation after modified radical mastectomy and breast conservation surgery among female breast cancer patients operated in a tertiary care hospital of Lahore. We attempted to identify patients at higher risk for seroma formation.

Results of this study would provide a baseline data and would identify high-risk patients for our subsequent studies. These studies, then, would investigate the effectiveness of surgical measures such as dead space obliteration by quilting sutures, use of tissue glue, pressure dressing, intraoperative hydrocortisone and tranexamic acid to reduce the risk of seroma formation and to reduce morbidity associated with this complication.^{4,5,6}

METHODS

This study was conducted in a not-for-profit tertiary care hospital of Lahore, Pakistan (Hijaz hospital Lahore, affiliated with FMH College of Medicine and Dentistry) for patients diagnosed as having breast cancer from 01 august 2020 to 30 September 2022. A retrospective cohort of consecutively operated breast cancer patients' data were collected and reviewed. Female patients aged 20 years and above, who were diagnosed to be having breast cancer and underwent modified radical mastectomy or breast conservation surgery were included in the study. Patients on anti-coagulants, uncontrolled diabetes, advanced liver disease, previous surgery in axilla or planned immediate reconstruction were excluded from study. Sample size was calculated using World Health Organization's sample size determination calculator developed by Lamesshow and Hosmer.¹⁴ Anticipated population proportion of 5.3 % was used,⁵ with margin of error (d) of 5%. 10 % of calculated sample size was added for anticipation of non-response, dropout or missing data, making the total sample of 83 for this study. However 197 patients were included to increase the generalizability of this study.

All the patients underwent modified radical mastectomy or breast conservation surgery as per NCCN guidelines. All surgeries were performed by single surgeon. Dissection was performed with electrocautery in all cases. Two drains were placed, one under flap and one in axilla for patients who underwent MRM while in breast conservation cases single drain was placed in axilla. Pressure dressing was not applied in any case and patients were encouraged to start shoulder exercise the very next

day. Flap drain was removed on day 6 and axillary drain was removed on day 12 or when output was less than 30ml per 24 hours. Any amount of fluid collection under mastectomy flaps after the removal of drain (12th post-operative day or when drain output was less than 30cc per day) was considered to be coming from seroma. Patients were routinely called after 1 month of surgery before referral for adjuvant treatment for any wound related complications in our unit. Any complication including seroma during this period was routinely documented. Patients were also educated about late complications including seroma (a visible swelling under wound or armpit), lymphedema, and follow-up plan with surgery department for systemic and local recurrence. Telephonic communication was used for those patients who did not come for routine follow-up visit.

A semi-structured pretested questionnaire comprised of close end questions was designed to collect a data. The different sociodemographic factors that were taken into consideration were age, education level, employment status, total household income, sedentary lifestyle, and marital status. Other factors taken into consideration were body mass index, diabetes, hypertension, cancer stage disease, whether neoadjuvant chemotherapy was given, total number of axillary lymph nodes removed during surgery, postoperative wound infection and postoperative radiation.

Data entries were double-checked by a senior research assistant and verified by the researchers. Hard copy data were entered into SPSS-26 after defining variables according to the specified scales. Inconsistencies were identified and corrected through frequency distribution checks.

The final dataset was de-identified by assigning unique identification numbers and securing it with a password accessible only to the principal investigator. A copy of the dataset was shared with the statistician for analysis. SPSS version 26 was used for data management and statistical analysis. Descriptive statistics were generated for categorical variables using frequency distributions, while continuous variables were summarized as mean $\pm$ SD. Normality was assessed using histograms for continuous variables, including age. Cross-tabulations was done to determine the

risk factors of seroma formation and Chi-square test was used to compare group proportions with a significance level of $p < 0.05$.

Informed verbal consent was taken from participants before start of interview (new enrolments) and also telephonically to discharged patients to review their clinical files. Participants had the right to withdraw from study any time. Confidentiality of data was maintained by using secure passwords and de-identification of dataset. Participation was voluntary and no monetary benefit was given.

RESULTS

In this study 197 patients were selected based on inclusion criterion. However, 13 patients were not ready to share information and 25 patients' data was inaccurate or incomplete, so they were excluded. the results are therefore based on the information collected from 159 patients (Figure 1).

Analysis showed that in patients with age more than 50 years seroma formation was observed in 28.8% as compared to patients less than 50 years of age with ($p = 0.165$) showing no significant association. Similarly educational status, working status, diabetes mellitus, hypertension and postoperative radio showed no significant association with seroma formation. The bivariate analysis demonstrated that patients from urban and rural areas had a significantly higher incidence of seroma formation ($p = 0.013$) with more higher rates in urban population, as did those from lower socioeconomic backgrounds ($p = 0.042$). Additionally, a high body mass index (BMI) was strongly associated with increased drain output and seroma development ($p = 0.015$). Surgical factors also played a role, with a greater number of axillary lymph nodes removed ($p = 0.032$) and postoperative wound infections ($p < 0.001$) being linked to seroma formation (Table 1).

However, on multivariate analysis, only BMI ($p = 0.021$), the extent of axillary lymph node involvement ($p = 0.032$) and post operative infection ($p < 0.001$) maintained a significant association with seroma development Table # 2.

The Kaplan Meier curve indicated that majority of seroma occurred within 6 months of treatment. Those with high BMI were found to have more risk of seroma Figure #2

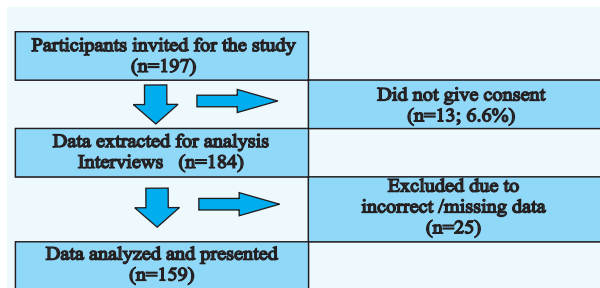


Figure 1: Recruitment of breast cancer patients undergoing modified radical mastectomy

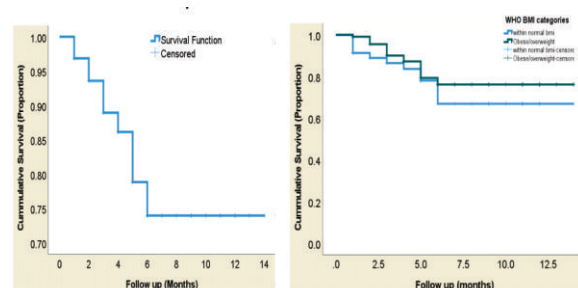


Figure 2: Kaplan-Meier curves showing seroma formation over time in relation to BMI

Table 1: Sociodemographic characteristics and the clinical features among breast cancer patients operated for modified radical mastectomy at a trust hospital in Lahore (n=159)

Characteristics	Seroma developed (n=37)		No seroma developed (n=122)		Total (n=159)	p-value
	Number	Percentage	Number	Percentage		
Age						0.165
≤ 50 years	18	19.4%	75	80.6%	93	
>50 years	19	28.8%	47	71.2%	66	
Educational status						0.458
No formal schooling	12	25.0%	36	75.0%	48	
Upto primary education	13	28.3%	33	71.7%	46	
More than Primary education	12	18.5%	53	81.5%	65	
Working status						0.570
Working	03	16.7%	15	83.3%	18	
Not Working	34	24.1%	107	75.9%	141	
Monthly family Income (Rs)						0.042
Upto25 K	24	32.0%	51	68.0%	75	
>25K to ≤ 50 K	08	13.8%	50	86.2%	58	
>50 K	05	19.2%	21	80.8%	26	
Area of residence						0.013
Urban	29	29.9%	68	70.1%	97	
Rural	08	12.9%	54	87.1%	62	
Body mass index (BMI)						0.015
Normal (18.5-24.9kg/m ²)	06	11.5%	46	88.5%	52	
Overweight/Obese (>25kg/m ²)	31	29.0%	76	71.0%	107	
Diabetes Mellitus						0.467
Yes	09	28.1%	23	71.9%	32	
No	28	22.0%	99	78.0%	127	
Hypertension						0.243
Yes	16	28.6%	40	71.4%	56	
No	21	20.4%	82	79.6%	103	
Post-operative infection						<0.001
Yes	21	47.7%	23	52.3%	44	
No	16	13.9%	99	86.1%	115	
Axillary lymph node involved						0.032
Yes	20	32.3%	42	67.7%	62	
No	17	17.5%	80	82.5%	97	
Post-operative radiation						0.561
Yes	34	23.9%	108	76.1%	142	
No	03	17.6%	14	82.4%	17	

Abbreviations: k, 1000; m, meter; kg, Kilogram

Table 2: Predictors of seroma formation in breast cancer patient undergoing radical modified mastectomy at a trust hospital of Lahore (n=159)

Predictors	Adjusted Odds Ratio (AOR)	95% CI. Of AOR	p-value
Age			
≤ 50 years	1	Reference	0.609
>50 years	1.26	0.52-3.09	
Body mass index (BMI)			
Normal (18.5-24.9kg/m ²)	1	Reference	0.021
Overweight/Obese (>25kg/m ²)	4.89	1.29-8.71	
Axillary lymph node involved			
Yes	2.88	1.18-7.05	0.031
No	1	Reference	
Post-operative radiation			
Yes	0.79	0.16-3.86	0.770
No	1	Reference	
Post-operative infection			<0.001
Yes	6.23	2.54-15.28	
No	1	Reference	

DISCUSSION

The objective of our study was to assess the risk factors associated with seroma formation after breast cancer surgery in a trust hospital of Lahore. We found that seroma developed in 37 out of 159 patients (23%). Patients who had more seroma formation were those who had high body mass index, more number of total axillary lymph nodes removed and who had postoperative infection but we did not find any statistically significant difference in patients with Diabetes, hypertension, more age and post operative radiation.

The incidence of seroma formation in our study is 23%. Previous studies has reported incidence ranges from 15% to 90%.² Various factors have been evaluated to find with seroma formation like BMI, age, diabetes, hypertension, sedentary life style, number of lymph nodes removed, effect of early shoulder mobilization and number of drains. According to fabro et al.¹⁴ in a prospective cohort of 249 patients, being overweight or obese and those undergoing axillary clearance were not associated with seroma development risk factors. In our study, the consistent predictors were BMI, axillary lymph node clearance and post operative infection with a significant p value of 0.021, 0.031 and <0.001

respectively.

Presence of Diabetes, hypertension and old age have been associated with seroma formation in various studies. In study khanat et al¹⁵ the incidence of hypertension was found more in seroma formation group 31(51%) patients as compare to non-seroma group 8(13%) patients with odd ratio OR 1.488. In a study by Anjum et. al¹⁶ hypertension was the most consistent significant risk factor for seroma formation subsequent to modified radical mastectomy . Good pre, peri and post-operative blood pressure control was proposed to reduce the risk of seroma formation and the morbidity. In our study patients with hypertension did not have significant seroma formation. This can be attributed to good perioperative control in our unit. Diabetes has been known to increase wound related complications after many surgeries including MRM, but in our study its relation is not statistically significant. This has been observed in other studies by Narasimhappa et al, and Xiao feng et al. that Diabetes does not have clinically significant impact on seroma formation. Increased age is yet another factor that is significant in many studies like, results of SerMa pilot study¹⁹ showed that seroma formation is more common in elderly patients (median patient

age in patient cases with seroma 73 years vs. 52 years without seroma; $p < 0.001$. In the study by Chandreka kumari,²⁰ among the patients assessed with seroma formation, 59.02% were aged 56 or older, while 40.06% were under 56. This research indicates that advancing age is a risk factor for the development of seroma, however our study does not support this. This could be due to the fact that most of our patients were under 60 years of age which has been a cut off predicting value in most studies.

The pathophysiology of seroma formation remains unclear; which renders targeted therapies challenging.²¹ Several authors have suggested disruption in lymphatics due to excessive tissue dissection results in impaired fluid drainage. Tissue trauma itself cause inflammation and increased vascular permeability. This combined with fibrinolytic activity and the dead space created by breast tissue removal leads to collection of fluid in free dead space. That is why more seroma is seen in MRM than with BCS and total number of lymph nodes removed. Some patients are at high risk due to proinflammatory state like diabetes, obesity or poor vascular status as in hypertension, smoking or old age. Surgical technique variations, like use of single drain vs two, use of tranexamic acid, early shoulder mobilization, use of quilting stitch have all been used to reduce the incidence of seroma formation. However, the results show variation and no single risk factor or technique has been definitively established fact and it remains dilemma, to be labelled as consequence rather than a complication.^{22,23,24}

This study is valuable as it focuses on a uniform patient population from a lower socioeconomic background. The sociodemographic characteristics and disease stages were comparable among participants. However, additional factors like poor immunity and delayed presentation should be considered for this specific subset. The limitations of the study include its small sample size and single-center design, limiting generalizability. The findings highlight the need for national and international collaborations to explore factors affecting similar profiles, enhance sample size, and enable better causal stratification and reasoning. Furthermore, strategies for reducing seroma through risk

identification in this group can be developed.

CONCLUSION

We concluded that comparatively higher seroma formation was seen in our population. The predictors in our study were level of axillary nodal clearance, high BMI and postoperative infection. Diabetes, hypertension and increase age did not have a statistically significant relation. The findings emphasize the importance of identifying high-risk patients and suggest that addressing modifiable factors like BMI and postoperative care could help reduce seroma incidence and improve recovery outcomes

Ethical Approval: This study was approved by Ethical Review Committee of Fatima Memorial Hospital, Lahore, vide No. ERB No.: FMH-16/05/2022-IRB-1052.

Funding source: *None*

Conflict of interest: *None*

AUTHOR'S CONTRIBUTION

Conceptualization and study design	GQ, SQA, AZ, MS
Data Acquisition	GQ, SM, SQA,
Data Analysis/ interpretation	GQ, SQA, HN, AZ
Manuscript drafting	GQ, SM, HN, AZ, MS, MH
Manuscript review	GQ, SM, HN, AZ, MS

All authors read and approved the final draft.

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