ORIGINAL ARTICLE

Incidence and risk factors of upper limb lymphedema in breast cancer patients after surgery

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Abstract

Background: Upper limb lymphedema is a common and troublesome complication that follows breast cancer surgery. *Aim and Objectives:* To find the incidence and identify risk factors for the development of upper limb lymphedema among patients treated for breast cancer. *Material and Methods:* This was a prospective observational study of 135 patients who underwent different breast cancer surgeries for invasive breast cancer. A description of the patients' demographics and details related to the tumour and axillary clearance were recorded. Using the circumference measurements, lymphoedema was defined as a difference in volume of ⩾ 200 ml between the two arms after six months of surgery. *Results:* Age, type of surgery (mastectomy versus breast preserving surgery), and adjuvant radiotherapy were not risk factors for lymphedema (p = 0.9977, 0.7794 and 0.852 respectively).A significant correlation was found between BMI above 25 kg/m^2, advanced stage, higher number of excised lymph nodes and more than 5 involved lymph nodes, and the development of lymphedema (p = 0.0001, 0.002, 0.01 and 0.009 respectively). Positive lymph nodes was a powerful predictor of lymphedema (p = 0.0003). *Conclusion:* Lymphedema can affect every third patient who is operated on for breast cancer. Advanced stage, increased BMI above 25 kg/m^2, increased number of excised lymph node together with increased number of involved lymph nodes, are significant risk factors for breast cancer related lymphedema.

Keywords: Breast Cancer Lymphedema, Risk Factors, Upper Limb, Morbidity

Introduction

Breast cancer is the commonest cancer among females worldwide and it is the second most common cancer related death. Globally, 2.3 million new cases were registered in 2020 with 685,000 deaths. [1-2]. In early breast cancer (stage I and II), the three main prognostic factors are Lymph Node (LN) status, tumor size, and histological grade (assessed by Scarff-Bloom-Richardson's or Robinson's cytological grading) [3, 4]. An improved 5-year survival rate for breast cancer which reaches 90% is obviously related to better treatments. This led to a significant increase in the number of the long term complications such as Postmastectomy Lymphedema (PML). PML of the arm is one of the troublesome side effects related to breast cancer treatment with no possible cure but only possible to reduce the limb size with treatment [5-6]. Lymphoedema (LE) affect about 1 in each 3 patients managed by Axillary Lymph Node Dissection (ALND) [7]. PML occurs due to

impaired lymphatics' function, leading to interstitial lymph fluid retention which is protein-rich. This causes ipsilateral swelling in the axilla, arm and hand [8].

Fluid retention in the interstitium is followed by recurrent attacks of acute subcutaneous inflammation causing fibrotic thickening of the skin. Recurrent cellulitis also results in further damage to the lymphatic vessels and advancement of lymphoedema [6, 8]. Although physical limitation of the affected limb characterize advanced lymphedema, more than minimum swelling can cause symptoms, resulting in physical impairment. Such symptoms include limb swelling, feeling of heaviness and numbness, and pain [9]. Quality of life also get affected due to anxiety, emotional distress, and changes in body contour [9].

The principle treatment for Breast Cancer Related Arm Lymphedema (BCRL) is conservative with physiotherapy, with complete decongestive therapy and in selected cases, microsurgery. No known curative treatment for BCRL is available [6, 10]. Fear of developing lymphedema in at-risk patients has been revealed to impact patients' physical activity and quality of life through altered lifestyle and activity limitations [11].

Risk factors for lymphedema

Although, studies reported varying findings, most did not identify the age as a significant risk factor for lymphedema development. Despite that, the level of evidence of individual studies was low [12]. A high level of Body Mass Index (BMI) is considered a risk factor for BCRL. Despite BMI being unmodifiable risk factor, these patients might get benefit from close surveillance for lymphedema during follow up [13-14]. Advanced cancer stage is associated with more lymph nodes being involved by the disease and even the incidence of matted axillary lymph nodes rise with the increasing disease stage [15]. Advanced stage breast cancer is associated with significantly increased number of patients with BCRL when compared to early stages (I and II) breast cancer [16]. Many studies showed no statistical difference between Modified Radical Mastectomy (MRM) and Breast Preserving Surgery (BPS) with regard to PML as both of them involve axillary dissection [16-17].On the contrary, other studies identified BCRL being related more to MRM than BPS [15]. Many studies have showed that adjuvant radiotherapy is not a risk factor for the development of lymphedema [17-18].

Other studies revealed that radiotherapy can result in occlusion of veins within the irradiated field, lymphatic damage, and can even cause local muscle fibrosis which interfere with the lymphatic and venous circulation [19-20]. One large cohort study showed that regional lymph node irradiation significantly increased the risk of BCRL compared to breast/chest wall irradiation alone [21]. There is no doubt that ALND increases the risk of developing lymphedema and this risk increases with more lymph nodes being removed, together with increasing the number of positive lymph nodes. [22]. Both of ALND and the less invasive Sentinel Lymph Node Biopsy (SLNB) increase the risk of lymphedema due to removal of axillary lymph nodes [23]. Many studies also revealed that involved (positive) axillary lymph nodes is a strong risk factor for BCRL [24]. Positive lymph nodes is even a risk factor for preoperative lymphedema due to obstruction to the lymphatic flow through involved lymph nodes [25].

Material and Methods

This was a prospective observational study of 135 patients who underwent surgeries for invasive breast cancer. The study was carried out between January 2018 and September 2022 at Baquba Teaching Hospital, Diyala Province, Iraq.

Inclusion criteria

Female patients with invasive breast cancer (stage I-IV); unilateral axillary node clearance; no more than level II axillary dissection; age range of 20-75 years; good general condition; given a consent to participate; no contralateral lymphoedema; no defective skin barrier; and no affected kidney or liver function were included in the study.

Exclusion criteria

Women with recurrent ipsilateral breast cancer; prior ipsilateral axillary clearance for breast cancer, past history of mantle radiation and those who were known cases of immunodeficiency were excluded from the study.

The study was initiated after obtaining ethical approval from the Institutional Ethics Committee (Letter no 127/ Baquba Teaching Hospital for researches on Human Subjects 2018, dated 16/1/2018)

Definition of lymphoedema

In this study, the patients were assigned as having lymphedema when ⩾ 200-mL difference in arm volume was present for more than 6 months [26-27].

Risk factors

Participants were studied for the following independent risk factors for lymphedema: age; BMI; tumour stage (early stage I and II versus advanced stages III and IV); MRM versus BPS, adjuvant radiotherapy, total number of lymph nodes excised and the number of positive (involved) lymph nodes. All patients had level II axillary dissection as a maximum.

Data collection

Depending on the risk factor being studied, data were collected during preoperative assessment, intraoperatively and in the postsurgical period through histopathological examination. Baseline arm measurements were taken during preoperative assessment, and follow-up measurements at 6 months postoperatively. Demographic variables as age and BMI (kg/m^2) were reported during the preoperative assessment. Stage of the disease was ascertained by collecting clinical, radiological and postoperative histopathological results. Extent of breast surgery (MRM/BPS) and the number of excised lymph nodes were intraoperative findings. Positive lymph nodes and adjuvant radiotherapy data were collected postoperatively.

Measurement of lymphoedema

The circumference measurement was used for identifying lymphedema. Circumference measurements were converted to limb volume by applying the geometric formula for a truncated cone (frustum). In this method the patient was kept in sitting position with her hand pronated. A low-stretch tape with an accuracy of 1 mm was placed directly in contact with the skin around the arm without application of excessive pressure.

Measurements were done at two places; at the wrist, just below the ulnar styloid process (lower circumference), and at the upper arm, 20 cm proximal to the lateral epicondyle of the humerus (upper circumference). The arm volume was then calculated from these two circumference measurements by applying the frustum method (truncated

cone method), in which the lower circumference of the arm was indicated as (c) and the upper circumference was indicated as (C); both measured in centimeters (cm). Then, the formula $V=h\ (C^2 + Cc + c^2)/12\pi$ was applied, where 'h' was the distance between the upper and lower circumference (in cm). Both sides were measured; the contralateral side was used to compare with the affected one. Interlimb difference of 200 ml or more was described as being diagnostic of BCRL [26-27].

Statistical analysis

Bivariate analysis was used to study the effect of each of the independent variables on lymphedema development. This was applied for age, BMI, stage, type of surgery, adjuvant radiotherapy, number of excised lymph nodes and the number of involved lymph nodes. As both MRM and BPS are associated with dissection of the axilla, the relative risk of each for the development of lymph edema was calculated.

The inter-correlation effect (odds ratio) of the variables that appeared to significantly relate to lymphedema were examined using logistic regression. Value of $p < 0.05$ was considered statistically significant. Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS)22 for Windows.

Results

One hundred and thirty five patients treated for breast cancer were recruited in this study. Thirty eight (28.14%) patients developed lymphedema. Average age of the patients was 49.27 years. Most of the patients (37.8%) were in the age group 40-49 years, followed by the age group 50-59 years (28.9%), and followed by patients in the age group ⩾ 60 years (16.3%). Bivariate regression was applied to assess the effect of each of the independent factors on the development of postoperative lymphedema.

Taking all age groups together, there was no statistical significant correlation between patients' age and the development of postoperative lymphedema ($p = 0.9977$). By applying bivariate regression in each age subgroup, it was shown that the age group 30-39 was significantly associated with BCRL ($p = 0.035$) (Table 1).

Table 1: Incidence of lymphedema among different age groups (Bivariate regression)

Age groups	Total	Developed edema	Not developed edema	*p*	CI
20-29	6	1	5	0.432^{NS}	-0.436-0.836
30-39	17	3	14	0.03518*	-0.14-0.005
40-49	51	13	38	0.7538^{NS}	-0.05-0.036
50-59	39	11	28	0.9633^{NS}	-0.06-0.05
⩾ 60	22	10	12	0.2645^{NS}	-0.03-0.11
Total	135	38	97	0.9977^{NS}	-4.002-4.118

*NS: Not significant, *significant at p < 0.05*

With regards to BMI, the current study revealed statistically significant correlation between BMI above normal and the development of postoperative lymphedema. There was significant correlation ($p = 0.0001$; CI = 0.01-0.03); for patients with BMI 25-29.9 ($p = 0.041$; CI = 0.005- 0.22); for patients 30-39.9 ($p = 0.038$; CI = 0.002-0.08) and for patients ⩾ 40 ($p = 0.039$; CI = 0.017-0.61) (Table 2).

Our study revealed significant correlation between the stage of breast cancer and the development of lymphedema ($p = 0.002$; CI = 0.07-0.29). For highlighting the effect of specific disease stage in the development of lymphedema, the relative risk was calculated comparing early breast cancer (stage I and II) with locally advanced and metastatic breast cancer (stage III and IV), it was 0.43 and 2.3 respectively. It indicated that the probability of developing lymphedema was lower for early breast cancer compared to locally advanced and metastatic breast cancer (Table 3).

Table 2: Associations between body mass index and lymphedema

Body mass index	Total	Developed edema	Not developed edema	*p*	CI
18-24.9	31	8	23	0.75^{NS}	-0.08-0.12
25 -29.9	46	14	32	0.041*	0.005-0.22
30-39.9	43	10	33	0.038*	0.002-0.08
⩾ 40	15	6	9	0.039*	0.017-0.61
Total	135	38	97	0.0001**	0.01-0.03

NS: Not significant, significant at $p < 0.05$, highly significant**at $p \leq 0.001$*

Table 3: Associations between stage of the cancer and lymphedema

Stage	Total	Developed edema	Not developed edema	*p*	CI
(I-IV)	135	38	97	0.002*	0.07-0.29
				Relative risk	
Stage I	64	11 (17.1)	53 (82.81)	0.43	
Stage II	57	19 (33.33)	38 (66.6)		
Stage III/IV	14	8 (57.14)	6 (42.86)	2.3	

*NS: Not significant, *significant at $p < 0.05$*

With regard to the type of surgery, our study revealed no significant correlation between the type of surgery and the development of lymphedema (p = 0.7794; CI = -0.20- 0.152) (Table 4). Our study revealed no significant correlation between the development of lymphedema and adjuvant radiotherapy (p = 0.852; CI = -0.14- 0.17) (Table 5).

Our study revealed significant correlation between the number of excised lymph nodes and the development of lymphedema (p = 0.01; CI = 0.02-0.14). Also, the current study showed significant correlation between the number of positive (involved) lymph nodes and the development of lymphedema (p = 0.0007), and the later was specifically significant when the number of positive lymph nodes was ⩾ 5 compared to < 5 positive lymph nodes (p = 0.009, 0.273) respectively (Table 6).

Table 4: Associations between type of surgery and lymphedema

Surgery	Total	Developed edema	Not developed edema	*p*	CI
BPS	34	9	25	0.7794^{NS}	-0.20-0.152
MRM	101	29	72		
Total	135	38	97		

*NS: Not significant, *significant at p < 0.05*

Table 5: Associations between receiving adjuvant radiotherapy and development of lymphedema

Radiotherapy	Total	Developed edema	Not developed edema	*p*	CI
Adjuvant	80	23	57	0.852^{NS}	-0.14-0.17
No adjuvant	55	15	40		
Total	135	38	97		

*NS: Not significant, *significant at p < 0.05*

Table 6: Associations between number of excised lymph nodes and lymphedema

Excision	Mean ± SD	Developed edema	Not developed edema	*p*	CI
LN removed	11.45 ± 1.27	38	97	0.01^{*}	0.02-0.14
Positive lymph nodes	4.49 ± 0.82	38	97	0.0007^{**}	0.07 -0.25
≥ 5 positive lymph nodes	5.22 ± 0.48	24	41	0.009^{**}	0.08 -0.56
< 5 positive lymph nodes	3.82 ± 0.38	14	56	0.2735^{NS}	-0.11-0.39

NS: Not significant, significant at p < 0.05, highly significant**at p ≤ 0.001*

By applying a multivariate regression, the independent effect of BMI, disease stage, number of excised lymph nodes and the number of involved lymph nodes were studied as a risk factor for the development of lymphedema. The regression yielded that the number of involved lymph nodes was having the strongest correlation for developing lymphedema ($p = < 0.0001$), followed by the stage of the disease ($p = 0.0004$), BMI ($p = 0.002$) and the number of excised lymph nodes ($p = 0.03$) (Table 7).

Identification of the predictive factors for lymphedema development was done by applying a logistic regression analysis. The predictive factors of this analysis and their influences have been displayed in Table 8. The results of the current study revealed that every additional lymph node involvement, each one unit increase in the stage, every additional excised lymph node , and each one unit increase in the BMI could increase the odds of lymphedema by 3.14 , 3.08, 1.45 and 1.12 times respectively.

Table 7: Demographic and clinical characteristics of the patients

Variable	Coefficients	Standard Error	*p*	CI
Intercept	-2.03332	0.380766	0.000	-2.78- -1.28
Body mass index	0.016324	0.005243	0.002	0.006- 0.03
Stage	0.187336	0.05176	0.0004	0.08- 0.29
Number of excised lymph nodes	0.060147	0.027046	0.03	0.007- 0.12
Number of positive lymph nodes	0.184137	0.041489	0.000	0.10- 0.27

NS: Not significant, significant at $p < 0.05$, highly significant** at $p \leq 0.001$*

Table 8: Predicting factors of lymphedema

Predicting factors	Coefficients	Standard Error	*p*	CI
b_0	-15.7221	3.1066	0.000	1.486e-7 (-21.81-9.63)
Body mass index	0.1076	0.03706	0.004	1.12 (0.04-0.18)
Stage	1.1262	0.3620	0.002	3.08 (0.45-1.84)
Excised lymph nodes	0.3678	0.1821	0.043	1.45 (0.01-0.72)
Involved lymph nodes	1.1447	0.3162	0.0003	3.14 (0.52-1.76)

Discussion

Lymphedema is a known complication of cancer surgery as the later involve lymph node dissection. Arm edema can appear at any time following dissection of the axillary lymph nodes. Lymphedema may occur immediately or several years following surgery [28]. In our study, thirty eight (28.14%) patients developed lymphedema. Eighty-four cohort studies reviewed by Shen *et al.,* (2022) included 58,358 patients with breast cancer; the cumulative incidence of lymphedema was 21.9% [15]. Ugur *et al*.,(2013) revealed that the incidence of BCRL was 27% (124 out of 455 patients) [16]. Ren *et al*., (2022) showed that lymphedema prevalence was 6.8% at baseline, and it was 19.9% and 23.8% at 2 and 7 years, respectively, following lymphedema diagnosis [28]. Ribeiro Pereira *et al*., (2017) showed that the cumulative incidence of BCRL was 13.5% at two years, 30.2% at five years and 41.1% at 10 years of follow up [29].

Our study could not find any significant effect of age in the development of lymphedema (p = 0.9977). The age was significant risk factor only in the age group 30-39 (p = 0.035) and this could be explained by the low total number of patients in this age group and all of the three patients who developed lymphedema had involved lymph nodes $\geqslant$ 5. Our results are in accordance with that of Guliyeva *et al*., (2023) who performed systematic review of articles that were published between 1974 and 2020 (26 studies, 19,396 patients) concerning the risk factors for lymphedema development related to surgery for breast cancer with aim to determine age as a risk factor [12]. They found that 13 out 26 studies reported no correlation between age and lymphedema development.

Our study identified BMI above normal as a significant factor for the development of postoperative lymphedema (p = 0.0001). Leray *et al*., (2020) who retrospectively studied 74 patients with BCRL found that BMI was the only risk factor associated with severe lymphedema (p = 0.0132) [13]. Wu *et al*., (2019) in their meta-analysis of 12 studies with 8039 patients having CA breast found that patients with a BMI of 25–30 kg/m^2 had 1.42 times [OR 1.42 with 95% confidence interval 1.20-1.68] risk of developing BCRL compared to those with BMI < 25 kg/m^2; 1.39 times [OR 1.39 with 95% CI of 1.21-1.6) for those with BMI $\geqslant$30 kg/m^2 compared to BMI 25–30 kg/m^2 group, and 1.84 times [OR 1.84 with 95% CI of 1.47- 2.32] for BMI $\geqslant$ 30 kg/m^2 compared to BMI <25 kg/m^2 group [14]. Our study found advanced stages to be strongly correlated with BCRL (p = 0.002). Shen *et al.,* (2022) found higher cancer stage (III) being correlated more with the development of lymphedema when compared to early stages (I-II) [15]. Ugur *et al.,* (2013) followed up 455 patients found the incidence of lymphedema lesser in those with early breast cancer compared to those with advanced ones (24% and 35.3%, respectively, p = 0.018) [16]. Shahpar *et al.,* (2013) also identified advanced stage as a significant risk factor for BCRL [17]. Our study did not find the surgery type (MRM vs BPS) to be a risk factor for lymphedema (p = 0.7794. These results are in accordance with that of Ugur *et al.,* (2013), Shahpar *et al.,* (2013) and Hara *et al*., (2022) which showed no significant difference between the two procedures (p = 0.924, 0.817, and 0.70 respectively) [16, 17, 22]. On the contrary, Shen *et al.,* (2022) identified that BCRL is related more to MRM than BPS [15].

Our study revealed no significant correlation between the development of lymphedema and adjuvant radiotherapy ($p = 0.852$; CI = -0.14-0.17). Our results are in concordance with Shahpar *et al.,* (2013) and Lee *et al*., (2012) who recognized in their studies that radiotherapy was not a risk factor for BCRL ($p = 0.265$ and 0.440 respectively) [17, 18]. On the other hand, Zhu *et al*., (2014) had reviewed 25 studies with 12,104 patients and found that adjuvant radiotherapy increased the incidence of BCRL by 35% [19]. One possible explanation for the differences in the results between studies could be in the ways that radiotherapy had been given in recent years [20]. Warren *et al*., (2014) in their large prospective study showed that Regional Lymph Node Radiation (RLNR) increased the incidence of BCRL significantly (hazard ratio 1.7, $p = 0.025$) when compared to breast/chest wall radiation alone and suggested that clinicians should assess the potential benefit of RLNR considering its raised risk of lymphedema [21].

Our study showed that lymphedema significantly correlated to the number of excised lymph nodes ($p = 0.01$). Hara *et al*., (2022) showed that dissection of more than 18 lymph nodes significantly increased the risk of lymphedema compared to less than 18 lymph nodes excised ($p = 0.05$) [22]. Zhu *et al*., (2014) recognized axillary lymph node dissection as a significant risk factor for postmastectomy lymphedema, increasing the risk by 3.73% (OR = 3.73, 95%; CI 1.16 to 11.96) [19].

Also, our study showed significant correlation between the number of involved lymph nodes and the development of lymphedema ($\geqslant 5$ versus < 5 lymph nodes) with $p = 0.009$ and 0.273 respectively. Liu *et al*., (2023) also recognized positive lymph nodes as a strong predictor for the BCRL ($p = 0.04$) (odd ratio of 1.06; CI 1.00-1.13) and found that dissection of interpectoral lymph nodes greatly contributed to the development of severe lymphedema with a higher odds ratio (7.76; 95% CI: 3.87–15.54) [24]. Iyigun *et al*., (2018) identified that the number of positive lymph nodes was a significant risk factor for lymphedema ($p = 0.003$) [25]. Ren *et al*., (2022) also found that excision of more than five lymph nodes was associated with increased hazard by 2.65 (165%; CI 1.99-3.53) [28].

Of the aforementioned risk factors, our study showed that the number of involved lymph nodes was associated with the strongest correlation for the development of postoperative lymphedema ($p = <0.0001$), followed by the stage of the disease ($p = 0.0004$), BMI ($p = 0.002$) and the number of excised lymph nodes ($p = 0.03$). Iyigun *et al*., (2018) also identified on multiple regression that positive lymph nodes were the most significant risk factor for lymphedema ($p = 0.002$) [25].

The current study revealed that every additional lymph node involvement, each one unit increase in the stage, every additional excised lymph node , and each one unit increase in the BMI could increase the odds of lymphedema by 3.14, 3.08, 1.45 and 1.12 times respectively. These results are higher than those found by Shahpar *et al*., (2013) that every additional lymph node involvement and each unit increase of BMI, could increase the odds of arm swelling by 15% and 9% respectively [17].

Conclusion

Lymphedema can affect up to one third of breast cancer patients, affecting their quality of life. Advanced disease, increased BMI above 25 kg/m^2, increased number of excised lymph node together with increased number of positive lymph nodes,

are significant risk factors for breast cancer related lymphedema.

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