

## Peer Review File

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### Reviewer A

#### Comment 1:

References: The formatting of references is inconsistent. Some are in all caps, others capitalize the first letter before the use of lowercase letters. Please standardize this.

#### Reply 1:

Thanks for the reviewer's valuable comments. We modified the citation format of the full text to be consistent.

**Changes in the text: (Lines 33 page 9)**

#### Comment 2:

Methods Section (Lines 29–30, page 2): The sentence “A total of 1,049 questionnaires...” belongs in the Results section rather than the Methods. Please move it accordingly.

#### Reply 2:

Thanks for the reviewer's valuable comments. We put this sentence in the results section.

**Changes in the text: (Lines 21 page 4)**

The changes are as follows:

3.1 General information—A total of 1021 patients were included in this study, including 1018 females and 3 males; age 21-84 (50.75±11.70) years; Body Mass Index (BMI) 15.95-41.02 (22.97±3.10) kg/m<sup>2</sup> ; postoperative time 1-181 (10.48±21.69) months Surgical methods: reconstructive surgery 164 (16.0%) cases, breast-conserving surgery (24.7%) cases; axillary lymph node treatments: sentinel lymph node biopsy 264 (25.9%) cases, axillary lymph node dissection 757 (74.1%) cases; the number of axillary lymph node treatments 1-41 (15.74±8.31).

#### Comment 3:

Recurrent Infections and ISL Staging (Lines 37–49 page 2): The manuscript implies that recurrent infections may be associated specifically with stage 4 lymphedema. However, infections are not part of the ISL staging system and can occur across all stages of lymphedema. Could you clarify if this is an observational finding or if there was an assumption made about infections being exclusive to stage 4? If patients with recurrent infections were classified as stage 4 based solely on this symptom, what was the rationale behind this classification?

**Reply 3:**

Thanks for the reviewer's valuable comments. Our group agrees with the experts who point out that infection can occur at all stages of lymphedema. In this article, we want to show that patients with stage 3 lymphedema can have recurrent infections according to the ISL staging system. Recurrent infection is only one of the clinical manifestations of stage 3 lymphedema.

**Changes in the text:** None.

**Comment 4:**

Reference 8: Why does the study rely on the 2013 consensus document (reference no. 8) instead of the updated 2020 version (PMID: 32521126)? Using the most current guidelines would strengthen the study's credibility.

**Reply 4:**

Thanks for your careful checks. We have revised the references to the latest version.

**Changes in the text:** (Lines 23-24 page 10)

**Comment 5:**

Statistical Analysis: The Methods section states that normally distributed data are expressed as mean and SD, but the Results section begins with reporting the range, followed by mean and SD. Ensure consistency by either adjusting the presentation or amending the Statistical Analysis section to reflect this order.

**Reply 5:**

Thanks for the reviewer's valuable comments. We modified the statistics section accordingly.

**Changes in the text:**(Lines 1-8 page 4)

The changes are as follows:

Count data were expressed as frequency and percentage, measurement data conforming to normal distribution were expressed as mean  $\pm$  standard deviation (mean  $\pm$  sd), and measurement data not conforming to normal distribution were expressed as median (M) and interquartile range. Data were processed with t test, chi-square test and rank sum test, and the test level was  $\alpha = 0.05$ .

**Comment 6:**

Chi-Square Analysis (Lines 40–42 page 2): You describe a chi-square analysis method in the Results section, but it is not mentioned in the Methods section under your analysis section.

Include a description of this analysis in the Methods section for consistency.

**Reply 6:**

Thanks for your careful checks. We supplemented this accordingly in the statistical

## Methods section.

Changes in the text: **(Lines 1-8 page 4)**

The changes are as follows:

Count data were expressed as frequency and percentage, measurement data conforming to normal distribution were expressed as mean  $\pm$  standard deviation (mean  $\pm$  sd), and measurement data not conforming to normal distribution were expressed as median (M) and interquartile range. Data were processed with t test, chi-square test and rank sum test, and the test level was  $\alpha = 0.05$ .

### **Comment 7:**

Table 2: The table is unclear, particularly regarding the naming of the second column, where “lymphedema staging” is mentioned twice. Could there be an error in the column headers?

### **Reply 7:**

Thanks for your careful checks. Table 2 describes the differences in the number of axillary lymph nodes retrieved between patients with stage 3 lymphedema and those with stage 0, 1, and 2 lymphedema.

**Changes in the text: None.**

### **Comment 8:**

Results Clarification (Lines 43–45 page 3): This result is unclear. Are you indicating that patients with lymphedema stage 3 had a significantly higher number of axillary lymph node dissections compared to those in stages 0, 1, and 2? You only mention that there was a difference, but the exact difference or its direction is not provided. Additionally, in lines 28–30 page 4, you refer to the number of lymph nodes removed rather than the number of lymph node dissections performed, which is not discussed in the Results section (line 43-45 page 3). Please clarify these findings and ensure they are fully presented in the Results section before being discussed.

### **Reply 8:**

Given this valuable advice, statistical differences were interpreted accordingly.

**Changes in the text: (Lines 31-34 page 4)**

The changes are as follows:

The mean number of axillary lymph node dissection in stage 3 patients was significantly higher than that in other stages.

### **Comment 9:**

Table 3: Use consistent formatting, such as only numbers or roman numerals (e.g., i, ii, etc.), to avoid confusion.

### **Reply 9:**

Thanks for your careful checks. We uniformly use numbers for labeling.

**Changes in the text: (Lines 6-9 page 6)**

The changes are as follows:

① The difference is statistically significant when compared with the stage 0 edema group; ②The difference is statistically significant when compared with the stage 1 edema group; ③The difference is statistically significant when compared with the stage 2 edema group; and ④The difference is statistically significant when compared with the stage 3 edema group.

**Comment 10:**

Table Descriptions: Expand the table descriptions to clearly explain what each table represents, including what the numbers signify (e.g., mean values of questionnaire outcomes).

**Reply 10:**

In view of this valuable comment, we have supplemented the relevant content.

**Changes in the text: (Lines 28-29、 31-34 page 4 ; Lines 19-20 page 5 ; Lines 1-2 page 6)**

The changes are as follows:

Table I describes the general data of patients with different stages of lymphedema and the results of univariate analysis.

Table 2 illustrates the  $2 \times 2$  comparison between different stages of lymphedema and the number of lymph nodes dissected.

Table 3 covers the mean scores and standard deviation values of the scores of patients with different stages of lymphedema in each dimension of the questionnaire, and compares the occurrence of related symptoms.

**Comment 11:**

Two-by-Two Comparison (Results Section 3.2): The two-by-two comparison presented in the Results section is not mentioned in the Methods section. Include this analysis in the Methods section and provide justification for performing this comparison in addition to the ANOVA.

**Reply 11:**

In view of this valuable comment, we supplemented this in the statistical Methods section.

**Changes in the text: (Lines 5-8 page 4)**

The changes are as follows:

Analysis of variance (ANOVA) was used to compare the frequency of symptoms, symptom severity, and symptom distress among multiple groups, and two-by-Two

Comparison were used to determine which specific groups had significant differences.

**Comment 12:**

Overall, Strengths: Your article provides a critical evaluation of BCRL and highlights challenges in diagnosis and symptom overlap with surgery-related issues. I particularly appreciate the attention given to the limitations of relying solely on increased arm circumference for diagnosing early-stage lymphedema.

**Reply 12:**

[Thank you for your recognition.](#)

**Changes in the text:** [None.](#)

**Comment 13:**

Overall article: Your article lacks a methodical and precise writing style, with insufficient clarity in reporting the methodology, including detailed descriptions of statistical analyses and measured outcomes. The results should be presented transparently, accompanied by a thorough discussion of their implications.

With these revisions, your article will provide a clearer and more comprehensive understanding of the topic.

**Reply 13:**

[Thanks for the reviewer's valuable comments. We have supplemented the section on methodology, statistical analysis and measurement results in detail.](#)

**Changes in the text: (Lines 1-8 page 4)**

The changes are as follows:

2.5 Statistical analysis

SPSS 22.0 software (IBM Corp., Armonk, NY, USA) was used for the data analyses. Count data were expressed as frequency and percentage, measurement data conforming to normal distribution were expressed as mean  $\pm$  standard deviation (mean  $\pm$  sd), and measurement data not conforming to normal distribution were expressed as median (M) and interquartile range. Data were processed with t test, chi-square test and rank sum test, and the test level was  $\alpha = 0.05$ . Analysis of variance (ANOVA) was used to compare the frequency of symptoms, symptom severity, and symptom distress among multiple groups, and two-by-Two Comparison were used to determine which specific groups had significant differences.

**Reviewer B**

**Comment 1:**

Many references are outdated , should be redone.

**Reply 1:**

Thanks for your careful checks. We have updated references.

**Changes in the text: (Lines 33 page 9)**

**Comment 2:**

3 males were included out of over 1000 female patients, these should be included as they are senseless in this series and cause bias and confusion

**Reply 2:**

Thanks for your careful checks. We have modified statements that are likely to cause discrimination and confusion.

**Changes in the text: (Lines 21 page 4)**

The changes are as follows:

A total of 1021 patients were included in this study; age 21-84 ( $50.75 \pm 11.70$ ) years; Body Mass Index (BMI) 15.95-41.02 ( $22.97 \pm 3.10$ ) kg/m<sup>2</sup> ; postoperative time 1-181 ( $10.48 \pm 21.69$ ) months Surgical methods: reconstructive surgery 164 (16.0%) cases, breast-conserving surgery (24.7%) cases; axillary lymph node treatments: sentinel lymph node biopsy 264 (25.9%) cases, axillary lymph node dissection 757 (74.1%) cases; the number of axillary lymph node treatments 1-41 ( $15.74 \pm 8.31$ ).

**Comment 3:**

There is no mention of lymphoscintigraphy nor fluorescence imaging which are both baseline examinations to detect early lymphedema. Include + reference

**Reply 3:**

In view of this valuable comment, we have made a corresponding supplement in the text.

**Changes in the text: (Lines 32-34 page 8)**

The changes are as follows:

Lymphatic radionuclide imaging or fluorescence is also the gold standard for the detection of early lymphedema, but most diagnosis and treatment institutions do not have professional equipment and personnel.

**Comment 4:**

page 5 line 47 - you mention a 2 cm difference interlimb as a cutoff to detect lymphedema, but no consideration has been given to dominance of the upper limbs (dominant limb can be 2 cm larger in normal condition !

**Reply 4:**

In view of this valuable comment, we have made corresponding supplementary modifications.

**Changes in the text: (Lines 28-32 page 8)**

The changes are as follows:

However, some patients have subjective edema symptoms before the limb circumference changes, suggesting the presence of early lymphedema. At the same time, most people have a dominant hand, and the dominant limb can be more than 2cm larger than the non-dominant limb under normal circumstances. Therefore, it is difficult to diagnose lymphedema by measuring arm circumference.

**Comment 5:**

table 1 is not clear – “whether or not preserve the breast”, “ whether or not armpit is clear”, “axillary treatments” ???

**Reply 5:**

[In view of this valuable suggestion, we modified the table accordingly.](#)

**Changes in the text: (page 5)**

The changes are as follows:

Variables
Age (years, □ X±S)
BMI (kg/m <sup>2</sup> , □ X±S)
Post-operative time (months)
Breast-conserving surgery
Axillary lymph node dissection
Number of axillary treatments (No., □ X±S)

**Comment 6:**

table 3 - P-values of 0.000 - although this is the outcome seen in SPSS, please put in consensus format of <0.001.

**Reply 6:**

[In view of this valuable suggestion, we modified the table accordingly.](#)

**Changes in the text: (page 6)**

The changes are as follows:

P-value
<0.001
<0.001
<0.001
<0.001
0.300

0.785

0.680

<0.001

0.932

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## Reviewer C

### Comment 1:

The main classification systems for lymphedema are described in the Discussion section of this article:

Forte AJ, Sisti A, Huayllani MT, Boczar D, Cinotto G, Ciudad P, Manrique OJ, Lu X, McLaughlin S. Lymphaticovenular anastomosis for breast cancer-related upper extremity lymphedema: a literature review. *Gland Surg.* 2020 Apr;9(2):539-544. doi: 10.21037/gs.2020.03.41. PMID: 32420289; PMCID: PMC7225471.

Please, cite and discuss the article, along with the main classification systems.

### Reply 1:

[We cite and discuss the article in the introduction.](#)

### Changes in the text: (Lines 19-22 page 2)

The changes are as follows:

Based on the subjective and objective data, researchers have developed many classification methods for lymphedema, including Campisi classification, MD Anderson classification of lymphedema, and Cheng's grading scale.

### Comment 2:

In the Introduction Section, cite and discuss the following fundamental article:

Sisti A, Huayllani MT, Boczar D, Restrepo DJ, Spaulding AC, Emmanuel G, Bagaria SP, McLaughlin SA, Parker AS, Forte AJ. Breast cancer in women: a descriptive analysis of the national cancer database. *Acta Biomed.* 2020 May 11;91(2):332-341. doi: 10.23750/abm.v91i2.8399. PMID: 32420970; PMCID: PMC7569667.

### Reply 2:

[We cite and discuss the article in the introduction.](#)

### Changes in the text: (Lines 2-3 page 2)

The changes are as follows:

In recent years, the incidence of breast cancer has been increasing rapidly, and the prevalence increases with age.



**Comment 3:**

Cite and discuss the following articles:

K R J, D K V, Sugumaran V, Pathinarupothi RK. A comprehensive review of computational diagnostic techniques for lymphedema. *Prog Biomed Eng (Bristol)*. 2025 Jan 9. doi: 10.1088/2516-1091/ada85a. Epub ahead of print. PMID: 39787703.

Chen JG, Perez CB, Coogan A, Kim T, Sanchez-Johnsen L, Ohara K, Nelson C, Rizzo DM, Matt J, Watson EJ, Sowden MM, Ahern TP. Classification of Breast Lymphedema in a Racially Diverse Cohort. *Lymphology*. 2024;57(2):84-96. PMID: 39536330.

Sharifi N, Ahmad S. Breast cancer-related lymphedema: A critical review on recent progress. *Surg Oncol*. 2024 Oct;56:102124. doi:10.1016/j.suronc.2024.102124. Epub 2024 Aug 23.

PMID: 39208532.

Fourgeaud C, Vignes S. New insights in breast cancer-related lymphedema. *J Med Vasc*. 2024

Sep;49(3-4):135-140. doi: 10.1016/j.jdmv.2024.06.001. Epub 2024 Jul 10. PMID: 39278693.

**Reply 3:**

[We cite and discuss the article in the introduction.](#)

**Changes in the text: (Lines 8-11, Lines 17-23 page 2)**

The changes are as follows:

In recent years, the incidence of breast cancer has been increasing rapidly, and the prevalence increases with age <sup>[1]</sup>. With the continuous progress of multidisciplinary diagnostic and therapeutic methods, the survival rate of patients has shown a significant increasing trend, and the prognosis and long-term survival have been improving <sup>[2]</sup>. Breast cancer-related lymphedema (BCRL) is an edema formed due to the accumulation of lymphatic fluid in the interstitium of the affected limb or region as a result of damage to the lymphatic system, which can cause physical symptoms such as swelling and numbness of the affected limb, pain, skin changes, and functional disability, etc. Its risk factors include genetic susceptibility, manual lymphatic drainage, physical activity, body weight, etc <sup>[3]</sup>. Nearly 20% of patients develop lymphedema after breast cancer treatment that includes axillary lymph node dissection <sup>[4]</sup>. BCRL is a chronic and progressive process, and once it occurs, it is difficult to treat and can affect patients' quality of life in the long term <sup>[5]</sup>, and patients may experience psychological symptoms such as negative self-perception of body image and emotional distress <sup>[6]</sup>. Therefore, BCRL focuses on prevention, early detection and early intervention. Currently, the diagnostic evaluation of breast cancer lymphedema consists of the collection of objective clinical data (bioelectrical impedance measurements, infrared measurements, water displacement method, limb circumference measurements) <sup>[7]</sup> and patient-reported subjective symptoms. In addition to traditional assessment

methods, innovative technologies such as computer algorithms and AI integration are also being explored in the early detection of lymphedema<sup>[8]</sup>. Based on the subjective and objective data, researchers have developed many classification methods for lymphedema, including Campisi classification, MD Anderson classification of lymphedema, and Cheng's grading scale<sup>[9]</sup>. Chen JG et al. explored methods for classifying breast lymphedema on the basis of findings from breast ultrasonography, physical examination, and patient reports<sup>[10]</sup>. It has been shown that patients with early lymphedema present with symptoms, and that the symptom experience worsens as the edema worsens, so symptom evaluation is useful for early detection of lymphedema<sup>[11, 12]</sup>. However, it is unknown how symptoms characterize and develop in patients with different lymphedema stages. Therefore, the aim of this study was to understand the occurrence of lymphedema in postoperative breast cancer patients, to explore the characteristics of the associated symptoms in patients with different lymphedema stages, and to provide guidance for the early diagnosis and symptom management of lymphedema.