Risk factors and prediction model for persistent breast-cancer-related lymphedema: a 5-year cohort study

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Abstract
Purpose Breast-cancer-related lymphedema (BCRL) can be a transient or persistent condition. The aims of this study were to (1) identify and weigh the risk factors for persistent lymphedema (PLE) among all patients with BCRL and (2) establish a prediction model for the occurrence of PLE.

Methods A cohort of 342 patients with BCRL with a median follow-up of 5 years after the onset of swelling was analyzed. PLE was defined as a hardening of the subcutaneous tissue, the persistence of the circumferential difference (CD) between arms, or a flare-up of swelling during follow-up. Multiple logistic regression was used to identify risk factors for PLE, including tumors, treatments, and patient-related factors. The prediction accuracy of the model was assessed using the area under the receiver operating characteristic curve (AUC).

Results Of the 342 patients with BCRL, 229 (67%) had PLE. Multiple logistic regression analysis revealed that the number of lymph node metastases \( p = 0.012 \), the maximal CD between arms at the first occurrence of swelling \( p < 0.001 \), and the largest difference during follow-up \( p < 0.001 \) were significant predictors for PLE. The corresponding AUC was 0.908. Although inclusion of body weight gains \( p = 0.008 \) and maximal CD at the latest follow-up \( p = 0.002 \) increased the analytical accuracy \( \text{AUC} = 0.920 \), the resulting AUC values \( p = 0.113 \) were not significantly different.

Conclusions BCRL is persistent in two thirds of patients. Patients with more lymph node metastases, weight gain, and larger CD since the onset of swelling and during follow-up have an increased likelihood of developing PLE.

Keywords Lymphedema · Breast cancer · Persistent lymphedema · Risk factors · Prediction model

Lymphedema is a distressing side effect of breast cancer and can have a devastating effect on a patient’s quality of life [1, 2]. Although lymphedema is defined as a chronic progressive disorder, most cases of breast-cancer-related lymphedema (BCRL) are mild or vanish spontaneously [3–5]. By contrast, in some cases, the condition may fluctuate or increase in severity [4, 6, 7]. Because no cure exists for lymphedema, identifying the underlying risk factors for persistent lymphedema

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(PLE) is necessary for the development of more efficient surveillance programs [5, 6, 8].

Individual studies have reported that 3–42% of women develop lymphedema after breast cancer treatment [3–7, 9–12]. This broad range of results may be because (a) lymphedema can be defined and measured in different ways [4, 5, 11, 13], (b) some studies contained a small sample size [3, 10], or (c) the periods of follow-up were different [4, 5, 7–9, 11, 12]. A comprehensive meta-analysis revealed that patients receiving axillary lymph node dissection (ALND) were four times more prone to have lymphedema than those who underwent sentinel lymph node dissection (SLNB) [11]. Additionally, tumors spreading to the axillary lymph nodes, higher body mass index (BMI), chemotherapy (CT), and radiotherapy (RT) have all been reported as risk factors for BCRL [6–9, 14–17]. Despite these findings, several vital issues must be highlighted: (1) the time between surgery and the onset of BCRL is crucial because it reflects the individual’s functional reserve of their lymphatic system after treatment; (2) taxane-based regimens are currently the first line of CT for node-positive breast cancers; however, whether taxanes induce lymphedema remains inconclusive; and (3) RT can cause fibrosis in the treated area and impair collateral lymphatic pathways, leading to varying degrees of lymphedema.

We report here a retrospective longitudinal cohort study that demonstrates risk factors associated with PLE development. Specifically, we focused on three crucial aspects: (1) tumor factors, including the stage of cancer, tumor stage, lymph node (N) stage, presence of supraclavicular (SC) or internal mammary (IM) node metastasis (diagnosed by positron emission tomography–computed tomography or magnetic resonance imaging, or confirmed via pathiology), and locally advanced breast cancer; (2) treatment factors, such as the type of surgery, CT with paclitaxel, docetaxel, or other regimens, and RT to different locations; and (3) patient factors, namely age, changes in body weight and BMI, the circumferential difference (CD) of both arms during serial follow-ups, the severity of swelling, and comorbidities.

Materials and methods

Recruitment of patients

All patients with BCRL recruited in this study were diagnosed, treated, and followed up at Koo Foundation Sun Yat-Sen Cancer Center, Taiwan. The follow-up protocols were developed by the breast cancer treatment team: all patients with breast cancer visited the oncologist every 3 months in the first 2 years after surgery, every 6 months in the third to fifth years, and once per year after that. Patients were routinely asked whether they noticed arm swelling, indentations, heaviness, or firm skin by a case manager; they were also examined by an oncologist for arm swelling and skin texture during each follow-up. In the follow-up clinic, patients with either subjective or objective arm swelling were referred to a physiatrist experienced in lymphedema diagnosis and management. Patients could also visit the physiatrist directly any time during the follow-up period if they noticed arm swelling.

The initial screening of the database between January 1, 2005, and December 31, 2015, identified 488 patients with BCRL. The inclusion criteria were as follows: (1) patients who exhibited CD in both arms of > 1 cm as measured by the physiatrist and (2) CD in both arms of < 1 cm, but manifesting as pitting edema or subcutaneous tissue hardening, or having symptoms of arm swelling, heaviness, or tight clothes. Among these patients, 146 were excluded from the study. The exclusion criteria were as follows: (1) stage IV cancer (n = 53), (2) having chest wall or axillary local recurrence (n = 37), (3) bilateral breast cancer (n = 34), (4) incomplete lymphedema treatment or being lost to follow-up (n = 7), (5) having cellulitis-induced swelling (n = 7), (6) having swelling before breast cancer surgery (n = 3), (7) having considerable heart or renal diseases (n = 3), or (8) having edema caused by deep vein thrombosis (n = 2). The resulting study population was 342 patients with breast cancer with unilateral arm swelling. This study was approved by internal review board of the hospital (IRB: 20170418A).

Definition of transient and persistent lymphedema

Transient lymphedema was defined as cases that fulfill all three of the following conditions: (1) decreasing CD of both arms after the onset of arm swelling, (2) no subcutaneous tissue fibrosis or pitting edema, and (3) no subjective symptoms of arm swelling. Persistent lymphedema was defined through the following symptoms: (1) having increasing CD or maintaining the same CD between both arms and (2) having any one of the following conditions:
texture hardening of the subcutaneous tissue, subjective feeling of arm swelling or discomfort even after edema treatment, and experiencing flare-up of swelling during follow-ups [19, 20].

**Lymphedema treatment**

Complete decongestive therapy (CDT) [6, 19–21] was the standard treatment for all patients with BCRL. For those who could not tolerate short-stretch bandages, pressure garments were applied. For patients with a lymphedema flare-up, another course of CDT was performed depending on the severity.

**Breast cancer treatment**

Surgery involved modified radical mastectomy (MRM, i.e., simple mastectomy + ALND), simple mastectomy (SM) with SLNB, and breast-conserving surgery (wide excision of the tumor) with either ALND or SLNB.

Adjunctive CT was suggested for patients who were node-positive or high-risk node-negative. A dose-dense paclitaxel-containing regimen was prescribed for N3 patients. A regimen containing docetaxel was administrated to N1 and N2 patients and high-risk N0 patients. Patients who were node-negative with moderate risk received nontaxane regimens. For patients with locally advanced tumors, neoadjuvant CT with a docetaxel-based regimen was prescribed before surgery.

| Table 1 Demographics and disease characteristics of 342 patients with lymphedema |

| Variables                              | Transient LE (n = 113) | Permanent LE (n = 229) | p value |
|----------------------------------------|------------------------|------------------------|---------|
| Age at surgery (years)                 | 48.62 ± 11.24          | 51.28 ± 10.71          | 0.017   |
| Age at onset of swelling (years)       | 50.47 ± 11.78          | 53.22 ± 10.88          | 0.011   |
| Follow-up after onset of swelling (years) | 4.96 ± 2.97  | 5.65 ± 2.99            | 0.035   |
| Follow-up after surgery (years)        | 7.22 ± 3.67            | 7.75 ± 3.64            | 0.203   |
| Laterality of surgery                  |                        |                        |         |
| Right                                  | 50 (30.7%)             | 113 (69.3%)            | 0.421   |
| Left                                   | 63 (35.2%)             | 116 (64.8%)            |         |
| SC/IM LN metastasis                    |                        |                        |         |
| Yes                                    | 7 (28.0%)              | 18 (72.0%)             | 0.663   |
| No                                     | 106 (33.4%)            | 211 (66.6%)            |         |
| Initial LABC, postneoadjuvant CT       |                        |                        |         |
| Yes                                    | 12 (26.7%)             | 33 (73.3%)             | 0.397   |
| No                                     | 101 (34.0%)            | 196 (66.0%)            |         |
| AJCC cancer stage                      |                        |                        |         |
| 0                                      | 3 (100.0%)             | 0 (0.0%)               | 0.001   |
| I                                      | 16 (53.3%)             | 14 (46.7%)             |         |
| IIA                                    | 31 (43.1%)             | 41 (56.9%)             |         |
| IIB                                    | 28 (29.5%)             | 67 (70.5%)             |         |
| IIIA                                   | 20 (29.9%)             | 47 (70.1%)             |         |
| IIIB                                   | 0 (0.0%)               | 1 (100.0%)             |         |
| IIIC                                   | 15 (20.3%)             | 59 (79.7%)             |         |
| AJCC tumor stage                       |                        |                        |         |
| T0                                     | 5 (62.5%)              | 3 (37.5%)              | 0.169   |
| T1                                     | 40 (38.1%)             | 65 (61.9%)             |         |
| T2                                     | 61 (29.5%)             | 146 (70.5%)            |         |
| T3                                     | 7 (35.0%)              | 13 (65.0%)             |         |
| T4                                     | 0 (0.0%)               | 2 (100.0%)             |         |
| AJCC node stage                        |                        |                        |         |
| N0                                     | 32 (47.8%)             | 35 (52.2%)             | 0.004   |
| N1                                     | 49 (33.8%)             | 96 (66.2%)             |         |
| N2                                     | 21 (30.4%)             | 48 (69.6%)             |         |
| N3                                     | 11 (18.0%)             | 50 (82.0%)             |         |

LE lymphedema, SC supraclavicular, IM internal mammary, LN lymph node, LABC locally advanced breast cancer, AJCC American Joint Commission on Cancer
followed by another two courses after surgery if complete remission was achieved. If residual cancer cells persisted, CT regimens were prescribed following the criteria for adjuvant CT.

RT was delivered using computed-tomography-based treatment to all patients receiving breast-conserving surgeries, as well as those who underwent mastectomy and were axillary-node-positive. The principle RT was administered at a dose of 45–50 Gy in 23–25 fractions to the breast or chest wall with tangential fields and a median 10-Gy boost to the tumor bed. SC and IM node RT were administered to patients with positive axillary lymph nodes [22]. Axillary node RT was delivered to some of the pN3 patients according to the judgment of the radiation oncologist.

### Statistical analysis

All statistical analyses were performed using SPSS software version 24 (SPSS for Windows, SPSS Inc., Chicago, IL, USA). Descriptive statistics were expressed as mean ± standard deviation for continuous variables and number of

### Table 2  Treatment characteristics of 342 patients with lymphedema

| Variables | Transient LE (n = 113) | Permanent LE (n = 229) | p value |
|-----------|------------------------|------------------------|---------|
| Type of surgery | | | |
| MRM (SM+ALND) | 80 (28.9%) | 197 (71.1%) | 0.002 |
| WE+ALND | 27 (47.4%) | 30 (52.6%) | |
| SM+SLNB | 3 (75.0%) | 1 (25.0%) | |
| WE+SLNB | 3 (75.0%) | 1 (25.0%) | |
| No. of LN dissected | 22.65 ± 9.18 | 24.11 ± 9.18 | 0.241 |
| No. of LN metastasis | 3.18 ± 4.64 | 6.21 ± 8.44 | < 0.001 |
| Chemotherapy (CT) | | | |
| No | 10 (52.6%) | 9 (47.4%) | 0.079 |
| Yes | 103 (31.9%) | 220 (68.1%) | |
| CT with taxane | | | |
| Without taxane (T) | 30 (36.6%) | 52 (63.4%) | 0.337 |
| With taxane | 73 (30.3%) | 168 (69.7%) | |
| All patients according to different types of taxane, or no taxane | | | |
| No CT+CT without T | 40 (39.6%) | 61 (60.4%) | 0.030 |
| Docetaxel only | 63 (34.3%) | 121 (65.1%) | |
| Paclitaxel only | 7 (15.6%) | 38 (84.4%) | |
| Docetaxel+paclitaxel | 3 (25.0%) | 9 (75.0%) | |
| CT with different regimens | | | |
| Not done | 12 (60.0%) | 8 (40.0%) | 0.030 |
| AC-T (docetaxel) | 52 (34.9%) | 97 (65.1%) | |
| ATC (paclitaxel) | 9 (18.8%) | 39 (81.2%) | |
| TC-AC-T (docetaxel) | 0 (0%) | 2 (100.0%) | |
| TC-CAF (docetaxel) | 5 (31.3%) | 11 (68.7%) | |
| TC (docetaxel) | 8 (36.4%) | 14 (63.6%) | |
| CAF | 19 (39.6%) | 29 (60.4%) | |
| Others | 8 (21.6%) | 29 (78.4%) | |
| Radiation therapy (RT) | | | |
| Not done | 22 (55.0%) | 18 (45.0%) | 0.004 |
| Yes | 91 (33.1%) | 211 (66.9%) | |
| Radiation therapy to regional LN | | | |
| SC RT (yes vs. no) | 83 (29.2%) | 201 (70.8%) | 0.002 |
| IM RT (yes vs. no) | 74 (27.9%) | 191 (72.1%) | < 0.001 |
| Axillary RT (yes vs. no) | 2 (7.4%) | 25 (92.6%) | 0.002 |

LE lymphedema, MRM modified radical mastectomy, SM simple mastectomy, ALND axillary lymph node dissection, WE wide excision, SLNB sentinel lymph node biopsy, LN lymph node, T taxane, A doxorubicin (adriamycin), C cyclophosphamide, D docetaxel, F fluorouracil, SC supraclavical, IM internal mammary
patients (%) for categorical variables. The between-group comparisons were conducted using the Mann–Whitney U and Fisher’s exact tests. Univariate logistic regression was used to assess the potential risk factors of PLE, ignoring the effects of other factors. For the risk factors with $p < 0.05$ denoting statistical significance in the univariate analysis, multiple logistic regression was used to identify those that were significantly associated with PLE after adjusting for the effects of other factors in the model. Multiple logistic regression analyses with variable selection in a stepwise fashion were used to develop the multivariate models for predicting PLE. When constructing the most parsimonious model to explain the data, we sought one with optimal prediction accuracy that minimized the number of variables. We based our model choice not only on likelihood ratio and Akaike information criterion but also on the basis of clinical availability, statistical significance, and prediction accuracy. The preliminary prediction model was based on the final results of the multiple logistic regression. The area under the receiver operating characteristic (ROC) curve (AUC) was the index of prediction accuracy. Comparisons of prediction accuracy or the equivalent AUCs were assessed using STATA/SE V 13.0 (Stata Corporation, College Station, TX). All statistical tests were two-tailed, and a $p$ value of $< 0.05$ was considered statistically significant.

### Results

This study involved 342 patients with breast cancer with unilateral arm swelling and a mean age of $52.31 \pm 11.25$ years. Among them, 229 (67%) were patients with PLE. The comparison of demographics and disease, treatment, and swelling characteristics between PLE and transient lymphedema (TLE) are presented in Tables 1, 2, and 3, respectively. As shown in Table 1, the average age at surgery or onset of swelling was

| Variables                                      | Transient LE ($n = 113$) | Permanent LE ($n = 229$) | $p$ value |
|------------------------------------------------|--------------------------|--------------------------|-----------|
| Onset time of swelling after surgery (months)  | 27.06 ± 27.03            | 25.54 ± 29.32            | 0.316     |
| Body weight (kg)                                |                          |                          |           |
| Presurgery                                      | 59.46 ± 10.78            | 59.36 ± 9.48             | 0.683     |
| Onset of swelling                               | 60.71 ± 10.72            | 61.68 ± 9.66             | 0.190     |
| Weight changes from presurgery to onset of swelling | 1.25 ± 4.11              | 2.32 ± 4.54              | 0.012     |
| At latest follow-up                             | 59.75 ± 11.16            | 60.03 ± 10.04            | 0.671     |
| BMI at the onset of swelling                    | 24.71 ± 4.47             | 25.09 ± 3.93             | 0.181     |
| Maximal CD of both arms                         |                          |                          |           |
| Onset of swelling                               | 1.63 ± 1.03              | 2.46 ± 1.53              | <0.001    |
| Largest during FU                               | 1.71 ± 1.00              | 3.59 ± 1.87              | <0.001    |
| At the latest FU                                 | 1.21 ± 0.64              | 2.95 ± 2.14              | <0.001    |
| Initial severity of LE                          |                          |                          |           |
| Mild, CD $\leq 2$ cm                            | 81 (42.6%)               | 109 (57.4%)              | <0.001    |
| Moderate, CD 2.1–3 cm                           | 24 (27.3%)               | 64 (72.7%)               |           |
| Severe, CD $>3$ cm                              | 8 (12.5%)                | 56 (87.5%)               |           |
| Onset time of swelling correlated with CT       |                          |                          |           |
| No CT or swelling before CT                     | 13 (65.0%)               | 7 (35.0%)                | 0.008     |
| Swelling during CT                              | 14 (27.5%)               | 37 (72.5%)               |           |
| Swelling after CT                               | 86 (31.7%)               | 185 (68.3%)              |           |
| Onset time of swelling correlated with RT       |                          |                          |           |
| Swelling before RT                              | 15 (23.8%)               | 48 (76.2%)               | 0.005     |
| Swelling during RT                              | 9 (50.0%)                | 9 (50.0%)                |           |
| Swelling after RT                               | 67 (30.5%)               | 153 (69.5%)              |           |
| No RT                                          | 22 (53.7%)               | 19 (46.3%)               |           |
| Cellulitis after swelling                      | 0 (0%)                   | 34 (100.0%)              | <0.001    |
| Cormobidity with DM                             | 18 (32.7%)               | 37 (67.3%)               | 1.000     |
| Cormobidity with other cancers                  | 14 (31.8%)               | 30 (68.2%)               | 1.000     |

LE lymphedema, BMI body mass index, CD circumference difference, CT chemotherapy, RT radiation therapy, DM diabetes mellitus
significantly higher for patients with PLE than those with TLE ($p = 0.017$ and $p = 0.011$, respectively). The risk of PLE for patients with breast cancer (after the onset of swelling) significantly increased with respect to the severity of the AJCC (American Joint Commission on Cancer) cancer stage ($p = 0.001$). A similar phenomenon was observed for the AJCC node stage ($p = 0.004$), but not the AJCC tumor stage ($p = 0.169$). As shown in Table 2, patients treated with MRM had

| Parameter                                      | $B$       | Std. error | Wald chi-square | $p$ value | Odds ratio | 95% CI for odds ratio |
|------------------------------------------------|-----------|------------|-----------------|-----------|------------|----------------------|
| Age at onset of swelling (years)               | 0.023     | 0.0106     | 4.490           | 0.034     | 1.023      | 1.002 1.044          |
| AJCC cancer stage                              |           |            |                 |           |            |                      |
| (3B,3C) vs. (0,1)                              | 1.692     | 0.4554     | 13.799          | $<0.001$  | 5.429      | 2.224 13.253         |
| 3A vs. (0,1)                                   | 1.160     | 0.4420     | 6.886           | 0.009     | 3.189      | 1.341 7.584          |
| 2B vs. (0,1)                                   | 1.178     | 0.4180     | 7.941           | 0.005     | 3.247      | 1.431 7.367          |
| 2A vs. (0,1)                                   | 0.585     | 0.4251     | 1.894           | 0.169     | 1.795      | 0.780 4.129          |
| AJCC node stage                                |           |            |                 |           |            |                      |
| N3 vs. N0                                      | 1.425     | 0.4132     | 11.886          | 0.001     | 4.156      | 1.849 9.341          |
| N2 vs. N0                                      | 0.737     | 0.3582     | 4.235           | 0.040     | 2.090      | 1.036 4.217          |
| N1 vs. N0                                      | 0.583     | 0.3011     | 3.749           | 0.053     | 1.791      | 0.993 3.232          |
| Type of surgery                                |           |            |                 |           |            |                      |
| WE+SLNB vs. MRM (SM+ALND)                      | −2.000    | 1.1623     | 2.960           | 0.085     | 0.135      | 0.014 1.321          |
| SM+SLNB vs. MRM (SM+ALND)                      | −2.000    | 1.1623     | 2.960           | 0.085     | 0.135      | 0.014 1.321          |
| WE+ALND vs. MRM (SM+ALND)                      | −0.796    | 0.2966     | 7.201           | 0.007     | 0.451      | 0.252 0.807          |
| No. of LN metastasis                           | 0.077     | 0.0234     | 10.793          | 0.001     | 1.080      | 1.031 1.130          |
| Chemotherapy (CT)                              |           |            |                 |           |            |                      |
| Yes vs. no                                     | 0.864     | 0.4747     | 3.314           | 0.069     | 2.373      | 0.936 6.018          |
| All patient according to different types of taxane, or no taxane | | | | | | |
| Docetaxel+paclitaxel vs. (no CT+CT without taxane) | 0.677     | 0.6970     | 0.942           | 0.332     | 1.967      | 0.502 7.712          |
| Paclitaxel only vs. (no CT+CT without taxane)   | 1.270     | 0.4589     | 7.656           | 0.006     | 3.560      | 1.448 8.750          |
| Docetaxel only vs. (no CT+CT without taxane)    | 0.231     | 0.2560     | 0.812           | 0.368     | 1.259      | 0.763 2.080          |
| Radiation therapy (RT)                         |           |            |                 |           |            |                      |
| Yes vs. no                                     | 1.042     | 0.3417     | 9.295           | 0.002     | 2.834      | 1.451 5.536          |
| Radiation therapy to regional LN               |           |            |                 |           |            |                      |
| Supraclavicular RT (yes vs. no)                | 0.956     | 0.2976     | 10.320          | 0.001     | 2.601      | 1.452 4.661          |
| Internal mammary RT (yes vs. no)               | 0.975     | 0.2685     | 13.183          | 0.000     | 2.651      | 1.566 4.487          |
| Axillary RT (yes vs. no)                       | 1.913     | 0.7443     | 6.606           | 0.010     | 6.773      | 1.575 29.132         |
| Weight changes from presurgery to onset of swelling | 0.057     | 0.0272     | 4.322           | 0.038     | 1.058      | 1.003 1.116          |
| Maximal CD of both arms                        |           |            |                 |           |            |                      |
| Onset of swelling                              | 0.530     | 0.1100     | 23.230          | $<0.001$  | 1.699      | 1.370 2.108          |
| Largest during FU                              | 1.270     | 0.1584     | 64.227          | $<0.001$  | 3.559      | 2.609 4.855          |
| At the latest FU                                | 1.618     | 0.2065     | 61.372          | $<0.001$  | 5.042      | 3.364 7.558          |
| Initial severity of lymphedema                 |           |            |                 |           |            |                      |
| Severe vs. mild                                | 1.649     | 0.4054     | 16.543          | $<0.001$  | 5.202      | 2.350 11.515         |
| Moderate vs. mild                              | 0.684     | 0.2807     | 5.935           | 0.015     | 1.982      | 1.143 3.435          |
| Onset time of swelling correlated with chemotherapy |           |            |                 |           |            |                      |
| Swelling after CT vs. no CT or swelling before CT | 1.385    | 0.4866     | 8.101           | 0.004     | 3.995      | 1.539 10.369         |
| Swelling during CT vs. no CT or swelling before CT | 1.591    | 0.5641     | 7.953           | 0.005     | 4.908      | 1.625 14.829         |
| Onset time of swelling correlated with radiation therapy |           |            |                 |           |            |                      |
| No RT vs. swelling before RT                   | −1.310    | 0.4308     | 9.243           | 0.002     | 0.270      | 0.116 0.628          |
| Swelling after RT vs. swelling before RT       | −0.337    | 0.3301     | 1.045           | 0.307     | 0.714      | 0.374 1.363          |
| Swelling during RT vs. swelling before RT      | −1.163    | 0.5565     | 4.368           | 0.037     | 0.313      | 0.105 0.930          |

*Std* standard, *CI* confidence interval, *AJCC* American Joint Commission on Cancer, *WE* wide excision, *SLNB* sentinel lymph node biopsy, *MRM* modified radical mastectomy, *SM* simple mastectomy, *ALND* axillary lymph node dissection, *LN* lymph node, *CD* circumference difference
the highest risk of PLE among the four types of surgery. The average number of lymph node metastases was significantly higher for patients with PLE than for those with TLE ($p < 0.001$). The risks of PLE were significantly associated with RT ($p = 0.004$) and RT to regional lymph nodes (SC-RT, IM-RT, and axillary-RT; $p = 0.002$, $p < 0.001$, and $p = 0.002$, respectively). The results in Table 3 indicate that, among the various swelling characteristics, significant differences existed between the two types of lymphedema in the following variables: weight changes from presurgery to onset of swelling ($p = 0.012$), the maximal CD of both arms ($p < 0.001$), the initial severity of lymphedema ($p < 0.001$), the onset time of swelling associated with CT and RT ($p = 0.008$ and 0.005, respectively), and cellulitis after swelling ($p < 0.001$).

One of the aims of this study was to establish a predictive model. The results of the univariate logistic regression shown in Table 4 reveal that (1) higher age at the onset of swelling significantly increased the risk of PLE, and the odds of PLE increased 2.3% per year of age at the onset of swelling ($p = 0.034$). (2) The odds ratio (OR) of PLE significantly increased with respect to the AJCC cancer stage (OR = 3.247, 3.189, and 5.429 for stages 2B, 3A, and 3B or 3C, respectively, versus stages 0 or 1; $p = 0.005$, $p = 0.009$, and $p < 0.001$, respectively), with a similar phenomenon observed for the AJCC node stage. (3) The odds of PLE increased by 8% for each one-unit increase in the number of lymph node metastases ($p = 0.001$). (4) The OR of PLE for RT (yes vs. no) was 2.834 with a 95% confidence interval of 1.451–5.536. (5) The ORs of PLE for SC-RT, IM-RT, and axillary-RT (yes vs. no) were 2.601, 2.651, and 6.773, respectively ($p = 0.001$, $p < 0.001$, and $p = 0.010$, respectively). (6) The odds of PLE increased by 5.8% for each 1-kg increase in weight from presurgery to the onset of swelling ($p = 0.038$). (7) The ORs of PLE for the maximal CDs of both arms at the onset of swelling, the highest CDs during follow-up, and the CDs at the latest follow-up were 1.699, 3.559, and 5.042, respectively (all $p < 0.001$). (8) The ORs of PLE for the initial severity of lymphedema (moderate and severe vs. mild) were 1.982 and 5.202, respectively ($p = 0.015$ and $p < 0.001$, respectively).

Multiple logistic regression revealed that five risk factors were significantly associated with PLE after mutually adjusting for the effects of other factors in the model (Tables 5 and 6). To demonstrate the accuracy of the prediction model using those five predictors’ multiple logistic regressions, the predicted value of this model was used as the test variable, with the corresponding ROC curve illustrated in Fig. 1. The corresponding AUC was 0.920. To establish a parsimonious model, we attempted to reduce the number of predictors in the model without sacrificing accuracy. The final prediction model is presented in Table 6, and the corresponding ROC curve is shown in Fig. 1. Its corresponding AUC was 0.908. The

### Table 5

| Parameter                        | $B$   | Std. error | Wald chi-square | $p$ value | Odds ratio | 95% CI for odds ratio |
|----------------------------------|-------|------------|----------------|-----------|------------|-----------------------|
| (Intercept)                      | −3.470| 0.5015     | 47.893          | $<0.001$  | 0.031      | 0.012–0.083           |
| No. of LN metastasis             | 0.075 | 0.0331     | 5.100           | 0.024     | 1.078      | 1.010–1.150           |
| Weight changes from pre-surgery  | 0.105 | 0.0394     | 7.084           | 0.008     | 1.111      | 1.028–1.200           |
| Maximal CD of both arms          |       |            |                 |           |            |                       |
| Onset of swelling                |       |            |                 |           |            |                       |
| Largest during follow-up         | 2.842 | 0.5502     | 26.683          | $<0.001$  | 17.148     | 5.833–50.411          |
| At the latest follow-up          | 1.083 | 0.3553     | 9.284           | 0.002     | 2.952      | 1.471–5.923           |

Std standard, CI confidence interval, AJCC American Joint Commission on Cancer, WE wide excision, SLNB sentinel lymph node biopsy, MRM modified radical mastectomy, SM simple mastectomy, ALND axillary lymph node dissection, LN lymph node, CD circumference difference

### Table 6

| Parameter                        | $B$   | Std. error | Wald chi-square | $p$ value | Odds ratio | 95% CI for odds ratio |
|----------------------------------|-------|------------|----------------|-----------|------------|-----------------------|
| (Intercept)                      | −2.962| 0.4469     | 43.943          | $<0.001$  | 0.052      | 0.022–0.124           |
| No. of LN metastasis             | 0.078 | 0.0311     | 6.314           | 0.012     | 1.081      | 1.017–1.149           |
| Maximal CD of both arms          |       |            |                 |           |            |                       |
| Onset of swelling                | −2.340| 0.4582     | 26.080          | $<0.001$  | 0.096      | 0.039–0.236           |
| Largest during follow-up         | 3.437 | 0.4951     | 48.196          | $<0.001$  | 31.091     | 11.782–82.042         |

Std standard deviation, CI confidence interval, LN lymph node, CD circumference difference
results of chi-square testing (with one degree of freedom) indicated no significant difference between the two AUC values ($\chi^2 = 2.54$, $p = 0.1113$).

**Discussion**

Lymphedema is considered a progressive disease without curative treatment; however, through proper intervention, stage I lymphedema can be reversed [19, 20]. It is unclear if and how patients with stage I lymphedema progress to more severe, chronic, or persistent conditions. Our data indicated that most patients with BCRL (78.9%) started to experience swelling within 3 years after surgery. One third of patients with BCRL did not progress further, or even resolve without any flare-up, whereas two thirds of patients with BCRL were diagnosed with PLE during follow-up [6]. The goal of this study was to identify underlying risk factors of PLE that may lead to more effective prevention and treatment strategies.

We revealed that the number of metastatic lymph nodes and body weight changes from presurgery to the onset of swelling, the maximal CD of both arms at the onset of swelling, and the largest CD during follow-up were strongly associated with PLE development. This study employed a cohort of 342 patients with BCRL and comprehensive records regarding the patients, treatments, and swelling characteristics, as well as potential confounding factors such as bilateral breast cancer, local recurrence, stage IV disease, and swelling after infection. The median 7- and 5-year follow-ups after surgery and after the onset of swelling, respectively, were longer than those in most related studies. The diagnosis of BCRL was reliably performed through patients’ perceptions of arm swelling, observations by case managers and oncologists, and examination and repeated measurements by physiatrists.

Our result revealed that axillary lymph node metastasis and advanced cancer stages were related to the development of PLE. The increment of one instance of lymph node metastasis increased the risk of PLE by 8%. Lymphatic function could be impaired by tumor growth and further damaged by the surgical removal of the lymph nodes. Abnormal accumulation of water and proteins in the subcutaneous tissue, subsequent tissue proliferation, and fibrosis development gradually result in PLE [19, 20, 23].

Progression of mild arm lymphedema has been shown to be associated with morbid obesity [7], defined as a BMI of 35 kg/m$^2$ or greater. McLaughlin et al. reported that lymphedema was associated with greater body weight, higher BMI, and infection or injury in the ipsilateral arm after surgery [12]. Our results indicated that obesity could not only be a contributor to the initial lymphatic overload responsible for the onset of lymphedema [17] but also contribute to the pathophysiology changes responsible for its progression [7, 24]. Notably, changes of body weight measured before surgery and at the onset of swelling were even more significantly related to PLE [25]. This finding is consistent with the theory of lymphatic overload [7, 17, 26].

We utilized the number of metastatic lymph nodes, the CD at the first visit, and the largest CD during follow-up to construct a prediction model for PLE. The accuracy of this predictor is denoted by an AUC of 0.908. The purpose of this prediction model was to not only explore the potential risk factors of PLE but also to provide a corresponding reference index of the accuracy of the prediction. In contrast to related studies [6–9, 12, 14, 15, 27, 28], investigating the risk factors for BCRL, AJCC cancer stage, node stage, ALND, and RT were not identified as risk factors of PLE in the final prediction model; however, they were significantly associated with PLE in the univariate logistic regression model.

Although not identified as a significant risk factor for PLE, RT is considered a major factor leading to BCRL [9, 14]. Regional lymph node irradiation (e.g., SC-RT and axillary-RT) has been found to increase the risk of BCRL by 2–5 times [6, 7, 9, 14, 29]. However, little attention has been given to IM-RT. SC-RT and IM-RT were associated with improved overall survival and are recommended for patients who are node-positive or high-risk node-negative patients [22]. Using univariate logistic regression analysis, we revealed that women receiving IM-RT or SC-RT had a 2.6-fold higher risk of developing PLE.

The role of CT in BCRL remains controversial. Studies have indicated that CT—especially with taxanes—is a risk factor for the development of lymphedema [6, 8, 16].

![ROC Curve](image)
However, only limited analyses for types of taxane (e.g., docetaxel and paclitaxel) are available. A large prospective cohort study by Swaroop et al. [30] concluded that neither docetaxel nor paclitaxel increased the risk of lymphedema. In this report, the cumulative incidence of lymphedema over 2 years was only 5.27%, which was much lower than in other studies [4, 6, 7]. Our data showed that patients treated with taxane-based CT were more prone to develop PLE, and patients who did not receive CT or underwent CT without taxane tended to exhibit TLE. In addition, patients receiving paclitaxel were at a higher risk of developing PLE than those who underwent treatment with docetaxel or other types of taxane. The mechanisms for such differences remain unclear [31, 32].

The limitations of this study were as follows: (1) we did not measure the circumference of both arms before surgery; a preexisting difference, though usually small [33], between dominant and nondominant arms might mask the effects of CD reported here [12]. (2) Patients without lymphedema were not included in this study, so the patients investigated were generally in more advanced stages and received more adjuvant therapies after surgery than in other reports. Most reports in the literature have described risk factors associated with the development of lymphedema in breast cancer survivors [9, 11, 12, 14–17, 28–31]. In the present study, we focused on the risk of developing persistent lymphedema in patients with already established arm edema. The topic of this investigation reflected the primary concern of the breast cancer survivors, that is, “whether the complication would go away.” The strength of our study was that we used a large sample size combined with a median 5-year follow-up.

In conclusion, we demonstrated a prediction model for PLE using three risk factors: more lymph node metastases, more weight gain from surgery to the onset of swelling, and larger CD between arms. On the basis of these results, we encourage the early diagnosis of breast cancers, appropriate body weight control for postoperative patients, and early education on manual lymph drainage for high-risk patients [8, 34].

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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