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ORIGINAL ARTICLE

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 (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 pathology), 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).

Diagnosis and measurements of lymphedema

The texture of skin and subcutaneous tissue of the whole arm was palpated, and circumferential measurement of both arms was performed. The physiatrist measured the circumference of the bilateral upper limbs at the metacarpophalangeal joint, the wrist, 10 cm distal to the antecubital fossa of the elbow, the elbow, and 10 and 20 cm proximal to the elbow [18]. Patients exhibiting CDs between both arms ≥ 1 cm, or those showing CD < 1 cm but with evident pitting edema or subcutaneous tissue hardening were defined as having lymphedema. The degrees of lymphedema were classified as mild, moderate, or severe if the CDs of any measured site were ≦ 2 (n = 190), 2.1–3 (n = 88), or > 3 cm (n = 64), respectively [7]. Patients with BCRL were treated and followed up in surveillance clinics.

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.

Adjuvant 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 patients 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 (65.7%)	
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 (paciltaxel)	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 (30.1%)	211 (69.9%)	
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 ± 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

Table 3 Swelling characteristics of 342 patients with lymphedema

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 ≦ 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* circumeference difference, *CT* chemotherapy, *RT* radiation therapy, *DM* diabetes mellitus

Table 4 Results of univariate logistic regression

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 mammory 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

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

Table 5 Results of multiple logistic regression

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 to onset of swelling	0.105	0.0394	7.084	0.008	1.111	1.028	1.200
Maximal CD of both arms							
Onset of swelling	−2.387	0.4717	25.594	< 0.001	0.092	0.036	0.232
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* circumferencel 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 6 Results of multiple logistic regression (three factors)

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

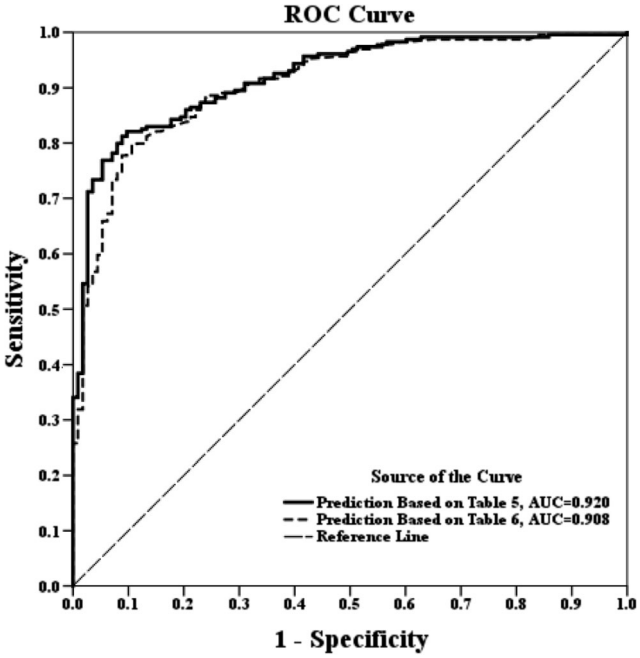

Fig. 1 ROC curves based on the multiple logistic regression prediction models

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 pathophysiologic changes responsible for its progression [7, 24]. Notably, change of body weight measured before surgery and at the onset of swelling was 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].

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 or 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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