Development and validation of a nomogram to predict the risk of breast-cancer-related lymphedema among Chinese breast cancer survivors

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Abstract

Purpose: Breast Cancer-Related Lymphedema (BCRL) is a major long-term complication for post-surgery breast cancer survivors. Although several risk factors have been identified, lifestyle characteristics have been neglected in previous studies. The aim of this study was to develop and validate a nomogram for estimating this population's risk of developing lymphedema, taking into consideration their demographic, clinical, and personal lifestyle behaviors.

Methods: In a cross-sectional study, we collected data from 775 post-operative breast cancer survivors who had attended a follow-up session in the recent ten years (primary cohort). Lymphedema was assessed using the Norman telephone questionnaire, self-reported by patients. Multiple logistic regression was used to identify risk factors for lymphedema, including demographic, clinical, and lifestyle-related factors. A nomogram was constructed based on those factors and was validated using a separate group of 314 breast cancer patients (validation cohort).

Results: The factors independently associated with lymphedema were higher body mass index (BMI), modified radical mastectomy (MRM), postsurgical infection, chemotherapy, radiotherapy, exercise of the affected arm, and the active participation in physical activity ($P<0.05$). The Area under curve (AUC) values of the primary and the validation cohorts were 0.721 (95% confidence interval: 0.685–0.756) and 0.702 (95% confidence interval: 0.646–0.759), respectively.

Conclusions: BCRL risk factors include MRM, radiotherapy, chemotherapy, and higher BMI, while the active physical activity behavior of patients appears to be a protective factor against lymphedema. The nomogram incorporating the patients' clinical and lifestyle factors might be useful for predicting lymphedema in breast cancer survivors.

Keywords: breast cancer, lymphedema, risk factors, lifestyle behaviors, nomogram

Introduction

Breast cancer survival rates have been significantly improved in recent decades from ongoing advancements in surgical and treatment approaches [1]. However, complications from treatment that affect the long-term quality of life of patients have become a significant concern. Breast cancer-related lymphedema (BCRL) is a painful and potentially devastating complication of lymph node damage caused by surgery and/or radiotherapy [2,3]. Pain, stiffness, disfigurement, and altered body image are distinct features of lymphedema, which is incurable and can profoundly diminish the quality of life of patients [4]. Breast cancer survivors have a lifelong risk of developing lymphedema, with the incidence of developing lymphedema among post-operative breast cancer survivors, ranging widely from 9% to 52% differences in the prospective and retrospective studies, the use of measurement techniques [5-7] and the length the follow-up periods [8-10].

Several disease and treatment risk factors for BCRL, including modified radical mastectomy (MRM) and radiotherapy, have been demonstrated as major risk factors for BCRL due to the damage done to the axillary lymphatic reflow [8,9,11,12,10,13,14]. Although treatment-related risk factors are largely not modifiable, substantial scope exists for the modification of lifestyle behaviors aimed at minimizing the incidence of lymphedema in those at risk, defined as patients who have had their lymph nodes removed or who has undergone radiation therapy during treatment for cancer. A higher body mass index (BMI) is a major risk factor related to BCRL; It can increase the initial lymphatic overload responsible for the onset of lymphedema and contribute to the pathophysiological changes responsible for its progression [8,15].

Meanwhile, physical activity has also been shown to be an important factor associated with BCRL [16,17]. The physiological theory supporting the role of physical activity is that the physical contraction of the skeletal muscles of the upper extremity acts as a “muscle pump” in the lymphatic flow mechanism. This “muscle pump” is considered to be the primary channel for lymphatic drainage throughout the body; thus, the consequent development of lymphedema is significantly related to a decrease in the lymphatic pump function of the muscles [18-20]. A systematic review revealed that the risk of developing BCRL was higher among patients who did not participate regularly physical activity than for those who did [8]. Thus, primary or secondary prevention, in particular, through the administration of a physical activity intervention is recommended under various guidelines when there is a considerable risk that a patient will develop BCRL [16,21]. In addition, some precautionary behaviors such as avoiding the drawing of blood, injections, blood pressure readings, and trauma to the at-risk arm have been recommended under various lymphedema risk-reduction guidelines to prevent overload of the lymphatic system of the at-risk limb or affected limb [22,23]. However, the evidence remains inconclusive on the association between exposure to these behaviors and the development of BCRL [24,25]. Since patients need to continuously avoid engaging in certain lifestyle behaviors throughout their life for fear of developing BCRL, it is essential to specify well-substantiated lifestyle factors in this setting [26].

Although models for predicting the risk of developing BCRL exist, they have either been derived from patient disease and treatment characteristics or have not been validated [10,27-30]. Prediction models that include and/or identify lifestyle behaviors as factors associated with BCRL have seldom been developed. The primary objective of the present study was to identify multiple risk factors for BCRL based on the demographic, disease and treatment, and lifestyle behaviors of patients in order to develop

a predictive tool (nomogram). Secondary objectives were the development and validation of the nomogram to predict the risk of developing lymphedema in breast cancer survivors.

Methods

Study Design and Participants

A cross-sectional study was conducted to recruit participants using the following criteria: (i) age 18 years or older; (ii) diagnosis with unilateral breast cancer after 2011; (iii) completed breast cancer surgery at least 6 months earlier; and (iv) proficiency in the Chinese language. The exclusion criteria were as follows: (i) failed to complete radiation and/or chemotherapy treatment; (ii) other conditions that could cause edema (e.g., congestive heart failure, renal diseases and malnutrition etc); (iii) have a history of major trauma, surgery, or infection in the upper limbs or neck; and; (iv) unable to complete the study questionnaire.

Data collection procedures

Seven hundred and seventy-five eligible patients were recruited consecutively between April 2019 and September 2019 from three general hospitals in Beijing and the Rehabilitation Branch of China anti-cancer association in Beijing, who made up the primary cohort of the present study, to identify the risk factors of lymphedema from data on the demographic, clinical, and lifestyle behavior characteristics of breast cancer survivors. Using the same selection criteria as for the primary cohort, 314 patients were recruited into the validation cohort between September 2019 to December 2019 at a general hospital in Shenyang, China.

The online-version advertisements for the study were posted on websites dedicated to breast cancer. Managers of the Rehabilitation Branch of China Anti-Cancer Association recommended that the

association members participate in the study according to the inclusion criteria, the first and fifth authors worked in the anti-cancer association as volunteers and recruited breast cancer patients. In addition， the potential participants were screened by oncology nurses at the breast cancer clinic in each of the four hospitals, and then referred to the first and sixth to eighth authors of this report. They explained verbally and in writing the purpose and procedures of the study. Participants were given the opportunity to ask questions and allowed adequate time to consider their participation. Assurances of confidentiality were provided. Informed consent was obtained from all participants before they filled in the questionnaires. The first author was available to answer any questions about the questionnaire. She also read the questionnaire and recorded the responses for those patients who were illiterate. Researchers checked the completeness of the questionnaires returned by the participants. Participants who completed the questionnaire received a gift voucher. Ethical approval was obtained from the Medical Ethical Committee of the Capital Medical University (No. Z2019SY022).

Analytic variables

All of the participants were asked to complete a set of structured questionnaires. The data collected for each patient included information on their sociodemographic, clinical, and lifestyle behavior characteristics. The socio-demographic information included facts about their age, marital status, level of education, and monthly family income. Clinical information such as disease and treatment characteristics included the duration of their illness, the surgery site, Tumor, Node, Metastases (TNM) staging, operative site, surgical types, and the occurrence of postsurgical infection; the use of chemotherapy, radiotherapy, hormonal therapy, or Chinese medicine; whether or not the tumor had recurred, and any chronic diseases such as cardiovascular disease, diabetes, or osteoporosis. We assessed

148 the performance of lifestyle behaviors through 20 items, including the level of physical activity, skin
149 care, the avoidance of limb constriction, the wearing of compression garments, and exposure to extreme
150 temperatures. We assessed the level of physical activity by asking the participants the frequencies of
151 physical activity per week with four-point responses (1 = almost every day, 2 = 2-4 days per week, 3 =
152 occasionally, and 4 = never). According to their frequencies of physical activity, we assessed whether
153 they had performed physical activity actively, participants reporting more than 2 days of physical activity
154 per week were classified as active, those who do not practice physical activities or practice occasionally
155 were classified as insufficiently active [31]. We assessed the performance of other lifestyle behaviors by
156 asking the participants whether they had performed each lifestyle behavior after breast cancer surgery,
157 instructing them to choose either “Yes” or “No” to confirm whether they performed the listed behaviors
158 daily [22,32].
159

160 **Evaluation of BCRL events**

161 The outcome “lymphedema” was assessed using the Chinese version of the Norman telephone
162 questionnaire. The questionnaire is a self-reported, subjective measure with adequate validity, which
163 predicts BCRL by using self-reports of discharged breast cancer survivors [12,33,34]. The Norman
164 telephone questionnaire, which was originally developed by Norman et al. [33]. Liu et al. [35] had
165 translated this questionnaire into Chinese and reported that its sensitivity was 0.56, its specificity was
166 0.61, and its accuracy was 0.6. Using the Chinese version of this questionnaire, We asked patients
167 whether their right and left hands seem to be differ in size from each other (Norman et al.), and the
168 question was repeated separately for the lower arms and upper arms. Patients who did not report
169 difference at a location were assigned a degree score of 0. If they observed a difference in size, they

were asked: “would you say that, on average, the different in the sizes of your hands/lower arms/ upper arms were: (1) very slight; you are the only person who would notice this, (2) noticeable to people who know you well but not to strangers, or (3) very noticeable.” Patients were classified as mild (1-3 scores), moderate (4-6 scores), or severe (7-9 scores) volume of lymphedema. Moreover, to increase the accuracy of the measurement of BCRL, we collected the patients’ self-report of their diagnosis of BCRL by asking the following “Yes” or “No” question: “Have you been diagnosed as having BCRL by a doctor or physiatrist?”. Consequently, patients were identified as having lymphedema if their Norman telephone questionnaire score was ≥ 1, or if they had been diagnosed as having BCRL by a doctor or physical therapist.

Statistical analysis

Data were analyzed using the STATA 15.0 for Mac (StataCorp Texas, USA) and R software version 3.4.1 (rms package; R Project, Vienna, Austria; http://www.Rproject.org). Categorical variables were summarized as frequencies and percentages; continuous data were presented as means, standard deviation, and range. A Chi-square test and Mann-Whitney U test were used to conduct the between-group comparisons. Univariate and multivariable logistic analysis was used to select the predictive features from the primary cohort. Candidate variables with significance (those with a P value of ≤ 0.20) under the univariate analysis were entered into the multivariate analysis model using the forward stepwise logistic regression. The nomogram for predicting BCRL was constructed based on the independent risk factors that resulted from the multivariable logistic regression analysis. A receiver operating characteristics (ROC) curve was drawn and the area under the curve (AUC) value was calculated to measure the discrimination of the BCRL nomogram. It is generally accepted that AUC

values of 0.7–0.8 represent reasonable discrimination, and values above 0.8 represent good discrimination [36]. Calibration of the nomogram was examined graphically by plotting the calibration curve, with the predicted BCRL risks plotted on the x-axis and the observed BCRL risks plotted on y-axis. The 45-degree gray line represents a perfect prediction. The solid black line represents the predictive performance of the nomogram, of which a closer fit to the 45-degree gray line represents a better predictive performance of the model [37].

Results

Characteristics of the primary and validation cohorts

The primary cohort comprised 775 patients (median age: 55 years; interquartile range: 48–62 years), and 398 patients (51.4%) had BCRL: 140 patients (35.4%) were mild, 148 patients were moderate, and 109 patients (37.2%) were severe. The validation cohort consisted of 314 patients (median age: 54 years; interquartile range: 47–60 years) and 137 patients (43.6%) had BCRL：74 patients (54.0%) were mild, 36 patients (26.3%) were moderate, and 27 patient (19.7%) were severe. A comparison of patient characteristics between the primary and validation cohorts are shown in **Table 1**. In general, distributions were similar regarding patients' disease and treatment characteristics and statistically significant differences were found in Duration of illness, TNM staging, Hormonal therapy, Chinese medicine conditioning, Osteoporosis ($P < 0.05$); In terms of lifestyle related characteristics, 6 of 21 factors showed significant difference between the primary and validation cohorts($P < 0.05$), including "Avoid punctures, such as injections and blood draws, in the affected arm", "Avoid having blood pressure taken on the at-risk extremity", "Use care with razors to avoid nicks and skin irritation" , "If a rash, itching, redness, pain, increased skin temperature, or fever symptoms occur, contact your physician immediately

for early treatment", "Keep extremely clean and dry", "Wear well-fitted compression garment for strenuous activities (prolonged standing or running)".

Development and validation of the BCRL nomogram

In the univariate analysis, 17 of the 38 factors tested were associated with the occurrence of BCRL and were entered into the multivariate analysis (**Table 2**). In the multivariate analysis, 7 factors were identified as independent predictors of BCRL ($P<0.05$). A significant increase in the risk of developing BCRL was found in women with a higher BMI, those who had undergone a modified radical mastectomy, experienced a postsurgical infection, or who had undergone chemotherapy or radiotherapy, whereas a decreased risk of developing lymphedema was found in those who exercised their affected arm regularly or active participation in physical activity. The specifics of the predictors of BCRL are presented in **Table 3**. A model incorporating the above independent predictors was developed and presented as the nomogram (Fig. 1). A total point is the sum of points for each variable and the probability of BCRL is the corresponding number of the total points in the nomogram. For instance, if a total point is >300, the probability of BCRL is >70 %. The AUC for the nomogram in our primary cohort was 0.721 (95% CI: 0.685–0.756). As shown in Fig. 2, the calibration plot of the nomogram on the probability of BCRL indicated good agreement between the prediction and actual observation, where the ideal calibration and the logistic calibration curve were represented by the 45-degree gray line and the solid line accordingly.

The BCRL nomogram was validated in the independent validation cohort, the AUC for the nomogram in our validation cohort was 0.702 (95% CI: 0.646–0.759). The calibration plot showed that the probabilities of BCRL predicted by the nomogram were sometimes not in good agreement with the

actual probabilities observed in the validation cohort, indicating the need for improvement of the calibration for this nomogram (Fig. 3).

Discussion

Using data from a large cohort, we examined the demographic, disease, treatment, and lifestyle characteristics of the patients that may affect their development of secondary lymphedema after surgery for breast cancer. We identified seven key predictors of BCRL: a higher BMI, MRM, postsurgical infection, chemotherapy, radiotherapy, exercise of the affected arm, and the level of physical activity. Among them, a higher BMI, MRM, radiotherapy, chemotherapy and postsurgical infection are important risk factors for BCRL [8-10,12,29]. Recently, exercise of the affected arm, and the active participation in physical activity have also been identified as potential predictors for lymphedema [16].

Several trends arising from the data added to the research base, which is important to clinical practice with regard to educating patients on risk reduction. Among the lifestyle-related factors, we found that women who exercised their affected arm and engaged in active physical activity per week appeared to have a lower risk of developing lymphedema than those who did not perform those activities. The association between exercise and the risk of developing lymphedema has been shown in Park's cohort study and in another study conducted by Disipio et al. [8,16]. A possible mechanism by which physical activity decreases the risk of developing lymphedema is through the activation of the "muscle pump," which can theoretically enhance the lymphatic fluid drainage and decrease the individual's risk of developing BCRL [18,38]. Baumann et al. [17] revealed that moderate exercise training improved the functional capacity and improved subjective and objective parameters in patients with BCRL. Notably, dynamic, moderate, and high-frequency exercise appeared to provide the most positive effects.

Meanwhile, guidelines recommended that breast cancer survivors actively engaged in physical activity in daily life. However, fewer than half of patients in our primary and validation cohort were still insufficiently physically active. Moreover, many post-operative breast cancer survivors might face a significantly decrease of the physical activity level for a long time comparing to their preoperative value [39]. Misconceptions that exercise is associated with the development of lymphedema, lack of sufficient information regarding exercise and the exercise programs might prevent the patients from being physical active. In addition, many breast cancer survivors received conflicting advice on exercise, which may have further limited them from engaging in active exercise [40,41]. Thus, it is important that therapists provide their patients with correct information about exercise and exercise programs.

We found no significant association between BCRL and engagement in such lifestyle behaviors as getting blood pressure readings, having blood drawn, receiving injections, and engaging in air travel. Asdourian et al. [24] reported similar findings in a study involving 327 patients who underwent bilateral breast cancer surgery as those in a study by Ferguson et al. [25] involving women 6 to 60 months after they had received a diagnosis of cancer. Considering that the lifestyle behaviors relating to lymphedema risk have not been well established, when determining education strategies active consideration should be given to providing individual-based lifestyle instructions in order to alleviate unnecessary distress and anxiety for those at risk of developing lymphedema.

Our results are in agreement with the majority of studies showing an association between postsurgical infection and an increased risk of developing lymphedema [8,42,27]. The mechanism may be that the immune response caused by postsurgical infection increased the load on the lymphatic system. Similarly, Indelicato et al. [43] found that patients with BCRL were more likely to develop delayed breast cellulitis, suggesting a vicious circle between the development of cellulitis and BCRL.

Furthermore, we developed a nomogram based on a cohort with an long duration of disease (Median: 42 months, IQR: 15-94 months) and the AUC was 0.721(95% CI: 0.685–0.756), which performed well on the primary cohort on measures of discrimination and calibration. For the external cohort, the nomogram was accurate with an AUC of 0.702 (95% CI: 0.646–0.759), indicating the need for further cohort study to evaluate the calibration of this nomogram. Therefore, this nomogram may represent an convenience and available tool for clinicians to estimate the BCRL risk of individuals within the follow-up period. Notablely, different from other BCRL prediction tools based on clinical data [12,10,29,28]. the variables in our proposed model consisted of clinical and exercise characteristics. This would be helpful for optimizing lymphedema surveillance efforts and for guiding efforts to minimize the risk of lymphedema through refining individual lifestyle behaviors following their breast cancer treatment.

Meanwhile, though the nomogram is acceptable for BCRL risk estimation, its discrimination and accuracy of nomogram need to be improved comparing with similar studies [10,28,29] due to several limitations. Firstly, It was worth noting that the predicted probabilities were higher than the actual probabilities in the calibration Plot (Figure 3) of the validation cohort. This is likely because patients with arm asymmetry were misdiagnosed as mild lymphedema due to the absence of baseline measurement of the arm swelling. A study reported that 28.3% patients were with 5% of arm asymmetry and 10 % patients with 2.9 % of arm asymmetry, respectively [44]. Secondly, participants of our study may be considered as mild lymphedema, and this might reduce the predictive power of the model. Thirdly, the risks for lymphedema of axillary lymph node dissection (ALND) and sentinel lymph node biopsy (SLND) are completely different (25-34.1% vs, 5.6-10%, respectively) [12,8,45]. However, the clinical factors included in the nomogram of this study did not specify whether the patients had ALND or SLND. It was because the final nomogram was formulated based on a cohort consisted of women who were

diagnosed before 2011 when sentinel lymph node biopsy was less common [46]. Thus, the nomogram was unable to clarify the risk of lymphedema with different axillary node status, and the risk of lymphedema in patients with SLND might be overestimated. Furthermore, as the process of gradually adopting new institutional radiotherapy policies, different irradiation ranges caused different impacts, regional lymph node irradiation has been found to increase the risk of BCRL by 2-4 times, whereas the breast/chest wall alone is not associated with lymphedema [10]. The radiotherapy included in this nomogram did not specify whether it included regional lymph nodes or breast / chest wall alone, Thus, when applying this nomogram to estimate the risk of BCRL in patients with radiotherapy, clinicians need to differentiate their different radiotherapy regimens.

Moreover, the previous studies also reported that chemotherapy played a crucial role for BCRL. Taxane-based chemotherapy can lead to the accumulation of extracellular fluid and accelerate peripheral edema [47]. Furthermore, taxanes-based chemotherapy with or without trastuzumab can increase the risk of BCRL. Herceptin-based therapy can reduce the direct proliferative effects of vascular endothelial growth factor on tumor cells, and diminish the operation of lymph angiogenesis website, prevent lymphatic regeneration, and thereby promote lymphedema [48]. Thus, development and validation including different chemotherapy or trastuzumab warrants further clarification in future studies.

Our study has also some methodological limitations. Firstly, the convenience sampling method may have decreased the representativeness of the sample. Asymptomatic patients may have refused to participate in the collection of information on symptoms, while affected patients might have been more motivated to fill in the questionnaire. Secondly, in the current study, we adopted a subjective method (the patient self-report lymphedema), with high sensitivity and specificity compared to expert physical measurements [49]. However, this method may result in recall bias, especially in elderly people.

Therefore, combing with the objective measurements such as clinical and physical examinations, the measurement bias could be reduced in the future study.

Conclusion

Active engagement in physical activity including exercising the affected arm appear to be a protective factor against BCRL. These results may be valuable for guiding lymphedema surveillance strategies and patient education in clinical practice. Moreover, in this study a nomogram incorporating both the exercise signature and clinical risk factors was constructed. This nomogram can be conveniently used during the follow-up session to screen groups that are at a high-risk of developing BCRL. Further investigations involving larger, multi-center, prospective cohorts are warranted.

Declarations

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

Ethics approval: Approval was obtained from the Medical Ethics Committee of Capital Medical University (Z2019SY022). The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

Consent to participate: Informed consent was obtained from all of the participants in this study.

Consent for publication: Not applicable.

Availability of data and material: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code availability: The statistical analyses were conducted using STATA 15.0 for Mac (StataCorp Texas, USA) and R software version 3.4.1 (rms package; R Project, Vienna, Austria; http://www.Rproject.org).

Authors' contributions: Conceptualization: Yi Zhu, Jun-E Liu, Hui Qiu, Yan-fei Liu; Methodology: Yan-fei Liu, Jun-E Liu, Yim Wah Mak, Yi Zhu; Data collection: Yan-fei Liu, Hui Qiu, Li-hui Liu, Shen-shen Yang, Shao-hua Chen; Formal analysis and investigation: Yan-fei Liu, Hui Qiu, Shen-shen Yang, Shao-hua Chen; Writing-original draft preparation: Yan-fei Liu, Jun-E Liu; Writing - review and editing: Yan-fei Liu, Jun-E Liu, Yim Wah Mak. All authors read and approved the final manuscript.

References

1. DeSantis CE, Ma J, Gaudet MM, Newman LA, Miller KD, Goding Sauer A, Jemal A, Siegel RL (2019) Breast cancer statistics, 2019. CA Cancer J Clin 69 (6):438-451. doi:10.3322/caac.21583

2. Michelotti A, Invernizzi M, Lopez G, Lorenzini D, Nesa F, De Sire A, Fusco N (2019) Tackling the diversity of breast cancer related lymphedema: Perspectives on diagnosis, risk assessment, and clinical management. Breast 44:15-23. doi:10.1016/j.breast.2018.12.009

3. Invernizzi M, Corti C, Lopez G, Michelotti A, Despini L, Gambini D, Lorenzini D, Guerini-Rocco E, Maggi S, Noale M, Fusco N (2018) Lymphovascular invasion and extranodal tumour extension are risk indicators of breast cancer related lymphoedema: an observational retrospective study with long-term follow-up. BMC Cancer 18 (1):935. doi:10.1186/s12885-018-4851-2

4. Rockson SG (2019) Lymphedema after Breast Cancer Treatment. N Engl J Med 380 (7):694. doi:10.1056/NEJMc1817537

5. Shah C, Vicini FA (2011) Breast cancer-related arm lymphedema: incidence rates, diagnostic techniques, optimal management and risk reduction strategies. International journal of radiation oncology, biology, physics 81 (4):907-914. doi:10.1016/j.ijrobp.2011.05.043

6. Rupp J, Hadamitzky C, Henkenberens C, Christiansen H, Steinmann D, Bruns F (2019) Frequency and risk factors for arm lymphedema after multimodal breast-conserving treatment of nodal positive breast Cancer - a long-term observation. Radiat Oncol 14 (1):39. doi:10.1186/s13014-019-1243-y

7. Norman SA, Localio AR, Potashnik SL, Simoes Torpey HA, Kallan MJ, Weber AL, Miller LT, Demichele A, Solin LJ (2009) Lymphedema in breast cancer survivors: incidence, degree, time course, treatment, and symptoms. J Clin Oncol 27 (3):390-397. doi:10.1200/JCO.2008.17.9291

8. DiSipio T, Rye S, Newman B, Hayes S (2013) Incidence of unilateral arm lymphoedema after breast cancer: a systematic review and meta-analysis. The Lancet Oncology 14 (6):500-515. doi:10.1016/s1470-2045(13)70076-7

9. Ribeiro Pereira ACP, Koifman RJ, Bergmann A (2017) Incidence and risk factors of lymphedema after breast cancer treatment: 10 years of follow-up. Breast 36:67-73. doi:10.1016/j.breast.2017.09.006

10. Byun HK, Chang JS, Im SH, Kirova YM, Arsene-Henry A, Choi SH, Cho YU, Park HS, Kim JY, Suh CO, Keum KC, Sohn JH, Kim GM, Lee IJ, Kim JW, Kim YB (2019) Risk of Lymphedema Following Contemporary Treatment for Breast Cancer: An Analysis of 7617 Consecutive Patients From a Multidisciplinary Perspective[published online ahead of print]. Ann Surg. doi:10.1097/SLA.0000000000003491

11. McLaughlin SA, DeSnyder SM, Klimberg S, Alatriste M, Boccardo F, Smith ML, Staley AC, Thiruchelvam PTR, Hutchison NA, Mendez J, MacNeill F, Vicini F, Rockson SG, Feldman SM (2017) Considerations for Clinicians in the Diagnosis, Prevention, and Treatment of Breast Cancer-Related Lymphedema, Recommendations from an Expert Panel: Part 2: Preventive and Therapeutic Options. Ann Surg Oncol 24 (10):2827-2835. doi:10.1245/s10434-017-5964-6

12. Zou L, Liu FH, Shen PP, Hu Y, Liu XQ, Xu YY, Pen QL, Wang B, Zhu YQ, Tian Y (2018) The incidence and risk factors of related lymphedema for breast cancer survivors post-operation: a 2-year follow-up prospective cohort study. Breast Cancer 25 (3):309-314. doi:10.1007/s12282-018-0830-3

13. Skuli SJ, Sheng JY, Bantug ET, Zafman N, Riley C, Ruck JM, Smith KC, Snyder CF, Smith KL, Stearns V, Wolff AC (2019) Survivorship care visits in a high-risk population of breast cancer survivors. Breast Cancer Res Treat 173 (3):701-708. doi:10.1007/s10549-018-5028-z

14. Kim M, Shin KH, Jung SY, Lee S, Kang HS, Lee ES, Chung SH, Kim YJ, Kim TH, Cho KH (2016) Identification of Prognostic Risk Factors for Transient and Persistent Lymphedema after Multimodal Treatment for Breast Cancer. Cancer Res Treat 48 (4):1330-1337. doi:10.4143/crt.2015.463

15. Penn IW, Chang YC, Chuang E, Chen CM, Chung CF, Kuo CY, Chuang TY (2019) Risk factors and prediction model for persistent breast-cancer-related lymphedema: a 5-year cohort study. Support Care Cancer 27 (3):991-1000. doi:10.1007/s00520-018-4388-6

16. Park JH, Lee WH, Chung HS (2008) Incidence and risk factors of breast cancer lymphoedema. Journal of clinical nursing 17 (11):1450-1459. doi:10.1111/j.1365-2702.2007.02187.x

17. Baumann FT, Reike A, Hallek M, Wiskemann J, Reimer V (2018) Does Exercise Have a Preventive Effect on Secondary Lymphedema in Breast Cancer Patients Following Local Treatment? - A Systematic Review. Breast Care (Basel) 13 (5):380-385. doi:10.1159/000487428

18. Gashev AA (2002) Physiologic aspects of lymphatic contractile function: current perspectives. Ann N Y Acad Sci 979:178-187; discussion 188-196. doi:10.1111/j.1749-6632.2002.tb04878.x

19. Stanton AW, Modi S, Mellor RH, Levick JR, Mortimer PS (2009) Recent advances in breast cancer-related lymphedema of the arm: lymphatic pump failure and predisposing factors. Lymphat Res Biol 7 (1):29-45. doi:10.1089/lrb.2008.1026

20. Hashemi HS, Fallone S, Boily M, Towers A, Kilgour RD, Rivaz H (2019) Assessment of Mechanical Properties of Tissue in Breast Cancer-Related Lymphedema Using Ultrasound Elastography. IEEE Trans Ultrason Ferroelectr Freq Control 66 (3):541-550. doi:10.1109/TUFFC.2018.2876056

21. Park JH (2017) The effects of complex exercise on shoulder range of motion and pain for women with breast cancer-related lymphedema: a single-blind, randomized controlled trial. Breast Cancer 24 (4):608-614. doi:10.1007/s12282-016-0747-7

22. NLN Medical Advisory Committee (2011) Position statement of the National Lymphedema Network: lymphedema risk reduction practices. Lymphnet.org website. Available from: www.lymphnet.org/pdfDocs/nlnriskreduction.pdf/ (accessed 15 September 2020).

23. Chinese Anti-Cancer Association Committee of Breast Cancer Society (2019) Clinical Practice Guidelines of Breast Cancer(Version 2019). China Oncology, vol 29. doi:10.19401/j.cnki.1007-3639.2019.08.009

24. Asdourian MS, Swaroop MN, Sayegh HE, Brunelle CL, Mina AI, Zheng H, Skolny MN, Taghian AG (2017) Association Between Precautionary Behaviors and Breast Cancer-Related Lymphedema in Patients Undergoing Bilateral Surgery. J Clin Oncol 35 (35):3934-3941. doi:10.1200/jco.2017.73.7494

25. Ferguson CM, Swaroop MN, Horick N, Skolny MN, Miller CL, Jammallo LS, Brunelle C, O'Toole JA, Salama L, Specht MC, Taghian AG (2016) Impact of Ipsilateral Blood Draws, Injections, Blood Pressure Measurements, and Air Travel on the Risk of Lymphedema for Patients Treated for Breast Cancer. J Clin Oncol 34 (7):691-698. doi:10.1200/JCO.2015.61.5948

26. Asdourian MS, Skolny MN, Brunelle C, Seward CE, Salama L, Taghian AG (2016) Precautions for breast cancer-related lymphoedema: risk from air travel, ipsilateral arm blood pressure

measurements, skin puncture, extreme temperatures, and cellulitis. The Lancet Oncology 17 (9):e392-405. doi:10.1016/s1470-2045(16)30204-2

27. Wang L, Li HP, Liu AN, Wang DB, Yang YJ, Duan YQ, Zhang QN (2016) A Scoring System to Predict Arm Lymphedema Risk for Individual Chinese Breast Cancer Patients. Breast Care (Basel) 11 (1):52-56. doi:10.1159/000443491

28. Bevilacqua JLB, Kattan MW, Changhong Y, Koifman S, Mattos IE, Koifman RJ, Bergmann A (2012) Nomograms for Predicting the Risk of Arm Lymphedema after Axillary Dissection in Breast Cancer. Annals of Surgical Oncology 19 (8):2580-2589. doi:10.1245/s10434-012-2290-x

29. Gross JP, Whelan TJ, Parulekar WR, Chen BE, Rademaker AW, Helenowski IB, Donnelly ED, Strauss JB (2019) Development and Validation of a Nomogram to Predict Lymphedema After Axillary Surgery and Radiation Therapy in Women With Breast Cancer From the NCIC CTG MA.20 Randomized Trial. International journal of radiation oncology, biology, physics 105 (1):165-173. doi:10.1016/j.ijrobp.2019.05.002

30. Li F, Lu Q, Jin S, Zhao Q, Qin X, Jin S, Zhang L (2020) A scoring system for predicting the risk of breast cancer-related lymphedema. International journal of nursing sciences 7 (1):21-28. doi:10.1016/j.ijnss.2019.12.007

31. Matoso LBBMM, Boing L, Korpalski T, Dias M, Moratelli J, Fausto DY, Guimarães ACdA (2020) Relationship of fatigue with depressive symptoms and level of physical activity in women with breast cancer diagnosis. Revista Brasileira de Cineantropometria & Desempenho Humano 22:e59189. doi:10.1590/1980-0037.2020v22e59189

32. Fu MR, Axelrod D, Haber J (2008) Breast-cancer-related lymphedema: information, symptoms, and risk-reduction behaviors. J Nurs Scholarsh 40 (4):341-348. doi:10.1111/j.1547-5069.2008.00248.x

456 33. Norman SA, Localio AR, Kallan MJ, Weber AL, Torpey HA, Potashnik SL, Miller LT, Fox KR,
457 DeMichele A, Solin LJ (2010) Risk factors for lymphedema after breast cancer treatment. Cancer
458 Epidemiol Biomarkers Prev 19 (11):2734-2746. doi:10.1158/1055-9965.EPI-09-1245
459 34. Togawa K, Ma H, Sullivan-Halley J, Neuhouser ML, Imayama I, Baumgartner KB, Smith AW,
460 Alfano CM, McTiernan A, Ballard-Barbash R, Bernstein L (2014) Risk factors for self-reported
461 arm lymphedema among female breast cancer survivors: a prospective cohort study. Breast cancer
462 research : BCR 16 (4):414. doi:10.1186/s13058-014-0414-x
463 35. Liu J, Lu, Q., Ou, Y.Q., Hou, X.T., Liu, F., Shi, S., Li, C.Y. (2015) Validation of Norman telephone
464 questionnaire in detection of Iymphedema for breast cancer patients after radical rection. Journal of
465 Nursing Science 30 (24):35-37
466 36. Shin HC, Han W, Moon HG, Cho N, Moon WK, Park IA, Park SJ, Noh DY (2012) Nomogram for
467 predicting positive resection margins after breast-conserving surgery. Breast Cancer Res Treat 134
468 (3):1115-1123. doi:10.1007/s10549-012-2124-3
469 37. Moons KG, Altman DG, Reitsma JB, Ioannidis JP, Macaskill P, Steyerberg EW, Vickers AJ,
470 Ransohoff DF, Collins GS (2015) Transparent Reporting of a multivariable prediction model for
471 Individual Prognosis or Diagnosis (TRIPOD): explanation and elaboration. Ann Intern Med 162
472 (1):W1-73. doi:10.7326/M14-0698
473 38. Nelson NL (2016) Breast Cancer-Related Lymphedema and Resistance Exercise: A Systematic
474 Review. Journal of strength and conditioning research 30 (9):2656-2665.
475 doi:10.1519/JSC.0000000000001355

476 39. De Groef A, Geraerts I, Demeyer H, Van der Gucht E, Dams L, de Kinkelder C, Dukers-van Althuis
477 S, Van Kampen M, Devoogdt N (2018) Physical activity levels after treatment for breast cancer:
478 Two-year follow-up. The Breast 40:23-28. doi:10.1016/j.breast.2018.04.009
479 40. Kim S, Han J, Lee MY, Jang MK (2019) The experience of cancer-related fatigue, exercise and
480 exercise adherence among women breast cancer survivors: Insights from focus group interviews.
481 Journal of clinical nursing 29 (5-6):758-769. doi:10.1111/jocn.15114
482 41. Panchik D, Masco S, Zinnikas P, Hillriegel B, Lauder T, Suttmann E, Chinchilli V, McBeth M,
483 Hermann W (2019) Effect of Exercise on Breast Cancer-Related Lymphedema: What the
484 Lymphatic Surgeon Needs to Know. J Reconstr Microsurg 35 (1):37-45. doi:10.1055/s-0038-
485 1660832
486 42. Gillespie TC, Sayegh HE, Brunelle CL, Daniell KM, Taghian AG (2018) Breast cancer-related
487 lymphedema: risk factors, precautionary measures, and treatments. Gland surgery 7 (4):379-403.
488 doi:10.21037/gs.2017.11.04
489 43. Indelicato DJ, Grobmyer SR, Newlin H, Morris CG, Haigh LS, Copeland EM, 3rd, Mendenhall NP
490 (2006) Delayed breast cellulitis: an evolving complication of breast conservation. International
491 journal of radiation oncology, biology, physics 66 (5):1339-1346.
492 doi:10.1016/j.ijrobp.2006.07.1388
493 44. Sun F, Skolny MN, Swaroop MN, Rawal B, Catalano PJ, Brunelle CL, Miller CL, Taghian AG (2016)
494 The need for preoperative baseline arm measurement to accurately quantify breast cancer-related
495 lymphedema. Breast Cancer Res Treat 157 (2):229-240. doi:10.1007/s10549-016-3821-0
496 45. Keeley V (2020) The Early Detection of Breast Cancer Treatment-Related Lymphedema of the Arm.
497 Lymphat Res Biol. doi:10.1089/lrb.2020.0097

46. Jiang ZF, Li, J.B. (2020) Development of guidelines and clinical practice for breast cancer. Chinese Journal of Surgery 58 (2):85-90. doi:10.3760/cma.j.issn.0529-5815.2020.02.002

47. Invernizzi M, Michelotti A, Noale M, Lopez G, Runza L, Giroda M, Despini L, Blundo C, Maggi S, Gambini D, Fusco N (2019) Breast Cancer Systemic Treatments and Upper Limb Lymphedema: A Risk-Assessment Platform Encompassing Tumor-Specific Pathological Features Reveals the Potential Role of Trastuzumab. J Clin Med 8 (2). doi:10.3390/jcm8020138

48. Schoppmann SF, Tamandl D, Roberts L, Jomrich G, Schoppmann A, Zwrtek R, Dubsky P, Gnant M, Jakesz R, Birner P (2010) HER2/neu expression correlates with vascular endothelial growth factor-C and lymphangiogenesis in lymph node-positive breast cancer %J Annals of Oncology. 21 (5)

49. A NS, T ML, B EH, F NM, R M (2001) Development and validation of a telephone questionnaire to characterize lymphedema in women treated for breast cancer. %J Physical therapy. 81 (6)

Figure Captions

Fig. 1 Nomogram for predicting the probability of lymphedema

Rows 2 through 8 represent variables. By drawing a vertical line between each variable and the Points' axis to determine the effect of each variable by a defined number of points, which should be summed and located in row 9 (Total Points). Vertical line should be made between the row 9 and 11 (Risk of lymphedema) to obtain the predicted probability of BCRL.

Fig. 2 Calibration curve of the BCRL nomogram in the primary cohort

Fig. 3 Calibration curve of the BCRL nomogram in the validation cohort