

Defining breast cancer-related lymphedema (BCRL) prevalence and risk factors: A pragmatic approach to lymphedema surveillance

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ABSTRACT

Introduction: We presented the key findings from Singapore's Changi General Hospital Breast Centre's lymphedema surveillance strategy that used patients' reported symptoms, standard arm circumference measurements and clinical assessment in the diagnosis of breast cancer-related lymphedema (BCRL). Our secondary aim was to highlight and discuss important elements of a surveillance strategy that can be implemented to track this outcome measure of breast cancer treatment for future research.

Method: We conducted a cross-sectional study of 511 breast cancer patients to assess the prevalence of BCRL and its associated risk factors. We defined BCRL prevalence rates based on patients' self-reporting, objective arm circumference measurements and clinical diagnosis based on International Society of Lymphology (ISL) staging.

Results: The median follow-up of patients was 88.8 months. The cumulative prevalence rate in the cohort was 30.9%. The cohort of BCRL patients were older (58.4 versus [vs] 54.9 years), had higher mean Body Mass Index (27.7 vs 25.2), higher proportion of mastectomy (77% vs 64.3%), axillary clearance, less likely breast reconstruction, higher-grade tumour, more lymph nodes excised, more advanced nodal disease, and had undergone adjuvant chemotherapy. However, clinically apparent BCRL was only 6.5% (33 out of 511 patients). The proportion of clinically significant BCRL in patients undergoing sentinel lymph node biopsy (SLNB) or axillary sampling was 1.7% compared to 9.9% in patients who had undergone axillary clearance. Majority of the BCRL were subclinical or mild in severity.

Conclusion: Our study showed that our rates of BCRL were comparable to international rates and highlighted similar patient profiles who were at risk of developing the disease. Having a comprehensive lymphedema surveillance strategy is paramount in paving the way for future studies.

Ann Acad Med Singap 2024;53:80-9

Keywords: cancer, cancer survivorship, general surgery, lymphedema, prevalence, surveillance

CLINICAL IMPACT

What is New

- This study is the first to highlight prevalence and risk factors of developing breast cancer-related lymphedema in Singapore.
- Findings underscore the importance of a comprehensive lymphedema surveillance strategy in any breast unit.

Clinical Implications

- The study highlights the effectiveness of simple assessment tools such as patient questionnaires, regular arm circumference measurement before and after treatment, clinical assessment matrix for diagnosis of BCRL and timely intervention.
- This data can potentially inform guidelines for lymphedema surveillance strategy in Singapore.

INTRODUCTION

Breast cancer-related lymphedema (BCRL) is a chronic progressive pathological condition of the lymphatic system that can lead to significant impact on the quality of life after breast cancer treatment.¹ It is characterised by swelling and accumulation of protein-rich fluid in body tissues, leading to pain, tightness, skin changes such as fibrosis/thickening

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or recurrent infections, impaired mobility, and function of the affected arms. BCRL has an insidious onset and can occur even without precipitating events, years after treatment. Systematic reviews have shown that interventions tend to be more effective in the initial stages of lymphedema, before permanent changes such as fibrosis set in.^{2,3} However, due to a lack of standardised diagnostic criteria, BCRL is still notoriously difficult to detect in its early stages.⁴ Hence, it is important to have a lymphedema surveillance strategy that starts as early as from the time of cancer diagnosis and persists beyond treatment.

The incidence of BCRL has been reported to range from 0% to 94% of the breast cancer survivors.³⁻¹² This wide variation in incidence is largely owing to a difference in study designs, diagnostic methods, a lack in consistency of objective measures of BCRL, and varying timing of measurements. The lack of local data on the prevalence of BCRL in Singapore makes it difficult to quantify the extent of the morbidity or to study the effectiveness of interventions aimed at curtailing them.

In this paper, we present the key features of Singapore's Changi General Hospital Breast Centre's approach to lymphedema surveillance that has been using standard arm circumference measurements as an adjunct objective reading to aid in the diagnosis of BCRL. Finally, we conducted a cross-sectional study of our centre's breast cancer survivors to examine the performance of a set of predefined subjective and objective assessment tools, to assess for the prevalence of BCRL along with its associated risk factors. Our aim is to highlight and discuss the importance of a surveillance strategy that is evidence-based and can be implemented readily to track the magnitude and severity of BCRL as an outcome measure of breast cancer treatment.

METHOD

Lymphedema surveillance programme

A comprehensive lymphedema surveillance programme, started in 2019 at Changi General Hospital Breast Centre, included patient education on the condition, advice on arm care, and range-of-motion exercises (Fig. 1). These were taught to the patients prior to the initiation of any treatment and reinforced at each touch point by their respective treating clinicians and nurses. Baseline arm circumference measurements were also obtained by both trained nurses and clinicians.

Criteria for BCRL diagnosis

- Arm circumference was taken at 10 cm below and above the olecranon and a difference ≥ 2 cm from the contralateral arm or from baseline was taken to be indicative of BCRL.
- Patients' self-reported diagnosis of BCRL and/or subjective complaints of persistent arm swelling for more than 1 month were considered to be indicative of BCRL.
- All clinicians assessed for the presence of BCRL based on patient symptoms and arm circumference measurements. If present, clinicians graded the severity of lymphedema according to International Society of Lymphology (ISL) (Fig. 2).

Patients who were assessed to have risk factors and fulfilled any of the diagnostic criteria of BCRL or presence of triggers were offered referrals to our specialised lymphedema therapist for further evaluation and appropriate interventions.

A total of 511 patients who were treated and on follow-up for breast cancer surveillance in Changi General Hospital Breast Centre were recruited by convenient sampling between March and September 2021 for the cross-sectional study. The prevalence of lymphedema using patients' subjective complaints or self-reporting method, objective arm circumference measurements and clinicians' independent assessments were analysed for agreement. Patients who had metastatic breast cancer, bilateral breast cancer, disease recurrence or declined curative surgery were excluded. Based on the cumulative diagnosis of BCRL, we analysed the clinical risk factors associated.

This study was approved by SingHealth Centralised Institutional Review Board 2021/2068 to be conducted in Changi General Hospital.

Statistical analysis

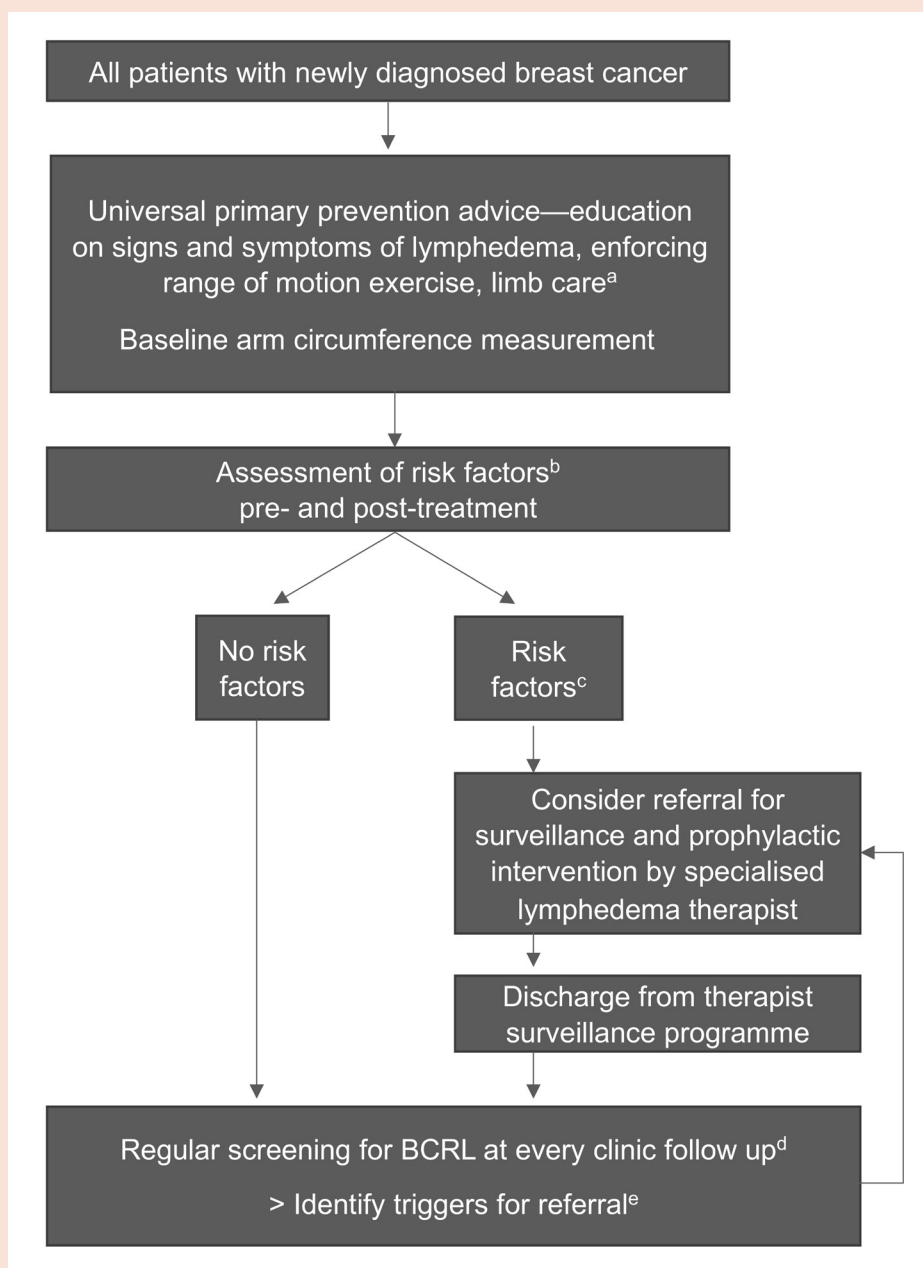
Percent agreement and Cohen's kappa coefficient were used to analyse inter-rater variability between the assessment tools. Categorical variables were analysed using the chi-square or Fisher's Exact test, and continuous variables were analysed using the Student's t-test. A *P* value of <0.05 was considered statistically significant. Statistical analysis was performed in March 2022 using Stata SE version 17 (StataCorp, College Station, TX, US).

RESULTS

Patients' clinical demographic and risk factors associated with BCRL

The median follow-up of patients was 88.8 months (Table 1). The cumulative prevalence rate in the

Fig. 1. Our surveillance strategy for breast cancer related lymphedema (BCRL).



^a Universal primary prevention advice:

- 1) Maintain a healthy weight
- 2) Avoid trauma/injury to at-risk limb if possible. However, isolated blood pressure measurement, venipuncture and peripheral intravenous line placement in the ipsilateral arm not affected by lymphedema has not been shown to affect the occurrence of lymphedema
- 3) Regular surveillance of signs and symptoms of BCRL

^b Risk factors:

- 1) Elevated body mass index (BMI ≥ 25)
- 2) Higher pathological stage ($\geq T3$ or $\geq N1$)
- 3) History of axillary clearance
- 4) Chemotherapy

^c Screening for lymphedema signs and symptoms (PESTS):

- 1) Pain
- 2) Elevate the arm (check for fatigue, weakness, restricted range of motion)
- 3) Swelling
- 4) Tightness and altered sensation (including heaviness, numbness)
- 5) Skin changes (including thickening, signs of infection)

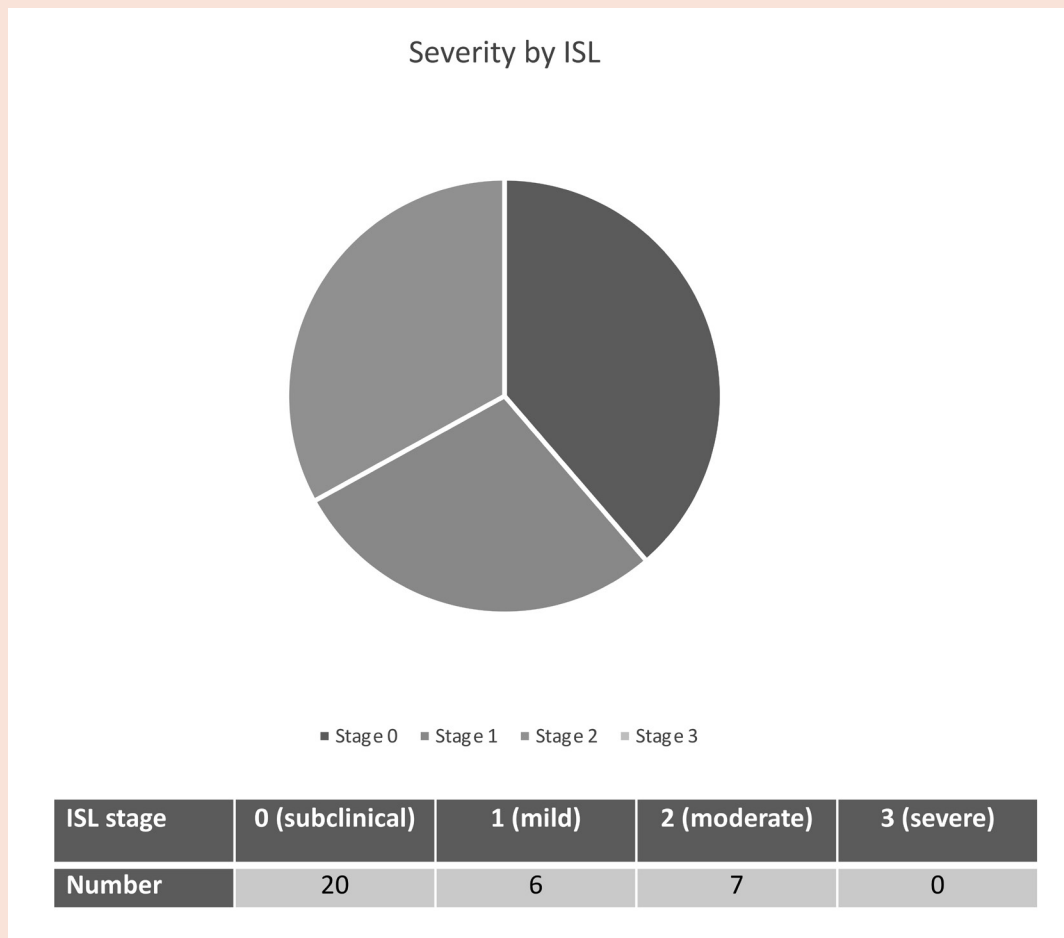
^d Screening for confounding conditions:

- 1) Musculoskeletal conditions (e.g. frozen shoulder/osteoarthritis/fracture/carpal tunnel syndrome/others)
- 2) Neurological conditions (e.g. stroke/dystonia/cervical spondylosis/others)
- 3) Fluid retention/third spacing from organ failure
- 4) Vascular causes (e.g. deep vein thrombosis/central vein stenosis/arteriovenous fistula)
- 5) Other treatment associated morbidities
 - a) Chemotherapy-induced peripheral neuropathy (CIPN)
 - b) Aromatase inhibitor-induced musculoskeletal syndrome (AIMS)
 - c) Radiation fibrosis
 - d) Axillary web syndrome/cording/post mastectomy pain syndrome

^e Triggers for referrals to lymphedema therapist:

- 1) Symptomatic without other attributable medical causes
- 2) Number of limb infections ≥ 1 per year
- 3) Arm circumferential measurement difference ≥ 2 cm

Fig. 2. Severity of BCRL diagnosed according to International Society of Lymphology (ISL).



cohort was 30.9% when using any of the diagnostic criteria. This cohort of BCRL patients had a higher mean age (58.4 vs 54.9 years), higher mean BMI (27.7 vs 25.2), higher proportion of whom have undergone mastectomy (77% vs 64.3%), axillary clearance, less likely breast reconstruction, higher-grade tumour, more lymph nodes excised, more advanced nodal disease, and had undergone adjuvant chemotherapy.

Prevalence by various assessment tools and inter-rater reliability

Based on our study, the prevalence of BCRL diagnosed by arm circumference measurements was the highest at 18.9% (89 out of 511), whereas clinicians' assessment was the lowest at 6.5% (33 out of 511). When using any of the diagnostic criteria, the cumulative prevalence was 30.1% (154) (Table 2). Although there was a high percent agreement rate of >80% between self-reported symptoms/arm circumference and clinical diagnosis of BCRL, the Cohen's kappa agreement for inter-rater reliability was only fair (0.19–0.31, $P < 0.001$).

Clinically significant BCRL determined by attending clinician

The overall clinical BCRL diagnosed by clinician was only 6.5% (33 out of 511). Of note, the observed proportion of clinical BCRL in patients undergoing SLNB/axillary sampling was 1.7% compared to 9.9% in patients who undergone axillary clearance (Table 3). Majority of the BCRL severity were subclinical or mild (ISL stages 0–1), while only 7 out of 33 were considered moderate (ISL stage 2). None were severe (ISL stage 3) nor required radical resection with or without lymphatic reconstruction (Fig. 2). Only 33% (11 out of 33) of patients with BCRL had active therapist review. These patients were given reinforcement on skin care advice and offered compression sleeve prescription (ISL stages 0–1), or received manual lymphatic drainage, and compression bandage (ISL stage 2). Although suitable cases were discussed for lymphatic restoring procedures, there was little uptake. The rest either defaulted due to poor compliance or were discharged to self-therapy.

Table 1. Demographic of all patients cumulatively diagnosed with BCRL by self-reported symptoms, arm circumference measurements, or clinician assessment.

	All (n=511)	BCRL (n=154)	No BCRL (n=346)	P value
Age, median (years)	56.0 ± 12.6	58.4 ± 12.5	54.9 ± 12.5	0.003
BMI	26.0 ± 7.7	27.7 ± 9.0	25.2 ± 6.8	0.002
Breast surgery				0.01
BCS	135 (27.9%)	28 (17.7%)	107 (30.3%)	
Mastectomy	349 (72.1%)	122 (77.2%)	227 (64.3%)	
Axillary surgery				0.09
SLNB/Axillary sampling	210 (45.4%)	60 (41.4%)	150 (47.2%)	
Axillary clearance	253 (54.6%)	85 (58.6%)	168 (52.8%)	
Reconstruction	48	11 (8.6%)	37 (14.5%)	0.10
Time interval from operation, months	88.8	80.1	92.6	0.09
Histology				0.19
DCIS	87 (17.0%)	23 (14.6%)	64 (18.1%)	
Ductal	318 (62.2%)	97 (61.4%)	221 (62.6%)	
Lobular	23 (4.5%)	5 (3.2%)	18 (5.1%)	
Others	83 (16.2%)	33 (20.9%)	50 (14.1%)	
Grade				0.047
1	72 (14.9%)	14 (9.3%)	58 (17.4%)	
2	226 (46.6%)	71 (47.0%)	155 (46.4%)	
3	187 (38.6%)	66 (43.7%)	121 (36.2%)	
Tumour stage				0.05
0	109 (21.3%)	32 (20.3%)	77 (21.8%)	
1	175 (34.3%)	42 (26.6%)	133 (37.7%)	
2	177 (34.6%)	65 (41.4%)	112 (31.7%)	
3	36 (7.1%)	12 (7.6%)	24 (6.8%)	
4	14 (2.7%)	7 (4.4%)	7 (2.0%)	
Nodal stage				0.01
0	366 (71.6%)	103 (65.2%)	263 (74.5%)	
1	93 (18.2%)	32 (20.3%)	61 (17.3%)	
2	31 (6.1%)	10 (6.3%)	21 (6.0%)	
3	21 (4.1%)	13 (8.2%)	8 (2.3%)	
No. of lymph node positive, mean	1.4 ± 4.0	2.5 ± 6.1	0.9 ± 2.5	0.0001
No. of lymph node excised, mean	11.7 ± 8.5	13.1 ± 9.2	11.1 ± 8.1	0.02
NPI				0.02
Good	151 (34.6%)	38 (28.4%)	113 (37.3%)	
Moderate	214 (49.0%)	65 (48.5%)	149 (49.2%)	
Poor	72 (16.5%)	31 (23.1%)	41 (13.5%)	
Receptor profile				0.18
ER+	382 (78.3%)	111 (74.5%)	271 (80.0%)	
TNBC	39 (7.6%)	16 (10.1%)	23 (6.5%)	0.15
Her2+	117 (26.5%)	33 (24.4%)	84 (27.5%)	0.51
Adjuvant chemotherapy	256 (50.1%)	91 (57.6%)	165 (46.7%)	0.02
Adjuvant endocrine therapy	352 (68.9%)	107 (67.7%)	245 (69.4%)	0.70
Adjuvant radiotherapy	247 (48.3%)	76 (48.1%)	171 (48.4%)	0.94

BCS: breast-conserving surgery; BMI: body mass index (kg/m²); DCIS: ductal carcinoma-in-situ; ER: estrogen receptor positive; Her2+: human epidermal growth factor receptor 2 positive; NPI: Nottingham Prognostic Index; SLNB: sentinel lymph node biopsy; TNBC: triple negative breast cancer

Table 2. Prevalence by assessment tools and inter-rater reliability.

Prevalence			
Clinical diagnosis	Self-reported symptoms	Arm circumference	Cumulative
n=33 (6.5%)	n=83 (16.2%)	n=92 (18.0%)	154 (30.1%)
Clinical diagnosis of BCRL			
Self-reported symptoms	Yes	No	Percent agreement 407/479 (85.0%); Kappa 0.3188; P<0.001
Yes	24	59	Sensitivity 24/33 (72.7%)
No	9	383	Specificity 383/446 (88.5%)
Clinical diagnosis of BCRL			
Arm circumference >2 cm	Yes	No	Percent agreement 388/478 (81.1%); Kappa 0.192; P<0.001
Yes	19	73	Sensitivity 19/33 (57.6%)
No	14	369	Specificity 369/445 (82.9%)

BCRL: breast cancer-related lymphedema

DISCUSSION

Local prevalence rates are comparable to internationally observed data despite higher rates of mastectomy and axillary dissection

This study highlighted the prevalence rates of BCRL in a single tertiary breast unit with an established lymphedema surveillance strategy. Comparable to other studies in our literature review, the prevalence of BCRL was estimated to be less than a third of the cohort (6.5–30.8%).^{3–12} This was lower than expected despite the cohort having a higher rate of mastectomy and axillary clearance performed (>50%). These risk factors were hypothesised to contribute to the rates of BCRL due to their extent of surgical disruption of the draining lymphatics.^{10,12} The proportion of breast surgery performed was at least reflective of the practice in Singapore and other Southeast Asian countries in the last decade, whereby rates of mastectomy with or without axillary dissection may be higher due to reasons such as breast cancer being diagnosed at a more advanced stage, and psychosocial reasons such as fear of cancer relapse, perception that health is more important than breast retention, possibility of involved margins.^{13–17}

However, breast surgery has seen a trend of de-escalating axillary treatment aimed at producing equivalent survival outcomes and omitting previously routine surgical therapies such as axillary lymph node dissection or radiation in select group.^{18–22} This is expected to further improve arm morbidities outcome assessment such as BCRL and shoulder dysfunctions. The rates of BCRL will continue to form an important part of performance

indicators of any contemporary breast unit. This study is therefore important to set a benchmark for prevalence rates not only as a cumulative rate, but identify the relative risk of BCRL associated with various treatment and risk factors.

Differentiating clinical BCRL from other causes

The result demonstrated variation in the estimation of prevalence of BCRL depending on the type of assessment tools used. Patient-reported BCRL was higher compared to clinician-diagnosed BCRL. However, the latter also represented the most clinically significant BCRL requiring interventions that were not due to other medical causes. Clinical surveillance post-cancer treatment was aimed at excluding disease recurrences, and other breast cancer treatment-related morbidities that could also impair functional outcomes and quality of life. This required clinicians to take into account patients' underlying risk factors and potential competing diagnosis. Patient-subjective complaints of shoulder dysfunction or altered limb sensation may be caused by common conditions such as frozen shoulder or adhesive capsulitis, carpal tunnel syndrome, tenosynovitis.^{23,24} Other contributing conditions such as chemotherapy-induced peripheral neuropathy (CIPN), aromatase inhibitor-induced musculoskeletal syndrome (AIMS), radiation-induced fibrosis, axillary cording syndrome may often co-exist (Fig. 1).^{25–30} Similarly, arm swelling could be due to other causes such as fluid overload, venous disorders or disease recurrence. These should be excluded with the relevant tests. Rates of BCRL by patients' reporting may therefore be an overestimation due to any of these confounding factors.^{30,31}

Table 3. Demographic of patients with clinical BCRL diagnosed by physician.

	BCRL (n=33)	No BCRL (n=478)	P value
Age, median (years)	61.1 ± 12.9	55.6 ± 12.5	0.02
BMI	27.2 ± 8.3	25.9 ± 7.6	0.38
Breast surgery			
BCS	2 (6.5%)	133 (29.4%)	0.02
Mastectomy	29 (93.5%)	320 (70.6%)	
Axillary surgery			
SLNB/Axillary sampling	5 (16.7%)	205 (47.3%)	0.008
Axillary clearance	25 (83.3%)	228 (52.7%)	
Reconstruction	0	48	0.02
Time interval from operation, months	84.6 ± 15.5	89.0 ± 3.5	0.75
Histology			
DCIS	3 (9.1%)	84 (17.6%)	0.29
Ductal	23 (69.7%)	294 (61.7%)	
Lobular	0	23 (4.8%)	
Others	7 (21.2%)	76 (15.9%)	
Grade			
1	0	72 (15.8%)	0.05
2	15 (50.0%)	211 (46.4%)	
3	15 (50.0%)	172 (37.8%)	
Tumour stage			
0	6 (18.2%)	103 (21.6%)	0.005
1	4 (12.1%)	171 (35.8%)	
2	15 (45.6%)	162 (33.9%)	
3	5 (15.5%)	31 (6.5%)	
4	3 (9.1%)	11 (2.3%)	
Nodal stage			
0	16 (48.5%)	350 (73.2%)	<0.001
1	6 (18.2%)	87 (18.2%)	
2	6 (18.2%)	25 (5.2%)	
3	5 (15.2%)	16 (3.4%)	
No. of lymph node positive, mean	5 ± 8	1.2 ± 3.5	<0.001
No. of lymph node excised, mean	16.9 ± 8.9	11.4 ± 8.4	<0.001
NPI			0.001
Good	4 (12.9%)	147 (31.6%)	
Moderate	12 (38.7%)	202 (43.4%)	
Poor	12 (38.7%)	60 (12.9%)	
Receptor profile			
ER+	21 (72.4%)	361 (78.7%)	0.43
TNBC	4 (12.2%)	35 (7.3%)	
Her2+	7 (24.1%)	110 (25.3%)	
Adjuvant chemotherapy	24 (72.7%)	232 (48.6%)	0.007
Adjuvant endocrine therapy	21 (63.6%)	331 (69.3%)	0.51
Adjuvant radiotherapy	20 (60.6%)	227 (47.5%)	0.15

BCS: breast-conserving surgery; BMI: body mass index (kg/m²); DCIS: ductal carcinoma-in-situ; ER: estrogen receptor positive; Her2+: human epidermal growth factor receptor 2 positive; NPI: Nottingham Prognostic Index; SLNB: sentinel lymph node biopsy; TNBC: triple negative breast cancer

These factors ultimately explained the relatively low Cohen's kappa coefficient because the patients' signs and symptoms can be wrongly alluded to BCRL. This highlighted a significant difference and lack in objectivity across the assessment tools. However, given the limitations of the available measurement tools, the authors proposed to include all of the findings collectively from directed questioning of patient symptoms, objective measurement of arm circumference and finally, an assessment matrix to consider various confounding diagnosis in the lymphedema surveillance strategy.³¹

Focus on evidence-based recommendations

The clinical risk factors associated with BCRL identified in our current study corroborated with those in literature review.³⁰ These risk factors included elevated BMI, higher tumour and nodal pathological stage, presence of axillary clearance and chemotherapy. This at-risk group may benefit from a more intensive lymphedema surveillance strategy and recommendation. Risk factors directly related to disease and treatment factors may be unavoidable, but certain modifiable targets such as obesity or weight gain after treatment, and minimising infections or injury to the at-risk limb can be emphasised during patient education.³⁰⁻³² Our institutional practice was to address clinical risk factors in accordance with established lymphedema clinical guidelines and avoid precautionary advice or primary prevention strategies that may engender unnecessary fear, restrictions or confusion from the inconsistency messaging. For example, avoiding of air travel, avoiding extreme of temperatures, vigorous exercise or the restrictions of use of the at-risk limb for blood pressure taking, venipuncture and/or peripheral intravascular line placement—to date, these have largely not been shown to be conclusively associated with development of lymphedema and their level of supporting evidence remained debatable.³²⁻³⁸

Strengths and limitations

The strength of the findings was derived from a comprehensive lymphedema surveillance strategy that was practised consistently by all participating clinicians after reviewing the latest available literature.³⁰ The merits of this surveillance strategy included its ease of implementation as it did not rely on sophisticated tools for an objective measurement, and showcased a practical use of classical patient reported symptoms, regular arm circumference measurements to guide independent clinician assessment and grading per ISL staging. Patient education largely focused on typical signs and symptoms, risk factors that were

supported by the latest evidence and avoided unnecessary precautionary advice.^{31,32,39} Specialised lymphedema therapy may also be a scarce resource and we defined specific referral criteria for right-siting patients to avoid taking up unnecessary resources. This improved the sustainability of the lymphedema surveillance strategy and allowed wider implementation.

A limitation of the study was the nature of the convenience sampling method and the relatively low frequency of moderate-to-severe BCRL observed. These could be due to sampling bias and retrospective nature of the study. To address this issue, the study used the cumulative prevalence diagnosed by either of the 3 assessment tools to include a larger sample of patients with possible BCRL. We accounted for the overestimation of BCRL by patient-reported symptoms and arm measurements compared to clinical BCRL that was likely due to the presence of other distracting conditions that warranted different management. This study did not claim to have a diagnostic gold standard for BCRL but highlighted the important aids to make an accurate clinical diagnosis.³ Although arm circumference measurement was relatively inexpensive, it required rigorous training of our staff to standardise the method of recording to improve accuracy and reduce inter-assessor variability. Educating on BCRL, addressing its risk factors, implementing regular surveillance, and timely referral for appropriate management remain cornerstone to any comprehensive lymphedema service.³⁰ Based on our results, we could still generate important hypothesis on the risk factors relevant to our population, better understand the limitations of the current diagnostic process and plan for future research based on this set of standardised outcome assessment.

Future implications

We aim to safely reduce the morbidity of BCRL by providing the optimal breast cancer treatment necessary without compromising on oncological outcomes. This includes reviewing our patient selection criteria for various axilla therapies including axillary lymph node dissection or radiotherapy and to avoid practices deemed to be of low value.¹⁸

Fortunately, the observed severity of BCRL in our cohort was largely limited to subclinical and mild. These may be contributed by timely detection and referral for specialised therapy, although we would require a larger sample size and direct studies to confirm the effectiveness of our lymphedema surveillance strategy. Lastly, there is an emerging role for lymphatic preserving

or restoring procedures that have shown promising results at reducing the severity of BCRL for those whose disease and treatment factors cannot be modified otherwise.⁴⁰ However, it would require validation of other assessment tools to diagnose, assess the severity of lymphoedema, and progress following conservative or surgical treatment.³⁹

CONCLUSION

In conclusion, our study showed that our rates of BCRL were comparable to international standards and highlighted similar patient profiles who were at risk of developing BCRL. Although the severity of BCRL were largely subclinical or mild, having a comprehensive lymphedema surveillance strategy is paramount to address and further reduce the impact of this debilitating condition.

Conflict of interest

None to declare.

Acknowledgement

The authors acknowledge and thank the rest of the breast care nurses and team in the Changi General Hospital Breast Centre.

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