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Original Article

Preoperative inter-arm differences and normative-based thresholds for lymphedema in Chinese breast cancer patients: Insights from a large cohort study

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A R T I C L E I N F O

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A B S T R A C T

Objective: Early detection and diagnosis of lymphedema are crucial for effective treatment and prevention of its progression. Normative-based diagnostic thresholds can enhance diagnostic accuracy in the absence of preoperative measurements. This study aimed to investigate preoperative inter-arm differences and the associated factors, as well as to determine normative-based thresholds for lymphedema in Chinese breast cancer patients.

Methods: This study utilized baseline data from a large cohort of Chinese breast cancer patients. Bilateral arm circumferences were measured at the wrist and at 10 cm intervals proximally up to 40 cm. Arm volumes were calculated using the truncated cone formula. Paired *t* test, repeated measures analysis of variance, and regression analysis were performed.

Results: A total of 1707 breast cancer patients were included. Paired *t* tests showed that the dominant arm circumferences and volumes were significantly larger than those of the nondominant arm ($P < 0.001$). Regression analysis and repeated measures analysis of variance revealed that hand dominance was the influencing factor of inter-arm differences ($P < 0.05$). Normative-based thresholds determined by two standard deviations above the mean inter-arm volume ratio were 1.057 for the dominant arm and 1.079 for the nondominant arm.

Conclusions: The absolute and relative normative-based thresholds for Chinese breast cancer patients differed slightly from the commonly used diagnostic criteria and those reported in Western populations and among Chinese healthy women. The normal variability and asymmetry associated with arm dominance underscore the importance of preoperative baseline assessments. Implementing normative-based diagnostic thresholds can facilitate more accurate lymphedema diagnosis when preoperative measurements are unavailable.

Trial registration: Registration No. ChiCTR2200057083.

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Introduction

Lymphedema is a pathological condition characterized by localized fluid retention and tissue swelling due to an impaired lymphatic system. Secondary lymphedema is often induced by cancer treatments, including lymph nodes dissection or regional lymph nodes radiation.[1] Arm lymphedema following breast cancer treatment is the most commonly reported type of cancer-related secondary lymphedema.[2] It can manifest months or even years after treatment, characterized by swelling in the arm on the same side as the surgery or radiation. A systematic review of 84 cohort studies concluded that upper limb lymphedema affects 21.9% (95% CI: 19.8%–24.0%) of breast cancer patients.[3] Lymphedema negatively impacts the quality of life of breast cancer patients, both physically and psychosocially. It causes chronic swelling, pain, and reduced arm mobility, hindering daily activities, and increasing the risk of infections.[4] Moreover, it leads to psychological distress, including anxiety, depression, and body image issues, affecting social interactions and emotional well-being.[4] Lymphedema is a chronic and progressive condition, without timely and effective management, long-term accumulation of lymph fluid can stimulate connective tissue hyperplasia, adipocyte deposition, and fibrosis.[5] Currently, there are no curative treatments for lymphedema. However, early diagnosis and intervention at the early stages of lymphedema, which is still reversible and manageable, are well acknowledged and highly recommended. These measures improve patient outcomes, reduce the need for intensive treatments (e.g., comprehensive decongestive therapy), and lower medical costs, etc.[6,7] Early diagnosis involves regular monitoring of limb circumferences and volumes using validated tools to detect subtle changes. Identifying lymphedema at an early stage enables patients to receive timely and effective treatments.

Clinical practice guidelines recommended incorporating objective measurements, self-reported symptoms, and physician-conducted clinical examination into the prospective screening for breast cancer-related lymphedema to facilitate early diagnosis and prevent progression.[2,8] Commonly used objective measurements include water volumetry, girth measurement, Perometry, bioimpedance spectroscopy, lymphoscintigraphy, three-dimensional scanning technology, etc.[2,9,10] Among these, indirect volumetry by circumference measurements with a girth has been demonstrated to be reliable, validated, inexpensive, convenient, and most frequently accepted and used in the clinical setting.[2,9] For optimal diagnostic accuracy, objective arm measurements should ideally be conducted at baseline (at diagnosis or preoperatively) and at regular follow-up intervals. Without baseline measurements, diagnosing lymphedema can be inaccurate due to the natural asymmetry of the arms.[2] A previous study involving 1028 breast cancer patients revealed that 28.3% had preoperative arm asymmetry of $\geq$ 5%, and 2.9% had asymmetry of $\geq$ 10%. Furthermore, nearly half of lymphedema cases would be misdiagnosed without baseline measurements.[11]

Although preoperative baseline measurements were highly recommended by guidelines and supported by increasing evidence, they are not universally implemented in research studies or clinical settings. Logistical barriers such as limited access to specialized equipment, lack of trained personnel, and time constraints, especially in less developed districts with restricted resources, hinder the practice.[11,12] Given these challenges, diagnosing lymphedema often relies on calculated volume differential between sides of $\geq$ 200 mL or 10%, or normative-based thresholds of two or three standard deviations (SD) above the mean of a control population.[8,13,14] However, these criteria do not account for preoperative arm asymmetry and are primarily based on studies of Western population.[8,11,15] Normative-based thresholds are cutoff values derived from healthy populations to identify abnormal or clinically significant changes.[15,16] These thresholds, established by calculating the mean and SD from a normative sample, provide a standardized approach to detect deviations from typical values.[15] This is crucial for assessing lymphedema, as comparing patient measurements to these thresholds allows for a more accurate evaluation of its presence and severity. Considering differences in body habitus between populations, and the relatively smaller body size of Asian populations, the diagnostic criteria and the normative-based thresholds for lymphedema should be customized based on studies of Asian populations, taking into account arm asymmetry.[16]

To date, only one study by Wang H et al. has been conducted on the Chinese population.[16] However, this study examined the normative-based threshold in a sample of healthy Chinese women. Considering the potential differences between healthy women and breast cancer patients, detailed information on normal variability in pre-treatment arm volumes is necessary to determine if increases in volume following breast cancer treatment are clinically meaningful. Therefore, using preoperative baseline arm volume to calculate the normative threshold is more reasonable and with reference value. Additionally, Wang et al.'s study incorrectly used mean + 2SD/3SD to calculate thresholds despite the data not following a normal distribution.[16] To date, only age, hand dominance, height, weight, body mass index (BMI), and side of cancer have been examined for their association with inter-arm differences. These studies suggest that age and hand dominance might correlate with inter-arm differences, but the results have been inconsistent.[15–17] Hence, this study aims to investigate the pre-operative inter-arm differences and the associated factors, as well as to determine the normative-based threshold for lymphedema in Chinese breast cancer patients.

Methods

Study design

This study is part of a large, prospective longitudinal cohort study investigating the risk factors of breast cancer-related lymphedema in women who underwent breast cancer surgery. The cohort study is registered in the Chinese Clinical Trial Registry (Registration No. ChiCTR2200057083). This study adheres to STROBE guidelines and includes the required information accordingly.

Participants and setting

The parent study recruited newly diagnosed breast cancer patients using a convenience sampling method from a national cancer centre in northern China, between February 15, 2022 and June 21, 2023. Eligibility criteria included being newly diagnosed with unilateral breast cancer confirmed by pathology, having undergone radical mastectomy or modified radical mastectomy, being aged 18 years or older, and providing informed consent. Exclusion criteria were the presence of malignant tumours in non-breast locations, tumour recurrence or metastasis, a history of lymphatic diseases, arm injury or surgery, and inability to use smartphones for completing online follow-up assessments.

Out of the 1967 breast cancer patients approached, 1707 were finally enrolled and completed baseline data collection and arm circumference measurements. For this study, we included only those participants with complete arm circumference data. Consequently, this analysis included data from 1707 breast cancer patients.

Pyle-Eilola et al. emphasized the importance of a minimum sample size of 120 per partition for establishing health-associated reference intervals, representing the central 95% of a healthy population.[18] In this study, we calculated normative-based thresholds for two groups of participants: those with the dominant arm affected ($n = 865$) and those with the non-dominant arm affected ($n = 842$), both meeting the minimum sample size requirement.

Data collection and arm measurement

Based on literature review and group discussion,[15–17] we extracted data on variables that could affect inter-arm volume differences. These variables included age, height, weight, BMI, marital status, education level, residence, family care roles, monthly income, employment, exercise habit, dominance side, side of cancer, tumor laterality and tumor location.

Data of bilateral arm circumference data were also extracted. Arm circumference was measured following well-established protocol.[19] Baseline measurements of arm circumference were undertaken by well-trained research nurses. Before measurement, patients were instructed to sit with their arms extended forward at a 90-degree angle, palms facing down on the table. Measurements were taken using a 1 cm-wide retractable, non-stretch soft tape measure. The tape measure was calibrated in metric units, with divisions marked every 0.1 cm. The measurements start from the midpoint of the ulnar styloid (wrist), designated as the "0 cm" mark, and continuing at 10 cm intervals up to 40 cm proximal to the ulnar styloid.[20,21] To enhance the precision of marking intervals, an adhesive paper strip ruler was aligned with the zero point at the midpoint of the ulnar styloid process and affixed parallel to the arm.

The volume of each arm segment was calculated using the truncated cone formula: $V = h(C_1^2+C_1C_2+C_2^2)/12\pi$, where h represents the height of the cone, which is 10 cm in this study, and C_1 and C_2 are the circumferences of the upper and lower bases of the cone, respectively.[21] To determine the total arm volume, the calculated volumes of all the four segments (Segment A: 0–10 cm, Segment B: 10–20 cm, Segment C: 20–30 cm, Segment D: 30–40 cm) were summed together.[22] Ninety-four participants with insufficient arm lengths were not measured for 40 cm circumferences, and thus, Segment D data was unavailable.

Data analysis

Data analysis was conducted using SPSS 26.0. Continuous variables that followed a normal or approximately normal distribution were presented as means ± SD. For non-normally distributed data, medians and interquartile ranges (IQR) were used. Categorical variables were summarized as frequencies and percentages. Paired *t* test was performed to compare the preoperative inter-arm volume differences between dominant and nondominant arms.

We calculated the absolute and relative inter-arm differences for the circumferences and volumes for each measurement location and segment along the arm, as well as for the whole arm. Absolute differences were calculated by subtracting the circumference or volume of one arm from the corresponding circumference or volume of the other arm. Relative differences were determined by expressing the circumference or volume of one arm as a ratio of the corresponding circumference or volume of the other arm. Inter-arm circumference or volume differences were used to establish diagnostic cut-offs of lymphedema, considering the dominant and non-dominant arm.

Given that the absolute inter-arm circumference or volume differences showed non-normal distribution, the 95th and 99th percentiles were calculated to determine the cut-offs that encompass 95% and 99% of the population, respectively. For the relative inter-arm differences, the diagnostic cut-offs were set at the mean plus two or three times the SDs to include 95% and 99.7% of the population.[16,23] Absolute inter-arm volume differences were set as the dependent variable, while demographic and clinical factors were set as independent variables. Multivariate regression analysis was conducted to analyse the demographic and clinical factors associated with absolute inter-arm volume differences. Repeated measures analysis of variance (RM-ANOVA), with one within-subjects factor and one between-groups factor, was conducted to assess the main effects of dominance and side of cancer, as well as to evaluate the interaction between these two factors, on absolute inter-arm volume differences. Significance was set at $P < 0.05$ for all tests.

Ethical considerations

The study was approved by the Biomedical Ethics Committee of Peking University (IRB No. 00001052-21124) and the Research Ethics Committee of Tianjin Medical University Cancer Institute & Hospital (IRB No. bc2023013). All participants provided written informed consent.

Results

Participants characteristics

Among the 1707 breast cancer patients, the average age was 47.63 years (SD = 9.24). Notably, 51.4% of them aged between 35 and 49 years old, and 49.1% had a BMI ≥ 24 kg/m^2, classifying them as overweight according to the classification of Chinese population.[24] The majority of them were married (91.8%) and predominantly right-side dominant (90.4%). Clinically, 50.7% of the tumours located on dominant side, while 52.1% were on the left side of the body. Additionally, 45.0% of the tumours situated in upper outer quadrant of the breasts. The demographic and clinical characteristics of the participants are summarized in Table 1.

Preoperative inter-arm differences between dominant and nondominant arms

Paired *t* tests showed that the circumferences and volumes of the dominant arm were consistently larger than the nondominant side at all locations (all $P < 0.001$). The mean inter-arm circumference difference at the 40 cm measurement was the largest: 0.21 cm (95% CI: 0.18–0.25 cm), while the smallest inter-arm circumference difference was found at the wrist measurement: 0.04 cm (95% CI: 0.02–0.06 cm) (Table 2). The mean inter-arm volume differences gradually increased from Segment A to

Table 1
Participants characteristics ($N = 1707$).

Variables	Mean (SD), *n* (%)	Variables	Mean (SD), *n* (%)
Age, years	47.63 (9.24)	**Monthly income (RMB)**	
20-34	132 (7.7%)	< 2000	255 (14.9%)
35-49	877 (51.4%)	2000–3999	579 (33.9%)
50-64	620 (36.3%)	4000–5999	415 (24.3%)
65-75	78 (4.6%)	> 6000	458 (26.8%)
Height (cm)	161.43 (4.94)	**Employment**	
Weight (kg)	63.04 (9.48)	Unemployed	527 (30.9%)
BMI (kg/m^2)	24.18 (3.44)	Employed	666 (39.0%)
< 18.5	45 (2.6%)	Retired	410 (24.0%)
18.5–23.9	824 (48.3%)	Other	104 (6.1%)
24.0–27.9	615 (36.0%)	**Regular exercise**	
≥ 28.0	223 (13.1%)	Yes	670 (39.3%)
Marital status		No	1037 (60.7%)
Single	44 (2.6%)	**Dominance side**	
Married	1567 (91.8%)	Left dominance	164 (9.6%)
Divorced	66 (3.9%)	Right dominance	1543 (90.4%)
Widowed	30 (1.8%)	**Side of cancer**	
Education level		Dominant side	865 (50.7%)
Primary school or below	96 (5.6%)	Nondominant side	842 (49.3%)
Middle school	483 (28.3%)	**Tumor laterality**	
High school	376 (22.0%)	Left	890 (52.1%)
College	295 (17.3%)	Right	817 (47.9%)
Undergraduate	404 (23.7%)	**Tumor location**	
Postgraduate	53 (3.1%)	Upper outer quadrant	769 (45.0%)
Residence		Lower outer quadrant	288 (16.9%)
Urban areas	1106 (64.8%)	Upper inner quadrant	331 (19.4%)
Town or county	362 (21.2%)	Lower inner quadrant	112 (6.6%)
Rural or suburban area	239 (14.0%)	Areola area	108 (6.3%)
Family roles		Unclear	99 (5.8%)
Mainly cared for by others	86 (5.0%)		
Mainly caring for others	502 (29.4%)		
Caring for oneself	175 (10.3%)		
Caring for each other	944 (55.3%)		

Table 2
Preoperative inter-arm circumference and volume differences between dominant and nondominant arms.

	n	Dominant	Nondominant	Inter-arm difference	*t*	*P*
		Mean (SD)	Mean (SD)	Mean (95% CI)		
Circumferences (cm)						
Wrist	1707	16.36 (1.12)	16.32 (1.12)	0.04 (0.02, 0.06)	4.401	< 0.001
10 cm	1707	21.71 (1.95)	21.58 (1.97)	0.13 (0.10, 0.16)	8.637	< 0.001
20 cm	1707	24.28 (1.86)	24.21 (1.88)	0.07 (0.05, 0.10)	5.833	< 0.001
30 cm	1707	26.49 (2.71)	26.38 (2.75)	0.11 (0.08, 0.14)	7.323	< 0.001
40 cm	1613	30.90 (3.38)	30.68 (3.40)	0.21 (0.18, 0.25)	10.894	< 0.001
Volumes (mL)						
Segment A	1707	292.05 (45.85)	289.42 (46.07)	2.63 (2.02, 3.24)	8.458	< 0.001
Segment B	1707	423.98 (68.07)	420.40 (68.66)	3.59 (2.80, 4.38)	8.927	< 0.001
Segment C	1707	517.32 (92.29)	513.65 (93.05)	3.67 (2.74, 4.61)	7.681	< 0.001
Segment D	1613	662.59 (138.83)	655.09 (139.51)	7.50 (6.12, 8.89)	10.617	< 0.001
Whole arm	1613	1893.43 (331.37)	1875.51 (333.36)	17.92 (14.79, 21.05)	11.223	< 0.001

Note: Paired *t* test. Circumference measurements begin at the wrist (ulnar styloid) and continue proximally at 10 cm intervals up to 40 cm. Volume measurements are derived from 10 cm segments, starting at the wrist (Segment A) and progressing in 10 cm increments to Segment D (30–40 cm proximal to the wrist). Whole arm refers to the total volume from Segment A to Segment D.

Segment D, ranging from 2.63 mL (95% CI: 2.02–3.24 mL) of Segment A to 7.50 mL (95% CI: 6.12–8.89 mL) of Segment D (Table 2). The mean inter-arm volume of the whole arm was 17.92 mL (95% CI: 14.79–21.05 mL).

4.4% (75/1707) of the patients had an absolute inter-arm circumference difference $\geq$ 2 cm. Among the breast cancer patients, the preoperative absolute inter-arm volume difference was $\geq$ 200 mL in 0.7% (11/1613) of all participants and $\geq$100 mL in 11.7% (188/1613) of the patients (Fig. 1). Additionally, 81.5%, 7.5%, and 1.0% of the breast cancer patients had an inter-arm volume ratio of < 5%, 5%–10%, and > 10%, respectively (Fig. 2). The volume ratio of the affected arm to the unaffected arm was 0.998 (SD = 0.035, range = 0.80–1.14). The volume ratio of the dominant arm to the undominant arm was 1.011 (SD = 0.034, range = 0.80–1.18). For dominant/non-dominant arm, 1.0% have asymmetry greater than 10% (< 0.9 or > 1.1), and 13.0% greater than 5%. For affected/unaffected arm, 0.6% and 12.8% have asymmetry greater than 10% and 5%, respectively.

Absolute and relative diagnostic cut-offs for lymphedema

The absolute diagnostic cut-offs for lymphedema in both dominant and non-dominant arms were based on 95th or 99th percentile of the absolute inter-arm differences. For the dominant arm, the circumference-based absolute cut-offs from the wrist to 40 cm ranged from 0.70 to 1.50 cm based on 95th percentile, while for the nondominant arm, these cut-offs ranged from 0.56 to 1.03 cm. The volume-based 95th percentile cut-offs for different arm segments ranged from 22.87 to 51.58 mL for the dominant arm, and from 17.89 to 39.04 mL for the nondominant arm. The volume-based 95th percentile cut-off for the whole arm was 120.30 mL for the dominant arm, and 89.74 mL for the nondominant arm (Table 3).

The relative diagnostic cut-offs for lymphedema were determined by values that were two or three SDs above the mean of the relative inter-arm differences. The relative inter-arm circumference ratio-based 2SD cut-offs ranged from 1.045 to 1.065 for the dominant arm, and from 1.044 to 1.052 for the nondominant arm. The relative inter-arm volume ratio-based 2SD cut-offs for each segment ranged from 1.084 to 1.099 for the dominant arm, and ranged from 1.067 to 1.078 for the nondominant arm. The relative inter-arm volume ratio-based 2SD cut-off for the whole arm was 1.079 for the dominant arm and 1.057 for the nondominant arm (Table 4). If the dominant arm was affected, 1.4% of the participants had an inter-arm volume difference ranging from 7.9% to 10%. Conversely, if the nondominant arm was affected, 2.3% of the participants had an inter-arm volume difference ranging from 5.7% to 10%.

Factors associated with inter-arm volume differences

Regression analysis revealed that right hand dominance ($\beta = 0.061$, $P = 0.016$) and cancer on nondominant side ($\beta = 0.076$, $P = 0.002$) were impact factors of the inter-arm volume difference of the whole arm (Table 5). To determine the effect of hand dominance and side of cancer on inter-arm volume difference, we performed RM-ANOVA and found

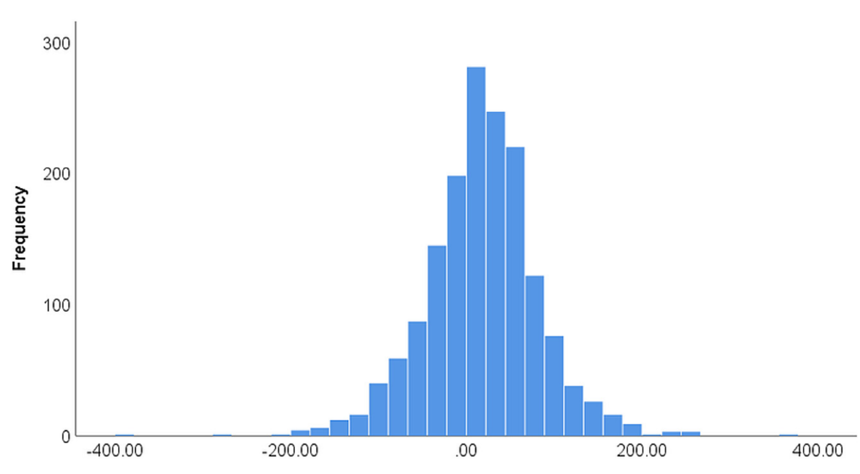

Fig. 1. Histogram of absolute inter-arm volume difference.

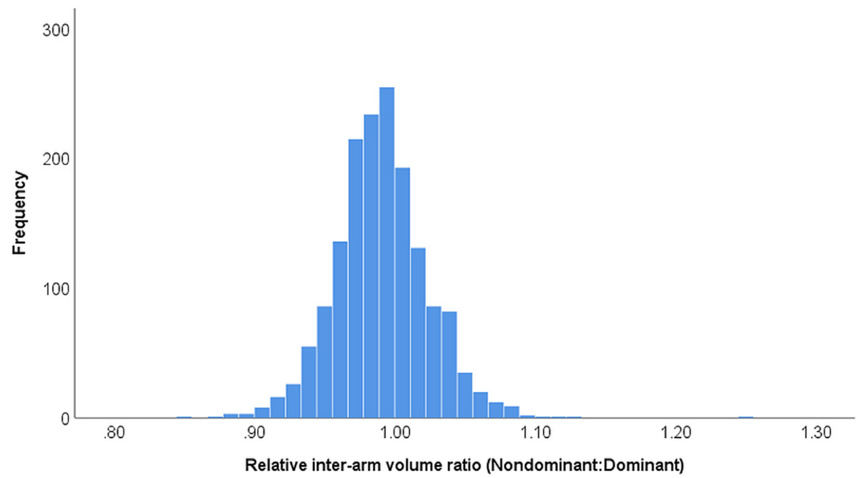

Fig. 2. Histogram of relative inter-arm volume ratio.

Table 3
Diagnostic cutoffs of absolute inter-arm circumference or volume differences.

Absolute inter-arm differences	Dominant arm affected	Cut-offs		Nondominant arm affected	Cut-offs	
	Median differences (P25, P75)	95th percentile	99th percentile	Median differences (P25, P75)	95th percentile	99th percentile
Circumferences (cm)	Dominant-nondominant			Nondominant- dominant		
Wrist	0.00 (−0.20, 0.20)	0.70	1.09	0.00 (−0.20, 0.20)	0.56	1.00
10 cm	0.10 (−0.20, 0.50)	1.10	1.70	−0.10 (−0.50, 0.20)	0.80	1.50
20 cm	0.00 (−0.20, 0.40)	0.90	1.20	0.00 (−0.40, 0.20)	0.80	1.20
30 cm	0.10 (−0.20, 0.50)	1.10	1.89	−0.10 (−0.50, 0.20)	1.00	1.50
40 cm	0.20 (−0.20, 0.60)	1.50	2.20	−0.20 (−0.60, 0.20)	1.03	1.80
Volumes (mL)						
Segment A	2.63 (−4.30, 9.75)	22.87	36.04	−2.63 (−9.75, 4.30)	17.89	31.89
Segment B	3.58 (−5.06, 13.43)	29.20	45.08	−3.58 (−13.43, 5.06)	23.97	39.31
Segment C	3.76 (−7.68, 15.07)	35.79	52.63	−3.76 (−15.07, 7.68)	28.68	49.63
Segment D	8.13 (−8.52, 23.76)	51.58	86.67	−8.13 (−23.76, 8.52)	39.04	64.88
Whole arm	18.17 (−18.40, 56.68)	120.30	179.83	−18.17 (−56.68, 18.40)	89.74	147.67

Note: Volume measurements are derived from 10 cm segments, starting at the wrist (Segment A) and progressing in 10 cm increments to Segment D (30–40 cm proximal to the wrist). Whole arm refers to the total volume from Segment A to Segment D.

that hand dominance showed significant main effects on inter-arm volume differences (all $P < 0.001$), while side of cancer did not (all $P > 0.05$) (Table 6).

Discussion

This study is the first to established preoperative normative inter-arm differences in a large sample of Chinese breast cancer patients. We found that the circumferences and volumes of the dominant arm were significantly larger than those of the nondominant arm at all locations and segments. Only a small proportion of patients had an inter-arm circumference difference ≥ 2 cm, or an inter-arm volume difference of ≥ 200 mL or ≥ 10%. We determined normative-based cut-offs, with the volume ratio-based 2SD cut-off for the whole arm being 1.057 for the dominant arm and 1.079 for the nondominant arm. Additionally, hand dominance was associated with inter-arm volume differences.

Given that arm volume measurements are more sensitive than circumferential changes, the results on absolute inter-arm circumference differences will not be discussed. However, we kept the results for reference if needed. Circumference measurements is a good choice of prospective surveillance of breast cancer-related lymphedema, especially when resources are limited and in undeveloped regions. Additionally, patients' self-measured arm circumferences showed high intra-rater reliability (intraclass correlation coefficient ≥ 0.86) with the measurements of a specialized physical therapist,[25,26] and arm volume calculated from self-measured circumferences correlated strongly with the perometry measurements ($r \geq 0.95$).[27] For patients who are self-monitoring their arm circumferences, inter-arm circumference differences can be used as a rough criteria for quick assessment.

Our study identified that the absolute preoperative arm volumes of breast cancer patients were smaller than those reported in Western population. For example, Sun et al.'s study reported dominant arm volumes with a mean of 2516 mL (range = 1346–5608 mL) and non-dominant arm volumes with a mean of 2502 mL (range = 1265–5726 mL).[11] Wiser et al.'s study (2020) reported a mean arm volume of 2216 mL (SD = 433 mL).[28] This difference could be could be attributed to variations in body morphology between Western and Asian populations. However, our measurements were larger than the arm volumes of heathy Chinese women (dominant arm: mean = 1670.1 mL, range = 262.3 mL; non-dominant arm: mean = 1642.1 mL, SD = 265.3 mL).[16] This might be due to the higher BMI levels in breast cancer patients compared to healthy women (mean = 23.3 kg/m^2, SD = 3.1 kg/m^2).[29] The characteristic variations between breast cancer patients and heathy women also imply the need for establishing normative-based threshold in Asian breast cancer population.

This study was conducted to validate and update previously reported normative-based thresholds in a cohort of Chinese breast cancer patients. For the dominant arm, the 95th percentile of the whole arm volume was 120.3 mL. If the commonly used clinical cut-off of 200 mL was applied for diagnosis, 4.32% of our cohort would be underdiagnosed. These patients would miss the optimal window for effective treatment and prevention of lymphedema progression.[11] Since absolute inter-arm difference is

Table 4
Diagnostic cutoffs of relative inter-arm circumference or volume differences.

Relative inter-arm differences	Dominant arm affected	Cut-offs		Nondominant arm affected	Cut-offs	
	Mean differences (SD)	2SD	3SD	Mean differences (SD)	2SD	3SD
Circumference ratios	Dominant: Nondominant			Nondominant: Dominant		
Wrist	1.003 (0.024)	1.051	1.075	0.998 (0.024)	1.046	1.070
10 cm	1.007 (0.029)	1.065	1.094	0.994 (0.029)	1.052	1.081
20 cm	1.003 (0.021)	1.045	1.066	0.996 (0.024)	1.044	1.068
30 cm	1.005 (0.024)	1.053	1.077	0.996 (0.024)	1.044	1.068
40 cm	1.007 (0.026)	1.059	1.085	0.993 (0.026)	1.045	1.071
Volume ratios						
Segment A	0.992 (0.043)	1.078	1.121	1.010 (0.043)	1.096	1.139
Segment B	0.992 (0.039)	1.070	1.109	1.010 (0.039)	1.088	1.127
Segment C	0.993 (0.037)	1.067	1.104	1.008 (0.038)	1.084	1.122
Segment D	0.989 (0.041)	1.071	1.112	1.013 (0.043)	1.099	1.142
Whole arm	1.011 (0.034)	1.079	1.113	0.991 (0.033)	1.057	1.090

SD, standard deviation. Volume measurements are derived from 10 cm segments, starting at the wrist (Segment A) and progressing in 10 cm increments to Segment D (30–40 cm proximal to the wrist). Whole arm refers to the total volume from Segment A to Segment D.

Table 5
Multivariate regression analysis of influencing factors for inter-arm volume differences.

Variables	*B*	*SE*	*β*	*t*	*P*
(constant)	−0.930	22.864		−0.041	0.968
Age	−0.183	0.245	−0.026	−0.750	0.453
BMI	−0.401	0.482	−0.021	−0.832	0.405
Education level	−1.167	1.688	−0.024	−0.691	0.490
Monthly income	0.541	1.828	0.009	0.296	0.767
Regular exercise (Ref. Yes)					
No	0.957	3.365	0.007	0.285	0.776
Dominance (Ref. Left dominance)					
Right dominance	13.436	5.565	0.061	2.414	0.016
Marital status (Ref. Married)					
Single	6.231	10.435	0.016	0.597	0.551
Divorced	−1.815	8.455	−0.005	−0.215	0.830
Widowed	−0.074	13.494	0.000	−0.005	0.996
Family roles (Ref. Mainly cared for others)					
Mainly cared for by others	−2.869	7.955	−0.010	−0.361	0.718
Caring for oneself	5.877	6.023	0.027	0.976	0.329
Caring for each other	−2.316	3.661	−0.018	−0.633	0.527
Residence (Ref. City)					
Town or county	0.338	4.132	0.002	0.082	0.935
Rural or suburban area	1.967	5.472	0.010	0.359	0.719
Tumor location (Ref. Upper outer quadrant)					
Lower outer quadrant	0.689	4.587	0.004	0.150	0.881
Upper inner quadrant	−3.110	4.372	−0.019	−0.711	0.477
Lower inner quadrant	9.904	6.710	0.038	1.476	0.140
Areola area	−4.960	6.704	−0.019	−0.740	0.460
Unclear	2.370	6.902	0.009	0.343	0.731
Employment (Ref. Employed)					
Unemployed	−2.572	4.800	−0.018	−0.536	0.592
Retired	−3.644	5.545	−0.024	−0.657	0.511
Others	0.672	7.310	0.002	0.092	0.927
Side of cancer (Ref. Cancer on dominant side)					
Cancer on nondominant side	9.790	3.227	0.076	3.034	0.002

BMI, body mass index.

associated with body size, an inter-arm ratio is recommended to achieve better accuracy in lymphedema diagnosis compared to using absolute inter-arm difference. This is particularly important when preoperative baseline measurements are unavailable to determine the relative volume change.

We evaluated baseline arm asymmetry using both the Affected/Unaffected ratio and the Dominant/Nondominant ratio. The Dominant/Nondominant ratio (1.011) was larger than the Affected/Unaffected ratio (0.998), demonstrating the arm dominance has a greater influence on arm asymmetry. Our results regarding arm asymmetry between the affected and unaffected arms were consistent with previous research.[11,30] Notably, we found that the affected arm had a 0.2% smaller volume compared to the unaffected arm at the preoperative baseline, which is inconsistent with previous findings.[11,24] Although preoperative ipsilateral lymphedema cases have been reported in breast cancer patients with extensive nodal involvement,[24,31] Smoot et al.'s study concluded that side of cancer did not influence the preoperative arm volumes of breast cancer patients.[17] In the present study, we cannot determine whether the asymmetry between affected and unaffected arm is caused by lymphedema or hand dominance. This limitation is due to the lack of precise measurements such as bioimpedance spectroscopy or lymphoscintigraphy. However, advancements in breast cancer screening and diagnosis are expected to reduce the proportion of locally advanced breast cancer. Consequently, the incidence of preoperative lymphedema will also decrease.

Our study confirmed the influence of hand dominance on preoperative arm differences.[15–17] It has been suggested that hand dominance

Table 6
Main and interaction effects of preoperative volume differences between dominant and nondominant arms.

Arm Volume	Cancer on dominant side	Cancer on nondominant side	Main effect of dominance		Main effect of side of cancer		Interaction effect (Dominance* side of cancer)	
	Mean (SD), $n = 865$	Mean (SD), $n = 842$	*F*	*P*	*F*	*P*	*F*	*P*
Segment A								
Dominant arm	291.87 (46.68)	290.80 (47.10)	73.760	<0.001	0.306	0.580	26.066	<0.001
Nondominant arm	292.23 (44.99)	288.00 (44.98)						
Segment B								
Dominant arm	423.25 (68.79)	424.73 (67.36)	81.707	<0.001	0.011	0.917	20.744	<0.001
Nondominant arm	421.46 (69.13)	419.30 (68.20)						
Segment C								
Dominant arm	516.50 (91.29)	518.17 (93.35)	59.434	<0.001	0.034	0.853	3.147	0.076
Nondominant arm	513.66 (91.57)	513.64 (94.59)						
Segment D								
Dominant arm	661.64 (136.07)	663.58 (141.71)	113.138	<0.001	0.024	0.877	1.548	0.214
Nondominant arm	655.00 (136.80)	655.19 (142.34)						
Whole arm								
Dominant arm	1889.97 (327.22)	1897.01 (335.77)	127.949	<0.001	0.010	0.922	11.643	0.001
Nondominant arm	1877.39 (328.88)	1873.57 (338.11)						

Note: Repeated measures analysis of variance, dominance as within group factor, side of cancer as between group factor. Volume measurements are derived from 10 cm segments, starting at the wrist (Segment A) and progressing in 10 cm increments to Segment D (30–40 cm proximal to the wrist). Whole arm refers to the total volume from Segment A to Segment D.

should be considered when defining the cut-offs for lymphedema diagnosis. Using a normative-based threshold of 3SD above the mean, the thresholds for the dominant arm (13%) and nondominant hand arm (9%) are close to the commonly recommended 10% inter–arm volume threshold.[8] While the 3SD-based threshold offers good specificity, it is conservative for diagnosing subclinical or mild lymphedema. Therefore, a 2SD-based threshold is recommended.[32] In this cohort, an inter-arm volume difference exceeding 7.9% is likely to indicate lymphedema when the dominant arm is affected, while a threshold of 5.7% applies when the non-dominant arm is affected. If the 10% inter-arm difference threshold was used in Chinese breast cancer patients, 1.4% and 2.3% would be under diagnosed. The current findings require further confirmation before being applied in clinical practice. The side of cancer (cancer on nondominant side vs. cancer on dominant side) showed no effects on preoperative inter-arm volume differences, consistent with previous reports.[17] The results indicated that lymph transport function remained unchanged before cancer treatment. Future studies are needed to verify our findings and explore additional potential variables which might be correlated with the inter-arm differences.

Previous evidence suggests that pre-operative bilateral baseline measurements should be a standard of quantification for diagnosing lymphedema. Without pre-operative baseline measurement, 40% to 50% of patients may be under or over diagnosed, especially in subclinical and early-stage cases.[11] Potential barriers for preoperative baseline measurements should be systematically explored and addressed. In situations where preoperative baseline measurement is unavailable, postoperative inter-arm comparisons should account for pre-existing arm variability and asymmetry. Our study presented normative-based thresholds for lymphedema diagnosis in Chinese breast cancer population. The thresholds have the potential to improve diagnostic accuracy in the absence of baseline assessments. However, further studies are needed to confirm and validate these normative-based thresholds before they can be implemented in practice.

Implications

Our findings have implications for both clinical practice and future research. Clinically, our results highlight the importance of preoperative bilateral arm measurements for accurate lymphedema diagnosis in post-operative breast cancer patients. Normative-based thresholds of arm lymphedema should be studied in different populations, considering the differences in body habitus, especially when pre-operative measurements are unavailable. Given that hand dominance significantly impacts inter-arm volume differences, healthcare providers should include the assessment of hand dominance during lymphedema evaluation. For Chinese breast patients, when preoperative assessments are unavailable, an inter-arm volume difference greater than 7.9% should be used as the diagnostic criterion for patients with tumors affecting the dominant side, while a difference greater than 5.7% should apply for those with tumors on the non-dominant side. As lymphedema might occurs in specific arm segments, identifying specific segments of the arm where volume differences exceed the established segment-specific cut-offs allows clinicians to detect early signs of lymphedema more precisely. Future research is warranted to test and verify these normative-based thresholds for arm lymphedema in the absence of pre-operative measurements across different settings, to establish well-evidenced normative-based thresholds for arm lymphedema in Chinese breast cancer patients.

Limitations

This study has several limitations. First, we determined hand dominance based on patients' self-report although validated questionnaires, such as the Edinburgh Handedness Inventory (EHI) are available. Nonetheless, research has demonstrated a strong correlation between the EHI and self-reported handedness. Second, all participants were recruited from a single medical centre, which might limit the representativeness of the sample and the generalizability of our findings. Further multi-centre studies should be conducted to include diverse Asian populations to confirm and validate the current findings. Third, hand volume was not considered due to the limitations of circumference measurement, as no formula is available for calculating hand volume with circumferences. Future studies should incorporate hand volume using appropriate measurement techniques. Another limitation is the potential influence of additional variables that were not explored. Future research should incorporate a broader range of potential variables such as detailed patient history and lifestyle factors to provide a more comprehensive analysis.

Conclusions

In conclusion, this study determined the preoperative inter-arm differences and identified the normative-based thresholds that consider hand dominance in a cohort of Chinese breast cancer patients. Hand dominance significantly influenced the inter-arm differences, with dominant arm circumference and volume being greater than the nondominant arm. The absolute and relative normative-based thresholds for Chinese breast cancer patients were slightly different from the commonly used diagnostic criteria and those reported in Western populations and Chinese healthy women. This study highlights the importance of preoperative baseline assessments due to the normal variability and asymmetry associated with arm dominance. While these thresholds have the potential to enhance diagnostic accuracy for postoperative comparisons in the absence of preoperative measurements, they still need to be validated in future multi-center and prospective studies.

Ethics statement

The study was approved by the Biomedical Ethics Committee of Peking University (IRB No. 00001052-21124) and the Research Ethics Committee of Tianjin Medical University Cancer Institute & Hospital (IRB No. bc2023013). All participants provided written informed consent.

CRediT authorship contribution statement

Aomei Shen: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Software; Validation; Roles/Writing – original draft; and Writing – review & editing. **Xin Li**: Investigation; Data curation; Roles/Writing – original draft; and Writing – review & editing. **Wanmin Qiang**: Conceptualization; Resources; Supervision; Writing – review & editing. **Hongmei Zhao**: Resources; Data curation; Validation; and Writing – review & editing. **Jingming Ye**: Resources; Validation; and Writing – review & editing. **Hongmeng Zhao**: Resources; Validation; and Writing – review & editing. **Yujie Zhou**: Resources; Validation; and Writing – review & editing. **Yue Wang**: Resources; Validation; and Writing – review & editing. **Zhongning Zhang**: Investigation; Data curation; Writing – review & editing. **Jingru Bian**: Investigation; Data curation; Writing – review & editing. **Liyuan Zhang**: Investigation; Data curation; Writing – review & editing. **Peipei Wu**: Investigation; Resources; and Writing – review & editing. **Qian Lu**: Conceptualization; Funding acquisition; Methodology; Project administration; Resources; Supervision; Validation; Writing – review & editing. Aomei Shen and Xin Li contributed equally. All authors had full access to all the data in the study, and the corresponding author had final responsibility for the decision to submit for publication. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Declaration of competing interest

The authors declare that they have no conflict of interests. The corresponding author, Prof. Qian Lu, is an editorial board member of *Asia-Pacific Journal of Oncology Nursing*. The article was subject to the journal's standard procedures, with peer review handled independently of Prof. Lu and their research groups.

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Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to ethical restrictions.

Declaration of generative AI and AI-assisted technologies in the writing process

No AI tools/services were used during the preparation of this work.

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