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Original Article

Risk factors of lymphedema on affected side of upper limb after breast cancer surgery — report from a single center of China

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Abstract: Objective: Lymphedema on affected side of upper limb is one of the most common complications after breast cancer surgery. This paper intends to discuss the morbidity of limb lymphedema and analyzes related risk factors, in hope of providing some guidance for early prevention of such complication. Method: 2,597 female patients with breast cancer who received operations in our hospital from December 2011 to December 2015 were sampled. According to patients' subjective feelings and Objective measurements, the morbidity of lymphedema on affected side of upper limb was evaluated. patients were asked if they discovered swelling on affected upper limb and whether they felt heavy or numb on the affected side of upper limb. If the answer was definite, it meant the existence of upper limb lymphedema. Objective measurements were made in combination with patients' subjective feelings. Patients' metacarpophalangeal joints, wrist joints and elbow joints were measured in about 20 cm, 15 cm, 10 cm and 5 cm above or below respectively. Then, all numerical values were added to determine the sum. Concerning patients' subjective feelings, patients were asked to answer following questions in the form of questionnaire. They were asked if they discovered swelling on affected upper limb and whether they felt heavy or numb on the affected side of upper limb. If the answer was definite, it meant the existence of upper limb lymphedema. If the sum of the numerical values of the affected side was 5 cm higher than the opposite side, or any measured part was 2 cm longer than the opposite side, it would be defined as true lymphedema. Results: After operation, the morbidity of lymphedema on affected side of upper limb was 10.7%. It was significantly and positively correlated to surgical approaches, postoperative infection, degree of lymph node metastasis and extent of lymph node dissection, but irrelated to age of patients, BMI, tumor size, breast reconstruction and neoadjuvant chemotherapy. The degree of lymph node metastasis (OR=1.301, P=0.011), extent of lymph node dissection (OR=2.149, P=0.000) and postoperative upper limb infection (OR=52.475, P=0.000) were discovered to be independent risk factors of lymphedema on affected upper limb. Conclusions: For patients with breast cancer who were detected with metastasis of many lymph nodes, wide extent of lymph node dissection and postoperative infection on upper limb, the morbidity of postoperative upper limb lymphedema was higher, and surgical approaches significantly impacted the morbidity of such lymphedema.

Keywords: Breast cancer, postoperative, affected side, upper limb, lymphedema, risk factors

Introduction

Lymphedema on affected side of upper limb is one of the most common complications after breast cancer surgery. It is caused usually by lymphatic obstruction and much protein-rich lymph fluid retention in interstitial space [1]. With the possibility of swelling or deformation of affected limb and upper limb disorders, the lymphedema seriously influences patients' mental health and quality of life [2]. Owing to differences in diagnostic criteria for upper limb lymphedema, methods of limb measurement, patients' cancer stage and surgical approaches and so on, the reported morbidity of lymphedema on affected side of upper limb after breast cancer surgery greatly varies from 7.2% to 42.9% home and abroad [3-5] and gradually

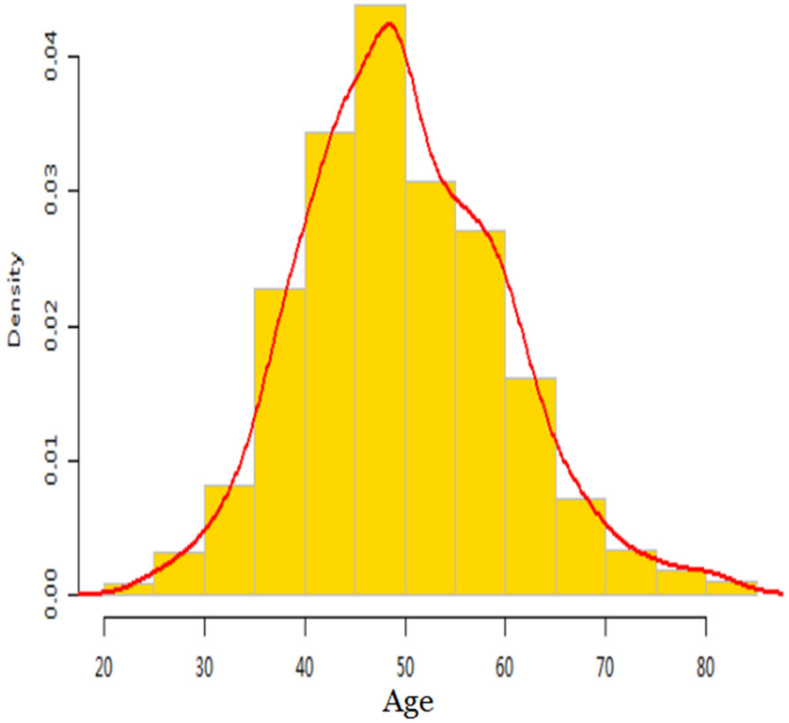

Figure 1. The age distribution of 2597 patients was shown in the above. Among those patients, the youngest was 23 and the oldest was 85, while their mean age was 49.

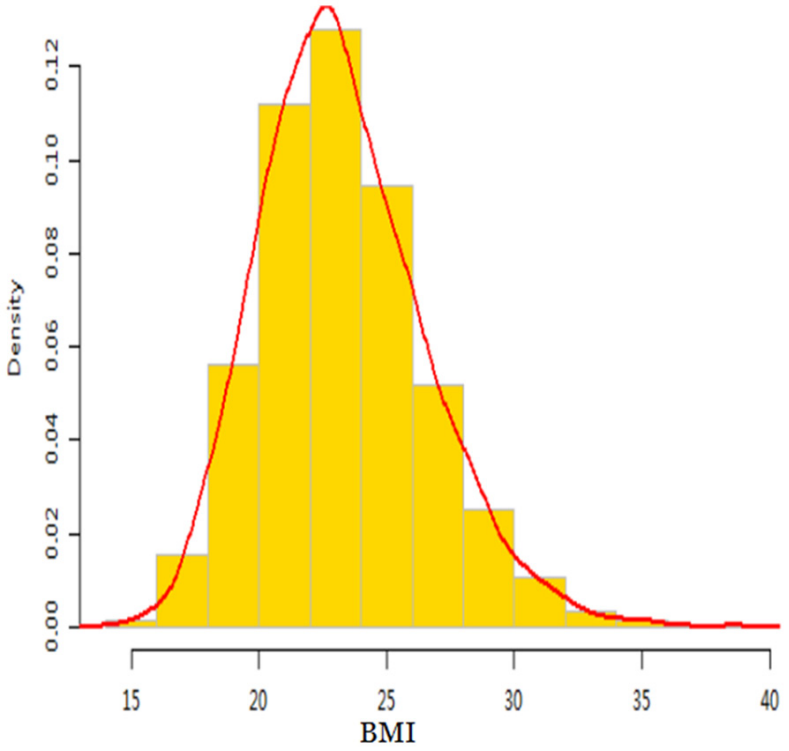

Figure 2. The BMI distribution of 2597 patients was shown in the above. Among those patients, the minimum was 14.4 and the maximum was 38.6, while their mean BMI was 23.2. BMI less than 25.8 accounted for 80%.

increases as time goes on [6]. At present, there are still no special effective measures for treating upper limb lymphedema [7]. Therefore, postoperative upper limb lymphedema for breast cancer shall be actively prevented in clinical practices [8]. If risk factors of the lymphedema can be identified and prevented earlier, it would be possible to decrease the morbidity of postoperative lymphedema on affected side upper limb, alleviate lymphedema and improve patients' quality of life. This paper investigated the morbidity of postoperative lymphedema on affected side of upper limb among nearly 3,000 female patients with breast cancer treated in our hospital and analyzed the related risk factors of the upper limb lymphedema, in hope of providing some guidances for early prevention.

Materials and methods

Case selection

Female patients with breast cancer who underwent surgical treatment in our hospital from December 2011 to December 2015 were selected. The inclusion criteria were described as follows. Firstly, they were pathologically diagnosed with breast cancer before or after operation. Secondly, they weren't complicated with other diseases such as pathological changes of lymphatic vessels or veins that would cause limb swelling or induce upper limn lymphedema before operation. Thirdly, the med-

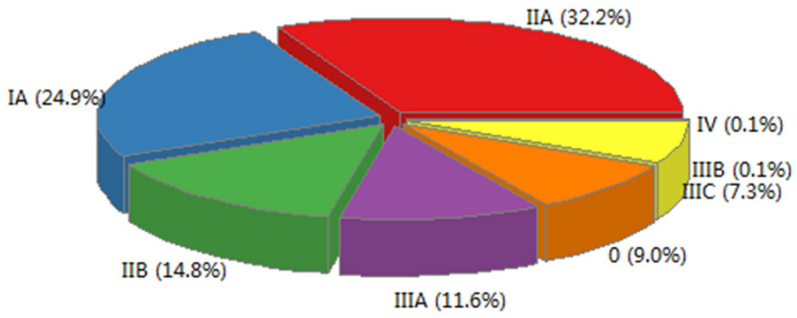

Figure 3. For TNM staging of 2,597 postoperative female patients, breast cancer was mostly in stages IIA (32.2%) and IA (24.9%), then was IIB (14.8%).

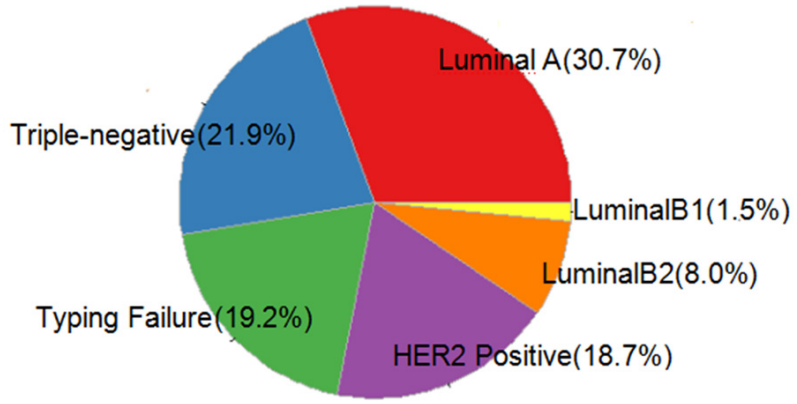

Figure 4. The molecular pathological type in this study is mainly Luminal A breast cancer patients (30.7%), followed by three negative breast cancer patients (21.9%), 489 cases (19.2%) of Her-2 (++) patients refused to use FISH examination, causes their molecular type cannot be judged.

ical records were complete. This study excluded ① Patients whose clinical data or follow-up data were seriously lost, ② those with communication barriers, and ③ those complicated with other diseases that could cause lymphedema. After selection, 2,597 postoperative female patients with breast cancer were included in this study.

Measurements of upper limb lymphedema and follow-up visits

Objective measurements were made in combination with patients' subjective feelings [9]. For objective measurements, limb circumference was measured as follows. Patients' metacarpophalangeal joints, wrist joints and elbow joints were measured in about 20 cm, 15 cm, 10 cm and 5 cm above or below respectively. Then, all numerical values were added to determine the sum. If the sum of the numerical values of the affected side was 5 cm higher than the opposite side, or any measured part was 2 cm longer than the opposite side, it would be defined as lymphedema. Concerning patients' subjective feelings, patients were asked to answer following questions in the form of questionnaire. They were asked if they discovered swelling on affected upper limb and whether they felt heavy or numb on the affected side of upper limb. If the answer was definite, it meant the existence of upper limb lymphedema. For the circumference of the upper limb, the postoperative follow-up visit lasted 6 to 60 months. To be exact, the patients were visited every three or six months. During the follow-up visit, upper limb lymphedema was found in 277 patients and its morbidity was 10.7%. The remaining patients did not occur upper limb lymphedema.

Data collection

A questionnaire survey was conducted by phone and outpatient follow-up visit. Patients' medical records in hospitals were consulted and collected to analyze related risk factors of postoperative upper limb lymphedema, including personal factors (e.g. age, height and weight), postoperative complications (e.g. infection of upper limb), tumor-related factors (e.g. tumor position, tumor size, TMN staging, pathological molecular types, lymph node metastasis and number of metastatic lymph nodes) and therapeutic factors (e.g. surgical approaches, extent of lymph node dissection and neoadjuvant chemotherapy).

Personal factors and postoperative complications: Among 2,597 postoperative female patients with breast cancer, the youngest was 23 and the oldest was 85, while their mean age was (49.9±10.1). Their age distribution was shown in **Figure 1** as follows. BMI (Body Mass Index) was calculated according to patients'

Table 1. Univariate analysis of factors impacting the morbidity of Edema

Variables	Assignment	N	Lymphedema n (%)	χ^2	*P*
Age					
	<40	451	37 (8.2)	3.472	>0.05
	≥40	2,146	240 (11.2)		
BMI				0.817	>0.05
	<25	1,915	198 (10.3)		
	≥25	682	79 (11.6)		
Postoperative Infection				34.631	0.000
	No	2591	272 (10.5)		
	Yes	6	5 (83.3)		
Part of Tumor				0.840	>0.05
	Double Breasts	52	4 (7.7)		
	Right Breast	1,236	135 (10.9)		
	Left Breast	1,309	138 (10.5)		
Tumor Size					
	<2 cm	1,109	113 (11.1)	0.489	>0.05
	2-5 cm	1,310	145 (10.2)		
	>5 cm	169	18 (11.1)		
	Unknown	9	0 (0)		
Pathological Molecular Type				2.104	>0.05
	HER2 positive	476	49 (10.3)		
	Luminal A	784	83 (10.6)		
	Luminal B1	39	3 (7.7)		
	Luminal B2	204	25 (12.3)		
	Triple-negative	559	69 (12.3)		
	Typing Failure	489	46 (9.4)		
	Missing Data	46	2 (4.3)		
Lymph Node Metastasis				21.119	0.000
	No	1,501	123 (8.2)		
	Yes	1,096	154 (14.1)		
Number of Metastatic Lymph Nodes				11.232	0.004
	≤3 (N1 Group)	2,145	212 (9.9)		
	4-9 (N2 Group)	267	32 (12.0)		
	≥10 (N3 Group)	185	33 (17.8)		
Surgical Approaches				28.400	0.000
	Breast-conserving Surgery	77	8 (10.4)		
	Breast-conserving Surgery + SLNB	112	7 (6.3)		
	Breast-conserving Surgery + ALND	164	20 (12.2)		
	Mastectomy	40	3 (7.5)		
	Mastectomy + SLNB	290	7 (2.4)		
	Modified Radical Mastectomy	1889	229 (12.1)		
	Radical Mastectomy	20	3 (15.0)		
	Others	5	0 (0)		
Extent of Lymph Node Dissection				19.244	0.000
	Sentinel Lymph Node Biopsy	245	6 (2.4)		
	Level I and II Lymph Node Dissection	2280	263 (11.5)		
	Level I, II and III Lymph Node Dissection	72	8 (11.1)		
	Others	30	0 (0)		
Breast Reconstruction				1.148	0.284
	Yes	73	5 (6.8)		
	No	2524	272 (10.8)		
Neoadjuvant Chemotherapy				1.300	0.254
	Yes	456	55 (12.1)		
	No	2141	222 (10.4)		

Notes: BMI, body mass index; SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection.

height and weight, equaling to (23.2±10.1) on average. There were 1,915 patients whose BMI was below 25 and 682 patients whose BMI wasn't lower than 25. The distribution of BMI was shown in **Figure 2** as follows. Six patients were infected on the upper limb after operation, and the morbidity of postoperative infection of affected limb was 0.23%.

Tumor-related factors: There were 1,309 patients with cancer on the left breast, 1,236 patients with cancer on the right breast, and 52 patients with cancer on both the left and right breasts. Tumors of most patients were smaller than 5 cm (including 2,419 cases altogether). For 9 patients, the records of their original tumor size couldn't be found after they received lumpectomy in other hospitals. Lymph node metastasis was detected in 1,096 patients and its rate was 42.2%. By further statistically analyzing the number of metastatic lymph nodes, it was discovered that there were 2,145 patients whose number of metastatic lymph nodes wasn't higher than 3 (N1 Group), 267 patients with 4 to 9 metastatic lymph nodes (N2 Group) and 185 patients whose number of metastatic lymph nodes was not below 10 (N3 Group). For TNM staging, breast cancer was mostly in stages IIA (32%) and IA (25%) (See **Figure 3**). Data about pathological molecular types of patients with breast cancer were collected and relevant records couldn't be found from medical records of 46 patients. 489 Her-2 positive patients with breast cancer rejected undertaking the FISH test because the cost of this test is very expensive, so their molecular types of breast cancer couldn't be judged (See **Figure 4**).

Therapeutic factors: The surgical approaches adopted in this study included modified radical mastectomy, mastectomy, mastectomy combined with sentinel lymph node biopsy, breast-conserving surgery, breast-conserving surgery combined with sentinel lymph node biopsy, and radical mastectomy, among which modified radical mastectomy was performed as the major surgical approach (1889 cases, 72.7%). 2,280 patients underwent stages I and II lymph node dissections, while stage I, II and III lymph node dissections were performed in 72 patients. 245 patients underwent sentinel lymph node biopsy in place of axillary lymph node dissection, and 30 patients only received breast cancer surgery without further lymph node dissection. 73 patients underwent Stage-I breast reconstruction after the breast cancer surgery, and 456 patients (17.6%) received neoadjuvant chemotherapy before operation.

Statistical methods

Data were classified and statistically analyzed by SPSS18.0, and a univariate analysis was performed by chi-square test. Relationships between several factors [including age, BMI, tumor size (T staging), number of metastatic lymph nodes (N1, N2 and N3 groups), chemotherapy and postoperative infection] and risks of lymphedema were evaluated by logistic regression. Besides, the connections of several factors such as age, BMI, tumor size (T staging), number of metastatic lymph nodes and extent of lymph node dissection with the disappearance of lymphedema after rest and several risks (including depression after finger pressing, limb thickening, skin roughness and hardening of tissues) were assessed by logistic regression. For both sides, it would be statistically significant when P was below 0.05.

Results

Univariate analysis

The univariate analysis suggested that the morbidity of upper limb lymphedema was significantly positively correlated to surgical approaches (χ^2=28.400, P=0.000), postoperative infection (χ^2=34.631, P=0.000), lymph node metastasis (χ^2=21.119, P=0.000), number of metastatic lymph nodes (χ^2=11.232, P=0.004) and extent of lymph node dissection (χ^2= 19.244, P=0.000), but irrelated to age, BMI, tumor position, tumor size, pathological molecular type, Stage I breast reconstruction and neoadjuvant chemotherapy (P>0.05), as shown in **Table 1**.

Different surgical approaches were further analyzed. The results suggested that the morbidity of upper limb lymphedema was lower for patients undertaking breast cancer dissection and sentinel lymph node biopsy than those receiving radical mastectomy (χ^2=9.494, P= 0.002), breast-conserving surgery combined with axillary lymph node dissection (χ^2=17.919, P=0.000) and modified radical mastectomy (χ^2=24.539, P=0.000), while no significant dif-

Table 2. Logistic regression results of multiple factors impacting edema

Variables	β	Wald	P	OR	OR 95% CI
Age	0.002	0.142	0.706	1.002	0.990-1.015
BMI	-0.092	0.397	0.529	0.912	0.685-1.214
Chemotherapy	-0.067	0.160	0.689	0.935	0.674-1.297
Extent of Lymph Node Dissection	0.765	13.219	0.000	2.149	1.423-3.247
Lymph Node Metastasis	0.263	6.429	0.011	1.301	1.062-1.595
T Staging	-0.048	0.190	0.663	0.953	0.766-1.185
Infection	3.960	12.778	0.000	52.475	5.983-560.258

Notes: Relationships between several factors (including age, BMI, chemotherapy, extent of lymph node dissection, lymph node metastasis, T staging and Infection) and risks of edema were evaluated by logistic regression. Patients with more metastatic lymph nodes, postoperative infection and a greater extent of lymph node dissection have a higher risk for lymphedema. The risk of lymphedema was irrelated to age, BMI, chemotherapy and T Staging.

Table 3. Logistic regression results of multiple factors affecting disappearance of edema after rest

Variable	β	Wald	P	OR	OR 95% CI
Age	0.001	0.046	0.830	1.001	0.989-1.014
BMI	-0.101	0.492	0.483	0.904	0.681-1.199
Extent of Lymph Node Dissection	0.738	12.563	0.000	2.091	1.391-3.145
Lymph Node Metastasis	0.268	7.007	0.008	1.307	1.072-1.594
T Staging	-0.045	0.167	0.683	0.956	0.772-1.185

Notes: Relationships between several factors (including age, BMI, extent of lymph node dissection, lymph node metastasis and T staging) and disappearance of edema after rest were evaluated by logistic regression. The disappearance of upper limb lymphedema after rest was related to extent of lymph node dissection and number of metastatic lymph nodes.

ference existed in morbidity of lymphedema among other groups (P>0.05). The morbidity of lymphedema in the group of sentinel lymph node biopsy was significantly lower compared with groups whose level I and II lymph nodes were dissected (χ^2=19.250, P=0.000) and those whose level I, II and III lymph nodes were dissected (χ^2=9.797, P=0.002). There were no significant differences in the morbidity of lymphedema between groups whose level I and II lymph nodes were dissected and those whose level I, II and III lymph nodes were dissected (P>0.05). Concerning lymph node metastasis, the morbidity of lymphedema was significantly higher in N3 Group than that of N1 Group (χ^2=10.914, P=0.001), but exhibited no significant differences between N1 Group and N2 Group, N2 Group and N3 Group (P>0.05).

Multivariate analysis

Multivariate analysis on risk factors of lymphedema: The results of this study suggested that the risk of lymphedema was higher for patients whose lymph nodes were dissected to a greater extent (OR=2.149, P=0.000) and those with more metastatic lymph nodes (OR=1.301, P=0.011). Meanwhile, the risk was higher for patients with postoperative infection than those without such infection (OR=52.475, P=0.000), as shown in **Table 2**.

Multivariate analysis on severity of lymphedema: The results of this study showed that the disappearance of upper limb lymphedema after that the affected limb remains stationary and relaxed was related to extent of lymph node dissection (OR=2.091, P=0.000) and number of metastatic lymph nodes (OR=1.307, P=0.008), as shown in **Table 3**. This indicated that the higher the degree of lymph node metastasis and the greater the extent of lymph node dissection, the higher the disappearance rate of patients' edema after their rest. Depression after finger pressing, limb thickening, skin roughness and hardening of tissues were irrelated to age, BMI, lymph node metastasis and extent of lymph node dissection (P>0.05).

Discussion

The etiologic and pathophysiological mechanisms of post-operative upper limb lymphedema are still unclear for patients with breast cancer. What is more, there is a lack of effective means for treating the lymphedema. The risk

factors of lymphedema have been hot research topics over the past few years. The results of clinical studies are not completely consistent and even conflict with each other. Numerous research findings have suggested that the morbidity of upper limb lymphedema is influenced by multiple factors, including surgical approaches, ways for treating axillary lymph nodes, number of dissected axillary lymph nodes, extent of axillary lymph node dissection and radiotherapy, whereas the relationships of lymphedema with age, body mass index and number of metastatic lymph nodes are still controversial [10-12].

In consideration that only a relatively small sample size was involved in exploring risk factors of lymphedema on affected side upper limb after breast cancer surgery in previous studies, nearly 3,000 surgical cases with breast cancer were included in this study, which involved the largest amount of cases among related studies. This study adopted more surgical approaches than previous reports, nearly including all current surgeries for treating breast cancer, which were compared from the perspective of morbidity of lymphedema. In addition, it discussed connections between pathological indexes about breast cancer and upper limb lymphedema completely. For instance, the relationships between pathological molecular types of breast cancer and upper limb lymphedema weren't mentioned in previous studies. In this study, it was discovered that the postoperative upper limb lymphedema was related to surgical approaches, postoperative infection, extent of lymph node dissection and number of metastatic lymph nodes, but irrelated to age of patients, BMI, part of tumor, tumor size, pathological molecular types, breast reconstruction and preoperative neoadjuvant chemotherapy.

At present, there are many surgical approaches for breast cancer, including mastectomy ± sentinel lymph node biopsy, modified radical mastectomy, radical mastectomy, breast-conserving surgery and breast reconstruction. In this study, the morbidity of lymphedema was the lowest for patients undertaking mastectomy plus sentinel lymph node biopsy, followed by breast-conserving surgery plus sentinel lymph node biopsy. The morbidity of lymphedema was significantly higher for patients receiving radical mastectomy, modified radical mastectomy, and breast-conserving surgery combined with axillary lymph node dissection. Their risks of lymphedema were 6.25, 5.04 and 5.08 times higher respectively compared with mastectomy plus sentinel lymph node biopsy. Previous studies [5, 13] also discovered that patients who received radical mastectomy or modified radical mastectomy faced higher risks of lymphedema than those undertaking mastectomy, possibly because extensive free flaps were needed and axillary fatty lymphatic tissues should be dissected in radical mastectomy or modified radical mastectomy. As a consequence, most lymphatic pathways were cut off.

Axillary lymph node dissection is one of commonly acknowledged risk factors of upper limb lymphedema at present. Under normal conditions, there are about 30 to 60 axillary lymph nodes [14]. It was reported that [15] when 16 to 25 lymph nodes were dissected, the relative risk of lymphedema was 1.78, but increased to 1.95 when more than 25 lymph nodes were dissected. The risk of lymphedema in undertaking radical axillary lymph node dissection was 4 times higher than that of sentinel lymph node biopsy [6]. Furthermore, this paper discovered that axillary lymph node dissection was an independent risk factor of lymphedema. The risks of lymphedema were 4.8 times higher for patients whose lymph nodes were dissected than that undertaking sentinel lymph node biopsy. To dissect axillary lymph nodes, it is necessary to cut off or ligate some lymph vessels, and the trauma extended towards lymph vessels along veins may obstruct or interrupt the lymphatic drainage, which would make lymph fluids retain in interstitial spaces and thereby cause lymphedema [16]. The sentinel lymph node biopsy may avoid lymph node dissection, greatly narrow the extent of axillary lymph node dissection and reduce risks of upper limb lymphedema, so it is worthy of being strongly advocated in practices.

For breast cancer, lymphatic metastasis is an important risk factor of upper limb lymphedema [11, 17], perhaps because normal functions of lymphatic system are damaged more severely for patients with invasive ductal carcinoma and lymph node metastasis, whose extent of surgical dissection is generally greater and who need more adjuvant therapies (e.g. chemotherapy and radiotherapy) before and after surgery, while these factors may aggravate damages to lymphatic system and surrounding tissues,

thereby leading to postoperative lymphedema on affected side of upper limb [18]. This study discovered that neoadjuvant chemotherapy didn't have evident impacts upon the morbidity of upper limb lymphedema, and lymphatic metastasis was an independent risk factor of upper limb lymphedema. When there were not fewer than 10 metastatic lymph nodes, the morbidity of lymphedema was 17.8%, and under this circumstance, the risk was 1.78 times higher compared with the situation when there were 3 or fewer metastatic lymph nodes, and 2.12 times higher than patients without lymph node metastasis. Shah C et al [19] retrospectively analyzed 1,497 patients. Their research showed that, the morbidity of upper limb lymphedema was 11.4% for stage N1 or N2 patients, and 6.3% for stage N0 patients. Nevertheless, it was still discovered that after rest, the response rate of lymphedema was higher for patients who had more metastatic lymph nodes and whose lymph nodes were dissected to a greater extent. Pertinent reasons are unclear and remain to be further studied.

After breast cancer surgery, the recovery of affected side of limb is important for recovery of the disease and the morbidity of upper limb lymphedema. Postoperative skin infection of upper limb may increase the risk of lymphedema. This study discovered that postoperative infection of upper limb was an independent risk factor of lymphedema for patients with breast cancer, the morbidity of lymphedema was far higher among infected patients (83.3%) compared with uninfected patients (10.5%), and the former patients faced 7.9 times higher risks than the latter. Postoperative skin trauma and infection may contribute to invasion of bacteria, causing lymphangitis and further damage remained lymphatic vessels, thus resulting in lymphedema because of damaged and blocked vessels [20]. In addition, recurrent infection would lead to thickening skin and subcutaneous tissues, skin keratinization, pigmentation and even elephantiasis [21]. In the past, a study [22] also discovered that after surgery, infection of the upper limb would increase the risk of lymphedema, and patients whose upper limb was infected would face 3.11 times higher risks than those who were uninfected on the upper limb.

Above all, we consider that patients who need to undertake any surgery for breast cancer shall try their best to reduce risk factors of upper limb lymphedema for early prevention. Among multiple risk factors, rate of lymph node metastasis is related to lymphedema, and breast cancer may be diagnosed and treated early by large-scale screening. In this way, the rate of lymph node metastasis may also decline among patients with breast cancer. For other risk factors, corresponding intervention measures may be taken, in order to lower the morbidity of postoperative lymphedema on affected side of limb for patients with breast cancer. For instance, if permitted by a patient's conditions, the trauma of selected surgical approaches shall be as mild as possible. In performing axillary lymph node dissection, it is inadvisable to blindly increase the extent of lymph node dissection. Provided that no lymph node metastasis is detected by the sentinel lymph node biopsy, such biopsy is advocated to be performed in place of axillary limb node dissection in case of no high risk factors, so as to avoid excessive damages to lymphatic system. To protect the lymphatic system of upper limb, ARM (Axillary Reverse Mapping) has been proposed over the past few years. ARM may protect the lymphatic system by tracing and labeling, to effective decrease the morbidity of postoperative lymphedema on affected side of upper limb [23]. Gennaro M et al [24] performed ARM for 60 patients with breast cancer, whose success rate was 75%, and the risk of upper limb lymphedema in retaining lymph nodes by ARM was 1/3 of that in undertaking ALND after the failed ARM. The effectiveness and safety of ARM deserve further exploration. Additionally, patients with breast cancer shall avoid skin infection on their upper limb as possible as they can, and those infected on their upper limb shall take active measures to control the infection.

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Disclosure of conflict of interest

None.

Authors' contribution

Zhang Xiping and Tang Binbin wrote this paper. Zou Dehong was the person in charge of this clinical project. The other authors participated

in the clincal design and statistical analysis. All authors approved the final version.

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