

# Recurrence of Lymphedema and Related Characteristics in Discharged Breast Cancer Patients During The COVID-19 Pandemic: A Multicenter, Cross-Sectional Survey

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## Research article

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# Abstract

## Background

To evaluate recurrence of lymphedema and its influencing factors in discharged breast cancer patients with treated lymphedema during the COVID-19 pandemic and to propose feasible improvements.

## Methods

A multicenter, cross-sectional, hospital-based survey of discharged breast cancer patients was conducted during the COVID-19 pandemic in eight first-class hospitals in Wuhan city, China. Norman Questionnaire was used for assessing lymphedema, and multivariable binary logistic regression was performed to risk factors of moderate or severe lymphedema. Difference in living characteristics, anxiety and depression between no or mild group and moderate or severe group were compared. Preference in management of lymphedema were collected.

## Results

202 valid patients were included. 191 participants reported recurred lymphedema (prevalence: 94.6%, 95%CI 90.5% to 97.3%). 134 of them was mild and 57 were moderate/severe. In the 191 patients, the main symptom was swelling (140, 69.3%) and pain (56, 27.7%). Multivariable regression showed that age (odds ratio, 1.06, 95%CI: 1.02-1.10), radical surgery (OR=4.35, 95%CI: 1.54-12.50) and fully complete radiotherapy (OR=2.62, 95%CI: 1.17-5.87, P=0.019) was associated with the risk of moderate or severe lymphedema. No significant difference in lifestyles was observed but moderate or severe group experienced higher rate of anxiety and depression. patients preferred treatment in hospital and self-care at home equally.

**Conclusion** The high recurrence rate of lymphedema in breast cancer patients with during COVID-19 should draw our great attention, continuous efforts should be made to identify patient at risk of lymphedema and distribute feasible guidance and education for self-management for these patients.

## Background

Anatomically and physiological, the breast has fifteen to 20 lobes that contain glands responsible for milk production in response to hormone stimulation, however, uncontrolled growth of cells in the breast can lead to tumors<sup>[1]</sup>. Breast cancer had become the world's most prevalent cancer in women based on the global cancer statistics 2020<sup>[2]</sup>. The breast tumor tends to spread lymphatically and hematologically, the axillary lymph nodes are often the first to be affected when breast cancer spreads. During treatment for breast cancer, some or all of the axillary lymph nodes under the arm are dissected and flow of lymph may be disrupted, the patients are at a high risk of lymphedema for the rest of their life. Meanwhile, possible regional lymph node radiation treatment may cause scarring and blockages in the under arm lymph nodes, which can further increase the risk of lymphedema. A review including 19 studies and 3035

breast cancer patients showed that 711 (23.43%) developed breast cancer related lymphedema (BCRL)<sup>[3]</sup>. Moreover, the disturbing recurrence of BCRL could be not ignored<sup>[4]</sup>. BCRL has been one of the serious complications that affect both quality of life and postoperative psychological status<sup>[5-6]</sup>. Early identification and treatment of lymphedema is important. Self-reported symptoms were considered as suitable instrument of early detection of BCRL<sup>[4]</sup>. Without timely treatment for lymphedema, the swelling will worsen, meanwhile, skin sores, infection in affected area or other problems can develop, all of which greatly deteriorate prognosis of breast cancer<sup>[7]</sup>.

In December 2019, the first case of Coronavirus disease 2019 (COVID-19) was identified in Wuhan city which was the epicenter of the COVID-19 outbreak in China. The COVID-19 spread rapidly and globally within a short period, which had been recognized as a global pandemic by the WHO<sup>[8-9]</sup>. At the beginning of the outbreak, the medical resources were limited with shortage of personal protection equipment and a large number of patients infected with COVID-19. About 51 local hospitals in Wuhan city were transformed into designated hospitals for patients infected with COVID-19, so patients with other diseases were delayed to get adequate and timely treatment, which also included breast cancer patients<sup>[10-11]</sup>. The delay due to the outbreak will cause overdue diagnosis and treatment of lymphedema. Meanwhile, a high prevalence of depression and anxiety were observed among general population during the pandemic<sup>[12]</sup>. A literature review showed that psychosocial issues were associated with breast cancer-related lymphedema<sup>[13]</sup>. So, it is of great significance to understand status of lymphedema and demands among the breast cancer patients with treated lymphedema.

Breast cancer patients in Wuhan city experienced a long city lockdown and a passive delay of treatments. Therefore, they could provide valuable information. In this study, we performed a multicenter cross-sectional survey in eight first-class hospitals from Wuhan city to investigate the status of lymphedema and demands in breast cancer patients with previous and cured lymphedema during the early pandemic. It can help to arrange optimal nursing plan and treatment for potential lymphedema in breast cancer patients during the ongoing global COVID-19 pandemic.

## **Materials And Methods**

### **Study Design, Setting, Participants**

From May 27, 2020 to June 10, 2020, a multicenter, cross-sectional, hospital-based survey was conducted in eight first-class hospitals in Wuhan city, China. This study was reviewed and approved by the ethical review of Tongji Medical College of Huazhong University of Science and Technology. A convenient sampling method was adopted to select accessible breast cancer patients. Patients were eligible for the inclusion if they: 1) female patients who were diagnosed with breast cancer before COVID-19; 2) discharged after treatment; 3) has lymphedema before COVID-19 pandemic and the lymphedema had been effectively treated and affected limbs had recovered to normal before January 2020; 4) lymphedema-related intervention was interrupted during COVID-19 from January to April 2020; 5) agreed

the informed consent and was volunteer to participate in this study. The exclusion criteria were 1) infection with COVID-19; 2) new recurrence or metastasis of breast cancer.

## Data Collection

A self-administered electronic questionnaire was designed to collect data. A structural and unified instructions was prepared to explain the purpose, meaning and filling method of the questionnaire. The link embed in a QR code was distributed through WeChat (a famous online communication tool in China). One WeChat account could only fill out the questionnaire once, and consumed time was recorded for further validation.

The questionnaire consisted of general characteristics, diagnostic questionnaire for lymphedema, patient-reported outcomes and preference in management of lymphedema. In the demographic characteristics, we collected age, height, weight, educational level, surgery (yes/no) and type of surgery, radiotherapy (yes/no), use of taxane drugs or hormones in the past 6 months(yes/no), knowledge level of lymphedema. Moreover, we queried participants' physical activity (yes/no), special protection for the affected limb (yes/no), emotional status and need for treatment after the lymphedema reappeared during COVID-19 pandemic. Secondly, to assess whether the patients have lymphedema symptoms by phone, a reliable and validated Norman Questionnaire was applied<sup>[14]</sup>. The researchers converted contents of phone assessment into easy-to-understand text, repeated proofreading and comparison to guarantee the consistent meaning. It queried about any swelling in 3 parts (the hand, forearm and upper arm) in the past 3 months. For each part, its score ranged from 0 to 3, 0 indicated no swelling, 1 score indicated a slight swelling where only the patient could perceive, 2 score indicated a moderate swelling where patients' acquaintances could notice in daily life, 3 score indicated a serious swelling where any stranger could notice. Finally, the scores of the three parts were summed. No lymphedema was developed if the sum equaled to 0, a total score of 1 to 4 scores indicated a mild lymphedema, 4 points or more implied a moderate to severe lymphedema. The symptoms of lymphedema were structurally assessed according to a review on patient reported outcomes for breast cancer<sup>[15]</sup>. We collected whether the patient reported swelling, pain, heaviness, numbness, stiffness or movement restriction in affected limbs. Finally, the participants' anxiety and depression were assessed using 7 items in the hospital anxiety and depression scale(HADS)<sup>[16]</sup>. Each item scored from 0 to 3 points, giving a total of 21 points. A total score greater than 8 suggested the presence of anxiety and depression which required medical attention.

## Statistical analysis

Data were extracted from the online questionnaire system and exported to SPSS software for statistical analysis. We first performed statistical description and group comparisons. Mean and standard deviation was used to describe continuous variables, and student's t test was performed for comparison between groups. Categorical variables were described using frequencies and percentages and were compared using chi-square test or Fisher's exact test. Participants were classified into none or mild lymphedema

group and moderate to severe lymphedema group, a multivariable binary logistic regression was conducted to explore potential and independent risk factors, odds ratio and corresponding 95% confidence interval (95% CI) were presented. Two-sided P values of less than 0.05 were considered statistically significant.

## Results

### General characteristics

A total of 228 questionnaires were collected, All but 16 participants were excluded for taking less than 90 seconds; no logical error was found. Finally, 202 records were included for final analysis. The included patients presented a mean age of 51.34 years old and a mean BMI 23.43 Kg/m<sup>2</sup>, and the majority of them (70.8%) reported a more than 10-years education background. 144 patients (71.8%) had received radical surgery. Affected by COVID-19 pandemic, only 10 (5.0%) underwent radiotherapy, while 71 (35.1%) did not receive radiotherapy and 121 (59.9%) experienced interrupted radiotherapy. 55 (22.3%) used taxane or hormone therapy in the past 6 months. Seen Table 1.

Table 1  
demographic characteristic of discharged breast cancer patients during COVID-19

Variable	Description
Age, years, mean+/-SD	51.34 ± 10.07
BMI, kg/m <sup>2</sup> , mean+/-SD	23.43 ± 3.08
Years of education, years, n(%)	
≤ 6	11(5.4%)
7–9	48(23.8%)
10–12	66(32.7%)
> 12	77(38.1%)
Type of surgery, n(%)	
Radical surgery	145(71.8%)
Others	57(28.2%)
Radiotherapy situation, n(%)	
Never	71(35.1%)
Fully completed	121(59.9%)
Interrupted	10(5.0%)
Medication, n(%)	
Used	45(22.3%)
Never used	121(59.9%)
Unknow	36(17.8%)
COVID-19, Coronavirus Disease 2019; BMI, body mass index; Medication, the use of taxane drugs or hormones in the past six months.	

## Prevalence of lymphedema and self-reported symptoms

Based on Norman Questionnaire using 8 as cutoff, 191 participants (prevalence: 94.6%, 95%CI 90.5–97.3%) reported recurred lymphedema, 134 of them were mild and 57 were moderate to severe, In the 191 patients, the main symptom was swelling (140, 69.3%), followed by pain (56, 27.7%), heaviness (55, 27.2%), numbness (55, 27.2%), stiffness 31 (15.3%), and movement restriction 31 (15.3%).

## Characteristics associated with degree of lymphedema

The participants were classified into two groups, no or mild lymphedema group (134, 66.3%) and moderate or severe lymphedema group (57, 28.2%). Description of two groups were presented in Table 2.

The age was  $49.79 \pm 10.14$  in the no or mild group and  $55.30 \pm 8.80$  in moderate or severe group. After adjustment, increased age was significantly and independently associated with severer lymphedema (OR = 1.06, 95%CI: 1.02–1.10, P = 0.004). The rate of radical surgery was 91.2% in moderate or severe group and 61.1% in another group, Multivariable regression showed that radical surgery methods were associated with a higher risk of severer lymphedema using othres surgery as reference (OR = 4.35, 95%CI: 1.54–12.50, P = 0.006). 42(73.7%) in no or mild group took fully complete radiotherapy, while the figures decreased to 79(54.5%) in moderate or severe group. Using no radiotherapy as reference, fully complete radiotherapy increased the risk of severer lymphedema (OR = 2.62, 95%CI: 1.17–5.87, P = 0.019). However, BMI, the months since surgery and use of drugs or hormones in the past six months were found not to be the risk factors after adjustment.

Table 2

Logistic regression analysis on the relationship between risk factors and risk of moderate or severe lymphedema

	Degree of lymphedema		Adjusted OR (95%CI)	P
	None or mild (n = 145)	Moderate or severe (n = 57)		
Age	49.79 ± 10.14	55.30 ± 8.80	1.06(1.02–1.10)	0.004
BMI	23.01 ± 2.99	24.33 ± 3.15	1.08(0.97–1.21)	0.176
Surgery until now(months)	25.34 ± 24.09	41.15 ± 32.51	1.01(0.99–1.02)	0.155
Surgical method				
Radical surgery	93(61.1%)	52(91.2%)	4.35(1.54–12.50)	0.006
Others	52(35.9%)	5(8.8%)	1.00	
Radiotherapy				
Never	57(59.7%)	14(24.6%)	1.00	
Fully completed	79(54.5%)	42(73.7%)	2.62(1.17–5.87)	0.019
Interrupted	9(6.2%)	1(1.8%)	0.60(0.05–6.91)	0.685
Medication				
Used	38(26.2%)	7(12.3%)	1.00	
Never used	81(55.9%)	40(70.2%)	1.46(0.53–3.97)	0.461
Unknown	26(17.9%)	10(17.5%)	1.84(0.51–6.68)	0.353
BMI, body mass index; Medication, the use of taxane drugs or hormones in the past six months;				

# Influence of lymphedema on lifestyle and psychological state

During the COVID-19 pandemic, after lymphedema recurred, less than 20% patients increased physical labor and more than 80% took protective measures for affected limbs. Meanwhile, about half of patients took less exercise at home and about one in five patients reported excessive housework during quarantine at home. The rate of accidental injuries, skin allergies and fungal skin infections of the hands were low. No significant differences in these lifestyles were observed between the two groups. However, a significantly higher proportion of both anxiety and depression were observed in moderate or severe group than that in no or mild group, 78.9% vs 54.4%, 24.6% vs 9.7%, respectively, seen Table 3.

Table 3  
 difference in lifestyles and psychological states between no or mild group and moderate or severe group

Parameters	Degree of lymphedema		P
	None or mild n(%)	Moderate or severe n(%)	
Manual labor			0.870
No change	78(53.8%)	29(50.9)	
Increase	26(17.9%)	12(21.1)	
decrease	41(28.3%)	16(28.1)	
Protective measures for affected limbs			
None	24(16.6%)	7(12.3)	0.448
Keep skin clean and intact	87(60.0%)	32(56.1)	0.616
No lift of heavy objects	114(78.6%)	50(87.7)	0.136
Postoperative functional exercise	64(44.1%)	21(36.1)	0.345
Living conditions			
Exercise less at home	75(51.7%)	36(63.2%)	0.142
Excessive housework	24(16.6%)	10(17.5%)	0.865
Accidental injuries	5(3.4%)	3(5.3%)	0.846
Skin allergies	15(10.3%)	2(3.5%)	0.196
Fungal skin infections of the hands	3(2.1%)	0(0.0%)	0.654
Psychological state			
anxiety	79(54.4%)	45(78.9%)	0.001
Depression	14(9.7%)	14(24.6%)	0.006
COVID-19, Corona Virus Disease 2019; BMI, body mass index;			

## Patients' needs for treatment of lymphedema during the COVID-19 pandemic

The survey showed that 70.8% of patients hoped to get treatment at hospital even though the COVID-19 greatly limited the accessibility. The same rate was observed for the need of self-care at home. Online consultation and family help were the secondary options, accounting for about 35.1% and 32.7%,

respectively. About one in five chose community service and only 11.4% of patients were willing to receive door-to-door services.

## Discussion

The COVID-19 was mainly characterized by high contagiousness and rapid spread<sup>[17]</sup>. City lockdown and home quarantine were considered as effective measures to prevent the spread of the virus during the early outbreak. Breast cancer patients were also restricted from going out and visiting the hospital, which caused their treatment to be interrupted. In this study, the prevalence of recurred lymphedema during the COVID-19 pandemic was 94.6% which was higher than 14–40% in previous studies. The mainly reported manifestation was swelling and pain, while lymphedema related swelling, infection and dysfunction in limbs could affect the patients' quality of life seriously<sup>[18–19]</sup>. Meanwhile, insufficient knowledge about lymphedema and lack of standard and professional guidance in monitoring swelling and implementing lymphedema drainage in the patients might led to further aggravation and decreased quality of life during the home quarantine.

The high prevalence of lymphedema should draw our great attention and were required to distribute effective and timely intervention.

Prevention of lymphedema in breast cancer patients is more important than treatment, it is of great significance to identify potential risk factors and targeted population. Exercise is important for managing lymphedema by working muscle and increasing the flow of lymph fluid. Generally, the elderly was characterized by decreased physical activity<sup>[20]</sup>. In our study, the mean age was about 51 years, and age was found to increase the risk of severer lymphedema. Cancer survivors experienced fatigue and barriers to physical activity in after treatment<sup>[21]</sup>. Moreover, home quarantine might make participants reduce exercise. Finally, the decreased activity resulted in increased risk of lymphedema. There were various surgery for breast cancer, including biopsy surgery of sentinel lymph node, breast-conserving surgery, breast reconstruction surgery and others<sup>[22]</sup>. Radical mastectomy was a type of surgery that involved the removal of both breast tissue, fatty lymphatic tissue and lymph nodes. Undoubtedly, it cuts off most of the lymphatic pathways in the upper extremities. axillary dissection. Previous study found that complete axillary lymph node dissection increased incidence of lymphedema to 36%<sup>[23]</sup>. We also found radiotherapy significantly increased the risk of lymphedema, which was consistent with conclusion of a large cohort study<sup>[24]</sup>. Nursing staffs should provide personalized and feasible guidance for functional exercises and prevention, monitoring, treatment and nursing of lymphedema for these patients at high risk. In lymphedema, an inflammatory process was developed progressively in affected limbs. A national study conducted during COVID-19 pandemic showed a higher proportion of infection in cancer patients than the overall incidence of cancer in China (1% vs. 0.29%)<sup>[26]</sup>. Nursing managers should pay attention to preventing secondary infection in breast cancer patients.

The COVID-19 pandemic was a public health emergency, it not only affected the routine diagnosis and treatment of patients, but also affected the psychology of patients to a certain extent. A systematic

review showed that concerns about the risk of infection with COVID-19 led to high rates of symptoms of anxiety and depression<sup>[25]</sup>. In our study, 61.4% breast cancer patients suffered from anxiety and 13.9% experienced depression, patients with moderate or severe lymphedema presented higher proportion of both anxiety and depression. The patients worried that delay in treatment would cause symptoms of lymphedema to worsen, meanwhile, presence of lymphedema limited the movements of the affected limbs and affected daily life and self-care ability, such as use of chopsticks, toileting and bathing. These conditions made the patient frustrated and depressed. So, psychological intervention should be carried out timely for breast cancer patients with lymphedema to increase their psychological resistance. Nursing management could conduct remote guidance and apply online courses to increase patients' self-management ability during the restricted condition. Furthermore, timely diagnosis and treatment of lymphedema were still effective and direct measures.

Our study showed that patients preferred treatment in hospital and self-care at home equally. Patients with severe lymphedema or psychological distressed were recommended to go for treatment in professional hospitals. However, immunodeficiency after anti-tumor treatment might make these patients be susceptible to COVID-19 infection. Requirement of frequent nucleic acid and chest CT test make the treatment complex. Self-care at home become the optimal alternative. Patients can develop self-care ability in management of symptoms, treatment and psychosocial adaptation when coping with chronic diseases<sup>[28-30]</sup>. Considering the ongoing pandemic, nursing education for lymphedema must be distributed for discharged patients. Telemedicine was a promising technology<sup>[31]</sup>. After patients mastered basic knowledge of lymphedema and basic nursing methods, healthcare workers could guide remote rehabilitation and online medical treatment through telephone, WeChat, video and other online methods during COVID-19 pandemic<sup>[32]</sup>.

There were several limitations in this study. Firstly, it was a cross-sectional study, no causal inference could be made, but it could be considered that risk factors occurred before the recurred lymphedema which provided clues for the temporal relationship. Secondly, data was collected using an online tool, selection bias might exist since patients who did not use smartphones failed to participate in this study, meanwhile, recall bias and self-reporting problems might influence the precision. Finally, the COVID-19 pandemic was still ongoing, a longitudinal study was required to track breast cancer patients' new problems and search new solutions.

## Conclusion

During the COVID-19 pandemic, high prevalence of lymphedema was observed in breast cancer patients. Age, radical surgery and fully completed radiotherapy were associated with increased risk of severer lymphedema. Meanwhile, the patients with severe lymphedema experienced psychological distress. While the Covid-19 pandemic was still raging, continuous efforts should be made to identify patient at risk of lymphedema and distribute feasible guidance and education for self-management in lymphedema.

# Declarations

## Ethical approval

This study passed the ethical review of Tongji Medical College of Huazhong University of Science and Technology.

## Consent for publication

Not applicable.

## Availability of data and materials

The data being used and analyzed during the current study are available from the corresponding authors upon reasonable request.

## Competing interests

The authors declare that they have no competing interests.

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## Authors' contributions

PX developed the idea, designed the study, and provided financial support for the study. PX and CRW designed the questionnaires and drafted the manuscript. RZL, YY, YYL, XY, WT, WJY, LF, PH, and LF were involved in the acquisition of the data. PX and CRW summarized the data and contributed to data interpretation. CJ and HQ critically revised the manuscript for important intellectual content. The corresponding author had full access to all the data in the study and was responsible for submission for publication.

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