



# Self-administration of complex decongestive therapy facilitated by the mobile application WeChat improves lymphedema and quality of life in breast cancer survivors: an observational study

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**Background:** Lymphedema is the most common complication of breast cancer patients. Complex decongestive therapy (CDT) is often recommended but the efficacy varies due to the complexity of management. This study investigated a novel model of CDT based on a mobile application with the aim of improving the management of lymphedema in China.

**Methods:** We developed a novel model of CDT for breast cancer survivors with lymphedema, including 5 days of CDT therapy with training provided by medical staff in the outpatient clinic and 3 weeks of self-administrated CDT with daily online instructions during phase I, and a life-long maintenance treatment with online instructions once a week for phase II, which delivered by WeChat public accounts. The breast cancer and lymphedema symptom experience index (BCLE-SEI) and the Short-Form Health Survey (SF-36) were used to assess lymphatic symptoms and quality of life. Arm volume and lymphatic symptoms were assessed at baseline, and at 5 days, 1 month, and 3 months post-treatment. The quality of life was assessed at baseline and at 3 months post-treatment.

**Results:** A total of 88 patients with lymphedema were recruited, of whom, 61 followed the protocols and were further analyzed for this study. The mean relative excess arm volume (EAV) was reduced from a baseline value of 30.72% to 22.05%, 18.46%, and 16.67% at 5 days, 1 month, and 3 months post-therapy, respectively ( $P=0.000$ ). The BCLE-SEI scores of lymphatic pain, heaviness, and impaired limb mobility were all significantly improved after 3 months of treatment ( $P<0.05$ ). Moreover, according to the subscale of SF-36, the general health and vitality were significantly improved after 3 months of therapy (56.64 vs. 62.93,  $P=0.008$ ; and 64.26 vs. 70.08,  $P=0.024$ , respectively).

**Conclusions:** The proposed model of CDT based on the mobile application WeChat achieved promising outcomes. The volume of the affected arm, the lymphedema symptoms, and the quality of life were all significantly improved.

**Keywords:** Breast cancer; lymphedema; self-administered; complex decongestive therapy (CDT)

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## Introduction

Breast cancer was the most diagnosed cancer worldwide in 2020, in both genders and all age groups. It is also the most prevalent malignancy among females in China (1). Breast cancer related lymphedema (BCRL) is a common complication in breast cancer patients with an incidence up to 21.4% (2). Women with BCRL often report physical impairments, such as shoulder dysfunction or pain (3). Some patients even relinquish their jobs due to loss of lifting, gripping, holding, and other fine and gross motor skills (4). Breast cancer patients with lymphedema may also experience higher levels psychological distress and reduced quality of life (5,6).

BCRL is a chronic condition for which there is no cure. However, early detection and initiation of treatment are essential for good patient prognosis. As an effective standard therapy for BCRL, Complex decongestive therapy (CDT) is a fourfold conservative treatment which includes manual lymphatic drainage (MLD), compression therapy (consisting of compression bandages, compression sleeves, or other types of compression garments), skin care, and lymph-reducing exercises (LREs), and consists of two phases, an intensive phase which is often short and a maintenance phase that may last for a life-time (7,8). The intensive phase aims to reduce the fluid volume at the extremities by draining with the residual lymphatic system, reduce fibrosis, and prevent complications and recurrences. The maintenance phase is designed to conserve the benefits gained in the intensive phase. The efficacy of CDT in treating lymphedema has been demonstrated by many studies (9,10).

The National Comprehensive Cancer Network (NCCN) Breast Cancer Panel suggested that continuity of lymphedema treatment was important for the long-term care of breast cancer survivors (11). Ochalek *et al.* demonstrated that the effects of phase I treatment could be well maintained if patients persisted in applying compression therapy, attending follow-up sessions systematically, and following the therapy instructions during the 5-year maintenance period (12). Szuba *et al.* showed that a significant decline in the excess arm volume (EAV) could also be achieved by sufficient and timely instructions even if the duration of the intensive therapy was short (13). Since lymphedema is a chronic condition that can cause irreversible morbidity, it is important to encourage patients to master the skills involved in CDT and to actively participate in the therapy. Ligabue and colleagues found

that lymphedema and arm pain were both relieved in patients who self-performed CDT well (14). However, to date, few studies have investigated the effects of the self-administered CDT in patients in China.

The main causes leading to worse compliance of patient were lack of knowledge of lymphedema and professional follow-up during the self-management. Evidence supports that increasing patient awareness can promote adherence for BCRL (15), with the development of e-health, the format of medical consultations has evolved. WeChat is an extremely popular social application in China. Many researchers have reported the effectiveness of WeChat in the management of chronic diseases (16-18). It is easy to operate and can offer multiple functions. Because of advantage for providing patients education and supervision, this application was applied for the management of BCRL.

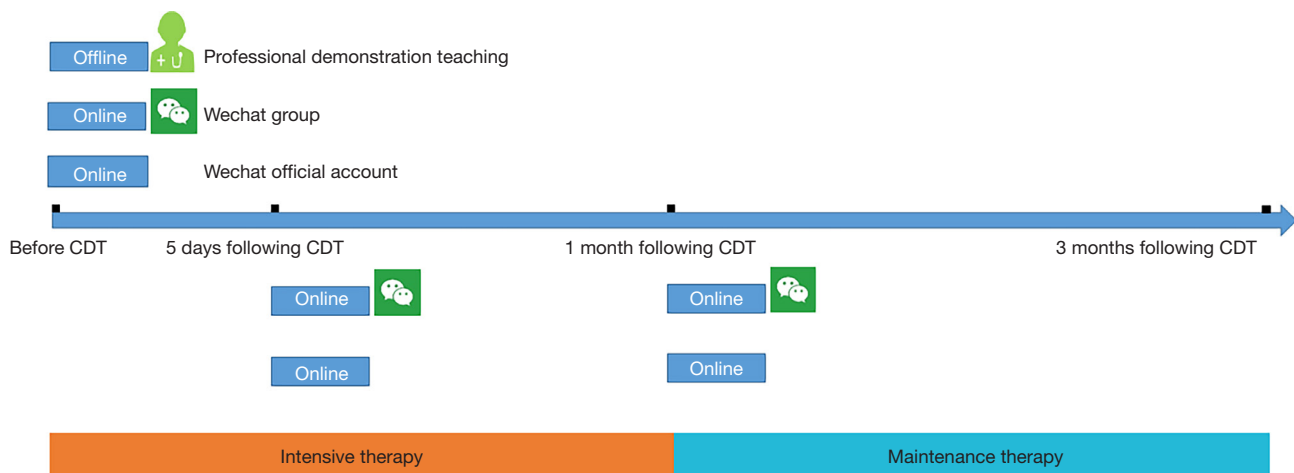
In previous studies, patients need to visit their therapist every-day during 2–4 weeks for intensive phase I to receive MLD and training for later self-management, which results in higher financial cost and labor (15,19,20). In this study, we develop a novel model with a much shorter period of outpatient phase I CDT and training, and a closely online instruction and supervision by WeChat to ensure the efficacy of self-administered CDT for longer period of phase II. The CDT treatment in our model was mainly performed by patients themselves at home, that was very different with traditional CDT, but might be preferable under COVID-19 circumstance. Therefore, this study aims to evaluate efficacy our CDT model, patients' symptoms and quality of life are also assessed to verify whether this model can improve the lymphedema condition in breast cancer patients.

We present the following article in accordance with the STROBE reporting checklist (available at <https://atm.amegroups.com/article/view/10.21037/atm-21-6662/rc>).

## Methods

### *Design and participants*

A longitudinal observational study was conducted at the CDT clinic in the Beijing Cancer Hospital, China. Patients with BCRL who were admitted to our clinic from December 1<sup>st</sup>, 2018 to December 31<sup>st</sup>, 2020 were recruited for this study. All participants had a medical history of breast cancer and presented with lymphedema, which was defined as a 10% or greater increase in the volume of the affected arm compared to the normal arm (9). Lymphedema



**Figure 1** The framework and timeline of the study. CDT, complex decongestive therapy.

staging was classified according to the International Society of Lymphology (ISL) (7).

All participants should have completed all the primary and (neo)adjuvant therapy, except for ongoing endocrine therapy or anti-Her2 therapy (trastuzumab with or without pertuzumab). Patients were excluded from this study if they presented with the following: relapse of breast cancer; other associated malignancies; bilateral lymphedema; deep venous thrombosis in the arm; uncontrolled infections; heart failure or renal failure; or inability to understand the study instructions. All participants were informed about the contents of the study and signed an informed consent form. This study was retrospectively registered in the Chinese Clinical Trial Registry (ChiCTR2100044957) on March 31<sup>st</sup>, 2021. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Approval was granted by the Medical Ethics Committee of Beijing Cancer Hospital (No. 2018KT106).

### Procedure

WeChat is the most widely used—and very friendly mobile application in China. After enrollment, all participants joined a WeChat group by scanning a two-dimensional code. Participants were also asked to review the WeChat official account (gh\_3de62c151351) containing operational videos related to CDT.

The framework and timeline of the proposed CDT model is illustrated in *Figure 1*. The treatment includes the intensive phase lasting for 1 month and the maintenance phase. During the first 5 days, the treatment was

conducted both offline and online. All patients received 5 consecutive sessions of CDT at the lymphedema clinic. Each session consisted of 4 components which included a 30–60-minute session of manual lymph drainage, skin care and moisturization, application of a multilayer short stretch bandage (Thuasne, Mobiderm, USA) or autofit (Thuasne, Mobiderm, USA), and remedial exercises. The bandage or autofit was applied for 23 hours per day, including the weekends. The treatment in the first 3 sessions were performed by a certified nurse. From the fourth session, patients were encouraged to conduct the treatments themselves. All participants were taught to master the CDT during the outpatient treatments. During the next 3 weeks, patients completed the CDT themselves at home. The instructions were delivered by the WeChat group and the official account. After 1 month, a follow-up visit was conducted in the lymphedema clinic.

After 1 month all patients entered the life-long maintenance treatment phase which was performed by patients at home with online instructions. During this period, the bandage was replaced by the garment and/or glove (MEDI) with class II compression (30 to 40 mmHg). All participants were encouraged to self-perform lymph drainage twice a day and wear the garment and/or glove only during the day. The instructions were mainly delivered via an online mode during this phase. After 2 months of maintenance treatment, another follow-up visit was conducted in the clinic.

The arm volume and symptoms were assessed pre-treatment, and again at 5 days, 1 month, and 3 months post-treatment. The quality of life was assessed pre-treatment

and at 3 months following treatment.

## Measures

### Demographics and clinical characteristics

A structured interview questionnaire including age, gender, height, weight, education, comorbidity, tumor location, types of surgery, types of adjuvant treatment (radiotherapy, chemotherapy), the time from surgery to lymphedema onset, and the time from onset to treatment was used to collate the required information. Medical records were carefully reviewed for supplementary data.

### The arm volume

The volume of each arm (denoted as  $V$ ) was calculated according to the arm circumferences measured at 5 points, namely, the space between the thumb and the index finger, the wrist, 10 cm above the wrist, the elbow, and 10 cm above the elbow.

The following volume calculation formula was used:

$$V = h \times (C1^2 + C1 \times C2 + C2^2) / 12\pi \quad [1]$$

where  $h$  is the length of the segment which is the distance between the two adjacent measurement points, and  $C1$  and  $C2$  are the arm circumferences at the top and base of the segment, respectively (21).

Three additional markers of EAVs, namely, the absolute excess of arm volume between the affected arm and the normal arm ( $EAV_{abs}$ ), the relative excess of arm volume between the affected arm and the normal arm ( $EAV_{relative}$ ), and the altered (in percentage) excess of arm volume during the follow-up visits and pre-treatment ( $EAV_{altered}$ ), were computed according to the following Eqs. [2-4]:

$$EAV_{abs} = V_{Affected} - V_{Normal} \quad [2]$$

$$EAV_{relative} = EAV_{abs} / V_{Normal} \times 100 / 100 \quad [3]$$

$$EAV_{altered} = \left( EAV_{baseline\ abs} - EAV_{follow-up\ abs} \right) / EAV_{baseline\ abs} \times 100 / 100 \quad [4]$$

### The breast cancer and lymphedema symptom experience index (BCLE-SEI) score

BCLE-SEI part I is a reliable and valid self-reporting survey used to assess the lymphatic pain, heaviness, and impaired limb mobility (shoulder, arm, elbow, wrist, and fingers) (22).

Each item is rated on a 5-point Likert-type scale from 0 to 4 as follows: 0= absence of symptoms; 1= minor symptoms; 2= somewhat severe symptoms; 3= moderate symptoms; 4= very severe symptoms. The BCLE-SEI has been translated into a Chinese version that has been demonstrated to be reliable and valid (23). Both English and Chinese versions have been authorized for use in this study. The BCLE-SEI score was assessed at baseline, and at 5 days, 1 month, and 3 months following CDT.

### Quality of life

The Short-Form Health Survey (SF-36) was used to evaluate the patient's quality of life. There are 8 multi-item scales in the SF-36, including physical functioning, role physical, bodily pain, general health, social functioning, role emotional, vitality (energy/fatigue), and mental health. Each multi-item scale is directly transformed into a 0–100 points scale with higher scores indicating better quality of life. The SF-36 was recommended to objectively assess the quality of life in BCRL practice guideline (24), and was translated into a Chinese version in 2003 and has been shown to be appropriate for use in the Chinese population (25). The quality of life was measured by the SF-36 survey at baseline and at the 3-month follow-up.

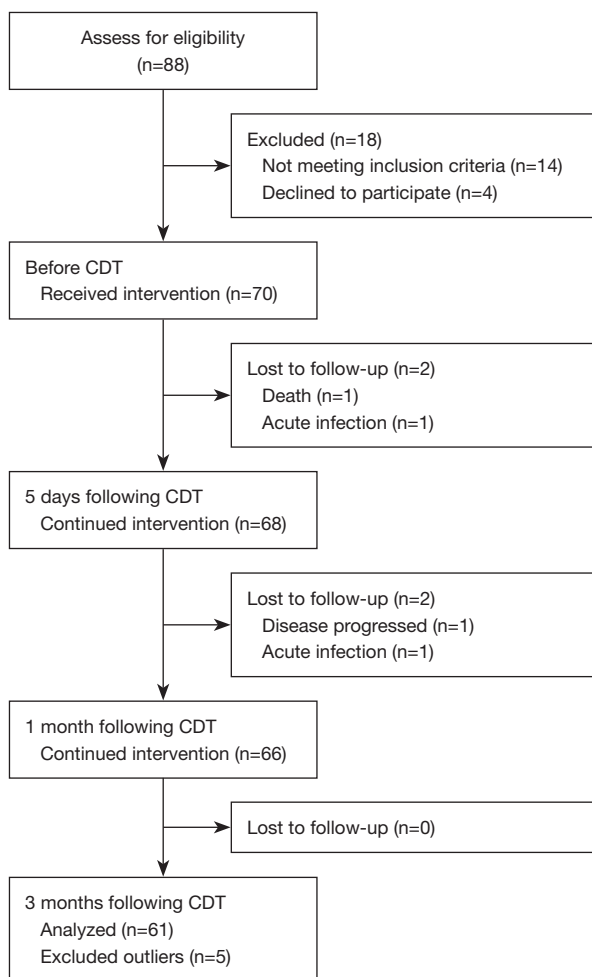
### Statistical analysis

Each continuous variable was presented as mean  $\pm$  standard deviation (SD) if it was distributed normally. Otherwise, it was described as median and interquartile range (Q1–Q3). All categorical variables were expressed as frequencies. The outliers were defined as data extremely large ( $> Q3 + 1.5 \times$  interquartile range) or small ( $< Q1 - 1.5 \times$  interquartile range) compared with others (26). Paired  $t$ -tests were applied to compare the quality of life at pre-treatment and 3 months following treatment. Repeated measure analysis of variance (ANOVA) was used to test whether the EAVs significantly altered with time. The IBM SPSS software (SPSS 19.0, USA) and the MATLAB software (Mathworks Inc., Natick, MA, USA) were used for statistical analyses. A two-sided  $P$  value less than 0.05 was considered statistically significant.

## Results

### Patient and clinical characteristics

From December 1<sup>st</sup>, 2018 to January 31<sup>st</sup>, 2020, 88 patients



**Figure 2** A schematic diagram showing the trial profile. CDT, complex decongestive therapy.

were screened, and 70 patients were enrolled to receive at least one intervention of the study treatment (Figure 2). Two patients were lost to follow-up in phase I of treatment, 1 died due to disease progression and the other patient had an acute infection (dermato cellulitis). Baseline characteristics of the 70 enrolled patients and the final 61 patients who completed the trial are shown in Table 1. The level of education was analyzed due to its impact on the compliance of e-health care. Education was defined as primary school or below, middle school, and college degree or above. Comorbidities included hypertension and diabetes. Out of the 70 patients, 61 (87.1%) completed the trial design and the CDT outcomes were analyzed. Nearly 90% of patients presented with stage II–III lymphedema. The demographics and clinical characteristics of the included patients are

presented in Table 1.

### Assessment of the arm volume

The arm volumes at pre- and post-treatment are summarized in Table 2. The mean  $EAV_{\text{altered}}$  was  $-38.87\%$  (SD,  $54.27\%$ ),  $-44.40\%$  (SD,  $43.23\%$ ), and  $-50.90\%$  (SD,  $44.58\%$ ) after 5 days, 1 month, 3 months following CDT, respectively. There was a significant decrease in the  $EAV_{\text{relative}}$  at different time points (Figure 3).

### Assessment of the pain, heaviness, and impaired limb mobility

The BCLE-SEI score of the lymphatic pain, heaviness, and impaired limb mobility were all significantly reduced after treatment ( $P < 0.05$ ; Table 2). All three symptoms reduced significantly in phase I and the treatment effects were maintained during phase II.

### Quality of life

The quality of life was assessed using the SF-36 survey (Table 3). The general health and vitality of the patients were significantly improved after 3 months of treatment.

### Discussion

In the current study, we proposed a novel self-administered CDT model for patients with BCRL based on the mobile application WeChat. In this model, the time spent on professional intensive therapy was greatly shortened to 5 days, and self-administration for maintenance phase was longer and started early. Self-administration means that patients try themselves to MLD and bandage compression at home, which is most important and longest part in CDT courses. For sure, patients do follow the guidance closely through WeChat. Nevertheless, the results showed that the proposed method can significantly reduce the EAV, relieve symptoms, and improve the patient's quality of life. Moreover, the therapeutic effect achieved in the intensive phase was well maintained in the maintenance phase.

The results revealed a mean decline of  $38.87\%$  in EAV after 5 days of clinic treatment. After 1 and 3 months of therapy, the EAV was further decreased by  $44.40\%$  and  $50.90\%$ , respectively. The  $EAV_{\text{altered}}$  results obtained in this study were very promising. The results in this current study were similar to the report by Vignes *et al.*, in

**Table 1** The baseline demographics and clinical characteristics of the included patients (n=70)

Characteristics	N (%) or mean [range]
Age, years	
Mean	54.3 (10.6)
Range	30–82
Gender	
Male	1 (1.4)
Female	69 (98.6)
BMI, kg/m <sup>2</sup>	
<25	41 (58.6)
25–30	25 (35.7)
≥30	4 (5.7)
Education	
Primary school or below	6 (8.6)
Middle school	28 (40.0)
College degree or above	36 (51.4)
Comorbidity	
Hypertension	10 (14.3)
Diabetes	19 (27.1)
None	41 (58.6)
Tumor location	
Left breast	33 (47.1)
Right breast	33 (47.1)
Bilateral	4 (5.7)
Surgery	
Mastectomy	61 (87.1)
Breast-conserving surgery	9 (12.9)
Radiotherapy	46 (65.7)
Chemotherapy	57 (81.4)
Time from surgery to lymphedema onset, months	28.9 [3–164]
Time from onset to treatment, months	23.9 [0–252]
Lymphedema stage	
Stage I	11 (15.7)
Stage II	43 (61.4)
Stage III	16 (22.9)

**Table 1** (continued)

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Characteristics	N (%) or mean [range]
Pression	
Autofit	29 (41.4)
Bandaging	41 (58.6)
Volume in the affected arm, mL	1,850.8 [1,054.1–3,813.2]
Volume in the normal arm, mL	1,473.0 [1,036.3–1,994.5]

BMI, body mass index.

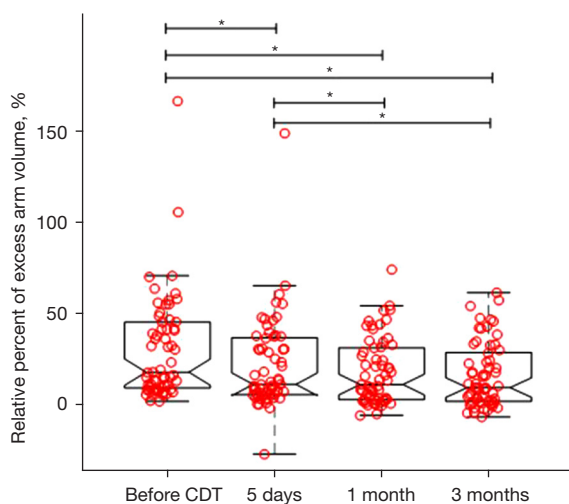
which 33% EAV reduction was obtained after 8 intensive therapy sessions (27). However, there are some studies which reported greater reductions in EAV. Andersen *et al.* demonstrated that patients who received 10 intensive therapy sessions achieved 43% and 60% EAV reduction after 1 and 3 months therapy, respectively (28). Didem *et al.* reported a reduction of 55.7% after 12 intensive therapy sessions over 4 weeks (29). In these latter 2 studies, patients with stage III lymphedema were all excluded and the larger reduction in EAV may result from the lower stages of the lymphedema. In our study cohort, 22.9% of patients presented with stage III lymphedema, while the reduction in edema volume was similar to the results of the study by Andersen *et al.* and Didem *et al.* (28,29). The results illustrated that short-term intensive phase I training and long-term mobile application assistance is effective at alleviating lymphedema.

This investigation also revealed that our CDT model can significantly alleviate pain, heaviness, and impaired limb mobility with BCLE-SEI score assessment. Many studies demonstrated that CDT can significantly relieve pain and heaviness intensity, and others showed CDT effects on mobility and improvements on arm flexion, abduction and external rotation (14,29–31). Relief of lymphedema related symptoms may bring improvement of quality of life, SF-36 survey as very useful generic questionnaire for BCRL, was used to objectively evaluate the quality of life in our study with all 8 items about physical and mental components. We found significant improvement with general health and vitality after 3 months treatment, but not with physical functioning, role of emotional and mental health. Consistent with our findings, Kim *et al.* demonstrated that CDT had a positive impact to the physical functioning, general health, and physical abilities (32). Sezgin Ozcan

**Table 2** Changes in the EAVs and lymphatic symptoms before and after treatment

EAVs	Before CDT, mean (SD)	Post CDT, mean (SD)			F	P
		5 days	1 month	3 months		
EAV <sub>abs</sub> , mL	383.23 (350.28) <sup>b,c,d</sup>	274.74 (299.25) <sup>a,c,d</sup>	226.50 (217.24) <sup>a,b</sup>	207.62 (218.12) <sup>a,b</sup>	25.503	0.000**
EAV <sub>relative</sub> , %	30.72 (28.37) <sup>b,c,d</sup>	22.05 (24.96) <sup>a,c,d</sup>	18.46 (18.05) <sup>a,b</sup>	16.67 (17.65) <sup>a,b</sup>	23.850	0.000**
BCLE-SEI score						
Lymphatic pain	1.66 (1.00) <sup>b,c,d</sup>	1.38 (0.69) <sup>a</sup>	1.39 (0.61) <sup>a</sup>	1.39 (0.67) <sup>a</sup>	3.349	0.031*
Heaviness	2.15 (1.12) <sup>b,c,d</sup>	1.59 (0.82) <sup>a</sup>	1.52 (0.79) <sup>a</sup>	1.62 (0.66) <sup>a</sup>	13.833	0.000**
Impaired limb mobility	1.72 (0.91) <sup>b,c,d</sup>	1.43 (0.62) <sup>a</sup>	1.32 (0.56) <sup>a</sup>	1.43 (0.80) <sup>a</sup>	8.862	0.000**

<sup>a</sup>, significant difference compared with pre-treatment,  $P < 0.05$ ; <sup>b</sup>, significant difference compared with 5 days post-treatment,  $P < 0.05$ ; <sup>c</sup>, significant difference compared with 1 month post-treatment,  $P < 0.05$ ; <sup>d</sup>, significant difference compared with 3 months post-treatment,  $P < 0.05$ ; \*\*, significant difference within different assessment time points,  $P < 0.01$ ; \*, significant difference within different assessment time points,  $P < 0.05$ . EAV, excess arm volume; CDT, complex decongestive therapy; SD, standard deviation; EAV<sub>abs</sub>, the absolute excess of arm volume between the affected arm and the normal arm; EAV<sub>relative</sub>, the relative excess of arm volume between the affected arm and the normal arm; BCLE-SEI, breast cancer and lymphedema symptom experience index.



**Figure 3** The values of EAV<sub>relative</sub> at pre- and post-treatment visits for all the included participants. Each dot represents the EAV<sub>relative</sub> of a participant at each corresponding visit. The box-plots illustrate the distribution of the EAV<sub>relative</sub> values for all participants at each visit. \* represents a significant difference in EAV<sub>relative</sub> values between different visits (repeated measure ANOVA,  $P < 0.05$ ). EAV<sub>relative</sub>, the relative excess of arm volume between the affected arm and the normal arm; ANOVA, analysis of variance; CDT, complex decongestive therapy.

*et al.* showed that CDT improved all 8 items in the SF-36 survey (30). However, *Dayes et al.* found no differences in the physical and mental components between baseline and any follow-up visit for patients receiving CDT (9). CDT

generally ameliorates the quality of life, and the different results may be attributed to the variability of the CDT protocol and the diversity in patient clinical characteristics.

Lymphedema is a chronic and irreversible disease. It is important to build an effective self-management model (33,34). Several studies have demonstrated that web-based multimedia intervention can provide patients with more self-care information compared to conventional educational pamphlets (35). As the most popular and powerful multimedia application with one billion users in China, WeChat is user-friendly for the older population, as well as for users with lower education levels. Therefore, patients can easily obtain training information and follow consultation guidelines. Saving time spent in outpatient clinics and on transport contributes significantly to patient compliance, especially cancer patients who do not want to be exposed to the danger of COVID-19. In China, generally, 4 weeks of CDT is required for each patient, averaging a total cost of \$1,200. In addition, pressure devices such as low elastic bandages and compression garment cost around \$500 each. Since these costs are not covered by medical insurance in China, many patients neglect or reluctantly receive therapy. Therefore, the novel CDT model proposed in this report may be the optimal treatment during the COVID-19 pandemic. The key point in the paper is that our novel CDT model was established to combine the mobile application WeChat with CDT treatment and implement individualized education and follow-up for patients through the mobile application, so

**Table 3** Changes in the quality of life at baseline and at the 3-month follow-up

SF-36 factor	Before CDT, mean (SD)	3 months post-treatment, mean (SD)	Change, mean (SD)	P value
Physical functioning	72.95 (18.65)	70.33 (22.65)	2.62	0.357
Role physical	27.05 (38.54)	32.79 (41.47)	-5.74	0.352
Bodily pain	71.69 (21.22)	72.48 (20.52)	-0.79	0.765
General health	56.64 (21.09)	62.93 (22.60)	-6.30	0.008**
Social functioning	67.83 (24.52)	70.29 (20.18)	-2.46	0.461
Role emotional	62.84 (42.21)	59.56 (42.65)	3.28	0.549
Vitality	64.26 (19.08)	70.08 (18.06)	-5.82	0.024*
Mental health	70.49 (19.12)	68.00 (16.83)	2.49	0.302

P values were derived from paired *t*-tests. \*\*,  $P < 0.01$ ; \*,  $P < 0.05$ . SF-36, Short-Form Health Survey; CDT, complex decongestive therapy; SD, standard deviation.

that patients can shorten their treatment time in hospital and improve self-management quality. In addition to these health benefits, patients may save time, labor and treatment costs.

To the best of our knowledge, this is the first experimental study to introduce self-administered CDT with the assistance of the WeChat application. Our finding showed very promising results. However, there were certain limitations in this study. First, the arm volume was calculated using the formula with arm circumferences. While several studies have reported a high correlation between the calculated volume and the direct volume measurement (36–39), the results should be verified using different measurement methods. Second, as a single arm observational study, the strength of our results are limited because of control arm missing. Furthermore, although establishing WeChat communication between therapist and patients might improve patients' compliance, we do recognize that our CDT model need to be validated in future trials with larger sample size, and compliance questionnaire will be performed to objectively assess the patients' compliance improvement.

In conclusion, this report demonstrated that the novel self-administered CDT model can reduce the arm volume and improve the symptoms and quality of life for patients with BRCL. This novel model can be well conducted under the current COVID-19 circumstances.

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## Footnote

**Reporting Checklist:** The authors have completed the STROBE reporting checklist. Available at <https://atm.amegroups.com/article/view/10.21037/atm-21-6662/rc>

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**Ethical Statement:** The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was performed in accordance with the principles of the Declaration of Helsinki (as revised in 2013). Approval was granted by the Medical Ethics Committee of Beijing Cancer Hospital (No. 2018KT106). Informed consent was obtained from all individual participants included in the study.

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