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Original Article

A multi-modal intervention for managing the fatigue–sleep disturbance–depressed mood symptom cluster in breast cancer patients undergoing chemotherapy: A pilot study

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ABSTRACT

Objective: To examine the feasibility and acceptability of a multi-modal intervention for managing the cancer-related fatigue–sleep disturbance–depressed mood (F-S-D) symptom cluster in patients with breast cancer (BC) and receiving chemotherapy in Hong Kong, and the preliminary effects of such intervention on the occurrence of the F-S-D symptom cluster in these patients.

Methods: This study was a single-blind randomized controlled trial. Patients with BC scheduled for chemotherapy were recruited. Intervention participants received a weekly nurse-led multi-modal intervention lasting 7 weeks. The feasibility parameters and adverse events were assessed using logbook records. Acceptability was evaluated using a program evaluation questionnaire. F-S-D symptoms and quality of life (QOL) were measured at baseline (T0), upon intervention completion (T1), and 3 months after intervention completion (T2). Generalized estimating equation analyses were used.

Results: Fifty participants were enrolled. The eligibility and enrollment rates were 11% and 87.7%, respectively. The rate of adherence to the intervention was 96%. No adverse events were reported. All participants were satisfied with the intervention, which had significant effects in terms of reducing the occurrence of the F-S-D symptom cluster at T2 ($P = 0.035$) and improving QOL at T1 and T2 (T1: $P = 0.035$; T2: $P = 0.012$).

Conclusions: The multi-modal intervention is a feasible, acceptable, and safe intervention that demonstrated preliminary positive effects in managing the F-S-D symptom cluster and improving QOL in patients with BC and receiving chemotherapy in Hong Kong. This study provides key insights into F-S-D symptom cluster management in patients with BC.

Trial registration: ChiCTR2100047819 (Chinese Clinical Trial Register).

Introduction

Breast cancer (BC) is the most commonly diagnosed cancer in women and contributes to approximately 12.5% of cancer incidence worldwide[1] and 28.4% new cancer cases in Hong Kong in 2020.[2] Moreover, there was a dramatic increase in the number of BC cases from 2010 to 2020, with a 64.9% increase in Hong Kong during this period.[2] Due to advances in medical care and early diagnosis, the overall 5-year survival rates for regional and localized BC have increased to 86% and 99%, respectively.[3] Hence, acute and long-term symptoms experienced by patients with BC as they progress along their cancer trajectory are increasingly recognized.[3]

Patients with BC who undergo chemotherapy experience severe and substantial distressful symptoms.[4,5] The three most distressful symptoms are cancer-related fatigue (CRF), sleep disturbances, and depressed mood, which have been reported to occur in 68%–90%, 54%–78%, and 58%–79% of patients with BC undergoing chemotherapy, respectively.[6–9] These symptoms can persist for up to 5 years after the cessation of treatment[10–13] and can co-occur and interact with each other, thereby having synergistic effects on patients' outcomes.[4,6,9,14,15] These three symptoms have also been described as a symptom cluster,[9,14,16] which is denoted as the CRF–sleep disturbance–depressed mood (F-S-D) symptom cluster and has considerable negative impacts on BC patients' quality of life (QOL).[9,17,18] The abilities of various interventions to manage the F-S-D symptom cluster have been examined,[13,19] but these systematic reviews have not focused on patients with BC and undergoing chemotherapy or examining relationships between the F-S-D symptom cluster and cancer-related QOL.

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Furthermore, there are no international guidelines on pharmacological and non-pharmacological interventions for managing the F-S-D symptom cluster. A recent systematic review was conducted to examine the effectiveness of pharmacological and non-pharmacological interventions in managing the F-S-D symptom cluster in patients with BC and receiving chemotherapy and the impact on cancer-related QOL.[20] Results from this review indicated that multi-modal intervention integrating psychological support, education in chemotherapy side effects and management, dietary advice, and exercise may be effective.[20] Therefore, a multi-modal intervention was developed based on the evidence reported in the above-mentioned systematic review and its efficacy was tested in this study.

The aim of this study was to explore the feasibility and acceptability of the multi-modal intervention in patients with BC and undergoing chemotherapy in Hong Kong and to obtain preliminary findings on the effects of the intervention on the occurrence of the F-S-D symptom cluster in these patients and on their QOL.

Methods

Study design

This pilot study involved a parallel two-armed, single-blind randomized controlled trial (RCT) and was conducted from June 2021 to June 2022.

Randomization and blinding

Fifty participants were enrolled and randomized into either the experimental or control group by permuted block randomization with a block size of four or six. An independent research assistant conducted the randomization sequence. The sequentially numbered, opaque, sealed envelope method was used to achieve allocation concealment.[21] Another independent outcome data assessor was blinded to group allocation of the participants during the study.

Study setting and participants

The participants were recruited via convenience sampling from an outpatient oncology clinic in an acute-care public hospital in Hong Kong. The inclusion criteria were (1) histologically proven BC (2) stage I to III BC, (3) age $\geq$ 18 years, (4) scheduled for adjuvant or neoadjuvant chemotherapy, (5) Eastern Cooperative Oncology Group Performance Status of 0–1, (6) ability to communicate in Cantonese and read Chinese, (7) availability to be contacted by telephone. The exclusion criteria were (1) receiving treatment for mental disorders, (2) a diagnosis of cognitive impairment, (3) pregnancy, (4) refusal to participate, (5) receiving another intervention eg, a dietary or exercise programme, or (6) started chemotherapy before commencement of the multi-modal intervention.

Sample size

The total sample size in pilot studies usually ranges from 20 to 40 for two comparative groups.[22] Therefore, a sample size of 40 is considered appropriate and adequate to provide the estimations of effect sizes for planning future studies.[22] Considering the highest attrition rate was 19% in a previous study examining a nurse-led multi-modal intervention which delivered the intervention by both face-to-face and telephonically in patients with BC and receiving chemotherapy,[23] and allowing for a 20% attrition rate, a total of 50 patients with BC (25 per arm) were recruited to participate in this study.

Experimental and control groups

Intervention development and implementation in the experimental group

The Predisposing, Reinforcing, and Enabling Constructs in Educational Diagnosis and Evaluation (PRECEDE)–PROCEED model is a framework providing planning in health education and health promotion. In which, the PRECEDE model provides clear guidelines for the development of intervention to improve outcomes. The PROCEED model was developed later which identifies policy and regulatory factors in the implementation. Therefore, a multi-modal intervention was developed based on the evidence from the systematic review and by adopting the PRECEDE model of health behavior. The PRECEDE model provides a framework to identify the three types of determinant factors of health behaviors that can drive behavioral change.[24] The three types of determinant factors are predisposing factors, enabling factors, and reinforcing factors. Predisposing factors can influence motivation to engage in behavioral change. Enabling factors can facilitate health behaviors and skills or resources required for health. Reinforcing factors can provide continuing incentives to perform health behaviors (Fig. 1).

The experimental group received a weekly nurse-led multi-modal intervention program that lasted 7 weeks and involved psychological support and education on chemotherapy side effects and their management, dietary suggestions, and exercise recommendations. The chemotherapy side effects were the eight commonly experienced side effects: suppressed marrow function, nausea, vomiting, decreased appetite, fatigue, hair loss, darkened skin, and hypersensitivity to chemotherapy. Common side effects of docetaxel, doxorubicin, and epirubicin treatment were also included.[23,25–28] The dietary advice comprised balanced diet and coping with nausea and vomiting, oral mucositis, poor appetite, suppressed marrow function, and fatigue.[29–33] The exercise recommendation was to perform at least 150 min of moderate-intensity exercise or 75 min of high-intensity exercise per week.[30,34–37].

The intervention was delivered by registered nurses who worked in the oncology unit. In the first session, they delivered a 25-min face-to-face session to educate the experimental group on the content of educational booklet before chemotherapy. This educational booklet consisted of four chapters that gave an introduction to F-S-D symptoms and their general management, an introduction to chemotherapy side effects and their management, dietary advice, and exercise recommendations, respectively. The subsequent intervention sessions lasted 20 min each and were delivered by telephone to each participant in the experimental group in weeks 2–3 and weeks 5–6. In these sessions, the nurses assessed the participants' knowledge, monitored their adherence to the intervention, and provided dietary advice, exercise recommendations, and feedback and suggestions on the management of chemotherapy side effects. The participants were also given a food diary and exercise diary to monitor their progress and assess their adherence to a balanced diet and recommended exercise. In weeks 4 and 7, the nurses conducted a routine assessment of the participants' F-S-D symptoms. The participants were reminded not to disclose the intervention they received to other participants.

Treatment fidelity

The intervention nurses were registered nurses who had obtained a master's degree in nursing and had at least 5 years of experience in oncology. In addition, the principal investigator (PI) delivered a 2-h session based on the standardized training manual to all of the nurses. This manual included details on the intervention materials, the log sheets to be used in the intervention sessions, the responsibilities of nurses in the intervention sessions, routine assessment materials (questionnaires used to assess F-S-D symptoms and their scoring methods), communication skills, adverse reactions, and drop-out issues.

In each intervention session, nurses were required to record the duration of the session on a log sheet and to record the compliance of participants with dietary advice and exercise recommendations on checklists. Questions about barriers to follow dietary advice and exercise recommendations were also included in the checklists.

The nurses' competency was assessed by the PI by observing their performance in role play and via a competency checklist. The competency checklist for the nurses who were to deliver the experimental group

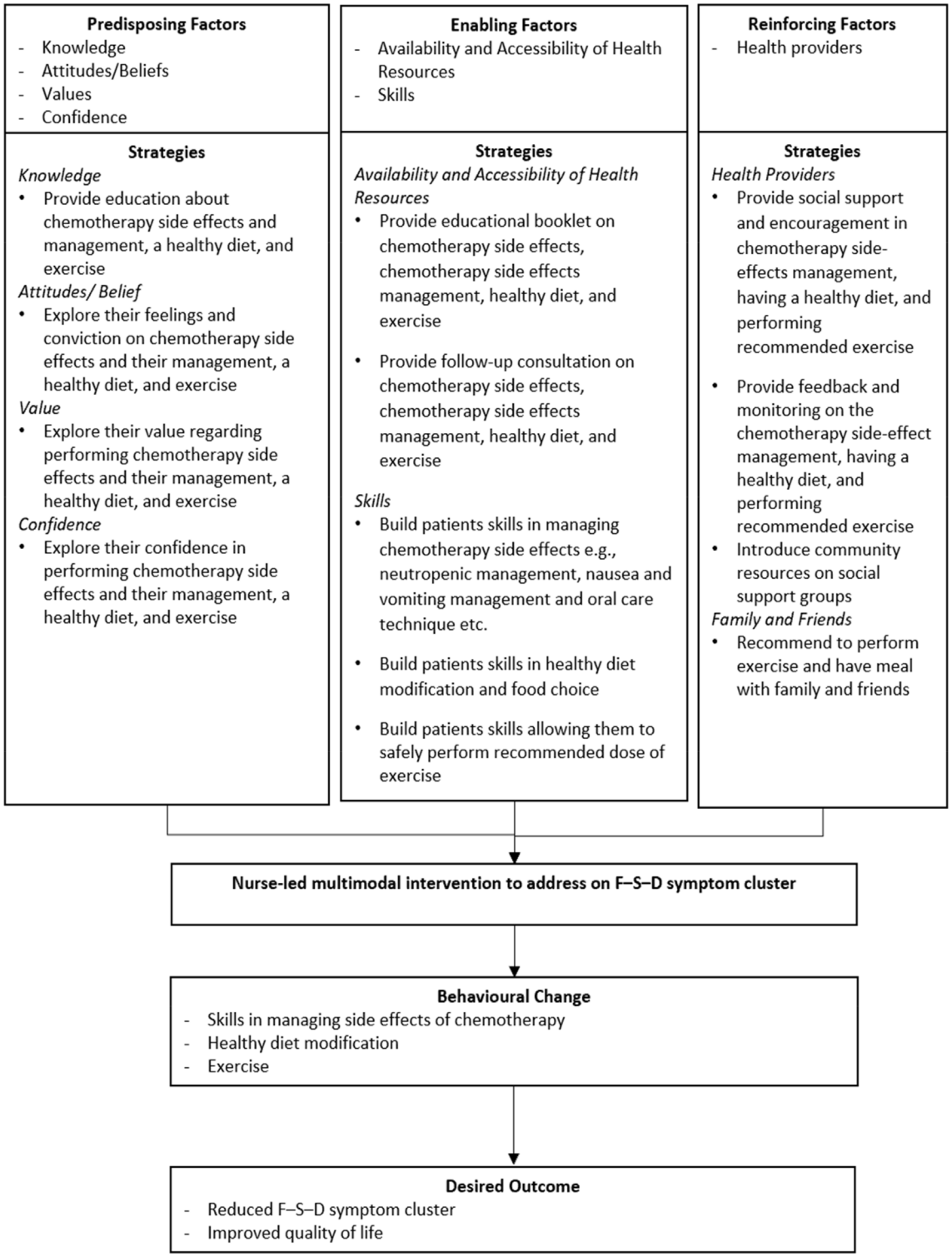

Fig. 1. Theoretical framework of multi-modal intervention. F-S-D, fatigue–sleep disturbance–depressed mood.

intervention and usual care in the control group, respectively, comprised 29 items and 13 items, respectively. In addition, the nurses' knowledge was assessed via a knowledge test comprising 50 true or false questions. The nurses were required to get 100% correct in both tests. Various sessions were audiotaped and reviewed by the PI to check whether the content suggested in the evidence-based protocol was delivered appropriately over time. Moreover, regular meetings were held for all trained nurses every 3 weeks to respond their queries.

Control group

The control group received usual care. In the first session, the control group was provided with 10 min of face-to-face education on chemotherapy side effects and management. They were also given paper materials on chemotherapy side effects education and management. In weeks 4 and 7, each of the participants in the control group was followed up by telephone. Each of these follow-up sessions lasted 15–20 min and assessed the participants' knowledge of chemotherapy side effect

management. This schedule is the usual schedule employed in the current clinical practice in Hong Kong. The participants were reminded not to disclose the intervention they received to other participants.

Outcome measures

Primary outcome: feasibility of the intervention

The feasibility of the intervention was assessed in terms of the eligibility rate, the enrollment rate, the rate of adherence to the intervention, the attrition rate, and the presence of adverse events.

The eligibility rate was calculated by dividing the number of eligible participants by the total number of screened participants. The enrollment rate was calculated by dividing the number of participants who were enrolled in the study by the total number who was eligible to participate in the study. The adherence rate was calculated by dividing the number of sessions attended by the participants by the total number of intervention sessions delivered. The attrition rate was calculated by dividing the number of participants who dropped out of the study before completion by the number of participants who had provided written consent. An adverse event was any kind of adverse event that was related to the intervention.

Primary outcome: acceptability of the intervention

The acceptability of the intervention was assessed using a self-developed program evaluation questionnaire on a 5-point Likert scale. The questionnaire consisted of seven questions on the appropriateness of the content and duration of the intervention sessions; the usefulness of information on F-S-D symptom cluster management, chemotherapy side effects and their management, dietary advice, and exercise recommendations; program satisfaction.

Secondary outcomes

The secondary outcome was the F-S-D symptom cluster. CRF was assessed using the validated nine-item Brief Fatigue Inventory (BFI) – Chinese version.[38] The BFI assesses the severity of CRF and the extent to which it affects the daily living. Each item is rated on an 11-point scale ranging from 0 (no fatigue or no interference) to 10 (the worst fatigue or complete interference). The total fatigue severity score is the mean score for all of the BFI items, and fatigue is categorized into four levels based on the mean score (0: no fatigue; 1–3: mild fatigue; 4–6: moderate fatigue; 7–10: severe fatigue).[38] The BFI is a reliable instrument, as it has a Cronbach's alpha of 0.90–0.92.[39]

Sleep quality was measured using the validated 19-item Pittsburgh Sleep Quality Index (PSQI)—Chinese version. The PSQI evaluates seven sleep-quality components: sleep efficiency, sleep disturbance, sleep duration, sleep latency, use of sleep medication, daytime dysfunction, and subjective sleeping quality. Each item is rated on a scale from 0 (better) to 3 (worse). The sum of the scores for all of the items in each sleep-quality component is determined and assigned a score from 0 (better) to 3 (worse) based on the PSQI scoring manual. The total score on the PSQI is calculated by summing all of the component scores. The total score of the PSQI ranges from 0 to 21. A total score of five or above indicates poor sleeping quality.[40] The PSQI has a satisfactory reliability (Cronbach's alpha = 0.85).[41]

Depressed mood was assessed using the validated 20-item Center for Epidemiologic Studies–Depression (CES-D)—Chinese version.[42] The items in the CES-D are rated on a 4-point Likert scale ranging from 0 (rarely or none of the time) to 3 (all of the time). The total score on the CES-D is the sum of the scores for all of the items. The total score ranges from 0 to 60, and total scores of 16–26 and 27–60 represent mild and major depression, respectively.[42] The CES-D has good reliability (Cronbach's alpha = 0.91).[42]

The F-S-D symptom cluster was defined as the presence of all three symptoms at the same time. The thresholds were a BFI score ≥ 1, a PSQI score ≥ 5, and a CES-D score ≥ 16.

Another secondary outcome was QOL and was assessed using the validated 37-item Functional Assessment of Cancer Therapy–Breast (FACT-B)-Chinese version.[43] The FACT-B consists of five subscales, which assess physical well-being, social/family well-being, emotional well-being, functional well-being, and BC.[44] The items are rated on a 5-point Likert scale ranging from 0 (not at all) to 4 (very much). The subscale score is calculated by multiplying the sum of the item scores by the number of items in the subscale, then dividing by the number of items answered. Then, the total score of the FACT-B is calculated by summing the subscale scores. The total score ranges from 0 to 148, where a low total score indicates a low QOL. The FACT-B has good reliability (Cronbach's alpha = 0.88).[44]

Data collection

The PI and research assistants screened the eligibility of all of the potential participants. All of the eligible participants were informed about the study and were provided an information sheet with details on the study. Informed written consent was obtained from all of the participants before the intervention was delivered. After the participants had provided their consent, their demographic and health information were collected at baseline (T0), before randomization. Primary and secondary outcomes were assessed at T0, at the completion of the intervention (T1), and at 3 months after the completion of the intervention (T2). At T0, all of the participants completed a set of self-administered questionnaires that measured the primary and secondary outcomes. At T1, an independent research assistant measured the primary and secondary outcomes and conducted a program evaluation via telephone call with the participants. At T2, all of the outcomes were assessed by the research assistants via telephone call. The schedule of enrollment, interventions, and assessment was designed according to the Standard Protocol Items: Recommendations for Interventional Trials (Fig. 2).

Data analysis

Appropriate descriptive statistics were used to summarize the participants' demographic and health information, the feasibility and acceptability indicators of the study, and the outcome variables across study timepoints. The normality of continuous variables was assessed using skewness statistics and normal Q–Q plots. The homogeneity of baseline characteristics between the experimental group and control group were assessed using independent *t*-tests for continuous variables and chi-square tests and Fisher's exact tests for categorical variables. The experimental and control groups' F-S-D symptom cluster levels and QOL were examined at T0, T1, and T2. Generalized estimating equation analyses were conducted to compare the differential changes in the F-S-D symptom levels and QOL at T1 and T2 with respect to T0 between the experimental and control groups. A binary logistic link function was used to assess the binary outcomes of the F-S-D symptom cluster, whereas an identity link function was used to assess all of the other continuous outcomes. All of the outcomes were analyzed in accordance with the intention-to-treat principle. All of the statistical tests were two-tailed with the level of significance set to 0.05. All of the statistical analyses were conducted using IBM Statistical Product and Service Solutions Version 27 (IBM Corp, Armonk, New York).

Ethical considerations

Ethical approvals were obtained from the Joint Chinese University of Hong Kong–New Territories East Cluster Clinical Research Ethics Committee (IRB No. 2021.179) and the Kowloon West Cluster Research Ethics Committee (IRB No. KW/FR-21-069[18-12]). All of the

			STUDY PERIOD			
	Enrolment	Allocation	Post-allocation			
TIMEPOINT	-T1	0 (After recruitment)	T0	intervention	T1	T2
ENROLMENT:						
Eligibility screen	X					
Informed consent	X					
Allocation		X				
INTERVENTIONS:						
Multi-modal intervention (experimental group)				X		
Educational intervention (control group)				X		
ASSESSMENTS:						
Baseline variables			X			
Outcome variable: BFI			X		X	X
Outcome variable: PSQI			X		X	X
Outcome variable: CES-D			X		X	X
Outcome variable: FACT-B			X		X	X

Fig. 2. Standard protocol items: Recommendations for interventional trials—schedule of eEnrollment, interventions, and assessments.
BFI, Brief Fatigue Inventory; PSQI, Pittsburgh Sleep Quality Index; CES-D, Center for Epidemiologic Studies Depression Scale; FACT-B, Functional Assessment of Cancer Therapy-Breast Cancer; T0: baseline; T1: at completion of intervention; T2: three months following the intervention.

procedures performed in this study were in accordance with the International Conference on Harmonization Good Clinical Practice Guidelines.[45]

Results

Feasibility of the study

Eligibility rate

Five hundred and nineteen potential participants were screened. Four hundred and sixty-two of them were excluded due to the following reasons: required hormonal therapy only ($n = 211$), had initiated chemotherapy in other sectors ($n = 72$), required radiotherapy only ($n = 52$), had not received treatment after surgery ($n = 27$), refused to receive chemotherapy ($n = 25$), had completed chemotherapy in other sectors before commencement of the multi-modal intervention ($n = 22$), had stage IV cancer ($n = 15$), had a psychiatric problem that was being actively treated ($n = 10$), required re-excision ($n = 9$), did not attend follow-up ($n = 7$), had an Eastern Cooperative Oncology Group performance status of 2 or above ($n = 7$), or were foreigners ($n = 5$). Thus, the eligibility rate was 11% (Fig. 3).

Enrollment rate

Fifty-seven eligible participants were informed about the study, and 50 participants consented to participate. Seven eligible participants declined to do so owing to a lack of interest ($n = 4$) or a lack of time ($n = 3$). Thus, the enrollment rate was 87.7% (Fig. 3).

Adherence rate

The rate of adherence to the multi-modal intervention was 96%. Most of the participants reported experiencing gastrointestinal problems, such as a loss of appetite, nausea, a distended stomach, abdominal pain, and diarrhea, which were the barriers to maintaining a balanced diet, whereas tiredness, dizziness, and arthralgia were the main barriers to performing the recommended exercise.

Attrition rate

Forty-seven participants completed the study. Two participants in the control group were lost to follow-up, and one participant in the experimental group exited the study because of disease progression. Thus, the overall attrition rate was 6% (Fig. 3).

Presence of adverse events

No adverse events or unexpected symptoms were reported.

Acceptability

Twenty-four participants completed the program evaluation questionnaire. All of these participants agreed that the content of the multi-modal intervention was appropriate and that the information on chemotherapy side effects was useful. More than 85% agreed that the duration of the multi-modal intervention was appropriate; more than 95% agreed that the information on F-S-D symptoms, the dietary advice, and the exercise recommendations were useful. All of these participants were satisfied with the program (Table 1).

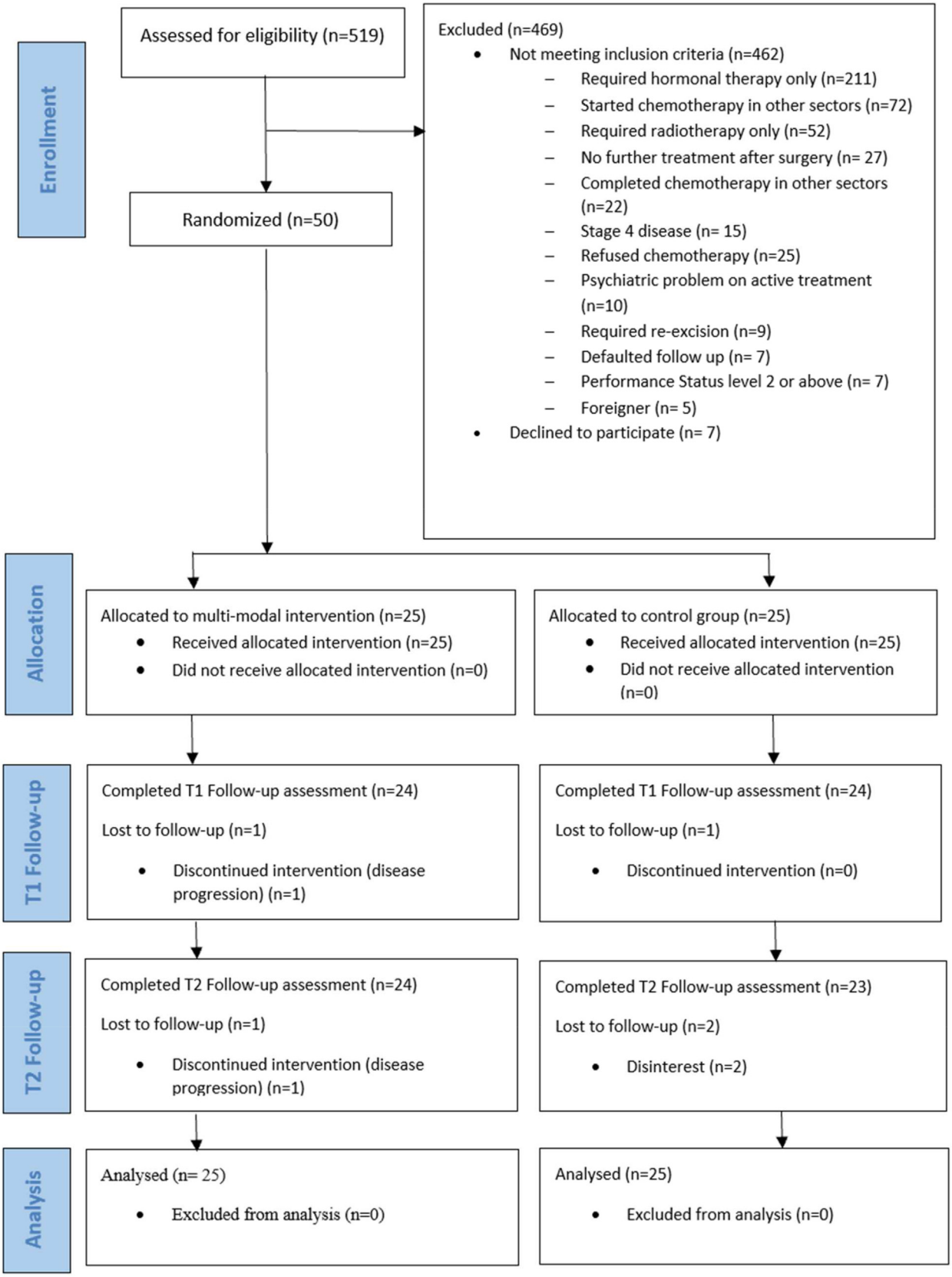

Fig. 3. Consolidated standards of reporting trials 2010 flow diagram.

Table 1
Programme evaluation results on the acceptability of the intervention.

Item	Strongly agree	Agree	No comment	Disagree	Strongly disagree
1. The contents of the multi-modal intervention are appropriate.	20.8	79.2			
2. The duration of the multi-modal intervention is appropriate.	8.3	79.2	12.5		
3. The information on cancer-related fatigue–sleeping disturbance–depressed mood is useful for me.	4.2	91.6	4.2		
4. The information on the side effects of chemotherapy is useful for me.	75	25			
5. The dietary advice is useful for me.	20.8	75	4.2		
6. The exercise recommendation is useful for me.	20.8	75	4.2		
7. Overall, I am satisfied with the multi-modal intervention.	29.2	70.8			

Baseline characteristics of the participants

The mean age of the participants was 54.14 years (standard deviation [*SD*] = 10.89) and ranged from 28 to 81 years. Ninety-eight percent were women, 64% were married, and 96% lived with others. Approximately 82% had a secondary school education or above, 60% had full-time or part-time jobs or were on sick leave, and 84% had stage II or III cancer. Approximately 76% had received adjuvant chemotherapy and 42% had received targeted therapy. Approximately 24% had experienced the F-S-D symptom cluster. The mean BFI, PSQI, and CES-D scores were 2.33 (*SD* = 1.90), 6.48 (*SD* = 3.72), and 14.38 (*SD* = 8.84), respectively. The mean FACT-B score was 98.72 (*SD* = 16.91). The mean scores on the physical well-being, social/family well-being, emotional well-being, functional well-being, and BC subscales of the FACT-B were 22.30 (*SD* = 4.54), 18.02 (*SD* = 5.96), 17.20 (*SD* = 3.51), 16.46 (*SD* = 5.64), and 24.72 (*SD* = 4.88), respectively. The baseline sociodemographic characteristics and outcome variables of the participants are presented in Table 2. There were no statistically significant differences in sociodemographic data and outcomes between the experimental group and control group at baseline.

Correlation between CRF, sleep quality, depressed mood, and QOL at baseline

At baseline, there were moderately positive correlations between CRF and sleep quality ($r = 0.40$, $P = 0.004$); CRF and depressed mood ($r = 0.47$, $P = 0.001$); and sleep quality and depressed mood ($r = 0.44$, $P = 0.001$).[46] In addition, at baseline, there were moderately negative correlations between CRF and QOL ($r = -0.49$, $P < 0.001$) and between sleep quality and QOL ($r = -0.50$, $P < 0.001$), whereas there was a strong negative correlation between depressed mood and QOL ($r = -0.71$, $P < 0.001$).[46]

Preliminary results of the multi-modal intervention

Effect of the multi-modal intervention on the occurrence of the F-S-D symptom cluster

The proportion of participants who experienced the F-S-D symptom cluster increased from T0 to T1. Compared with the experimental group, the control group showed a greater increase in the occurrence of the F-S-D symptom cluster at T1. From T1 to T2, the occurrence rates of the F-S-D symptom cluster in the experimental and control groups decreased. The occurrence rate of the F-S-D symptom cluster in the experimental group was lower than that in the control group. Compared with the control group, the experimental group showed a greater reduction in the log odds of the occurrence of the F-S-D symptom cluster at T1 relative to T0 (T1: −0.552, 95% confidence interval [CI] [−2.086, 0.981]); $P = 0.480$]) and at T2 relative to T0 (T2: −2.287, 95% CI [−4.417, −0.157]; $P = 0.035$). However, the between-group difference in change in log odds at T1 was not statistically significant (Table 3).

Effect of the multi-modal intervention on QOL and the subscales of the FACT-B

Compared with the control group, the experimental group showed significantly greater improvements in QOL at T1 (T1: β = 9.843, 95% CI [0.712, 18.975], $P = 0.035$) and T2 (T2: β = 12.375, 95% CI [2.675, 22.075], $P = 0.012$) with respect to T0 (Table 3).

Among the subscales of the FACT-B, the experimental group showed significant improvements in the physical and functional well-being and BC subscales. Specifically, in the physical well-being subscale, compared with the control group, the experimental group showed no significant improvements at T1 relative to T0 (T1: β = 1.222, 95% CI [−1.229, 3.673], $P = 0.329$). However, compared with the control group, the experimental group showed a significantly greater improvement in physical well-being at T2 relative to T0 (T2: β = 2.587, 95% CI [0.095, 5.079], $P = 0.042$). In the functional well-being subscale, compared with the control group, the experimental group showed significantly greater improvements at T1 (T1: β = 3.323, 95% CI [0.069, 6.577], $P = 0.045$) and T2 (T2: β = 4.876, 95% CI [1.614, 8.139], $P = 0.003$) relative to T0. In the BC subscale, compared with the control group, the experimental group showed a significantly greater improvement at T1 relative to T0 (T1: β = 3.104, 95% CI [0.138, 6.070], $P = 0.040$). However, no significant difference was found at T2 with respect to T0 in the experimental group (T2: β = 1.843, 95% CI [−1.733, 5.420], $P = 0.312$) (Table 3). In addition, there were no significant between-group differences in the social/family well-being and emotion well-being subscales of the FACT-B.

Estimation of effect sizes of the multi-modal intervention on the F-S-D symptom cluster

At T1, the odds ratio of the F-S-D symptom cluster was 0.58, 95% CI [0.17–1.91], whereas at T2, it was 0.10, 95% CI [0.01–0.89] (Table 4).

Discussion

Feasibility and acceptability of the multi-modal intervention

The eligibility rate was 11%. The three main reasons contributing to ineligibility were required hormonal therapy only (45.7%), had started chemotherapy in other sectors (15.6%), and required radiotherapy only (11.3%). Hong Kong guidelines recommend that patients with very early-stage BC and oestrogen-receptor-positive BC do not receive chemotherapy after surgery.[47] This subset of patients comprises ~56.3% of newly diagnosed BC cases in Hong Kong.[48] Furthermore, a new test—the Oncotype DX test—is increasingly used as it provides information on the risk of recurrence of BC and how likely it is that patients would benefit from chemotherapy.[49] Therefore, some patients with stage II BC may no longer be recommended to receive chemotherapy. Furthermore, at the time when this study was conducted, Hong Kong experienced the fifth wave of the coronavirus disease 2019 (COVID-19) pandemic, which overburdened the public hospital service much more than previous waves. Thus, some of the participants might have begun their chemotherapy in other sectors, due to concern about becoming infected with severe acute respiratory syndrome coronavirus 2, and thus experienced longer waiting times in public hospitals than during other times. Moreover, 12.5% of the BC cases in Hong Kong during the study period were stage 0.[50] Such patients are recommended to undergo radiotherapy if they do not undergo a mastectomy.[47]

Table 2
Baseline sociodemographic characteristic and outcome variables of the participants.

Variables	All ($n = 50$)	Control group ($n = 25$)	Experimental group ($n = 25$)	P value
Age (years)[a]	54.14 ± 10.89	56.60 ± 10.90	51.70 ± 10.50	0.117
Gender				0.999[c]
Female	49 (98.0)	24 (96.0)	25 (100.0)	
Male	1 (2.0)	1 (4.0)	0 (0.0)	
Marital status				0.239[b]
Single/divorce/widow	18 (36.0)	7 (28.0)	11 (44.0)	
Married/cohabitation	32 (64.0)	18 (72.0)	14 (56.0)	
Living alone				0.999[c]
No	48 (96.0)	24 (96.0)	24 (96.0)	
Yes	2 (4.0)	1 (4.0)	1 (4.0)	
Education				0.747[c]
Primary school or below	9 (18.0)	6 (24.0)	3 (12.0)	
Secondary school	30 (60.0)	14 (56.0)	16 (64.0)	
Post-secondary education	6 (12.0)	3 (12.0)	3 (12.0)	
University	5 (10.0)	2 (8.0)	3 (12.0)	
Had a part-time/full time job				0.083[b]
No	20 (40.0)	13 (52.0)	7 (28.0)	
Yes	30 (60.0)	12 (48.0)	18 (72.0)	
Cancer stage				0.693[c]
I	8 (16.0)	3 (12.0)	5 (20.0)	
II	26 (52.0)	13 (52.0)	13 (52.0)	
III	16 (32.0)	9 (36.0)	7 (28.0)	
Treatment type				0.185[b]
Neo-adjuvant	12 (24.0)	8 (32.0)	4 (16.0)	
Adjuvant	38 (76.0)	17 (68.0)	21 (84.0)	
Targeted therapy				0.390[b]
Yes	21 (42.0)	9 (36.0)	12 (48.0)	
No	29 (58.0)	16 (64.0)	13 (52.0)	
Chemotherapy regime				0.206[c]
AC × 4 then TT × 4	3 (6.0)	2 (8.0)	1 (4.0)	
TT + CTX × 4	15 (30.0)	9 (36.0)	6 (24.0)	
PACS01	17 (34.0)	10 (40.0)	7 (28.0)	
TCH × 6	15 (30.0)	4 (16.0)	11 (44.0)	
F-S-D symptom cluster[b]				0.990
Yes (three symptoms)	12 (24.0)	6 (24.0)	6 (24.0)	
No (zero to two symptoms)	38 (76.0)	19 (76.0)	19 (76.0)	
BFI[a]	2.33 ± 1.90	2.04 ± 1.58	2.62 ± 2.17	0.283
PSQI[a]	6.48 ± 3.72	6.44 ± 3.88	6.52 ± 3.63	0.940
CES-D[a]	14.38 ± 8.84	14.52 ± 10.05	14.24 ± 7.65	0.912
FACT-B − Total[a]	98.72 ± 16.91	100.02 ± 18.02	97.42 ± 15.99	0.591
FACT-B − Physical well-being subscale[a]	22.30 ± 4.54	22.01 ± 5.33	22.60 ± 3.67	0.650
FACT-B − Social/Family well-being subscale[a]	18.02 ± 5.96	18.94 ± 5.20	17.10 ± 6.60	0.278
FACT-B − Emotion well-being subscale[a]	17.20 ± 3.51	16.96 ± 3.60	17.44 ± 3.47	0.633
FACT-B − Functional well-being subscale[a]	16.46 ± 5.64	17.44 ± 5.29	15.48 ± 5.92	0.223
FACT-B − Breast cancer subscale[a]	24.72 ± 4.88	24.68 ± 5.07	24.76 ± 4.78	0.957

Continuous variables were analyzed using independent *t*-test.
AC, Doxorubicin Cyclophosphamide; CTX, Cyclophosphamide; PACS01, Fluorouracil; Epirubicin, Cyclophosphamide and Docetaxel; TCH, Docetaxel; Carboplatin, Trastuzumab; TT, Docetaxel.
[a] Presented as mean ± SD, all others are presented as *n* (%).
[b] Categorical variables were analyzed using Chi-square test.
[c] Fisher's exact test.

This may account for the abovementioned three reasons that contributed to ineligibility. In addition, the study hospital was a designated infectious disease center during the COVID-19 pandemic. Thus, BC patients might have received their chemotherapy at other public hospitals, causing the eligibility to be lower than had been expected.

The enrollment rate was 87.7%, which is higher than those in previous studies (56%–75%).[30,51] The rate of adherence to the intervention was 96% which is within the range in other previous studies (93%–100%).[52,53] Moreover, the attrition rate was 6%, which is lower than those in other studies (7.8%–19%).[30,54]

The satisfactory adherence rate and the low attrition rate may be attributable to the use of a theoretical framework and evidence from a systematic review in the development of the multi-modal intervention. Specifically, the PRECEDE model provides a framework to identify the predisposing, enabling, and reinforcing factors that contribute to health behavioral change. Therefore, compared with participants who receive an intervention not based on the PRECEDE model, those who receive an intervention based on the PRECEDE model are more likely to engage in health behavioral change, which increases the rate of adherence to the latter type of intervention.[55] Furthermore, in the program evaluation, more than 95% of the participants agreed that the information provided on the F-S-D symptom cluster, chemotherapy side effects, dietary advice, and exercise recommendation was useful. Nutritional advice is one of the common types of information needed by Chinese patients with BC.[56,57] Furthermore, we clearly explained the potential advantages of compliance with the multi-modal intervention, in terms of managing one's symptoms, cancer journey, and long-term health. This might have enhanced the participants' compliance with the intervention, as they might have perceived that the multi-modal intervention would be useful and important for them to follow.

Furthermore, the low attrition rate may be attributable to the participants being reminded about the next follow-up time or assessment time and being encouraged to mark these times in their schedules. We also suggested to the participants that they save the contact telephone numbers of nurses and research assistants, so that if they missed a telephone call, they could proactively contact the designated nurse or

Table 3
General estimating equation model comparing the cancer-related fatigue–sleeping disturbance–depressed mood (F-S-D) symptom cluster and quality of life between the experimental and control groups across the study.

	n (%)						Group × time effect[d]	
	T0	T1	T2	Group[b] β [95% CI]	T1[c] β [95% CI]	T2[c] β [95% CI]	Group × T1 β [95% CI]	Group × T2 β [95% CI]
F–S–D symptom cluster occurrence (three symptoms)				0.00 [−1.298, 1.298]	0.797 [0.091, 1.685]	0.284 [−0.653, 1.221]	−0.552 [−2.086, 0.981]	−2.287 [−4.417, −0.157]
Experimental group ($n = 25$)	6 (24.0)	7 (28.0)	1 (4.0)					
Control group ($n = 25$)	6 (24.0)	10 (40.0)	7 (28.0)					
P[e]				0.990	0.079	0.552	0.480	0.035
	***Mean* (*SD*)**						**Group × Time Effect[h]**	
	T0	**T1**	**T2**	**Group[f] β [95% CI]**	**T1[g] β [95% CI]**	**T2[g] β [95% CI]**	Group × T1 β [95% CI]	Group × T2 β [95% CI]
FACT-B-Total				−2.604 [11.856, 6.648]	2.610 [−3.718, 8.938]	6.505 [−0.559, 13.569]	9.843 [0.712, 18.975]	12.375 [2.675, 22.075]
Experimental group ($n = 25$)	97.42 (15.99)	108.66 (15.28)	115.45 (13.57)					
Control group ($n = 25$)	100.02 (18.02)	103.33 (20.77)	107.43 (19.01)					
P[e]				0.581	0.419	0.071	0.035	0.012
FACT-B – Physical well-being				0.592 [−1.894, 3.078[	−2.250 [−4.291, −0.210]	−1.914 [−4.161, 0.334]	1.222 [−1.229, 3.673]	2.587 [0.095, 5.079]
Experimental group ($n = 25$)	22.60 (3.67)	21.42 (4.46)	23.17 (2.78)					
Control group ($n = 25$)	22.01 (5.33)	19.96 (5.44)	20.26 (4.63)					
P[e]				0.641	0.031	0.095	0.329	0.042
FACT-B – Social/Family well-being				−1.844 [−5.073, 1.385]	0.266 [−1.623, 2.155]	1.312 [−0.880, 3.503]	2.735 [−0.455, 5.926]	2.330 [−1.354, 6.015]
Experimental group ($n = 25$)	17.10 (6.60)	19.83 (5.70)	20.58 (6.05)					
Control group ($n = 25$)	18.94 (5.20)	19.36 (5.37)	20.51 (5.16)					
P[e]				0.263	0.783	0.241	0.093	0.215
FACT-B – Emotional well-being				0.480 [−1.439, 2.399]	2.774 [1.334, 4.214]	3.385 [1.681, 5.090]	−0.791 [−2.777, 1.195]	0.363 [−1.778, 2.503]
Experimental group ($n = 25$)	17.44 (3.47)	19.29 (3.33)	21.13 (3.03)					
Control group ($n = 25$)	16.96 (3.60)	19.83 (3.40)	20.35 (3.05)					
P[e]				0.624	0.001	0.001	0.435	0.740
FACT-B – Functional well-being				−1.960 [−5.009, 1.089]	0.723 [−1.319, 2.765]	0.629 [−1.485, 2.742]	3.323 [0.069, 6.577]	4.876 [1.614, 8.139]
Experimental group ($n = 25$)	15.48 (5.92)	19.21 (4.81)	20.79 (4.23)					
Control group ($n = 25$)	17.44 (5.29)	18.25 (5.81)	18.26 (5.10)					
P[e]				0.208	0.488	0.560	0.045	0.003
FACT-B – Breast cancer subscale				0.076 [−2.600.2.752]	1.190 [−1.023, 3.403]	3.261 [0.458, 6.064]	3.104 [0.138, 6.070]	1.843 [−1.733, 5.420]
Experimental group ($n = 25$)	24.76 (4.78)	28.92 (4.6)	29.79 (4.09)					
Control group ($n = 25$)	24.68 (5.07)	25.93 (5.24)	28.04 (5.46)					
P[e]				0.956	0.292	0.023	0.040	0.312

[a]The control group and the baseline measurement were the reference categories in the generalized estimating equations model.
[b] Group effect corresponded to the mean baseline difference between the experimental and control groups in the log odds of occurrence of the symptom cluster.
[c] Time effect at T1 and T2 corresponded to the mean change in the log odds of the occurrence of symptom cluster at T1 and T2, respectively, with respect to T0 in the control group.
[d] Group × time effect at T1 and T2 corresponded to the mean difference of changes in the log odds of the occurrence of the symptom cluster at T1 and T2, respectively, with respect to T0 between the two groups (change in experimental group – change in control group).
[e] The *P* value for the group-by-time interaction terms at T1 and T2.
[f] Group effect corresponded to mean difference at baseline between the experimental and control groups.
[g] Time effect at T1 and T2 corresponded to the mean change in scores for the experimental group at T1 and T2, respectively, compared with T0.
[h] Group × time effect at T1 and T2 corresponded to the mean difference of change score at T1 and T2, respectively, with respect to T0 between the two groups (change in experimental group – change in control group).

Table 4
Odds ratio of the cancer-related fatigue–sleeping disturbance–depressed mood (F-S-D) symptom cluster.

	Presence of the symptom cluster of F-S-D		Odds ratio (95% Cl)
	Control group ($n = 25$), n (%)	Experimental group ($n = 25$), n (%)	
T0	6 (24.0)	6 (24.0)	1.00 (0.27–3.66)
T1	10 (40.0)	7 (28.0)	0.58 (0.17–1.91)
T2	7 (28.0)	1 (4.0)	0.10 (0.01–0.89)

research assistant. Moreover, a rapport was built in the weekly consultations that might have reduced the intention to drop out from the experimental group.[58] In addition, after completion of all of the assessments, the control group was given the whole set of materials that had been supplied to the experimental group. This might have incentivized the control group to complete all of the assessments.[59]

Effect of the multi-modal intervention on the F-S-D symptom cluster and QOL

The multi-modal intervention resulted in the lower rates of occurrence of the F-S-D symptom cluster. However, this result is significant at T2 but not at T1. Specifically, at T1, the occurrence rate of the F-S-D symptom cluster in the experimental group ($n = 7$) was lower than that in the control group ($n = 10$). This may be attributable to the small sample size. The experimental group's mean scores in the BFI, PSQI, and CES-D showed decreasing trends. Therefore, the insignificant result at T1 may have been because the multi-modal intervention required a certain amount of time to simultaneously affect all of the symptoms in the F-S-D symptom cluster. Furthermore, such results may be related to the delivery time for follow-up assessment not having followed the chemotherapy cycle. Moreover, the mean BFI, PSQI, and CES-D scores in the control group were lower than expected. Studies have shown that 48%–90% of patients with BC and undergoing chemotherapy experience moderate-to-severe levels of CRF,[12,60] and that such patients experience more intense and severe fatigue in the first week of every chemotherapy cycle than in later weeks.[52] Thus, given the moderate correlation between the individual symptoms of the F-S-D symptom cluster, sleeping quality and depressed mood may be worse in the first week of chemotherapy cycles than in later weeks. Thus, the assessments might not have reflected the true severity of symptoms during chemotherapy, ie, the participants' symptoms might have subsided by the time of follow-up assessment and the effect of the intervention might not have been fully detected. The odds ratio of the F-S-D symptom cluster was 0.1, which indicates that the experimental group had only 10% of the odds of developing the F-S-D symptom cluster as the control group.

Strengths

This study was the first to examine the ability of a theory-based, multi-modal intervention to manage the F-S-D symptom cluster in patients with BC and improve their QOL. Thus, it fills a key research gap and provides useful preliminary results on the efficacy of the multi-modal intervention. Other study strengths include the RCT design and allocational concealment. Moreover, the multi-modal intervention was the first to address BC patients' care needs in Hong Kong. Overall, the preliminary results of this study provide evidence to support a future large-scale study. This study could also provide guidance for the implementation of the multi-modal intervention in Hong Kong and worldwide.

Limitations

Several limitations should be acknowledged regarding the interpretation of the results. First, the findings of the study were obtained from participants who were recruited via convenience sampling from a single study hospital. Thus, although the study hospital is the major hospital in its region, selection bias could have been introduced. Second, this study was a pilot study that aimed to assess the feasibility, acceptability, and preliminary effects of the multi-modal intervention on the whole F-S-D symptom cluster. In future, a full-scale study with a larger sample size should be conducted to more comprehensively investigate these effects. Third, due to the nature of the study, we could only blind the outcome assessors; blinding the participants was not feasible because dietary and exercise interventions are not delivered in usual practice. Thus, the participants might have been aware of the group allocation. Finally, the delivery time of follow-up assessments did not follow chemotherapy cycles. Therefore, the highest intensity of symptoms might not have been observed, and the true effects of the multi-modal intervention might have been underestimated. Therefore, it is suggested that the future follow-up assessment timepoints can be determined by considering the timing of chemotherapy cycles.

Implications for future study and practice

In future, a study with a larger sample size study should be conducted to better determine the ability of the multi-modal intervention to alleviate the F-S-D symptom cluster in patients with BC undergoing chemotherapy. Based on the findings of such a study, nurses could develop evidence-based interventions for managing the F-S-D symptom cluster in such patients and improving their QOL. Furthermore, the multi-modal intervention was primarily delivered by telephone and had acceptable feasibility. Therefore, this study provides insights into using telemedicine for symptom cluster management in future clinical practice. Moreover, symptom cluster management can be further developed into patients with BC undergoing maintenance hormonal therapy. Therefore, patients with BC can have comprehensive and extended care in symptom clusters management along their cancer trajectory.

Conclusions

The multi-modal intervention is a feasible, acceptable, and safe intervention. Preliminary positive effects in terms of managing the F-S-D symptoms cluster in patients with BC and improving their QOL were demonstrated. A full-scale RCT should be conducted in the future to comprehensively characteristics the efficacy of the multi-model intervention in such patients.

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Declaration of competing interest

All authors have none to declare. The corresponding author, Prof. Winnie So, is Editor-in-Chief of *Asia-Pacific Journal of Oncology Nursing*. The article was subject to the journal's standard procedures, with peer review handled independently of Prof. So and their research groups.

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Ethics statement

The study was approved by The Joint Chinese University of Hong Kong–New Territories East Cluster Clinical Research Ethics Committee (IRB No. 2021.179) and the Kowloon West Cluster Research Ethics Committee (IRB No. KW/FR-21-069[18-12]). All of the participants provided written informed consent.

Data availability statement

The data that support the findings of this study are available from the corresponding author, So, W.K.W., upon reasonable request.

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