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Original Article

Changes in cytokine levels in breast cancer patients with CRCI before or after CALM intervention

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Abstract: To investigate the changes in cytokine (interleukin 1 beta (IL-1β), tumor necrosis factor alpha (TNF-α) and interleukin 4 (IL-4)) levels and cognitive function before and after managing cancer and living meaningfully (CALM) intervention, in early-stage breast cancer patients with chemotherapy-related cognitive impairment (CRCI). One hundred and twenty-eight breast cancer patients with CRCI enrolled in this study, there are fifty patients underwent with 6 CALM interventions and seventy-eight patient care as usual (CAU). Cytokine (IL-1β, TNF-α and IL-4) levels in the patients were assessed, and the patients were evaluated with the Mini-Mental State Examination (MMSE), Prospective Memory (PM) and Retrospective Memory (RM), and Quality-of-life (QOL) and Psychological Distress Thermometer (DT) assessments before CALM intervention (BCM), after CALM intervention (ACM) and care of usual (CAU). Measures at these two time points and two groups were compared. There were significant differences in the performance on the RM, PM, MMSE, QOL and DT measures after, compared to before (t=8.126, t=8.007, t=-10.789, t=9.236, t=17.649, respectively; P<0.05), the CALM intervention, compared to CAU (t=-7.408, t=-7.300, t=8.128, t=-8.851, t=-10.572, respectively; P<0.05). In addition, cytokine levels, including IL-1β, TNF-α and IL-4, were significantly different before and after the CALM intervention (t=5.073, t=4.228, t=5.815, respectively; P<0.05) and the two groups (ACM vs CAU) were distinctly different (t=-3.353, t=-2.694, t=-3.268, respectively; P<0.05). furthermore, the cytokine levels (IL-1β, TNF-α and IL-4) have linear correlation with cognitive function before and after CALM intervention (r=-0.343/r=0.538, r=-0.375/r=-0.330, r=-0.310/r=-0.541, respectively; P<0.05). The present results indicated that CALM intervention could alleviate CRCI and that this process is accompanied by changes in IL-1β, TNF-α and IL-4 levels. These results further confirm that cytokines may be involved in CRCI and that CALM may become an efficient method to relieve CRCI-related symptoms in breast cancer patients.

Keywords: Breast cancer, chemotherapy, cognitive impairment, cytokines, managing cancer and living meaningfully

Introduction

Female breast cancer has become the most commonly diagnosed cancer (11.7%) and the fifth leading cause of cancer-related death (6.9%) in worldwide [1]. Pertinently, the number of new breast cancer cases had increased from 0.3 million in 2015 to 0.42 million in 2020; therefore, breast cancer was estimated to be the fourth most common form of cancer in China [2]. In terms of breast cancer mortality in China, the number of cancer-related deaths increased from 70000 in 2015 to 117000 in 2020. During these years, China added 112000 breast cancer cases and 47000 cancer-related deaths in the population, accounting for 18.41% of global breast cancer cases and 17.11% of related deaths [2]. From 2012 to 2016, the incidence rate of breast cancer increased each year by approximately 0.3%. In contrast, the associated mortality rate decreased yearly. The total mortality rate decreased by approximately 40% from 1989 to 2017; this decrease corresponded to a reduction of 375900 deaths among breast cancer patients [3]. Pertinently, chemotherapy is one of the most important treatments for breast cancer. With the continuous updates to chemotherapy drugs and protocols, the 5-year survival rate of early breast cancer patients has

approached 90% [4], which has made people pay increasing attention to the side effects of these treatments. In addition to the common clinical side effects, such as nausea and vomiting, bone marrow suppression, and hair loss, the impact of chemotherapy on cognitive function is receiving increasing attention internationally.

Chemotherapy-related cognitive impairment (CRCI) refers to impairment in cognitive functions, such as memory, attention, information processing speed, executive function and visual space function, during or after chemotherapy in patients with malignant tumors [5]. It is estimated that approximately 35% to 70% of breast cancer patients develop CRCI after chemotherapy [4], which keeps survivors from being able to return to their precancer life even after treatment. Hence, this change has a considerable impact on their daily work and life and greatly reduces their quality of life (QOL). These are short-term symptoms in most patients but they can last months to years in approximately 35% of patients [6]. Although the symptoms of CRCI may be severe and persistent, there are usually no significant neuropathologic changes that occur in tandem. Standard neuroimaging does not show significant changes in patients, while more advanced imaging techniques reveal subtle changes in hippocampal volume and white matter structure [7]. Doxorubicin, a commonly used chemotherapy drug for breast cancer, can impair learning and memory in rodents; moreover, the scores on cognitive scales and the visuospatial skills of patients treated with doxorubicin are poor [8]. In breast cancer patients who underwent cyclophosphamide, methotrexate, and fluorouracil chemotherapy, cognitive testing revealed that patients' rapid-onset and delayed speech memory, processing speed, executive function, and speed of mental movement were significantly lower than those in controls. This phenomenon persisted even 20 years after the end of treatment [9]. In addition to chemotherapy, cancer itself can cause cognitive impairment. Unlike cognitive impairment caused by cancer, a defining feature of CRCI is the presence of associated symptoms after chemotherapy and a causal relationship between the symptoms and chemotherapy [10].

Research on CRCI has been extensive in recent years, but the exact mechanisms of CRCI remain unclear. However, several potential mechanisms of CRCI have been reported in the literature. (1) Changes in dendritic structures caused by chemotherapy have been related to impaired spatial memory [11]. (2) Free radical oxidative stress is not only a marker of aging and neurodegeneration but also a possible mechanism of CRCI. Reactive oxygen species generated by oxidative stress mainly regulate the viability and differentiation of neurons and glial cells, thus initiating and maintaining brain damage [12]. In animal models, rats treated with cisplatin can develop dendritic structures, exhibit mitochondrial activity, and sustain DNA damage that increase oxidative stress in the hippocampus [3]. (3) As a physical and metabolic barrier, the blood-brain barrier (BBB) can restrict transportation between peripheral blood and the central nervous system, effectively maintain the stability of the brain tissue physiological environment, and protect brain tissue from harmful substances circulating in the blood. Most chemotherapeutic drugs cannot pass through the BBB due to their large molecular weight, preventing them from directly damage the central nervous system. However, certain chemotherapeutics, such as paclitaxel and 5-fluorouracil, can directly or indirectly damage the integrity of the BBB, thereby making it easier for peripheral toxic substances and inflammatory mediators to enter the brain tissue, eventually leading to the death of local neurons related to cognition [13]. (4) In addition, polymorphic expression of apolipoprotein E (APOE) and catechol-O-methyltransferase (COMT) increases the risk of cognitive impairment in cancer patients [14]. In patients with breast cancer and lymphoma undergoing chemotherapy, carriers of the APOE E4 allele are more likely to have impaired visual memory, spatial ability, and psychomotor function [14, 15]. Breast cancer survivors with COMT Val alleles are more vulnerable to disruptions in attention, speech fluency, and speed of movement [15]. (5) Inflammation is thought to play an important role in long-term cognitive impairment; also, a strong correlation between markers of inflammation and cognitive performance has been observed in breast cancer survivors even 20 years after they completed chemotherapy [16]. In addition to regulating inflammation, cytokines can affect the

central nervous system by regulating neurons and glial cells, neuron regeneration and neurodegeneration, and cholinergic and dopaminergic pathways [17]. Furthermore, it has been speculated that cytokines may be related to cognition. Cytokines cause local inflammatory responses in the hippocampus and cytokine receptor-rich brain tissue through oxidation and nitrosation [18]. These reactions lead to decreased memory, attention, processing speed, and reaction speed. It has been reported in the literature that cytokines can actively penetrate the BBB in the area around the ventricle. Cytokines can bind to endothelial receptors in the cerebrovascular system and stimulate the release of a variety of inflammatory mediators, such as cell adhesion molecules, chemokines, nitric oxide, and prostaglandins. These mediators further destroy the integrity of the BBB and exert a significant effect on the brain, causing structural damage [18]. This article mainly explored the correlations between CRCI and cytokine levels.

Although a large number of studies in recent years have found that CRCI is widespread and has certain clinical characteristics, and though research on its mechanism has also made certain progress, it is still unclear how to provide appropriate treatment for patients with CRCI. Cancer managing and living meaningfully (CALM) is a structured short-term, spiritually purifying, supportive-expressive psychosocial intervention that can provide substantial psychological benefits, particularly a reduction in depression and decreased death or dying anxiety [19, 20]. CALM was invented by Gray Rodin and was designed to prevent psychological disorders and increase well-being. In previous studies, CALM was found to decrease anxiety and depression and increase meaning in life [21]. The CALM model is a combination of behavioral psychology and cognitive psychology and has a positive effect on the treatment of psychological disorders and improvement of chemotherapy-related cognitive impairment (CRCI) [22].

To date, CALM has been widely used for anxiety and depression symptoms, but there are few reports about the efficacy of CALM interventions on patients with CRCI. The mechanisms of cytokine changes involved in CALM intervention remain unclear. Therefore, we investigated 128 breast cancer patients with CRCI following chemotherapy, there were 50 patients undergoing a 6-week CALM intervention. All participants were administered a series of neuropsychological tests, and the levels of interleukin 1 beta (IL-1β), tumor necrosis factor alpha (TNF-α) and IL-4 were assessed.

Materials and methods

Participants

A total of 128 breast cancer patients with CRCI-related symptoms after chemotherapy were enrolled in this study in XXXX from August 2019 to June 2021. The study was approved by the Research Ethics Committee of XXXX, and all the subjects provided informed consent.

The inclusion criteria were as follows: (1) pathologically confirmed nonmetastatic breast cancer (stages I-III); (2) sufficient baseline bone marrow and organ function reserve-specifically, an absolute neutrophil count ≥ 1500/mm^3, a platelet count ≥ 100000/mm^3 and a hemoglobin concentration ≥ 8 g/dl; serum muscle enzyme levels ≤ 1.5 times the normal upper limit; aspartate aminotransferase and alanine aminotransferase levels ≤ 2.5 times the normal upper limit; bilirubin levels ≤ 1.5 times the normal upper limit; and left ventricular ejection fraction (LVEF) ≥ 50%; (3) indication of CRCI after neuropsychological questionnaire; and (4) education of elementary school level and above and capability to independently complete the relevant neuropsychological tests. The exclusion criteria were as follows: (1) combination of other serious diseases that would not allow full participation in this study; (2) previous mental illness or inability to accurately express inner thoughts; (3) severe anxiety, depression and other abnormal emotions; and (4) complement or acceptance other psychotherapy or psychiatric consulting previously.

Neuropsychological tests

The Mini-Mental State Examination (MMSE) primarily measures general cognition, including memory, orientation in time and place, working memory, visuospatial skills, object naming, writing, reading, and complex motor operations, with an overall score ranging from 1 to 30, with higher scores indicating better cognition. A score of 26 or less on the MMSE is considered to indicate cognitive impairment, while

Table 1. The demographic characteristics and clinical information of the patients

Variables	CALM (n=50)				CAU (n=78)				χ^2/t	P
	No.	%	Mean	SD	No.	%	Mean	SD		
Age	50		52.04	8.55	78		50.60	6.72	1.06	0.29
20-39 years old	6	12			3	3.8				
40-59 years old	36	72			65	83.3				
≥ 60 years old	8	16			10	12.8				
Education	50				78				0.11	0.99
Primary school	22	44			35	44.8				
Secondary school	26	52			39	50				
Technical school	1	2			2	2.6				
University	1	2			2	2.6				
KPS	50		86.20	5.68	78		87.9	4.06	-1.89	0.06
70-80	17	34			16	20.5				
81-90	33	66			62	79.5				
Surgery	50				78				2.25	0.33
Mastectomy	41	82			68	87.2				
Lumpectomy	2	4			5	6.4				
No surgery	7	14			5	6.4				
Tumor size	50				78				4.12	0.13
≤ 2 cm	8	16			25	32.1				
2-5 cm	33	66			41	52.6				
>5 cm	9	18			12	15.4				
Type of cancer	50				78				5.77	0.06
Infiltrative	26	52			37	47.4				
Invasive ductal	18	36			39	50				
Other	6	12			2	2.6				
HER-2	50				78				0.04	0.84
HER-2 (+)	39	78			62	79.5				
HER-2 (-)	11	22			16	20.5				

Note: KPS, Karnofsky performance status.

scores of 27 to 30 are considered to be in the normal range.

The Prospective and Retrospective Memory Questionnaire (PRMQ) evaluates memory failures in daily life with a 4-point scale, on which points 1-4 represent never, occasionally, often, and always, respectively. The PRMQ consists of 16 self-reported items that separately evaluate prospective memory (PM) and retrospective memory (RM). The higher the scores are, the more severe the memory impairments are.

The QOL scale is a reliable and effective scale to measure patients' health-related QOL. It mainly evaluates their physical condition, social/family condition, emotional condition and functional condition and includes 27 items to be answered and 9 additional concerns. The physical and emotional areas are scored on a scale of 1 to 5, representing never, a little, some, comparable, and very, respectively; the social/family and functional areas are scored on an opposite scale. All the scores are added up for a final total score. Higher scores indicate poorer QOL.

The psychological distress thermometer (DT) scale is similar to a normal thermometer, with an overall score of 1-10. Scores of 1 to 10 represent the range from no DT to extreme DT. The subjects rated themselves based on their assessment of their DT over the previous week. The higher the score was, the more severe the DT was.

Cytokine measurements

A 2-ml blood sample was drawn from each patient and placed in ethylenediaminetetraace-

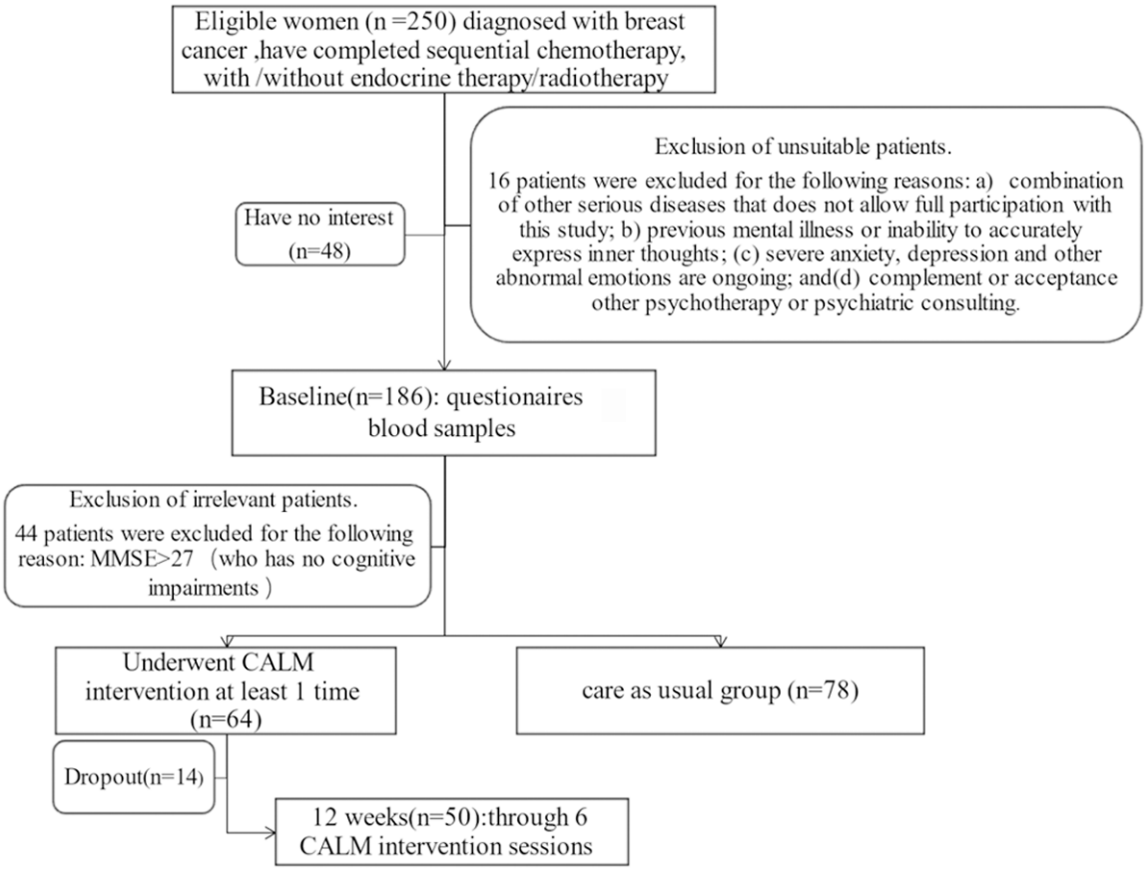

Figure 1. Flowchart of the study design, including the overall changes in participants.

Table 2. Comparison of PRMQ, MMSE, QOL and PD questionnaire scores before and after CALM intervention

Items	BCM (n=50)	ACM (n=50)	t	P
RM	18.00±2.61	15.30±2.51	8.126	0.000
PM	19.12±3.40	15.88±3.24	8.007	0.000
MMSE	21.92±2.90	26.30±3.27	-10.789	0.000
QOL	88.86±7.38	78.54±10.07	9.236	0.000
DT	4.74±1.26	2.56±1.15	17.649	0.000

tic acid (EDTA) tubes. All samples were centrifuged for 10 minutes at speeds of 2500 RPM and 4000 RPM. Finally, the plasma part of the blood sample was separated by centrifugation. At least 600 μl of each sample was reserved for use and stored aseptically at -80°C until analysis.

Study procedure

The experimental design was evaluated by experts in the research field to ensure that the experiment was feasible, practical and scientific. In this study, a total of 50 breast cancer patients were enrolled for 12 weeks, with a session once every two weeks for a total of 6 CALM interventions. The whole process was carried out in a quiet and comfortable environment, with soothing music as the background, and lasted approximately 30 to 60 minutes each time. These sessions involved communication with patients, popularizing knowledge related to breast cancer, changing patients' incorrect perceptions of breast cancer, relieving anxiety, making patients confident in their treatment regimen, helping patients achieve physical and mental relaxation, and encouraging patients to communicate with friends and relatives and integrate into society. In addition, the PM, RM, MMSE, QOL and DT scales were completed during the process. At baseline and after the last CALM intervention, IL-1β, TNF-α and IL-4 levels were detected.

78 breast cancer patients in CAU group received the normal health care, without receiving CALM intervention or other psychotherapy

Table 3. Comparison of PRMQ, MMSE, QOL and PD questionnaire scores before and after CALM intervention with CAU group

Items	CALM (n=50)		CAU (n=78)	t	*P*-value[1]	t	*P*-value[2]
	BCM	ACM					
RM	18.00±2.61	15.30±2.51	18.26±1.98	-0.630	0.530	-7.408	0.000
PM	19.12±3.40	15.88±3.24	19.79±2.77	-0.176	0.243	-7.300	0.000
MMSE	21.92±2.90	26.30±3.27	21.49±3.27	0.784	0.435	8.128	0.000
QOL	88.86±7.38	78.54±10.07	90.78±5.55	-1.578	0.118	-8.851	0.000
DT	4.74±1.26	2.56±1.15	4.79±1.20	-0.245	0.807	-10.572	0.000

Data are presented as the mean ± SD. Abbreviations: SD, standard deviation; MMSE, Mini-Mental State Examination; RM, retrospective memory; PM, prospective memory; QOL, quality of life; DT, psychological distress thermometer; BCM, before CALM; ACM, after CALM. [1]Change (*P*-value) between groups (comparison of BCM vs CAU). [2]Change (*P*-value) between groups (comparison of ACM vs CAU).

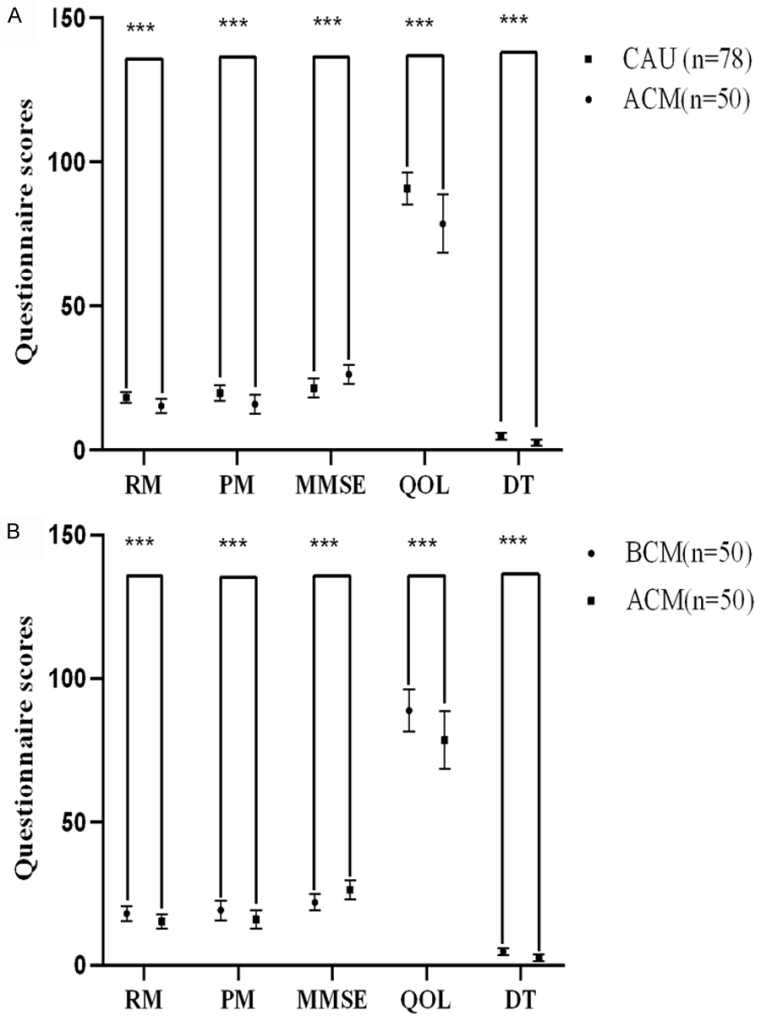

Figure 2. Study data histogram comparison questionnaire scores. A. Comparison questionnaire scores between CAU group and after CALM intervention. B. Comparison questionnaire scores before and after CALM intervention. Note: ***, P<0.001.

or psychiatric consulting. The questionnaires including PM, RM, MMSE, QOL and DT scales and the cytokine levels (IL-1β, TNF-α and IL-4) were tested at baseline.

Statistical analysis

All statistical analyses in this study were performed using the Statistical Package for Social Sciences (SPSS) version 23. The baseline data were analyzed in independent sample t test or Chi-square test. Paired sample t tests were used to compare the cytokine levels and scale scores before and after the CALM intervention. Independent sample t test were used to compare cytokine levels and scale scores between CAU group and CALM (after the CALM intervention) group. All tests were two-tailed with the significance level set to 0.05.

Results

Baseline demographics and clinical data

The baseline data of the 50 breast cancer patients accepted CALM and 78 breast cancer patients in CAU included in this study were age (52.04±8.55 years/50.60±6.72 years), and Karnofsky performance status (KPS) (86.20±5.68 scores/87.9±4.06 scores) that were proved to

Table 4. Comparison of IL-1β, TNF-α and IL-4 levels before and after CALM intervention

Items	BCM (n=50)	ACM (n=50)	t	P
IL-1β	63.48±27.96	45.93±15.46	5.073	0.000
TNF-α	65.51±27.42	50.12±16.80	4.228	0.000
IL-4	42.73±19.99	29.38±11.50	5.815	0.000

have no statistical difference (t=1.06, t=0.11, respectively; P>0.05). The data are expressed as the mean ± standard deviation. The two groups had the same education background. Surgical procedure, tumor size, pathological type of cancer, the expression of human epidermal growth factor receptor (Her-2) in CALM group and CAU group had no statistical difference (P>0.05). All subjects had undergone chemotherapy based on taxanes and anthracyclines, as shown in **Table 1** and **Figure 1**.

Neuropsychological assessments before and after CALM intervention and in CAU

Before and after CALM intervention, the scale scores, including RM (18.00±2.61/15.30±2.51, respectively), PM (19.12±3.40/15.88±3.24, respectively), MMSE (21.92±2.90/26.30±3.27, respectively), QOL (88.86±7.38/78.54±10.07, respectively) and DT (4.74±1.26/2.56±1.15, respectively) were significantly different (t=8.126, t=8.007, t=-10.789, t=9.236, t=17.649, respectively; P<0.05). The scores of RM (18.26±1.98), PM (19.79±2.77), MMSE (21.49±3.27), QOL (90.78±5.55), and DT (4.79±1.20) in CAU group had no statistical difference compared to before CALM intervention (t=-0.630, t=-0.176, t=0.784, t=-1.578, t=-0.245, respectively; P>0.05), but being significantly different from the scores after CALM intervention (t=-7.408, t=-7.300, t=8.128, t=-8.851, t=-10.572, respectively; P<0.05), as showed in **Tables 2**, **3** and **Figure 2**.

Cytokine levels before and after CALM intervention and in CAU

Before and after CALM intervention, levels of the cytokines IL-1β (63.48±27.96/45.93±15.46, respectively), TNF-α (65.51±27.42/50.12±16.80, respectively) and IL-4 (42.73±19.99/29.38±11.50, respectively) were significantly different (t=5.073, t=4.228, t=5.815, respectively; P<0.05). The levels of the cytokines IL-1β (63.63±35.19), TNF-α (64.45±35.08) and IL-4 (41.68±24.94) in CAU group had no difference with the levels before CALM intervention (t=-0.270, t=0.191, t=0.261, respectively; P>0.05), were significantly different compared to ACM (after CALM intervention) (t=-3.353, t=-2.694, t=-3.268, respectively; P<0.05), as shown in **Tables 4**, **5** and **Figure 3**.

The correlation between levels of cytokines and cognitive function

Before and after CALM intervention, and CAU group, levels of cytokines IL-1β, TNF-α and IL-4 were significantly correlated with MMSE (r=-0.343/r=-0.538/r=-0.741, r=-0.375/r=-0.330/r=-0.737, r=0.310/r=-0.541/r=-0.813, respectively; P<0.05), as shown in **Figures 4**-**6**.

Discussion

The present results showed that there were significant differences in neuropsychological test scores, including the PM, RM, MMSE, QOL and DT, in breast cancer patients after the CALM intervention, compared to before CALM intervention and CAU; also, this process was accompanied by changes in IL-1β, TNF-α and IL-4 levels. These data not only suggested the effectiveness of CALM intervention in patients with CRCI but also further confirmed the correlation between cytokines and CRCI. Additionally, CALM was indicated to be an effective intervention for increasing patients' QOL and for reducing DT.

Cytokines, important inflammatory factors in the body, not only play a role in diseases characterized by cognitive impairment, such as Alzheimer's disease and dementia [23] but also have been considered one of the possible mechanisms for CRCI [10]. It has been reported that the levels of various cytokines, such as IL-2, IL-4, IL-6 and TNF-α, increased in patients by approximately 1.5 times after chemotherapy [24]. In patients with traumatic brain injury, high levels of IL-1β were associated with a twofold increased risk of cognitive decline compared with patients with normal levels of IL-1β [25]. Higher levels of IL-1β were also observed in patients with CRCI [18]. In a mouse model, treatment with adriamycin led to excess TNF-α detected in peripheral blood and brain tissues, mainly in the hippocampus and cortex, which negatively affected cognitive

Table 5. Comparison of IL-1β, TNF-α and IL-4 levels before and after CALM intervention with CAU group

Items	CALM (n=50)		CAU (n=78)	t	*P*-value[1]	t	*P*-value[2]
	BCM	ACM					
IL-1β	63.48±27.96	45.93±15.46	63.63±35.19	-0.270	0.979	-3.353	0.001
TNF-α	65.51±27.42	50.12±16.80	64.45±35.08	0.191	0.849	-2.694	0.008
IL-4	42.73±19.99	29.38±11.50	41.68±24.94	0.261	0.794	-3.268	0.001

Data are presented as the mean ± SD. [1]Change (*P*-value) between groups (comparison of BCM vs CAU). [2]Change (*P*-value) between groups (comparison of ACM vs CAU).

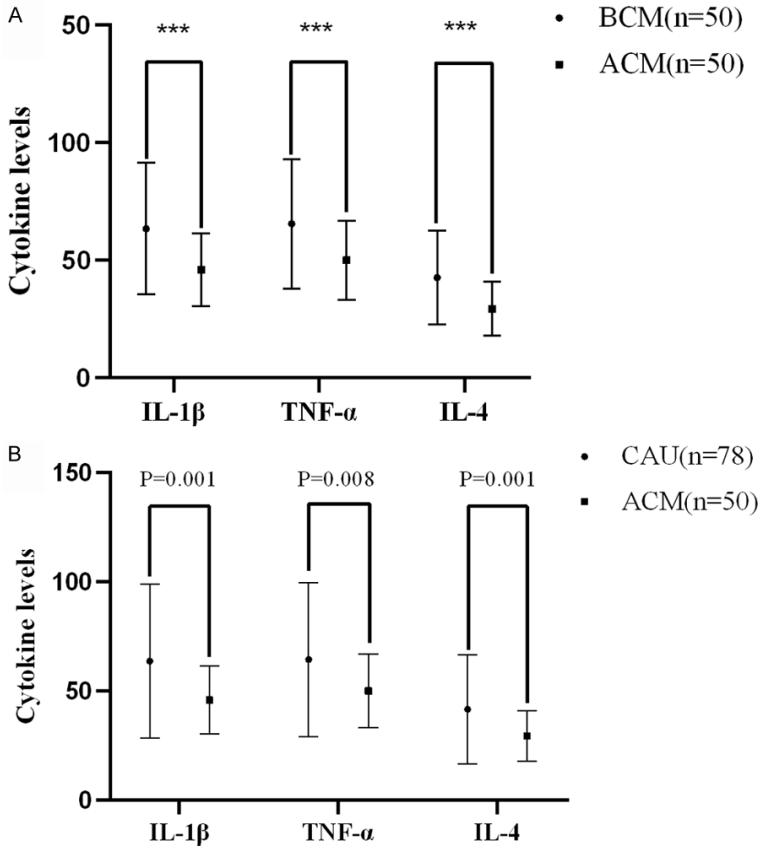

Figure 3. Study data histogram comparison plasma IL-1β, TNF-α and IL-4 levels. A. Comparison plasma IL-1β, TNF-α and IL-4 levels before and after CALM intervention. B. Comparison plasma IL-1β, TNF-α and IL-4 levels CAU group and after CALM intervention. Note: ***P<0.001.

function through the generation of reactive oxygen species and nitrogen, oxidative stress and mitochondrial damage [26]. Also, TNF-α and IL-1β work in concert to regulate and induce neuronal inflammation [27]. However, findings from previous studies on IL-4 remain controversial. Most studies have shown that IL-4 plays a protective role in cognitive function [18, 28], though a few studies have failed to observe a correlation between IL-4 and cognitive function [29, 30]. However, the results of this study suggested that cognitive function was alleviated after CALM intervention and accompanied by reduced IL-4 levels. This phenomenon indirectly indicates the negative effect of IL-4 on cognitive function, which is also contrary to most literature reports. Therefore, the role of IL-4 in CRCI remains to be further explored.

Research on CRCI in the current literature is relatively common. Although much of this research has focused on its clinical manifestations and biological mechanisms, how to effectively intervene is a realistic problem that needs to be urgently solved. Early psychological intervention may play a key role in the QOL of patients after treatment. Due to the side effects associated with drug treatment, psychological interventions seem to be more acceptable to patients. CALM interventions show great advantages among cancer patients by improving their systemic symptoms, depression and QOL. CALM intervention was proven to have the potential to not only relieve distress but also increase psychological growth and well-being [31]. CALM intervention can also help breast cancer patients avoid experiencing psychological symptoms and make final preparations for the possible event of their death [32].

The effectiveness of psychological interventions may be significantly individualized, so it is

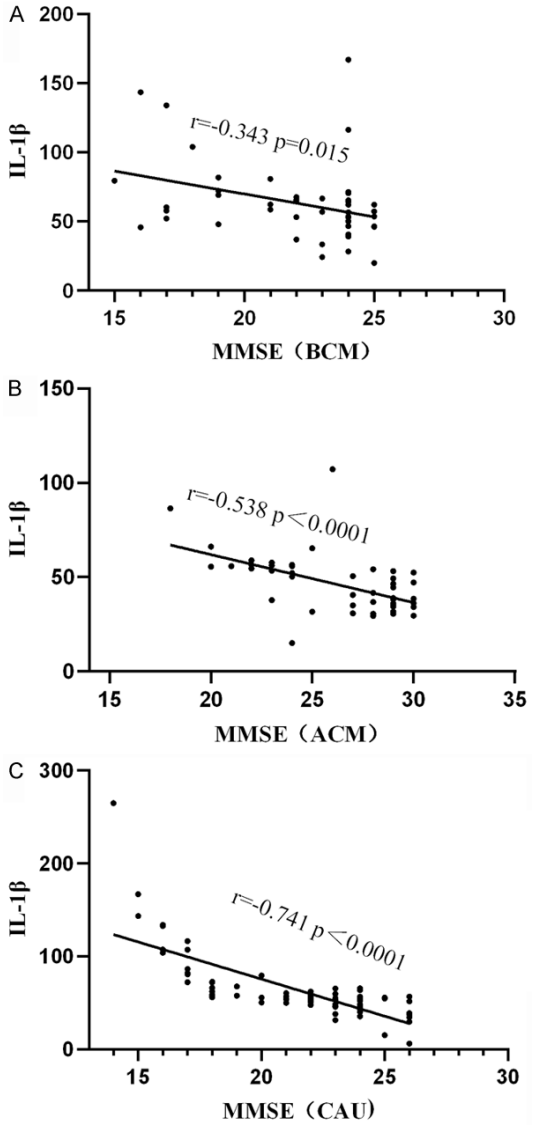

Figure 4. The linear correlation between MMSE scores and IL-1β. A. The linear correlation between MMSE scores and IL-1β before CALM intervention. B. The linear correlation between MMSE scores and IL-1β after CALM intervention. C. The linear correlation between MMSE scores and IL-1β in CAU group.

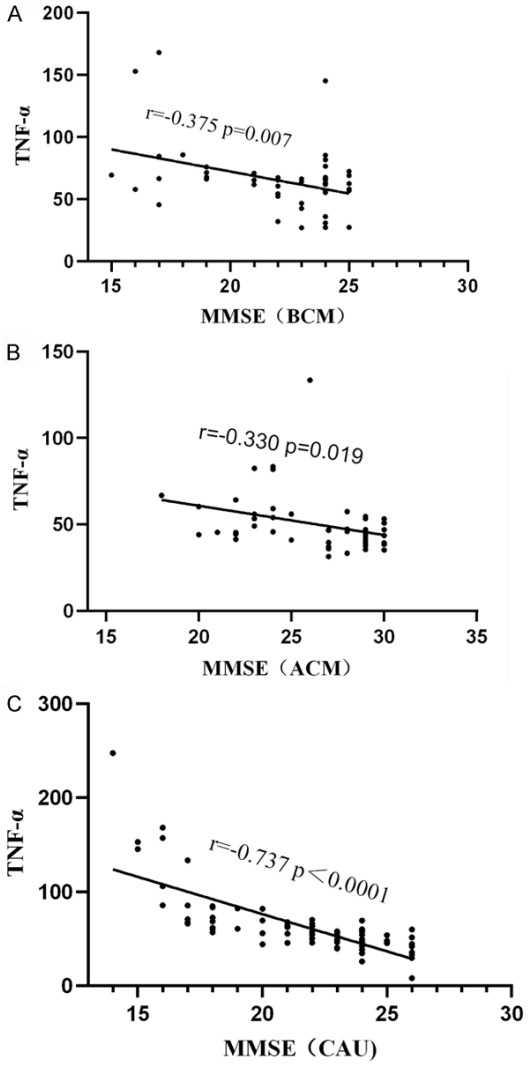

Figure 5. The linear correlation between MMSE scores and TNF-α. A. The linear correlation between MMSE scores and TNF-α before CALM intervention. B. The linear correlation between MMSE scores and TNF-α after CALM intervention. C. The linear correlation between MMSE scores and TNF-α in CAU group.

important to understand the characteristics of moderate treatment effects to determine who will benefit the most from the intervention [33]. Although these results are in line with other qualitative studies [34], including Canada, Germany [35], and Italy [21], and seem to confirm the efficiency of CALM intervention in reducing the level of depression, general anxiety, and death and increasing posttraumatic growth, it is controversial whether the CALM has an effect on emotional attachments and QOL. Little research has been done to determine whether education or psychological distress is a factor in CALM outcomes. Fully understanding the influencing factors of the effect of CALM interventions provides great value for theoretical testing and further improvements in related interventions. Although CALM interventions have achieved significant results in improving the symptoms of CRCI in breast cancer patients, due to the small sample sizes and very large differences among different ethnic groups and assessment tools, many studies are not comprehensive and need further research [36].

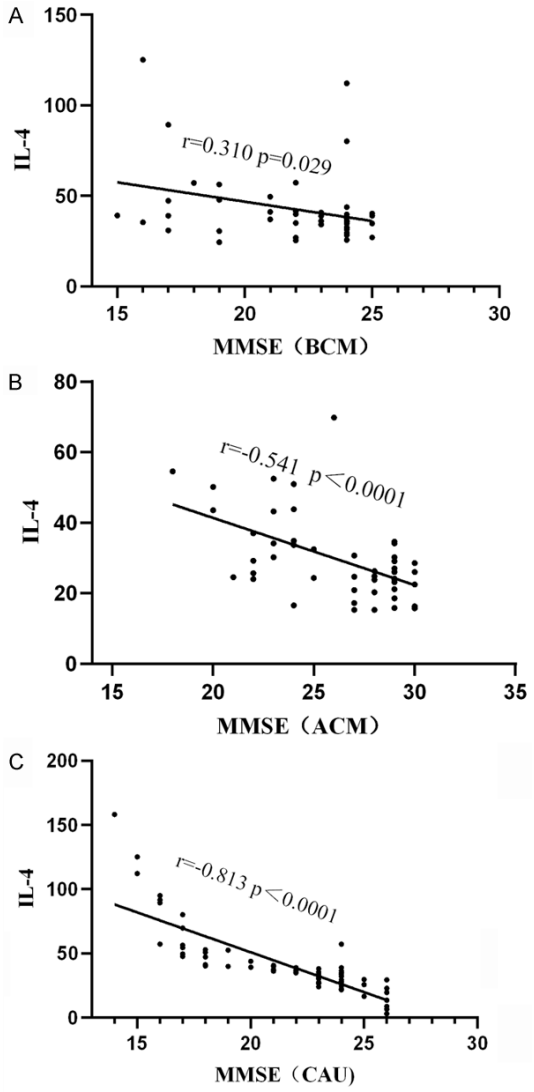

Figure 6. The linear correlation between MMSE scores and IL-4. A. The linear correlation between MMSE scores and IL-4 before CALM intervention. B. The linear correlation between MMSE scores and IL-4 after CALM intervention. C. The linear correlation between MMSE scores and IL-4 in CAU group.

Furthermore, our CALM intervention substantially improved patient QOL and alleviated their DT. During and even after cancer treatment, breast cancer patients experienced a variety of physical, psychological, social, and mental problems associated with the disease and its treatment. It has been reported that psychological distress is experienced by up to 50% of breast cancer patients [37]. Furthermore, physical symptoms such as fatigue and pain impair patients' social functioning and QOL [38]. The association between psychological distress and cognitive performance was confirmed by a recent study [39]. More importantly, investigations with larger samples have provided some evidence for associations between various measures of distress and both verbal memory and processing speed [40]. Therefore, we can speculate that DT may play an intermediary role in CRCI and that the CALM intervention ameliorated CRCI symptoms by improving DT and QOL. The exact mechanisms of CALM intervention in alleviating CRCI need to be further explored in the future.

One limitation of the study was the low number of breast cancer patients enrolled, and future research can be carried out with a larger sample size. The results of this experiment only suggested that CALM could improve CRCI. However, the specific biological mechanisms of this intervention remain unclear, so future studies should focus on this point for further exploration.

Conclusion

In brief, our study revealed improved cognitive function after CALM intervention in breast cancer patients with CRCI. Moreover, changes in IL-1β, TNF-α and IL-4 levels from before to after the intervention further demonstrated the correlation between cytokines and CRCI. This provides the theoretical basis that CALM may become an efficient method to relieve CRCI-related symptoms in breast cancer patients and improve their QOL. Finally, long-term studies are required to investigate whether these positive psychological and physiological responses are stable, increased, or decreased over time.

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Disclosure of conflict of interest

None.

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