Am J Cancer Res 2025;15(3):1148-1157
www.ajcr.us /ISSN:2156-6976/ajcr0163597

Original Article

The role of glymphatic system function in the managing Cancer and Living Meaningfully (CALM) intervention to improve chemotherapy-related cognitive impairment (CRCI) in breast cancer survivors

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Received January 27, 2025; Accepted March 7, 2025; Epub March 15, 2025; Published March 30, 2025

Abstract: Objective: This study employed the diffusion tensor image analysis along the perivascular space (DTI-ALPS) index to investigate the glymphatic system's involvement in Managing Cancer and Living Meaningfully (CALM) intervention to improve chemotherapy-related cognitive impairment (CRCI) in breast cancer survivors (BCs). Methods: 68 BCs were randomly assigned to the CALM (34 patients) or care-as-usual (CAU) (34 patients) groups. The Mini-Mental State Examination (MMSE) and Prospective and Retrospective Memory Questionnaire (PRMQ) were calculated for all patients before and after the intervention. Imaging data were collected from the CALM group to analyze the DTI-ALPS index before and after the intervention. Results: The CALM group showed significant improvements than the CAU group in MMSE (F = 6.612; *P* = 0.012), retrospective memory (RM) (F = 5.154; *P* = 0.027), and prospective memory (PM) (F = 8.731; *P* = 0.004) scores after the intervention. A significantly increased in the DTI-ALPS index was observed following CALM intervention compared to baseline (*t* = -2.111; *P* = 0.042). The ΔDTI-ALPS index was correlated with both ΔMMSE (*P* = 0.027, *r* = 0.378) and ΔRM (*P* = 0.026, *r* = -0.381) scores. Conclusion: CALM intervention improved CRCI and glymphatic function in BCs,with observed correlations between these enhancements.

Keywords: Breast cancer survivors, CALM intervention, CRCI, glymphatic system, DTI-ALPS

Introduction

Breast cancer (BC) is the most common cancer among women worldwide [1], and breast cancer survivors (BCs) account for 79-90% of cancer survivors globally [2]. Patients with BC with prolonged survival often experience different types of late toxic effects [3], such as chemotherapy-related cognitive impairment (CRCI). CRCI leads to varying degrees of impairment in various cognitive domains [4, 5], and has a significant negative impact on quality of life [6]. CRCI may last up to 20 years [7], therefore, CRCI poses a challenge to the long-term survival of cancer patients [6]. Surveys have shown that cancer survivors have an urgent need for interventions to improve CRCI, in addition to survival needs [8].

Various non-pharmacological interventions, such as cognitive behavioral therapy, meditation/positive thinking-based interventions, exercise/physical activity, and cognitive training, can alleviate CRCI in cancer survivors [9]. Managing Cancer and Living Meaningfully (CALM), a personalized, evidence-based psychotherapeutic intervention developed by Rodin et al. [10], includes the following four domains: symptom management and communication with healthcare providers, changes in

https://doi.org/10.62347/YWYC9782

self and relationships with close others, mental health and sense of meaning and purpose, and mortality- and future-oriented concerns. The CALM intervention has been shown to has been shown to reduce psychological distress [11], alleviate cancer-related fatigue [12], improve cognitive function [13] and quality of life [14] in cancer patients. However, its widespread use is limited because the mechanisms through which it improves cognitive function remain unclear.

Although the brain parenchyma lacks lymphatic vessels, cerebrospinal fluid (CSF)-interstitial fluid (ISF) exchange parallels peripheral glymphatic system functionality, leading researchers to designate this central nervous system (CNS) molecular exchange system as the "glymphatic system" [15]. The function of the glymphatic system is based on the bulk flow of CSF through the spaces that create it and cleanse the brain through this mechanism. In particular, glymphatic function involves CSF inflow from the periarterial space, CSF-ISF exchange, and ISF drainage from the brain into the peripheral glymphatic system through the extra-venous space [16]. While exogenous contrast agents can assess glymphatic function, their toxicity limitations prompted development of non-invasive alternatives like the diffusion tensor imaging along the perivascular space (DTI-ALPS) index [17]. The DTI-ALPS index is calculated by measuring the diffusivity of regions of interest (ROIs) located on association and projection fibers at the level of the lateral ventricles in the axial plane of a DTI scan, with higher ALPS indices indicating more efficient removal of waste products through the glymphatic system [18]. The DTI-ALPS index has been associated with various cognitive impairment [19, 20], which suggests that the glymphatic system protects cognitive function by facilitating the elimination of neurotoxic molecules from the brain [21].

The role of the glymphatic system in cognitive improvement in BCs with CRCI remains unclear. Moreover, the mechanisms through which the CALM intervention improves cognitive function should be elucidated to facilitate its widespread application in clinical settings. Therefore, in this study, we hypothesized that the function of the glymphatic system is correlated with cognitive function in BCs and the CALM intervention alleviates CRCI potentially by improving glymphatic enhancement.

Methods

Participants

BCs were recruited from the Second Affiliated Hospital of Anhui Medical University. The inclusion criteria were as follows: (1) patients aged ≥18 years with pathologically confirmed BC; (2) patients having completed 4-6 chemotherapy sessions containing paclitaxel and anthracycline, with a Karnofsky Performance Status (KPS) score ≥80 at 4-8 weeks post-final chemotherapy; (3) patients reporting subjective cognitive complaints; and (4) right-handed patients. The exclusion criteria were as follows: (1) patients with BC with other serious diseases or cancers; (2) patients with a history of psychiatric or neurodegenerative diseases such as depression, schizophrenia, dementia, and Alzheimer's disease; and (3) patients with malignant disease.

Sample size

This study was a single-blind randomized controlled trial in which an independent statistician performed statistical analysis and generated a random assignment sequence using a computer program. The sequence encapsulated in an envelope was kept confidential from the research team throughout the trial. The enrolled patients were randomly divided into the CALM and care-as-usual (CAU; control) groups. Referring to a previous study on the effects of CALM/CAU intervention on Mini-Mental State Examination (MMSE)scores (26.30 ± 3.27 vs. 21.49 ± 3.27) [22], we set the statistical power to 90% with a bilateral α value of 0.05. A sample size (n) of 15 cases was calculated based on the following formula: $n = 2(Z_\alpha + Z_\beta)^2 * \sigma^2/\delta^2$ [23]. Considering randomized grouping in a 1:1 ratio and a 20% loss of visits as well as refusal of visits, at least 18 cases were required in each group. Therefore, we needed to include at least 36 participants in this study. A flowchart of the study design is shown in **Figure 1**. Eventually, 34 patients were included in the CALM group, and 34 patients were included in the CAU group. All participants provided written informed consent, and this study was approved by the ethics committee of

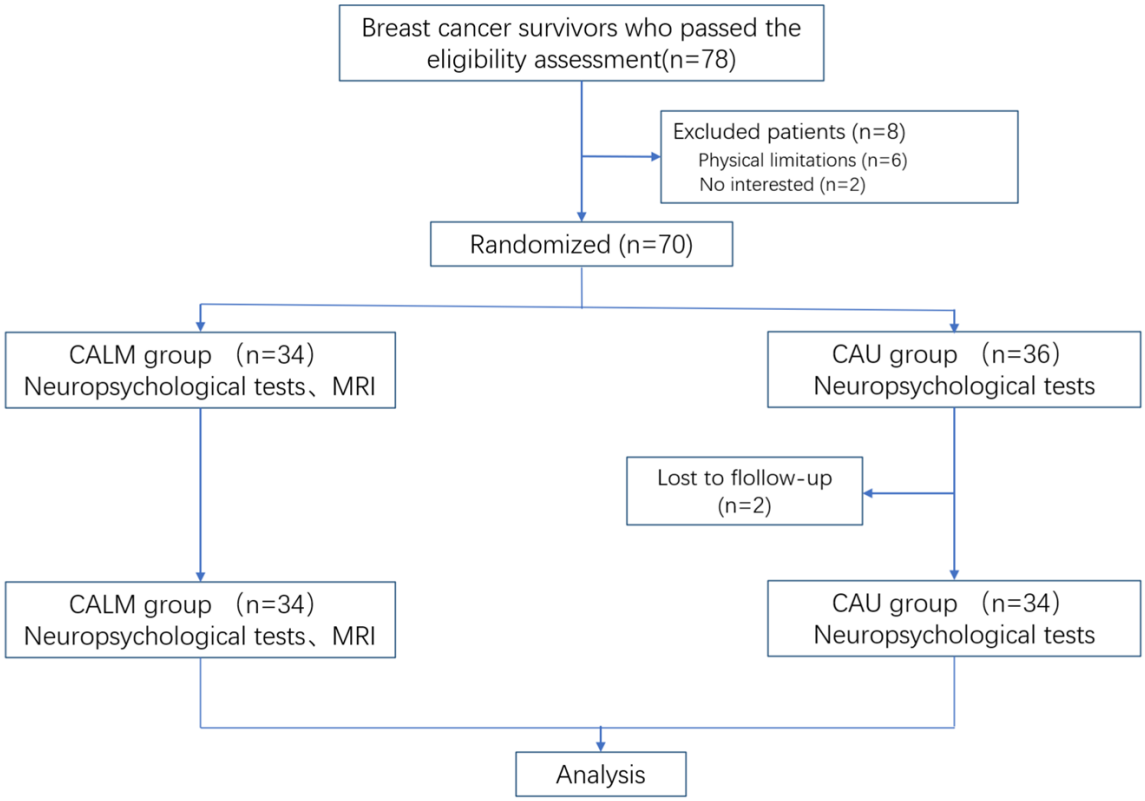

Figure 1. Flowchart of the study design.

the Second Affiliated Hospital of Anhui Medical University.

Interventions

BCs in the CALM group underwent the CALM intervention once every 2 weeks for six cycles. The entire process occurred in a comfortable and quiet environment with soothing background music, and each session lasted approximately 30-60 min. Patients in the CAU group did not receive any psychotherapy or counseling sessions. Detailed instructions for implementing the CALM intervention are shown in Supplementary Table 1.

Neuropsychological tests

MMSE was used to assess the general cognitive function of the patients. This tool measures memory, time and place orientation, working memory, visuospatial skills, object naming, writing, reading, and complex motor operations. The scale has a total score of 30, with higher scores indicating better cognitive performance [24].

Memory impairment was evaluated using the Prospective and Retrospective Memory Questionnaire (PRMQ) [25]. The PRMQ comprises 16 self-reported items that are equally divided to assess impairments in prospective memory (PM) and retrospective memory (RM), with higher scores indicating more severe impairment. The Chinese version of the PRMQ, which has been validated for use in Chinese populations, was used in this study [26].

Image acquisition

Magnetic resonance imaging (MRI) was performed on a Siemens 3.0 T scanner (Germany) with a 16-channel head coil at the Second Affiliated Hospital of Anhui Medical University. Each scan was completed in approximately 30 min. T1-weighted 3D-SPGR images were obtained with the following parameters: TR, 1900 ms; TE, 2.48 ms; FA, 9°; acquisition matrix, 256 × 256; FOV, 240 × 240 mm; thickness, 1.0 mm; gap, 0 mm; slice number, 176; and NEX, 1.0. The parameters of DTI were as follows: b-values, 0 and 1000 s/mm^2; number

of directions of diffusion gradients, 32; TR, 8400 ms; TE, 0.84 ms; FA, 90°; slice thickness, 3 mm; FOV, 256 × 2256 mm^2; gap, 0 mm; and imaging matrix, 128 × 128.

Image preprocessing and calculation of the DTI-ALPS index

The DTI-ALPS index was calculated by measuring the diffusivity of water molecules along the perivascular space. The method described by Liu et al. [27] was used to preprocess images and calculate the DTI-ALPS index.he perivascular space was assumed to be oriented in the same direction as the medullary vein at the level of the lateral ventricular body perpendicular to the ventricular wall, and this left-right direction was defined as the X-axis. In the plane of this region, projection fibers extended in the cephalad direction (Z-axis), whereas association fibers extended in the anteroposterior direction (Y-axis), which is orthogonal to the direction of the perivascular space (X-axis) [17]. The DTI-ALPS index was calculated as the ratio between the mean diffusivity (MD) in the area of projection fibers (Dxxproj) and association fibers (Dxxassoc) along the X-axis and the MD in the area of projection fibers (Dyyproj) along the Y-axis and association fibers (Dzzassoc) along the Z-axis; ALPS index = mean (Dxxproj, Dxxassoc)/mean (Dyyproj, Dzzassoc). The DTI-ALPS index was calculated for each patient to assess the function of the glymphatic system.

Images were preprocessed in the following steps: 1) conversion of data to the assessable nii format using MRIcroGL; 2) preprocessing of DTI images using the FSL (version 6.0.6.4) (https://www.fmrib.ox.ac.uk/fsl/) and MRtirx3 software; 3) deblurring of noise and Gibbs ringing artifacts; 4) correction of head motion and Eddy current using FSL; 5) calculation of dispersion tensor using Dtifit to obtain an anisotropic fraction (FA) map, FA color-coded map, and dispersion rate image; 6) linear alignment of individual A-images to the standard space template JHU-ICBM-FA using FSL; the acquired transformation matrix was applied to Dxx, Dyy, and Dzz maps; and 7) outlining of ROIs in the projection and association fibers, avoiding high-signal regions in the white matter as much as possible. ROIs were defined as spheres of 5 mm in diameter and were placed in the following regions: (A) projection fibers, left superior corona radiata (SCR) (center coordinates: 116, 110, 99); (B) association fibers, left superior longitudinal fasciculus (SLF) (center coordinates: 128, 110, 99); (C) projection fibers, right superior corona radiata (SCR) (center coordinates: 64, 110, 99); (D) association fibers, right superior longitudinal fasciculus (SLF) (center coordinates: 51, 110, 99). Finally, the ALPS index was calculated separately for the left and right hemispheres and the average index of the two hemispheres was used in subsequent analysis.

Statistical analysis

The IBM SPSS Statistics (version 27.0) and GraphPad Prism (version 9.3) software were used for statistical analysis and graphing. The independent-sample t-test was used to compare the age of patients between the CALM and CAU groups, whereas the Pearson chi-square test was used to compare educational qualification, KPS scores, tumor stage, and clinical stage between the two groups (shown in table). Non-parametric tests were used to compare MMSE and PRMQ scores between the two groups before the intervention, whereas analysis of covariance was used to compare the scores after the intervention (shown in table). The paired-sample t-test was used to analyze differences between the pre- and post-intervention DTI-ALPS index in the CALM group (shown in figure). Spearman and Pearson correlation analyses were used to analyze the relationship between MMSE and PRMQ score differentials and DTI-ALPS index differentials (shown in figure). The data are presented as mean ± standard deviation for continuous measures (e.g., age, DTI-ALPS index) and frequency (percentage) for categorical variables (e.g., education level, KPS scores). A p-value of <0.05 was considered statistically significant.

Results

Demographic and clinical characteristics did not differ between the two groups at baseline

The demographic and clinical characteristics of BCs in the CALM and CAU groups are shown in **Table 1**. No significant differences were observed between the two groups in terms of age, educational qualification, KPS scores, molecular types, and clinical stages.

Table 1. Demographic and clinical characteristics did not differ between the two groups at baseline

Variables	CALM (n = 34)	CAU (n = 34)	t/χ^2	*p*
Age (mean ± standard deviation, years)	52.94 ± 7.54	51.32 ± 6.26	0.962	0.339
Education level, n (%)			0.063	0.969
Primary school and below	19 (55.88)	20 (58.82)		
Junior high school	14 (41.18)	13 (38.24)		
University and above	1 (2.94)	1 (2.94)		
KPS scores, n (%)			0.066	0.798
80	12 (35.29)	11 (32.35)		
90	22 (65.71)	23 (67.65)		
Molecular type, n (%)			1.160	0.763
Luminal A BC	4 (11.76)	6 (17.45)		
Luminal B BC	19 (55.88)	18 (52.94)		
Her2-positive BC	7 (20.59)	8 (23.53)		
Triple-negative BC	4 (11.76)	2 (5.88)		
Tumor stage, n (%)			1.491	0.684
I	4 (11.76)	7 (20.59)		
II	15 (44.12)	16 (47.06)		
III	10 (29.41)	7 (20.59)		
IV	5 (14.71)	4 (11.76)		

Abbreviations: CALM, Managing Cancer and Living Meaningfully; CAU, care as usual.

Table 2. Comparison of neuropsychological outcomes between CALM and CAU groups

Group	MMSE scores (Mean ± standard deviation)		PRMQ scores (Mean ± standard deviation)			
			RM		PM	
	Pre-intervention	Post-intervention	Pre-intervention	Post-intervention	Pre-intervention	Post-intervention
CALM (n = 34)	25.97 ± 1.36	25.67 ± 2.21*	15.35 ± 2.92	13.94 ± 2.87*	13.50 ± 2.88	11.85 ± 3.15*
CAU (n = 34)	26.91 ± 1.31	26.00 ± 1.50#	15.65 ± 3.22	15.24 ± 2.61#	13.94 ± 1.70	13.56 ± 2.08#
z/f	z* = -0.330	F# = 6.612	z* = 0.519	F# = 5.154	z* = -1.419	F# = 8.731
p	0.741	0.012	0.603	0.027	0.156	0.004

*Comparison with CAU group pre-intervention; #Comparison with CAU group post-intervention.

Change in neuropsychological scale scores before and after the intervention was better in the CALM group than in the CAU group

As shown in **Table 2**, no significant differences were observed in MMSE or PRMQ scores between the CALM and CAU groups at the time of enrollment. However, after the intervention, the analysis of covariance showed that the MMSE scores were significantly higher in the CALM group than in the CAU group (26.91 ± 1.31 vs. 26.00 ± 1.50; F = 6.612; *P* = 0.012). In addition, RM (13.94 ± 2.87 vs. 15.24 ± 2.61; F = 5.154; *P* = 0.027) and PM (11.85 ± 3.15 vs. 13.56 ± 2.08; F = 8.731; *P* = 0.004) scores were significantly lower in the CALM group than in the CAU group after the intervention. Thus, the CALM intervention improved the performance of MMSE, PM, and RM better than the CAU intervention.

Significant increase in DTI-ALPS index before and after CALM intervention

As shown in **Figure 2**, the DTI-ALPS index was significantly higher after the intervention than before the intervention in the CALM group (1.45 ± 0.13 vs. 1.42 ± 0.11, *t* = -2.111; *P* = 0.042). This suggests that the clearance function of the glymphatic system improved after CALM intervention.

Changes in neuropsychological test scores before and after the CALM intervention correlate with changes in the DTI-ALPS index

As shown in **Figure 3**, the DTI-ALPS index was negatively correlated with RM scores (*P* = 0.041, *r* = -0.352) and positively correlated with MMSE scores (*P* = 0.043, *r* = 0.350) before

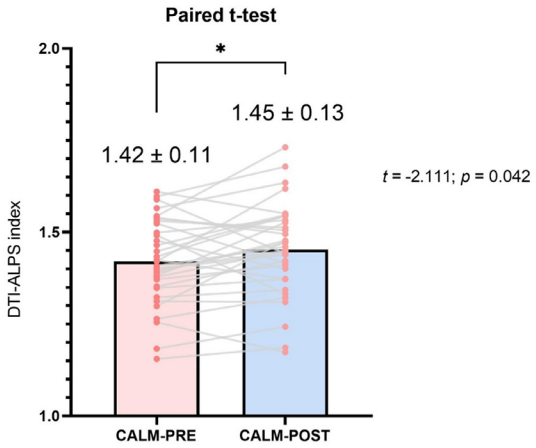

Figure 2. Pre-post intervention comparison of DTI-ALPS index. Data expressed in the results are the mean ± standard deviation.

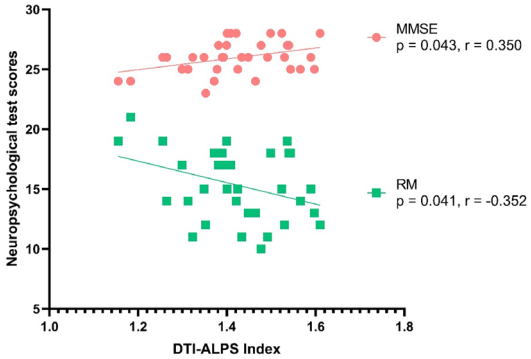

Figure 3. Bivariate correlation analysis between glymphatic function and cognitive performance. As shown in figure, at the baseline level, the DTI-ALPS index was negatively correlated with the RM score and positively correlated with the MMSE score.

the intervention in the CALM group. However, no significant correlation was observed between the DTI-ALPS index and PM scores (P = 0.103, r = -0.285). This suggests that at baseline level, the performance of MMSE and RM of BCs correlates with the clearance function of the glymphatic system.

As shown in **Figure 4**, the ΔDTI-ALPS index was correlated with both ΔMMSE (P = 0.027, r = 0.378) and ΔRM (P = 0.026, r = -0.381) scores after the CALM intervention. However, no significant correlation was observed between the ΔDTI-ALPS index and ΔPM scores (P = 0.097, r = -0.290). This suggests that improvements in cognitive function (RM and MMSE scores) in BCs correlate with improvements in glymphatic system clearance after CALM intervention.

Discussion

In this study, we found that the CALM intervention improved the overall cognitive function and memory of BCs. Pre-intervention analysis revealed correlations between the DTI-ALPS index and both MMSE and RM scores. The DTI-ALPS index increased significantly after the CALM intervention, and this increase was associated with improvements in both MMSE and RM scores. These findings suggest that glymphatic function is correlated with cognitive function in BCs. The CALM intervention can improve cognitive function in BCs, and improvement in glymphatic function may play an important role in the remission of CRCI in BCs.

The DTI-ALPS index is recognized as a non-invasive indicator of glymphatic function [28]. Multiple investigations demonstrate that the DTI-ALPS index can be used as a biomarker or predictive marker for neurodegenerative diseases. For example, glymphatic dysfunction in middle-aged and elderly chronic insomnia patients was associated with cognitive decline, detectable via DTI-ALPS during early disease stages [29]. Furthermore, the DTI-ALPS index can be used as a magnetic resonance (MR) biomarker for motor dysfunction in patients with subacute ischemic stroke [30]. To date, most studies on cognitive dysfunction have focused on Alzheimer's disease (AD). The DTI-ALPS index not only reflects glymphatic dysfunction and its correlation with cognitive dysfunction [17] but also serves as a predictive biomarker for cognitive decline in patients with AD [31]. Consistently, this study showed that the DTI-ALPS index was correlated with both cognitive function and RM in BCs. However, no significant correlation was observed between the DTI-ALPS index and PM, which may be attributed to factors such as the different neural mechanisms of RM and PM and the small number of study participants. Further investigation is required to determine DTI-ALPS's predictive value for BC-associated cognitive decline.

Studies have investigated why glymphatic function, as represented by the DTI-ALPS index, can affect the CNS and cognitive function. The brain is a highly active organ, and toxic metabolites (e.g., lactic acid, tau protein, and amyloid)

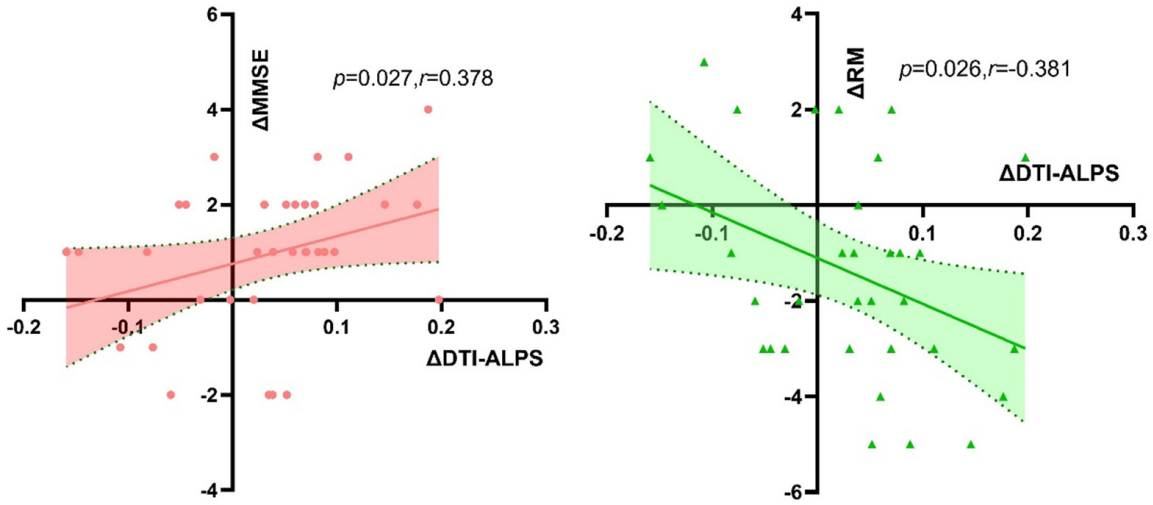

Figure 4. Intervention-effect correlation analysis with covariate adjustment. As shown in figure, the ΔDTI-ALPS index was positively correlated with the ΔMMSE (left panel) scores and negatively correlated with the ΔRM (right panel) scores after CALM intervention.

generated upon brain activity need to be eliminated from the brain parenchyma in a timely manner. Accumulation of these metabolites within the brain parenchyma can trigger and/or induce neurological damage [32]. A retrospective review [32] showed that waste is removed from the brain parenchyma primarily through CSF and the blood-brain barrier (BBB) via perivascular and periaxonal/perineural routes. Studies on the pathological mechanisms underlying CRCI have focused on BBB and CNS damage caused by chemotherapeutic drugs and inflammatory cytokines transported via the BBB [33]. However, owing to the lack of specific transport proteins, some waste products with large sizes, such as Aβ and other neuromodulators, are difficult to be eliminated through the BBB and need to be eliminated through the glymphatic system [15, 34, 35]. Accumulation of metabolic waste impairs neurological function. For instance, deposition of pathological proteins triggers neurotoxicity and inflammation [36], and accumulation of iron impairs synaptic transmission and neuronal function [37]. Therefore, injuries that lead to dysfunction of the glymphatic system can also impair cognitive function. Although we found a correlation between cognitive function and the DTI-ALPS index in BCs, glymphatic impairment's role in CRCI pathogenesis requires confirmation.

Studies have confirmed that accumulation of metabolic waste in the brain parenchyma impairs cognitive function. However, whether restoration of glymphatic function can effectively alleviate cognitive impairment in a timely manner remains unclear. Animal studies have shown that cognitive function can be improved by improving glymphatic function through voluntary exercise or supplementation with unsaturated fatty acids [38, 39]. Similar findings have been observed in studies on snoring, wherein the DTI-ALPS index improves and the cognitive function of the patient improves when the patient is surgically improved patient [40]. In this study, we found a correlation between the increase in the DTI-ALPS index and improvement in cognitive function after the CALM intervention in patients with BC. Therefore, we hypothesized that the CALM intervention improved cognitive function by increasing the DTI-ALPS index. However, owing to the lack of DTI data from non-chemotherapy-treated patients with BC, we could not clarify the changes in the DTI-ALPS index before and after chemotherapy or the role of the glymphatic system in these changes. Dynamic glymphatic alterations in CRCI demand further characterization.

Peripheral inflammation impacts the CNS [41], induces neuronal damage, and elevates neurodegeneration risk [42, 43]. Our prior work identified chronic inflammation mediated cognitive performance in BCs [44]. Aquaporin-4 (AQP4) facilitates the movement of CSF toward the brain parenchyma. Therefore, it is considered

the main fluid channel in the brain parenchyma and a key component of the glymphatic system [45]. Loss of vascular polarization of AQP4 due to chronic inflammation [46] is associated with reduced glymphatic flow, which reduces waste clearance. Therefore, an impaired glymphatic system can downregulate inflammatory cell clearance and exacerbate inflammation [45], inducing pathological damage that results in cognitive impairment. In our previous study, we found that the CALM intervention improved the inflammatory status of the brain in BCs and that this improvement was associated with improved cognitive function [47]. Given the relationship between inflammation and glymphatic function, we hypothesized that the CALM intervention improved cognitive function by improving glymphatic function and alleviating inflammation. A mutually reinforcing effect of these two changes is also possible. Bidirectional interactions between these systems merit comprehensive study.

Despite important findings, this study has some limitations. First, the relatively small sample size and single-center design of this study limit the diversity of the participants and hence the generalizability of the findings. Second, some concerns remain regarding the ability of the DTI-ALPS index to accurately reflect the function of the glymphatic system, as this index may also reflect the integrity of white matter fibers [48]. Third, although we found that the CALM intervention was more effective than CAU in improving the cognitive function of BCs, we could not validate whether this improvement was attributed to the improvement in glymphatic function, as the pre- and post-intervention DTI data were lacking for patients in the CAU group. In future studies, fMRI data should be collected before and after the intervention from both groups of patients simultaneously to increase the reliability of the results. Fourth and last, we collected longitudinal data at only two time points, that is, before and after the intervention, and failed to clarify the dynamic changes in the DTI-ALPS index in BCs with CRCI or their specific effects on cognitive function. Future longitudinal studies should conduct follow-up at more time points, such as pre-chemotherapy, post-chemotherapy, and post-intervention, to understand the dynamic changes in glymphatic function from treatment to recovery.

Conclusion

This study showed that glymphatic function is associated with cognitive function and memory in BCs. The CALM intervention alleviated CRCI in BCs, and improvement in the DTI-ALPS index was found to be correlated with improvement in cognitive function in BCs. Therefore, the role of the glymphatic system in the therapeutic efficacy of the CALM intervention warrants further investigation.

Acknowledgements

Thanks to the breast cancer patients whose dedication and perseverance have advanced the fight against cancer We sincerely wish these cancer survivors physical and mental health. We thank the reviewers for their valuable suggestions. This study was supported by the Shenzhen Natural Science Foundation Upper Level Project (JCYJ20240813145-301002) and The 2024 Take-Off project of Shenzhen Hospital of Southern Medical University (No. 23H3ATF01).

All included patients provided written informed consent.

Disclosure of conflict of interest

None.

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Supplementary Table 1. The details of each session in CALM intervention

Session	Topic	Content
Session 1	Managing sysptoms of patients and talking with their healthcare providers	This section requires the therapist to pay close attention to the patient's symptoms, physical condition. In order to change their misunderstandings about breast cancer, therapist will popularizing breast cancer-related knowledge, such as the occurrence and prevention of hair loss, cognitive impairment, fatigue, sleep disorders and other symptoms. Patients will learn that these symptoms will alleviated over time. Since the unknown is the source of fear, the therapist will introduce the mechanism of different treatment methods in an easy to understand way, thus will make patients more confident in their treatment plans. The therapist will communicate with their healthcare providers to understand the emotional state of the patient at home and make plans for the next session of intervention.
Session 2	Changes in themselves and relationships with close others	In this session, patients can discuss with the therapist about their changes after illness. The therapist will pay close attention to patient's relationships with their healthcare providers amd analyze the patient's relationship with family and friends from various perspectives. The patients will get some guidance to return to the normal life circle from the therapist.
Session 3	Review and summary	After two sessions, patients will be guided to establish positive patterns of thinking. In this session, patients will be directed to talking about their harvest in the process of the first two interventions and their recent changes in mentality. And the therapist will provide some methods such as mindfulness meditation to help patients relieving nervousness, which will help patients to relax physically and mentally.
Session 4	Spirtual wellbeing and a sense of meaning and purpose	In this session, therapists will help patients recall happy times during treatment and perceive spiritual wellbeing. Patients will learn that cancer is only a part of life setbacks, and many people's experiences are more painful. Learn to face these setbacks and span it to find sense of meaning and purpose.
Session 5	Concerns about mortality and future	Mortality and future are the greatest concerns of every patient, the therapist will communicate with patients about attitudes toward future and their fears about dying from cancer. The therapist may encourage patients to face up fears and anxieties, then facilitate attention to advanced care planning and death preparation.
Session 6	Review and summary	The patients will be guided to review their feelings of participating in CALM intervention, and summarize their feelings on the current state and their plans for future life to the therapist. The therapist will record the patient's feelings and help the patient summarize the coping measures for the unhealthy mentality.