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# Expression of inflammatory states in response to psychological distress in breast cancer survivors and its relationship to subjective memory function complaints

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## Abstract

**Background** Breast cancer (BC) survivors frequently endure psychological distress following chemotherapy, with subjective memory decline being a prevalent aspect of chemotherapy-related cognitive impairment (CRCI). This study aimed to assess the influence of psychological distress on subjective memory decline in BC survivors with CRCI and investigate potential underlying mechanisms.

**Methods** A total of 104 BC survivors who had completed chemotherapy were categorized based on the distress thermometer (DT) score into a no-psychological distress group (NPD group, $n=51$) and a psychological distress group (PD group, $n=53$). The groups were compared using the Mini-Mental State Examination (MMSE), the Prospective and Retrospective Memory (PM and RM) Questionnaire (PRMQ), cytokine levels (of interleukin-1β [IL-1β], tumor necrosis factor-alpha [TNF-α], and IL-4), and inflammatory markers (neutrophil-to- lymphocyte ratio [NLR], platelet-to-lymphocyte ratio [PLR], monocyte count-to-lymphocyte ratio [MLR], granulocyte-to-lymphocyte ratio [GLR], and systemic immune-inflammation index [SII]). Mediation analysis was performed to explore whether cytokine and inflammatory marker levels mediate the effect of psychological distress on subjective memory function complaints.

**Results** The NPD group performed significantly better in the PD group both RM ($z=-3.370$, $p=0.001$) and PM ($z=-1.967$, $p=0.049$). The IL-1β levels were substantially higher in the PD group than in the NPD group ($z=-2.920$, $p=0.004$). Similarly, NLR ($z=-2.585$, $p=0.010$), GLR ($z=-2.858$, $p=0.004$), and SII ($z=-2.747$, $p=0.006$) were higher in the PD group. Mediation analysis revealed that IL-1β partially mediated the relationship between DT and RM ($\beta=0.019$, $p=0.007$), while SII fully mediated the relationship between DT and PM ($\beta=0.003$, $p=0.017$).

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**Conclusion** BC survivors experiencing psychological distress exhibited worse subjective memory and elevated levels of IL-1β, NLR, GLR, and SII. These findings suggest that inflammation may be a cause of subjective memory function complaints in BC survivors with psychological distress.

**Keywords** Breast cancer, Cancer-related cognitive impairment, Psychological distress, Cytokines, Systemic immune-inflammation index

## Introduction

Breast cancer (BC) is the most prevalent cancer among women worldwide [1], representing a significant public health challenge. Advances in personalized and diversified treatment strategies have significantly improved survival rates, with the 5-year survival rate for patients with BC in China reaching 85% [2]. Chemotherapy remains a cornerstone of BC treatment [3], and is critical in adjuvant and palliative care. However, the cognitive side effects of chemotherapy, collectively termed chemotherapy-related cognitive impairment (CRCI), have garnered increasing attention for their potential impact on the long-term quality of life (QOL) of BC survivors. CRCI can persist for years after chemotherapy [4] and affects up to 75% of patients with BC [5]. This condition may manifest during or immediately after chemotherapy or as delayed episodes [6], with symptoms primarily involving impairments in learning, memory, processing speed, and executive function [7, 8]. The onset of CRCI can significantly diminish QOL and poses a long-term challenge for survivors [9], highlighting the need for effective strategies to address this issue.

The diagnosis of BC, the challenges of anti-tumor treatment, post-surgical changes in body image, and the fear of recurrence are profoundly stressful events that can lead to varying degrees of psychological distress in patients with BC. Chronic exposure to such stressors impacts cognitive functioning negatively [10]. Recent research has highlighted that cancer-induced post-traumatic stress can impair cognition in patients with BC [11], with anxiety and mood disorders further exacerbating cognitive impairment [12]. Those newly diagnosed with BC frequently report higher levels of psychological distress and poorer memory performance compared to the general population [13]. Furthermore, the complex interplay of negative emotions and psychological distress contributes to a dynamic and multifaceted phenomenon, where these factors mutually reinforce each other, leading to the worsening and persistence of cognitive problems [14]. A deeper understanding of the psychological distress experienced by BC survivors and its impact on subjective memory function complaints provides valuable insights for improving CRCI in this population.

Inflammation is considered a key mechanism in the development of cognitive impairment in patients with cancer [15]. Chronic stress resulting from adverse emotional states can trigger a sustained increase in circulating pro-inflammatory factors (such as interleukin-6 [IL-6], IL-1β, and C-reactive protein [CRP]). Prolonged elevation of these factors contributes to chronic inflammation, a condition linked to a poorer prognosis [16]. The relationship between psychological distress and inflammatory markers, including alterations in white blood cell counts, CRP, and cytokine levels, has been established [17]. However, the specific relationship between psychological distress and cognitive function in patients with BC remains underexplored, and the role of inflammation in this context is less well understood. Investigating the mechanisms by which psychological distress associated with cognitive functioning is crucial for designing effective interventions to mitigate CRCI in patients with BC.

In summary, the causes and underlying mechanisms of cognitive impairment in BC survivors remain incompletely understood. While current research predominantly emphasizes the physiological aspects of CRCI, psychological factors have received comparatively less attention. The aim of the present study was to investigate whether levels of inflammation are a potential mechanism linking psychological distress to subjective cognitive functioning complaints in BC survivors'. It was hypothesized that patients with concomitant psychological distress would have altered levels of inflammation and be associated with poorer cognitive functioning. These exploratory findings were expected to provide a hopeful outlook for early psychological interventions and strategies to improve the mental health of BC survivors.

## Methods

### Participants and sample size

This study included 104 female BC survivors with early/mid-stage BC who underwent treatment between August 2018 and March 2021 at the Department of Oncology, the Second Affiliated Hospital of Anhui Medical University. Clinical data were analyzed from the hospital's electronic medical record system. The inclusion criteria for this study were as follows: (1) patients diagnosed with BC who had undergone 4–6 cycles of paclitaxel- and anthracycline-based chemotherapy, were between 4 and 8 weeks post-treatment, and did not experience intolerable side effects; (2) adequate bone marrow and organ function, defined as neutrophils $\geq 2.0 \times 10^9$/L, platelets $\geq 100 \times 10^9$/L, hemoglobin $\geq 90$ g/L; (3) a minimum education level of elementary school, enabling independent questionnaire completion; (4) a Karnofsky

Performance Status (KPS) score of ≥ 80. Exclusion criteria were: (1) the presence of severe comorbidities, such as serious infections or autoimmune diseases; (2) a history of psychiatric or neurodegenerative conditions, including depression, schizophrenia, dementia, or Alzheimer's disease (AD); (3) advanced malignancy or distant metastasis.

This cross-sectional study was designed to examine the associations between psychological distress, inflammation levels, and subjective memory functioning in BC survivors. Based on previous studies [18], the expected standard deviations were 4.4914 (retrospective memory, RM) and 5.2401 (prospective memory, PM), with a two-sided test, $\alpha = 0.05$, and allowable errors of 1.2 (RM) and 1.3 (PM). Using the formula $n=(Z_{\alpha}^{2*}\sigma^2)/\delta^2$, the required sample sizes were calculated as 54 (RM) and 63 (PM). Accounting for a 5% invalid response rate, at least 67 cases were needed. Ultimately, 104 cases of BC survivors were included, as illustrated in Fig. 1.

## Assessment methods

### *Cognitive functioning*

Cognitive functioning was evaluated using the Mini-Mental Status Examination (MMSE) [19], a widely recognized cognitive screening tool that provides a rapid, comprehensive assessment of intellectual status and cognitive impairment. The Chinese version of the MMSE has demonstrated validity for application within Chinese populations [20]. The test has a maximum score of 30, with those ≤ 26 indicating cognitive impairment; lower scores denote more severe impairment.

### *Psychological distress*

Psychological distress was assessed using the Distress Thermometer (DT) as recommended by the National Comprehensive Cancer Network (NCCN) Distress Management Panel and previous studies [21]. The Chinese adaptation of the DT has been validated for use in Chinese populations [22]. Participants self-reported their psychological distress over the past week (including the current day) on a scale from 0 to 10, where higher scores reflect more significant distress. Scores ≥ 5 were classified as indicative of psychological distress [23]. Based on this threshold, patients were subsequently categorized into psychological distress (PD) and no-psychological distress (NPD) groups.

### *Memory assessment*

Memory impairment was evaluated using the Prospective and Retrospective Memory Questionnaire (PRMQ) [24]. The PRMQ comprises 16 self-reported items, equally divided to assess PM and RM impairments. Higher scores reflect more significant memory impairment. The Chinese version of the PRMQ has been validated for use in Chinese populations [25].

## Cytokine and inflammatory indicator collection and analysis

Hematologic specimens were collected within 24 h after participants completed the questionnaire assessments. Two milliliters of venous blood were drawn into ethylenediaminetetraacetic acid (EDTA) tubes and cryopreserved. Cytokine levels, including IL-1β, tumor necrosis factor-alpha (TNF-α), and IL-4, were measured

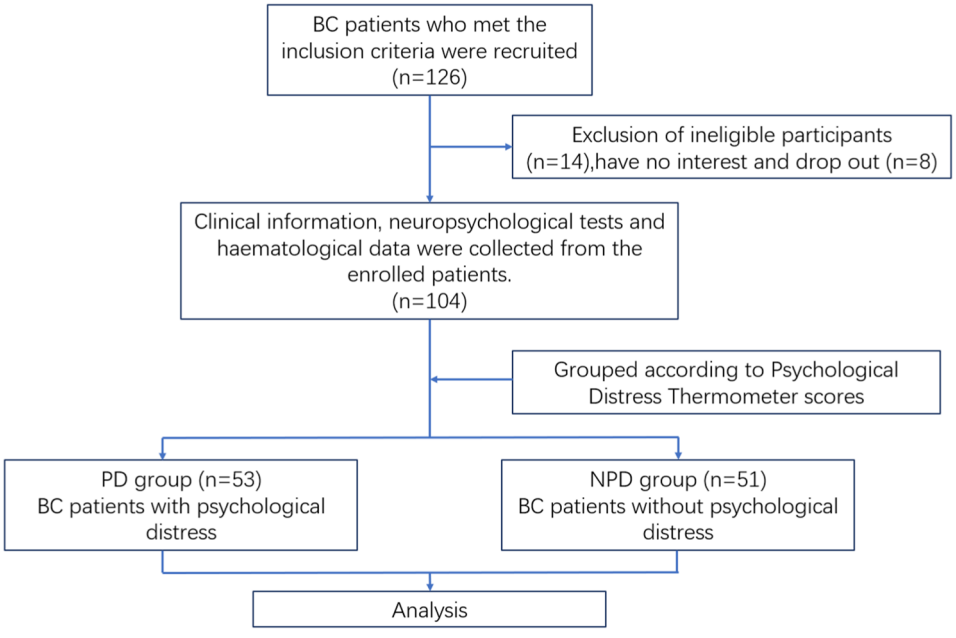


**Fig. 1** Flowchart of study design

via enzyme-linked immunosorbent assay (ELISA) kits (ml058059, ml077385, and ml058093, respectively) (Shanghai Tianhao Biological Company, Shanghai, China), with testing conducted using a 96-well microplate format. To evaluate pan-immune inflammatory markers, data from routine blood tests were used to calculate the following indices: neutrophil-to-lymphocyte ratio (NLR): neutrophil count/lymphocyte count; platelet-to-lymphocyte ratio (PLR): platelet count/lymphocyte count; monocyte-to-lymphocyte ratio (MLR): monocyte count/lymphocyte count; granulocyte-to-lymphocyte ratio (GLR): granulocyte count/lymphocyte count; and systemic immunoinflammatory index (SII): (platelet count × neutrophil count)/lymphocyte count.

### Statistical analysis

Data were analyzed using Statistical Package for the Social Sciences (SPSS) statistical software (version 27.0, International Business Machines Corporation, New York, USA). Statistical tests included:

- **Independent samples t-test**: for continuous variables with a normal distribution.
- **Mann-Whitney U-Test**: for continuous variables with a non-normal distribution.
- **Pearson chi-square test**: for categorical variables, including education level, KPS score, tumor stage, and molecular subtype.
- **Spearman correlation analysis**: to assess correlations between datasets.

Regression analysis was conducted to explore relationships between independent variables, mediators, and dependent variables. Mediation effects were analyzed using the Process plug-in, while the bootstrap method estimated total, direct, and indirect effects with confidence intervals. Given the limitations of mediated effects analyses in cross-sectional studies, the purpose of the current mediated effects analyses was to explore potential mechanisms of inflammation in psychological distress and memory impairment. Statistical significance was set at $p < 0.05$.

**Table 1** Demographic characteristics and clinical information of BC patients in both groups

| Variables | PD($n=53$) | NPD($n=51$) | t/$\chi^2$ | $p$ |
|---|---|---|---|---|
| **Age**(years) | 51.00 ± 8.06 | 50.94 ± 6.78 | 0.04 | 0.968 |
| **Education level**,n(%) | | | 1.005 | 0.605 |
| Primary school | 16(30.19) | 11(21.57) | | |
| Junior high school | 24(45.28) | 26(50.98) | | |
| University and above | 13(24.53) | 14(27.45) | | |
| **KPS scores** n(%) | | | 0.104 | 0.747 |
| 80 | 15(28.30) | 13(25.49) | | |
| 90 | 38(71.70) | 38(74.51) | | |
| **Molecular typing** n(%) | | | 3.375 | 0.292 |
| Luminal A | 4(7.55) | 2(3.92) | | |
| Luminal B | 36(67.92) | 28(54.90) | | |
| Her-2 overexpression | 9(16.98) | 16(31.37) | | |
| Triple-negative | 4(7.55) | 5(9.81) | | |
| **Pathological type** n(%) | | | 0.305 | 0.581 |
| Non-invasive carcinoma | 2(3.77) | 1(1.96) | | |
| Invasive carcinoma no special type | 51(96.23) | 50(98.04) | | |
| Invasive carcinoma special type | 0(0.00) | 0(0.00) | | |
| **Tumor stage** n(%) | | | 1.491 | 0.475 |
| I | 8(15.09) | 4(7.84) | | |
| II | 25(47.17) | 28(54.90) | | |
| III | 20(37.74) | 19(37.26) | | |

*Abbreviations* NPD, non-psychological distress; PD, psychological distress; KPS, Karnofsky Performance Status

## Results

### Demographic characteristics and clinical information

Table 1 presents the demographic and clinical characteristics of the patients in both groups. No significant differences were observed between the groups regarding age, education level, KPS score, molecular subtype, pathological type, or clinical staging.

### Cognitive functioning scale scores, cytokine levels, and inflammation markers

The MMSE scores were marginally higher in the NPD group compared to the PD group; however, the difference was insignificant (21.62 ± 3.05 vs. 22.59 ± 2.50, $z$ = -1.882, $p = 0.060$).

Patients in the NPD group demonstrated significantly better performance in RM(18.85 ± 1.99 vs. 17.29 ± 2.41, $z$ = -3.370, $p = 0.001$)and PM (19.94 ± 2.86 vs. 18.67 ± 2.17, $z$ = -1.967, $p = 0.049$)compared to the PD group.

Cytokine levels were generally elevated in the PD group relative to the NPD group. Among these, only the IL-1β levels were considerably higher(67.15 ± 35.18 vs. 56.04 ± 24.79, $z$ = -2.920, $p = 0.004$). Differences in TNF-α(65.48 ± 36.27 vs. 58.85 ± 20.58, $z$ = -0.481, $p = 0.630$)and IL-4(41.96 ± 25.04 vs. 39.12 ± 16.25, $z$ = -0.579, $p = 0.593$) were not significant.

Immunoinflammatory indexes were significantly higher in the PD group, with considerable differences in NLR($z$ = -2.585, $p = 0.010$), GLR($z$ = -2.858, $p = 0.004$), and SII($z$ = -2.747, $p = 0.006$).However, PLR($z$ = -1.460, $p = 0.144$) and MLR($z$ = -0.211, $p = 0.833$) showed no substantial differences. These results are summarized in Table 2.

### Correlation between psychological distress, PRMQ, cytokines, and inflammatory markers

Psychological distress was positively correlated with RM ($p = 0.001$, $r = 0.320$) and PM scores on the PRMQ scale

**Table 2** Results of cognitive function scale scores, cytokines, and inflammatory indicators in two groups of BC patients

| Variables | PD($n=53$) | NPD($n=51$) | $z^{\#}$ | $p$ |
|---|---|---|---|---|
| **Cognitive Scale Scores** | | | | |
| MMSE | 21.62 ± 3.05 | 22.59 ± 2.50 | -1.882 | 0.060 |
| RM | 18.85 ± 1.99 | 17.29 ± 2.41 | -3.370 | 0.001 |
| PM | 19.94 ± 2.86 | 18.67 ± 3.17 | -1.967 | 0.049 |
| **Cytokines Levels** (pg/ml) | | | | |
| IL-1β | 67.15 ± 35.18 | 56.04 ± 24.79 | -2.920 | 0.004 |
| TNF-α | 65.48 ± 36.27 | 58.85 ± 20.58 | -0.481 | 0.630 |
| IL-4 | 41.96 ± 25.04 | 39.12 ± 16.25 | -0.579 | 0.593 |
| **Markers of Systemic Inflammation Levels** | | | | |
| NLR | 2.91 ± 1.16 | 2.41 ± 1.01 | -2.585 | 0.010 |
| PLR | 165.75 ± 67.94 | 143.49 ± 51.67 | -1.460 | 0.144 |
| MLR | 0.33 ± 0.15 | 0.32 ± 0.13 | -0.211 | 0.833 |
| GLR | 3.07 ± 1.17 | 2.51 ± 1.02 | -2.858 | 0.004 |
| SII | 591.77 ± 264.68 | 473.91 ± 273.88 | -2.747 | 0.006 |

*Abbreviations*: NPD, non-psychological distress; PD, psychological distress; MMSE, Mini-Mental State Examination; RM, retrospective memory; PM, prospective memory; IL-1β, interleukin-1 beta; TNF-α, tumor necrosis factor-alpha; IL-4, interleukin-4; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; GLR, granulocyte-to-lymphocyte ratio; SII, systemic immune-inflammation index

[#]Mann–Whitney U test

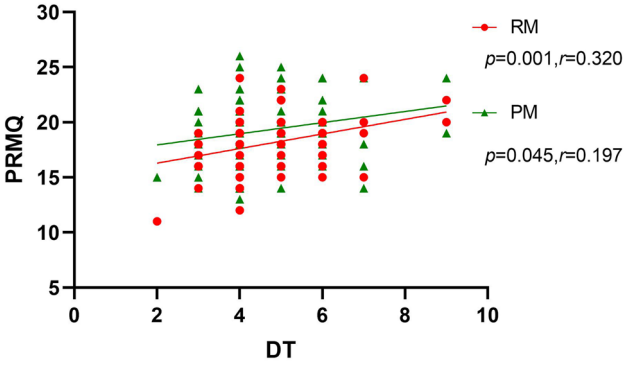


**Fig. 2** Correlation of DT scale scores with PRMQ scale scores

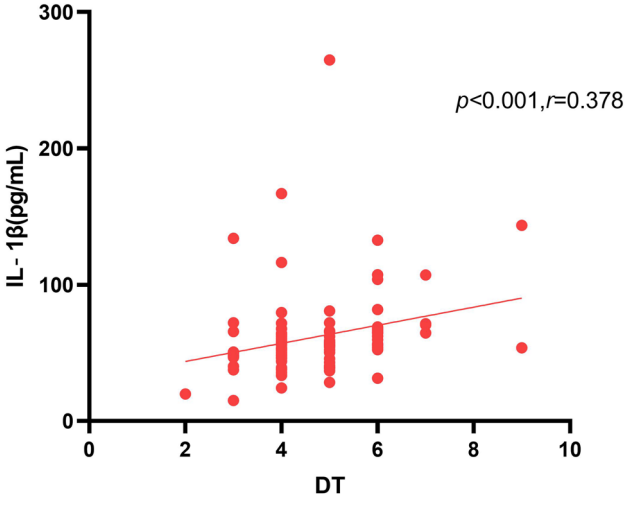


**Fig. 3** Correlation of DT scale scores with IL-1β

($p=0.045$, $r=0.197$) (Fig. 2). Among cytokines, psychological distress showed positive correlation with IL-1β ($p<0.001$, $r=0.378$) (Fig. 3). For systemic inflammatory markers, significant positive correlations were observed between psychological distress and NLR ($p=0.0021$, $r=0.301$), PLR ($p=0.024$, $r=0.221$), GLR ($p=0.001$, $r=0.323$), and SII ($p=0.001$, $r=0.317$) (Fig. 4).

### Analysis of mediation effects

As shown in Table 3, DT is correlated with RM ($\beta=0.663$, $p<0.001$) and PM ($\beta=0.506$, $p<0.001$); RM and PM were not highly correlated variables ($p=0.297$). Therefore, we will discuss the effects of variables in DT and cytokines/inflammatory response markers on PM/RM separately. The results, as shown in Table 4, showed that the independent variable DT had a significant effect on the mediating variables IL-1β ($\beta=6.642$, $p=0.007$), TNF-α ($\beta=4.868$, $p=0.042$), NLR ($\beta=0.295$, $p<0.001$), PLR ($\beta=12.650$, $p=0.010$), GLR ($\beta=0.319$, $p<0.001$) and SII ($\beta=70.286$, $p=0.001$) had a significant effect. Further results after regression analysis with simultaneous inclusion of the independent variable DT and significant mediator variables are shown in Table 5, the independent variable DT and IL-1β were able to positively and significantly predict RM simultaneously ($\beta=0.019$, $p=0.007$), and the independent variables DT and SII had an effect on PM ($\beta=0.003$, $p=0.017$). Bootstrap program was used to calculate the mediating effect as a percentage of the total effect. The results are shown in Tables 6 and 7; Fig. 5, mediation analysis revealed that IL-1β partially mediated the relationship between DT and RM(effect value = 0.128, 95% CI [0.021 to 0.256]). Conversely, the SII fully mediated the relationship between DT and PM (effect value = 0.117, *95% CI [-0.007 to 0.116]*).

## Discussion

The interplay between psychological distress, cognitive function, and chronic inflammation in BC survivors has garnered significant attention in recent years. Our findings indicate that BC survivors experience varying levels of psychological distress post-chemotherapy, with those exhibiting distress demonstrating more subjective memory complain. Furthermore, inflammation appears to be a potential factor linking psychological distress and subjective memory complain. Specifically, IL-1β may mediate the effects of psychological distress on RM function, whereas SII may mediate the effects of psychological distress on PM function.

CRCI may arise from diverse biological mechanisms, including blood-brain barrier disruption, systemic inflammation, accelerated cellular senescence, and neuronal stem cell dysfunction [26]. Chronic inflammation significantly contributes to cognitive decline [27, 28]. Elevated systemic inflammatory markers and peripheral

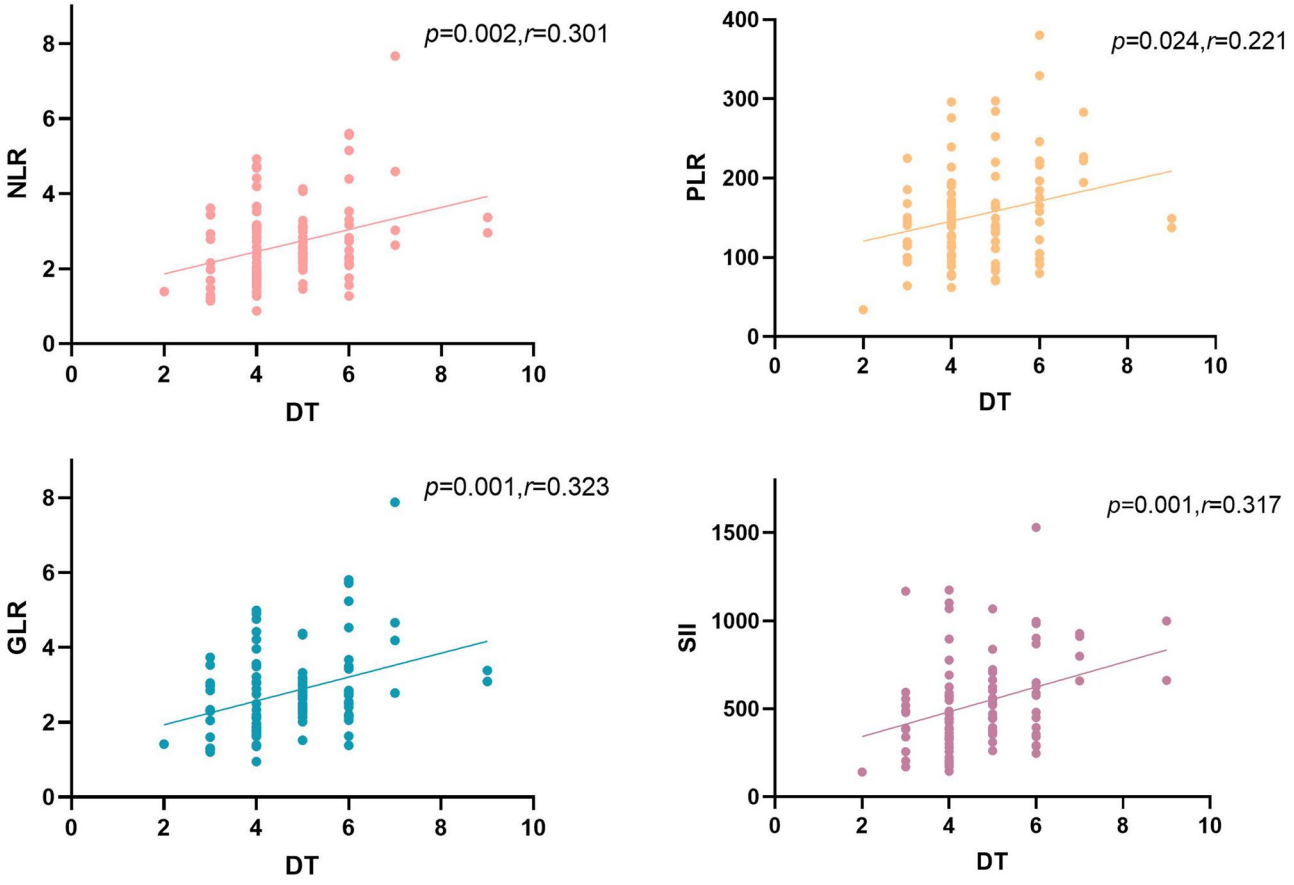


**Fig. 4** Correlation of DT scale scores with NLR, PLR, GLR, and SII

**Table 3** DT linkage to RM/PM

| Regression equation | | Model Fit Indicators | | Significance of regression coefficients | | | |
|---|---|---|---|---|---|---|---|
| Outcome Variables | Predictor variables | $R^2$ | $F$ | $\beta$ | *Standardized* $\beta$ | $t$ | $p$ |
| RM | Constant | 0.112 | 13.929*** | 14.965 | | 17.326 | < 0.001 |
| | DT | | | 0.663 | 0.347 | 3.732 | < 0.001 |
| PM | Constant | 0.031 | 4.292* | 16.936 | | 14.264 | < 0.001 |
| | DT | | | 0.506 | 0.201 | 2.072 | 0.041 |

*: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$

immune senescence can disrupt neuronal immune activity and reactivity. In patients with cancer, chemotherapy induces cellular damage and division, resulting in heightened inflammation, particularly pro-inflammatory cytokines, during and after treatment [29]. Evidence suggests that inflammation levels, including indices such as GLR and SII, can remain elevated for up to 20 years post-treatment and correlate with impaired cognitive performance [30]. Patients with BC undergoing chemotherapy also report increased psychological distress, including depression [31], which may act as a chronic stressor exacerbating cognitive impairment. Reduced stress levels are consistently associated with improved cognitive function in patients with cancer [32]. Chronic stress and adversity further alter immune cell behavior, influencing inflammatory signaling and immune cell activity in patients with BC undergoing treatment [16]. Exposure to repeated emotional stressors, as observed in post-traumatic stress disorder (PTSD)-related research, has been associated with significant neurobiological changes. These include increased synapse formation and dendritic growth in the basolateral amygdala, dendritic retraction in the hippocampus, and the emergence of anxiety-like behaviors in response to specific stimuli [10]. These findings suggest potential neural mechanisms underlying cognitive impairment associated with psychological distress. Similarly, our findings suggest that BC survivors with concomitant psychological distress may exhibit subjective cognitive functioning complaints. However, we did not find significant differences in general

**Table 4** Effect of cytokine/inflammatory markers on mediating variables

| Regression equation | | Model Fit Indicators | | Significance of regression coefficients | | | |
|---|---|---|---|---|---|---|---|
| Outcome Variables | Predictor variables | $R^2$ | $F$ | $\beta$ | *Standardized* $\beta$ | $t$ | $p$ |
| IL-1β | Constant | 0.060 | 7.540** | 30.410 | | 2.584 | 0.011 |
| | DT | | | 6.642 | 0.262 | 2.746 | **0.007** |
| TNF-α | Constant | 0.031 | 4.254* | 39.294 | | 3.422 | < 0.001 |
| | DT | | | 4.868 | 0.200 | 2.063 | **0.042** |
| IL-4 | Constant | 0.008 | 1.873 | 29.605 | | 3.580 | < 0.001 |
| | DT | | | 2.326 | 0.134 | 1.369 | 0.174 |
| NLR | Constant | 0.096 | 11.947*** | 1.275 | | 3.068 | 0.003 |
| | DT | | | 0.295 | 0.324 | 3.456 | **< 0.001** |
| PLR | Constant | 0.054 | 6.917* | 95.235 | | 4.070 | < 0.001 |
| | DT | | | 12.650 | 0.252 | 2.630 | **0.010** |
| MLR | Constant | 0.010 | 2.047 | 0.249 | | 4.533 | < 0.001 |
| | DT | | | 0.016 | 0.140 | 1.431 | 0.156 |
| GLR | Constant | 0.110 | 13.698*** | 1.293 | | 3.082 | 0.003 |
| | DT | | | 0.319 | 0.344 | 3.701 | **< 0.001** |
| SII | Constant | 0.089 | 11.034** | 202.327 | | 1.965 | 0.052 |
| | DT | | | 70.286 | 0.312 | 3.322 | **0.001** |

*: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$

cognitive functioning between the two groups (MMSE scale results), and we considered that it might be related to the lack of sensitivity of the MMSE in mild cognitive impairment.

Psychological distress and its manifestations of stress and depression are widely associated with elevated levels of pro-inflammatory cytokines across various populations, including patients with BC [18, 33]. The biological mechanisms underlying this phenomenon could involve dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and imbalance in the sympathetic-parasympathetic nervous systems. Such disruptions can alter catecholamines and cortisol secretion, promoting the release of pro-inflammatory mediators [34]. Among these, IL-1β is a crucial cytokine implicated in immune-mediated inflammatory diseases. The central nervous system (CNS) is particularly vulnerable to dysregulated cytokine networks, which can amplify inflammatory cascades by inducing further cytokine production in CNS-resident cells [35]. This inflammatory environment may compromise dopaminergic neuronal integrity and associated behaviors [36]. Elevated IL-1β levels have also been observed in Alzheimer's disease (AD), suggesting its involvement in the disease's early pathogenesis and progression [37, 38]. Animal models further corroborate the detrimental effects of IL-1β on synaptic structure and function, leading to memory deficits [39]. The PTSD studies similarly link psychological distress with increased inflammatory markers, including cytokines, and hypothesize that distress may serve as a biological pathway influencing chronic disease development [34]. Consistent with these findings, our study observed elevated IL-1βin patients with high psychological distress, which may partially explain its impact on RM.

Inflammation and immune dysfunction are critical contributors to AD-associated dementia. A study examining peripheral blood cell changes in patients with AD reported elevated NLRs and leukocyte counts compared to healthy controls, alongside reduced lymphocyte levels [40]. NLR has been proposed as a diagnostic biomarker for AD due to its sensitivity and specificity [41]. The SII is an emerging biomarker derived from neutrophil, lymphocyte, and platelet counts, offering a comprehensive measure of inflammatory and immune system activity. Unlike some markers affected by fluid imbalances [42], SII provided a stable representation of inflammatory pathways [43]. Recent research has linked elevated SII levels to cognitive impairment [44, 45]. This connection is attributed to leukocyte-mediated endothelial dysfunction, thrombosis, and the generation of superoxide radicals. Experimental studies have further supported this link, demonstrating that neutrophil depletion improves cerebral blood flow and enhances cognitive performance in mice [46]. Beyond molecular mechanisms, neuroimaging studies have explored the relationship between SII and cognitive impairment. For instance, investigations of coronavirus disease 2019 (COVID-19) survivors revealed that SII reflects systemic inflammation, and is associated with depression, PTSD, and microstructural alterations in white matter observed via magnetic resonance imaging (MRI) [47]. Similarly, research on cerebral small vessel disease found correlations between high SII levels and basal ganglia perivascular space enlargement [48]. The structural and functional brain changes secondary to elevated SII are hypothesized to impact cognitive function.

**Table 5** Significance of regression coefficients for RM/PM

| **Predictor variable: RM** | **Significance of regression coefficients** | | | |
|---|---|---|---|---|
| | **β** | **Standardized β** | **t** | ***p*** |
| Constant | 14.380 | | 16.631 | < 0.001 |
| DT | 0.535 | 0.280 | 2.997 | 0.003 |
| IL-1β | 0.019 | 0.255 | 2.729 | **0.007** |
| Constant | 14.431 | | 16.010 | < 0.001 |
| DT | 0.596 | 0.312 | 3.330 | 0.001 |
| TNF-α | 0.014 | 0.173 | 1.846 | 0.068 |
| Constant | 15.005 | | 16.542 | < 0.001 |
| DT | 0.672 | 0.351 | 3.563 | 0.001 |
| NLR | −0.031 | −0.015 | −0.152 | 0.880 |
| Constant | 14.746 | | 15.788 | < 0.001 |
| DT | 0.633 | 0.331 | 3.443 | 0.001 |
| PLR | 0.002 | 0.060 | 0.628 | 0.532 |
| Constant | 15.023 | | 16.559 | < 0.001 |
| DT | 0.677 | 0.354 | 3.564 | 0.001 |
| GLR | −0.045 | −0.022 | −0.220 | 0.826 |
| Constant | 14.798 | | 16.816 | < 0.001 |
| DT | 0.604 | 0.316 | 3.234 | 0.002 |
| SII | 0.001 | 0.097 | 0.995 | 0.322 |
| **Predictor variable: PM** | **Significance of regression coefficients** | | | |
| | ***β*** | ***Standardizedβ*** | ***t*** | ***p*** |
| Constant | 16.424 | | 13.525 | < 0.001 |
| DT | 0.394 | 0.157 | 1.572 | 0.119 |
| IL-1β | 0.017 | 0.169 | 1.699 | 0.092 |
| Constant | 16.250 | | 13.087 | < 0.001 |
| DT | 0.421 | 0.167 | 1.705 | 0.091 |
| TNF-α | 0.017 | 0.169 | 1.721 | 0.088 |
| Constant | 16.507 | | 13.330 | < 0.001 |
| DT | 0.406 | 0.162 | 1.579 | 0.118 |
| NLR | 0.336 | 0.122 | 1.190 | 0.237 |
| Constant | 16.509 | | 12.885 | < 0.001 |
| DT | 0.449 | 0.178 | 1.778 | 0.078 |
| PLR | 0.004 | 0.089 | 0.890 | 0.376 |
| Constant | 16.561 | | 13.346 | < 0.001 |
| DT | 0.413 | 0.164 | 1.590 | 0.115 |
| GLR | 0.290 | 0.107 | 1.035 | 0.303 |
| Constant | 16.390 | | 13.869 | < 0.001 |
| DT | 0.316 | 0.126 | 1.259 | 0.211 |
| SII | 0.003 | 0.241 | 2.418 | **0.017** |

**Table 6** Mediating effects of IL-1β in DT and RM

| | **Effect value** | **Effect percentage** | **95% LLCI** | **95% ULCI** |
|---|---|---|---|---|
| Total effect | 0.663 | | 0.310 | 1.015 |
| Direct effect | 0.535 | 80.7% | 0.181 | 0.889 |
| Indirect effects of IL-1β | 0.128 | 19.3% | 0.021 | 0.256 |

In this study, high psychological distress was associated with elevated SII levels. The results of the mediation effect analysis suggest that the PD-induced increase in SII levels may be associated with PM impairment.

**Table 7** Mediating effects of SII in DT and PM

| | **Effect value** | **Effect percentage** | **95% LLCI** | **95% ULCI** |
|---|---|---|---|---|
| Total effect | 0.505 | | 0.022 | 0.990 |
| Direct effect | 0.316 | 62.6% | -0.182 | 0.814 |
| Indirect effects of SII | 0.189 | 37.4% | 0.024 | 0.406 |

CRCI is influenced by various factors, including psychological distress and inflammation [14], which may jointly contribute to its onset and persistence [49]. Emotional distress can disrupt neural signaling via neuroinflammatory pathways and dysregulation of the HPA axis, potentially impairing neuroplasticity and cognitive function [50]. Similarly, cognitive impairment can exacerbate emotional distress, fatigue, and sleep disturbances, creating a vicious cycle [26]. In this study, BC survivors with psychological distress had higher levels of inflammation (including systemic markers of inflammation and cytokines) as well as poorer subjective memory function. The findings suggest that psychological distress significantly impacts memory performance, potentially mediated through inflammation. In addition, the vagus nerve also has great potential to modulate neuronal function and neuroinflammation, as well as having anti-inflammatory effects in the periphery, specifically by acting on tissue macrophages [51]. Vagus nerve activation improves cognitive responses and reduces systemic and brain inflammation induced by lipopolysaccharide endotoxemia [52]. Stimulation of the vagus nerve is even one of the potential therapies for early Alzheimer's disease [53]. Heart rate variability (HRV) is one of the objective and noninvasive measures to regulate the autonomic nervous system. Reduced HRV reflects vagal nervous system dysfunction and is associated with cognitive and affective dysregulation [54]. Previous studies have indicated that HRV can be used as one of the markers of psychological distress and recovery in cancer patients in the context of orthostatic interventions [55]. Our team's study based on non-small cell lung cancer (NSCLC) has also found that CALM intervention has a positive impact on overall physical and mental health, reduction of fatigue, quality of life, and autonomic dysfunction in NSCLC patients, and that HRV can be used as an observable indicator of physical and mental health [56]. Therefore, future studies need to focus more on the HPA axis and the role of vagal excitation and its cognitive impairment.

Improvements in CRCI are mainly categorised into pharmacological and non-pharmacological interventions, such as psychological interventions, exercise, etc. Due to the limited effect of medications [57], there is currently more focus on non-pharmacological interventions. CRCI is multifactorial and patients often experience high levels of fatigue, pain, anxiety and depression and are most likely to benefit from holistic approaches that include

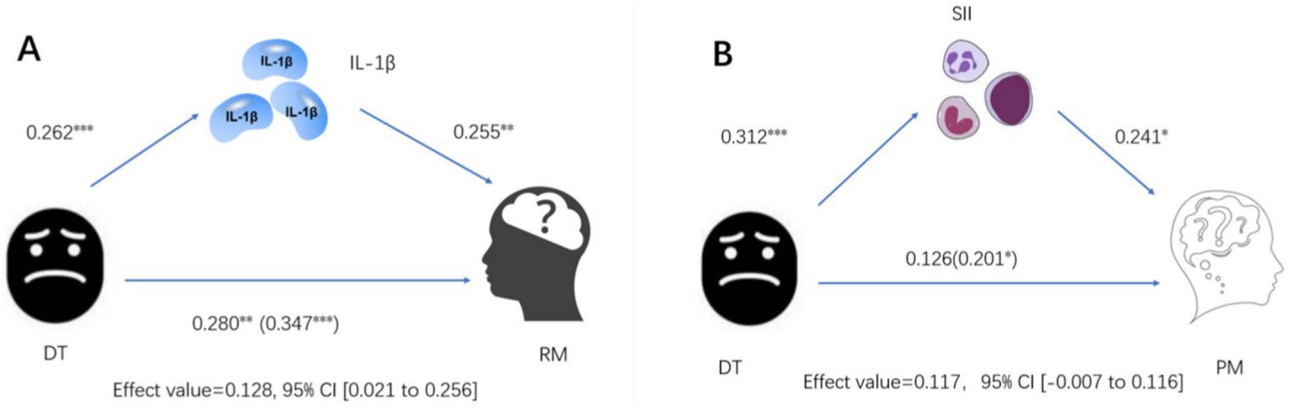


**Fig. 5** Mediating effects. **A**: Mediating effects of IL-1β in DT and RM; **B**: Mediating effects of SII in DT and PM

cognition, physical activity, relaxation, psychoeducation, group support and/or psychological counselling [57]. Similar to our findings, psychological factors may influence cognitive complaints [58] and thus negatively affect breast cancer survivors. Subsequent meta-analyses and clinical trials have shown [59–61] that both mindfulness-based psychological interventions and physical activity can help breast cancer survivors cope with fatigue, stress, anxiety, and depression and improve their quality of life. As CRCI is a multifactorial problem, an intervention that can simultaneously target the underlying mechanisms may be needed. At this point, understanding the underlying mechanisms of CRCI and their possible influences is important for specifying effective intervention strategies in the future.

The results of this paper provide novel insights for developing interventions to address CRCI. However, the cross-sectional design of this study limits the ability to establish a temporal sequence among psychological distress, inflammation, and subjective memory function complaints. Future large-scale longitudinal surveys and intervention trials are required to clarify these relationships. Psychological distress and cognitive impairment profoundly affect the daily lives of patients with BC and survivors, disrupting activities such as reading, financial management, and social interactions. Addressing these challenges, oncologists and psychologists aim to alleviate cognitive deficits and emotional distress in patients with BC following treatment to facilitate smoother reintegration into society. Based on the study findings, clinicians are recommended to routinely monitor inflammation levels during treatment and post-treatment follow-up, focusing on systemic inflammatory markers derived from routine blood results due to their accessibility and ease of measurement. Elevated levels of these markers should prompt heightened attention to potential cognitive impairment, and appropriate psychological interventions should be implemented to mitigate these effects.

Limitations: This study has several constraints. First, as a single-center study with a small sample size, its findings may lack generalizability. Expanding the cohort and collaborating with additional centers in future research could enhance representativeness and robustness. Second, the assessment of psychological distress was potentially influenced by transient emotional states, warranting repeated evaluations in subsequent studies to improve reliability. Third, this study did not capture long-term dynamic changes in psychological distress, cognitive function, or cytokine and inflammatory marker levels, limiting the ability to fully elucidate the intricate interactions among these variables. Moreover, the mediating effects analysis in this study was only used to explore the potential possible role of inflammation in psychological distress and subjective memory function complaints, and whether inflammation is one of the key mediating variables in psychological distress-mediated memory impairment needs to be further investigated in future longitudinal studies. Finally, age was not analyzed as a covariate in this study, although it was considered that there was no difference in age between the two groups. However, considering the possible differences in altered inflammation levels and subjective memory function complaints across age strata, future statistical analyses should consider integrating age to ensure more rigorous findings. In addition, since we enrolled BC survivors with a KPS ≥ 80 in general this limits our understanding of psychological distress and memory functioning, and inflammation levels in the whole population of BCs, and future studies should include a broad population of BC survivors. Considering the subjective nature of the PRMQ scale, it could be assessed in the future using more objective psychological software tests.

## Conclusion

This study evaluated the interplay between psychological distress, subjective memory complaints, cytokines, and systemic inflammatory markers in BC

survivors' post-chemotherapy. Findings revealed that survivors experiencing psychological distress exhibited worse memory performance and elevated levels of IL-1β, NLR, GLR, and SII. Inflammation may contribute to subjective memory function complaints in BC survivors with psychological distress. These findings offer valuable insights into potential strategies for mitigating cognitive impairment in BC survivors with CRCI.

**Abbreviations**

| | |
|---|---|
| BC | Breast Cancer |
| CRCI | Chemotherapy-Related Cognitive Impairment |
| DT | Distress Thermometer |
| NPD | No-Psychological Distress |
| PD | Psychological Distress |
| MMSE | Mini-Mental State Examination |
| PRMQ | Prospective and Retrospective Memory Questionnaire |
| PM | Prospective Memory |
| RM | Retrospective Memory |
| IL-1β | Interleukin-1β |
| TNF-α | Tumor Necrosis Factor-alpha |
| NLR | Neutrophil-to- lymphocyte ratio |
| PLR | Platelet-to-Lymphocyte Ratio |
| MLR | Monocyte Count-to-Lymphocyte Ratio |
| GLR | Granulocyte-to-Lymphocyte Ratio |
| SII | Systemic Immune-Inflammation Index |
| QOL | Quality of Life |
| CRP | C-reactive Protein |
| KPS | Karnofsky Performance Status |
| NCCN | National Comprehensive Cancer Network |
| SPSS | Statistical Package for the Social Sciences |
| PTSD | Post-Traumatic Stress Disorder |
| HPA | Hypothalamic-Pituitary-Adrenal |
| CNS | Central Nervous System |
| AD | Alzheimer's Disease |
| COVID-19 | Coronavirus Disease 2019 |
| MRI | Magnetic Resonance Imaging |
| HRV | Heart Rate Variability |
| NSCLC | Non-Small Cell Lung Cancer |

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**Author contributions**
Chen Gan: Conceptualization (equal); data curation (equal); methodology (equal); writing– original draft (equal); writing–review and editing (equal). Senbang Yao: Conceptualization (equal); data curation (equal); writing– original draft (equal); formal analysis (equal).Jingjing Zhao: Resources (equal); methodology (equal). Huangyuxin Shi: Formal analysis (lead); Jian Xu: Resources (equal); writing– review and editing (equal).Mingjun Zhang: Conceptualization (equal); methodology (equal).Huaidong Cheng: Conceptualization (lead); funding acquisition (lead); methodology (equal). Chen Gan and Senbang Yao contributed equally to this work.Mingjun Zhang and Huaidong Cheng are co-corresponding authors.

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**Data availability**
All data are available from the corresponding author upon reasonable request.

## Declarations

**Ethics approval and consent to participate**
The Biomedical Ethics Committee of Anhui Medical University approved this study (Project#20131028). Participants of this study signed informed consent before the study data was collected. The study followed the Declaration of Helsinki. The data in this study have not been tabulated in other articles.

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare no competing interests.

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## Publisher's note