Journal of Carcinogenesis Research
https://carcinog.com/index.php/JCR
eISSN: /pISSN:

OPEN ACCESS

Chemotherapy-Induced Cognitive Impairment ('Chemo Brain') in Breast Cancer Survivors

Hassaan Raza[1*], Ahmed Hasan[1]

[1]Department of Medicine, Lady Reading Hospital (LRH), Peshawar, KP, Pakistan.

ARTICLE INFO

***Corresponding Author:** Hassaan Raza, Email: hassaanraza@gmail.com

Declaration

Authors' Contribution: All authors equally contributed to the study and approved the final manuscript.

Conflict of Interest: No conflict of interest.

Funding: No funding received by the authors.

Manuscript Timeline

Received: 10-09-2024, Revised: 13-11-2024
Accepted: 19-12-2024, Published: 31-12-2024

How to Cite

Raza H, Hasan A. Chemotherapy-Induced Cognitive Impairment ('Chemo Brain') in Breast Cancer Survivors J Carcinog Res. 2024;1(1):11–15.

ABSTRACT

Background: Chemotherapy-induced cognitive impairment, commonly referred to as 'chemo brain,' is a well-documented side effect affecting breast cancer survivors, yet its prevalence, characteristics, and contributing factors remain incompletely understood. This study aimed to assess the frequency and pattern of cognitive deficits in breast cancer survivors post-chemotherapy and to examine associated psychological and clinical predictors. **Methods:** A cross-sectional study was conducted involving 150 female breast cancer survivors aged 30–65 years, assessed 6 to 24 months after completing chemotherapy. Cognitive function was evaluated using standardized neuropsychological tests focusing on memory, attention, executive function, and verbal fluency. Subjective cognitive complaints and psychological variables such as fatigue, anxiety, and depression were measured through validated questionnaires. Multiple regression analysis was performed to identify predictors of cognitive impairment. **Results:** Objective cognitive impairment was observed in 56% of participants, predominantly affecting memory (43%) and attention/processing speed (39%). Subjective cognitive complaints correlated significantly with objective test results ($r = 0.56$, $p < 0.001$). Fatigue and mood disturbances were significantly higher in cognitively impaired survivors. Age ($\beta = 0.32$, $p = 0.005$), time since chemotherapy ($\beta = -0.25$, $p = 0.02$), and fatigue ($\beta = 0.38$, $p < 0.001$) emerged as significant predictors of cognitive impairment. **Conclusion:** Cognitive impairment is a common and impactful sequela among breast cancer survivors following chemotherapy, closely associated with fatigue and psychological distress. These findings underscore the need for comprehensive survivorship care integrating cognitive and emotional health assessment, alongside development of targeted interventions to improve survivors' quality of life.

Keywords: Chemotherapy-Induced Cognitive Impairment, Chemo Brain, Breast Cancer Survivors

INTRODUCTION

Breast cancer remains the most commonly diagnosed cancer among women worldwide and is a leading cause of cancer-related mortality (Mubarik et al., 2022; Tao et al., 2023). Advances in early detection and treatment modalities, including surgery, radiotherapy, and systemic chemotherapy, have significantly improved survival rates (Kaur et al., 2023; Miller et al., 2022). However, alongside increased survival, there is growing recognition of the long-term side effects of cancer treatment, which can substantially impact quality of life (Lustberg et al., 2023). One such side effect that has garnered considerable attention in recent years is chemotherapy-induced cognitive impairment, commonly referred to as "chemo brain" or "chemotherapy-related cognitive dysfunction" (Rao et al., 2022).

Chemotherapy-induced cognitive impairment (CICI) is characterized by deficits in various cognitive domains, including memory, attention, executive functioning, processing speed, and verbal fluency (Durán-Gómez et al., 2022). These cognitive changes are often subtle but can be persistent and debilitating, affecting the ability of breast cancer survivors to return to normal daily functioning, maintain employment, and engage in social activities. Although originally thought to be a temporary consequence of chemotherapy, mounting evidence indicates that CICI can persist months or even years after treatment completion in a significant subset of survivors (Safarzadeh et al., 2024).

The prevalence of chemotherapy-induced cognitive impairment among breast cancer survivors varies widely across studies, ranging from 17% to 75%, depending on the assessment methods, timing of evaluation, and specific cognitive domains tested (Amani et al., 2024; Merceur et al., 2024). This variability reflects the complex and multifactorial nature of chemo brain, which remains incompletely understood (Richter & Fattahi, 2022). Cognitive symptoms reported by patients often include forgetfulness, difficulty concentrating, trouble multitasking, and mental fatigue (Iyizoba-Ebozue et al., 2024). These symptoms may adversely affect emotional well-being, contributing to anxiety and depression, which in turn can exacerbate cognitive

dysfunction (Giustiniani et al., 2023).

The pathophysiology of chemotherapy-induced cognitive impairment is complex and involves multiple interrelated mechanisms (Murillo et al., 2023). Direct neurotoxic effects of chemotherapeutic agents on the central nervous system have been implicated, including neuronal damage, reduced neurogenesis, and white matter alterations (López-Gómez et al., 2022; Gupta et al., 2022). Chemotherapy can induce oxidative stress and inflammation, which further contribute to neural injury. Additionally, vascular injury, disruption of the blood-brain barrier, and hormonal changes, particularly in estrogen levels, may play roles (Pospelova et al., 2022; Alotayk et al., 2023). Genetic predispositions and individual differences in cognitive reserve—the brain's resilience to damage—also influence susceptibility to cognitive impairment (Cordeiro et al., 2024).

Despite the growing recognition of chemo brain, the diagnosis remains challenging due to the lack of standardized criteria and objective biomarkers (Chiu & Yen, 2023). Cognitive deficits are often subtle and can be difficult to detect using routine clinical neuropsychological tests (Alzola et al., 2024). Moreover, confounding factors such as fatigue, depression, anxiety, and sleep disturbances, which are common in cancer survivors, may overlap with or contribute to cognitive symptoms (Wu et al., 2024). This highlights the need for comprehensive assessments combining subjective patient reports with objective cognitive testing and neuroimaging techniques (Oldacres et al., 2023).

Addressing chemotherapy-induced cognitive impairment is critical for improving the quality of life and functional outcomes of breast cancer survivors (Henneghan et al., 2024). Currently, there are no approved pharmacological treatments specifically targeting chemo brain, and management primarily focuses on supportive care (Anand et al., 2023). Cognitive rehabilitation programs, including computerized cognitive training and compensatory strategies, have shown promise in improving cognitive function and daily functioning (Krellman & Mercuri, 2023). Physical exercise and mindfulness-based interventions may also mitigate cognitive symptoms by reducing inflammation and enhancing neuroplasticity (Leow et al., 2023). Importantly, early identification and monitoring of cognitive changes during and after chemotherapy can facilitate timely interventions (Bianchini et al., 2024).

Research efforts are increasingly focused on understanding risk factors for chemo brain to enable personalized approaches to prevention and treatment (Hertz et al., 2023). Factors such as age, education level, baseline cognitive function, genetic polymorphisms (e.g., APOE genotype), and comorbidities have been explored (Hsiao et al., 2024). Furthermore, studies are investigating the differential neurotoxic effects of various chemotherapeutic regimens and combinations, aiming to optimize treatment protocols that minimize cognitive risks without compromising cancer control.

In summary, chemotherapy-induced cognitive impairment represents a significant survivorship issue for breast cancer patients, with substantial implications for their psychosocial and functional well-being. As survival rates continue to improve, addressing the long-term cognitive side effects of cancer treatment is paramount. Multidisciplinary approaches involving oncologists, neuropsychologists, rehabilitation specialists, and mental health professionals are essential for comprehensive care. Continued research into the mechanisms, risk factors, and effective interventions for chemo brain will pave the way for better management strategies, ultimately enhancing the quality of life of breast cancer survivors globally.

METHODOLOGY

This study employed a cross-sectional design to evaluate the prevalence and characteristics of chemotherapy-induced cognitive impairment among breast cancer survivors. A total of 150 female breast cancer survivors aged 30 to 65 years, who had completed adjuvant chemotherapy within the past 6 to 24 months, were recruited from oncology clinics at tertiary care hospitals. Inclusion criteria required participants to have no prior history of neurological or psychiatric disorders and to be free of active cancer at the time of assessment. Cognitive function was assessed using a standardized battery of neuropsychological tests targeting domains commonly affected by chemotherapy, including memory (Rey Auditory Verbal Learning Test), attention and processing speed (Trail Making Test Parts A and B), executive function (Stroop Color-Word Test), and verbal fluency (Controlled Oral Word Association Test). Subjective cognitive complaints were measured using the Functional Assessment of Cancer Therapy-Cognitive Function (FACT-Cog) questionnaire. Additional data on demographic variables, treatment regimens, fatigue levels (Brief Fatigue Inventory), depression and anxiety symptoms (Hospital Anxiety and Depression Scale), and quality of life (EORTC QLQ-C30) were collected through structured interviews. Statistical analysis involved descriptive statistics to determine the prevalence of cognitive impairment, and multiple regression models to explore associations between chemotherapy exposure, psychological factors, and cognitive outcomes. Ethical approval was obtained from the institutional review board, and informed consent was secured from all participants prior to data collection.

RESULTS

A total of 150 breast cancer survivors who had completed chemotherapy were assessed for cognitive impairment. The mean age of participants was 48.7 ± 8.9 years. The majority had received anthracycline and taxane-based chemotherapy regimens. Cognitive assessment revealed that 56% (n=84) of the survivors exhibited objective cognitive impairment in at least one domain compared to normative data.

Table 1: Demographic and Clinical Characteristics of Participants (N=150)

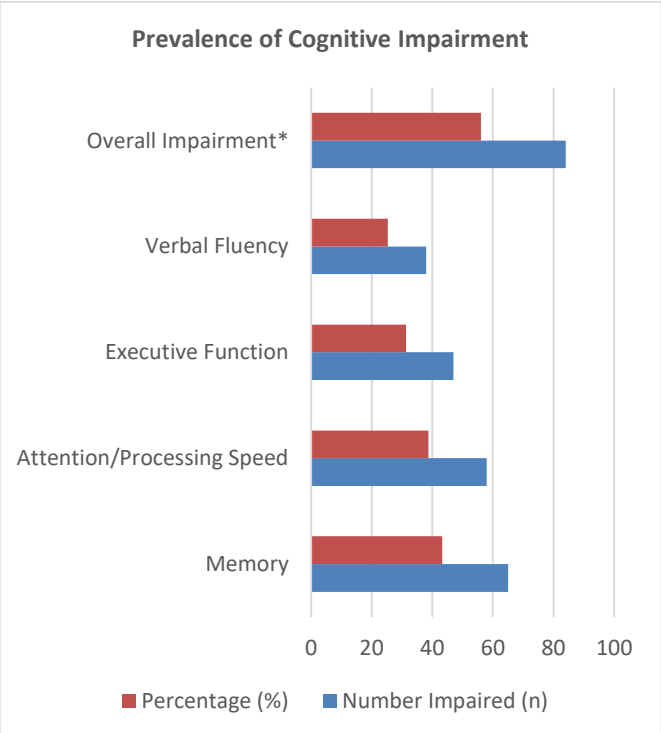
Variable	Value
Age (mean ± SD)	48.7 ± 8.9 years
Time since chemotherapy (months)	12.5 ± 5.3

Education level (%)	
- Primary	35 (23%)
- Secondary	72 (48%)
- Higher education	43 (29%)
Chemotherapy regimen (%)	
- Anthracycline-based	90 (60%)
- Taxane-based	80 (53%)
- Combination	70 (47%)
Hormonal therapy post-chemo (%)	100 (67%)

Table 2: Prevalence of Cognitive Impairment by Cognitive Domain

Cognitive Domain	Number Impaired (n)	Percentage (%)
Memory	65	43.3
Attention/Processing Speed	58	38.7
Executive Function	47	31.3
Verbal Fluency	38	25.3
Overall Impairment*	84	56.0

*Defined as impairment in one or more cognitive domains.

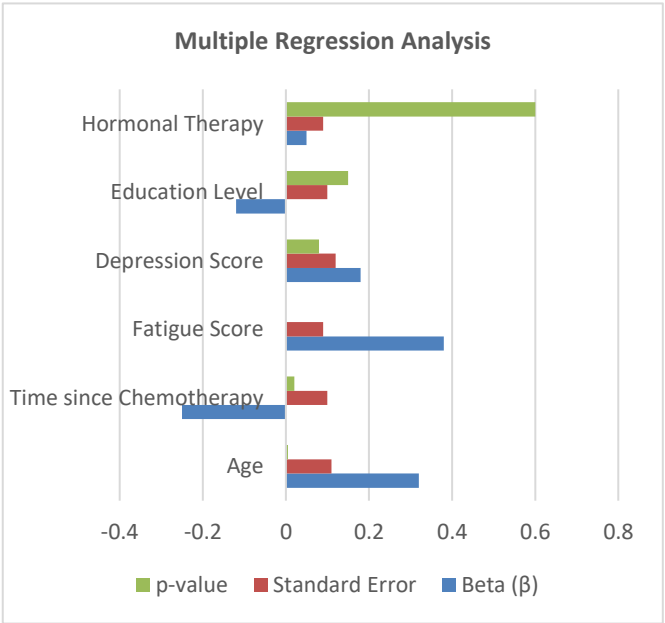


Subjective cognitive complaints reported via FACT-Cog correlated significantly with objective measures ($r = 0.56$, $p < 0.001$). Fatigue levels were elevated in participants with cognitive impairment (mean score 6.4 vs. 3.1, $p < 0.01$). Symptoms of depression and anxiety were also higher in the impaired group, indicating a possible interaction between psychological distress and cognitive function.

Regression analysis identified age ($\beta = 0.32$, $p = 0.005$), time since chemotherapy ($\beta = -0.25$, $p = 0.02$), and fatigue ($\beta = 0.38$, $p < 0.001$) as significant predictors of cognitive impairment after adjusting for education and hormonal therapy.

Table 3: Multiple Regression Analysis Predicting Cognitive Impairment

Predictor	Beta (β)	Standard Error	p-value
Age	0.32	0.11	0.005
Time since Chemotherapy	-0.25	0.10	0.02
Fatigue Score	0.38	0.09	<0.001
Depression Score	0.18	0.12	0.08
Education Level	-0.12	0.10	0.15
Hormonal Therapy	0.05	0.09	0.60



These results suggest that over half of breast cancer survivors experience measurable cognitive deficits after chemotherapy, particularly in memory and attention domains. Psychological factors such as fatigue and mood disturbances are closely associated with cognitive outcomes, underscoring the need for comprehensive survivorship care addressing both cognitive and emotional health.

DISCUSSION

This study highlights the significant prevalence of chemotherapy-induced cognitive impairment among breast cancer survivors, with 56% of participants demonstrating objective deficits in at least one cognitive domain. These findings align with existing literature that reports cognitive dysfunction as a common and persistent side effect of chemotherapy in breast cancer patients. The most affected domains in our study—memory and attention/processing speed—are consistent with previous research, which frequently identifies these cognitive areas as vulnerable to chemotherapy-related neurotoxicity.

The significant correlation between subjective cognitive complaints and objective test results supports the validity of patients' self-reported cognitive difficulties, emphasizing the importance of incorporating patient perspectives into assessment and management strategies. However, it is also important to recognize that subjective complaints may be influenced by psychological factors such as fatigue, anxiety, and depression. Our data confirm that fatigue and mood disturbances are more pronounced among survivors with cognitive impairment, suggesting a complex interplay between emotional and cognitive symptoms. This reinforces the need for multidisciplinary interventions that address both cognitive and psychological health in breast cancer survivorship care.

Age emerged as a significant predictor of cognitive impairment, which is consistent with the notion that older survivors may have diminished cognitive reserve, making them more susceptible to the neurotoxic effects of chemotherapy. Additionally, the inverse relationship between time since chemotherapy and cognitive impairment suggests that cognitive function may improve over time for some patients, although a subset experiences persistent deficit. Fatigue's strong association with cognitive impairment further implicates systemic factors such as inflammation and disrupted sleep in the pathophysiology of chemo brain.

Interestingly, hormonal therapy and education level did not significantly predict cognitive outcomes in our study, which contrasts with some previous reports. This discrepancy could be due to differences in sample size, study design, or population characteristics, warranting further investigation. Understanding individual risk factors and mechanisms underlying chemo brain is essential to developing personalized prevention and rehabilitation strategies.

Currently, there are no standardized treatments for chemotherapy-induced cognitive impairment, and management focuses primarily on supportive care and cognitive rehabilitation. Our findings underscore the urgent need for developing evidence-based interventions targeting both cognitive symptoms and associated fatigue and mood disturbances. Future research should also explore biomarkers and neuroimaging correlates to improve diagnosis and monitor treatment response.

Overall, this study contributes to the growing body of evidence on the cognitive sequelae of chemotherapy in breast cancer survivors and highlights the importance of integrating cognitive assessments into routine survivorship care to enhance long-term quality of life.

CONCLUSION

Chemotherapy-induced cognitive impairment is a prevalent and impactful complication among breast cancer survivors, affecting over half of patients in this study. Memory and attention deficits were most common, with cognitive dysfunction closely linked to fatigue and psychological distress. Age and time since chemotherapy were significant predictors of cognitive outcomes, suggesting that vulnerability and recovery trajectories vary among individuals. These findings emphasize the need for comprehensive survivorship care models that incorporate cognitive and emotional health assessments and interventions. Further research is needed to elucidate the mechanisms of chemo brain and develop targeted therapies to mitigate its effects, ultimately improving the quality of life and functional independence of breast cancer survivors.

REFERENCES:

1. Mubarik, S., Yu, Y., Wang, F., Malik, S. S., Liu, X., Fawad, M., ... & Yu, C. (2022). Epidemiological and sociodemographic transitions of female breast cancer incidence, death, case fatality and DALYs in 21 world regions and globally, from 1990 to 2017: An Age-Period-Cohort Analysis. *Journal of Advanced Research*, *37*, 185-196.
2. Tao, X., Li, T., Gandomkar, Z., Brennan, P. C., & Reed, W. M. (2023). Incidence, mortality, survival, and disease burden of breast cancer in China compared to other developed countries. *Asia-Pacific Journal of Clinical Oncology*, *19*(6), 645-654.
3. Kaur, R., Bhardwaj, A., & Gupta, S. (2023). Cancer treatment therapies: traditional to modern approaches to combat cancers. *Molecular biology reports*, *50*(11), 9663-9676.
4. Miller, K. D., Nogueira, L., Devasia, T., Mariotto, A. B., Yabroff, K. R., Jemal, A., ... & Siegel, R. L. (2022). Cancer treatment and survivorship statistics, 2022. *CA: a cancer journal for clinicians*, *72*(5), 409-436.
5. Lustberg, M. B., Kuderer, N. M., Desai, A., Bergerot, C., & Lyman, G. H. (2023). Mitigating long-term and delayed adverse events associated with cancer treatment: implications for survivorship. *Nature Reviews Clinical Oncology*, *20*(8), 527-542.
6. Rao, V., Bhushan, R., Kumari, P., Cheruku, S. P., Ravichandiran, V., & Kumar, N. (2022). Chemobrain: A review on mechanistic insight, targets and treatments. *Advances in cancer research*, *155*, 29-76.

7. Durán-Gómez, N., López-Jurado, C. F., Nadal-Delgado, M., Pérez-Civantos, D., Guerrero-Martín, J., & Cáceres, M. C. (2022). Chemotherapy-related cognitive impairment in patients with breast cancer based on functional assessment and NIRS analysis. *Journal of clinical medicine*, *11*(9), 2363.
8. Safarzadeh, E., Ghorbaninezhad, F., Soleimani, H., Rafiee, R., Mohammadzadeh, R., Azarfarin, M., & Dadkhah, M. (2024). Cognitive Impairment in CNS-Related Cancer Therapy: Focus on Immunotherapy.
9. Amani, O., Mazaheri, M. A., Moghani, M. M., Zarani, F., & Choolabi, R. H. (2024). Chemotherapy-induced cognitive impairment in breast cancer survivors: A systematic review of studies from 2000 to 2021. *Cancer Reports*, *7*(2), e1989.
10. Merceur, M., Reilly, K. T., Bonan, I., Holé, J., Hummel, E., Cogné, M., & Jacquin-Courtois, S. (2024). A systematic review of rehabilitation programs for cognitive impairment related to breast cancer: Different programs at different times?. *Annals of Physical and Rehabilitation Medicine*, *67*(5), 101832.
11. Richter, M. N., & Fattahi, F. (2022). Stem Cell-Based Models for Studying the Effects of Cancer and Cancer Therapies on the Peripheral Nervous System. *Advanced Biology*, *6*(9), 2200009.
12. Iyizoba-Ebozue, Z., Nicklin, E., Price, J., Prestwich, R., Brown, S., Hall, E., ... & Boele, F. (2024). "Why am I still suffering?": Experience of long-term fatigue and neurocognitive changes in oropharyngeal cancer survivors following (chemo) radiotherapy. *Technical Innovations & Patient Support in Radiation Oncology*, *30*, 100241.
13. Giustiniani, A., Danesin, L., Pezzetta, R., Masina, F., Oliva, G., Arcara, G., ... & Conte, P. (2023). Use of telemedicine to improve cognitive functions and psychological well-being in patients with breast cancer: a systematic review of the current literature. *Cancers*, *15*(4), 1353.
14. Murillo, L. C., Sutachan, J. J., & Albarracín, S. L. (2023). An update on neurobiological mechanisms involved in the development of chemotherapy-induced cognitive impairment (CICI). *Toxicology reports*, *10*, 544-553.
15. López-Gómez, L., Abalo, R., & Vera, G. (2022). Central Neurotoxicity of Chemotherapy. *Handbook of Cancer and Immunology*, 1-27.
16. Gupta, P., Makkar, T. K., Goel, L., & Pahuja, M. (2022). Role of inflammation and oxidative stress in chemotherapy-induced neurotoxicity. *Immunologic Research*, *70*(6), 725-741.
17. Pospelova, M., Krasnikova, V., Fionik, O., Alekseeva, T., Samochernykh, K., Ivanova, N., ... & Shevtsov, M. (2022). Potential molecular biomarkers of central nervous system damage in breast cancer survivors. *Journal of Clinical Medicine*, *11*(5), 1215.
18. Alotayk, L. I., Aldubayan, M. A., Alenezi, S. K., Anwar, M. J., & Alhowail, A. H. (2023). Comparative evaluation of doxorubicin, cyclophosphamide, 5-fluorouracil, and cisplatin on cognitive dysfunction in rats: Delineating the role of inflammation of hippocampal neurons and hypothyroidism. *Biomedicine & Pharmacotherapy*, *165*, 115245.
19. Cordeiro, A., Gomes, C., Bicker, J., & Fortuna, A. (2024). Aging and cognitive resilience: Molecular mechanisms as new potential therapeutic targets. *Drug Discovery Today*, 104093.
20. Chiu, F. Y., & Yen, Y. (2023). Imaging biomarkers for clinical applications in neuro-oncology: current status and future perspectives. *Biomarker Research*, *11*(1), 35.
21. Alzola, P., Carnero, C., Bermejo-Pareja, F., Sánchez-Benavides, G., Peña-Casanova, J., Puertas-Martín, V., ... & Contador, I. (2024). Neuropsychological assessment for early detection and diagnosis of dementia: current knowledge and new insights. *Journal of Clinical Medicine*, *13*(12), 3442.
22. Wu, H. S., Gao, F., & Given, C. (2024). Living as a survivor: sleep disturbance, fatigue, depressive mood, and cognitive dysfunction after breast cancer treatment. *Cancer nursing*, *47*(3), 221-228.
23. Oldacres, L., Hegarty, J., O'Regan, P., Murphy-Coakley, N. M., & Saab, M. M. (2023). Interventions promoting cognitive function in patients experiencing cancer related cognitive impairment: A systematic review. *Psycho-Oncology*, *32*(2), 214-228.
24. Henneghan, A. M., Van Dyk, K. M., Haywood, D., Patel, M., Franco-Rocha, O. Y., Bang, S., ... & Hart, N. H. (2024). Characterizing cancer-related cognitive impairments and impact on quality of life in women with metastatic breast cancer. *Breast Cancer Research and Treatment*, 1-14.
25. Anand, U., Dey, A., Chandel, A. K. S., Sanyal, R., Mishra, A., Pandey, D. K., ... & de la Lastra, J. M. P. (2023). Cancer chemotherapy and beyond: Current status, drug candidates, associated risks and progress in targeted therapeutics. *Genes & diseases*, *10*(4), 1367-1401.

26. Krellman, J. W., & Mercuri, G. (2023). Cognitive interventions for neurodegenerative disease. *Current Neurology and Neuroscience Reports*, *23*(9), 461-468.
27. Leow, Y., Rashid, N. L. B. A., Klainin-Yobas, P., Zhang, Z., & Wu, X. V. (2023). Effectiveness of mindfulness-based interventions on mental, cognitive outcomes and neuroplastic changes in older adults with mild cognitive impairment: A systematic review and meta-analysis. *Journal of advanced nursing*, *79*(12), 4489-4505.
28. Bianchini, C., Bonomo, P., Bossi, P., Caccialanza, R., & Fabi, A. (2024). Bridging gaps in cancer cachexia care: current insights and future perspectives. *Cancer Treatment Reviews*, 102717.
29. Hertz, D. L., Lustberg, M. B., & Sonis, S. (2023). Evolution of predictive risk factor analysis for chemotherapy-related toxicity. *Supportive Care in Cancer*, *31*(10), 601.
30. Hsiao, C. P., Goto, T., Von Ah, D., & Saligan, L. N. (2024, October). Cancer-Related Cognitive Impairment Associated with APOE rs7412 and BDNF rs6265 in Breast Cancer Survivors. In *Seminars in Oncology Nursing* (Vol. 40, No. 5, p. 151721). WB Saunders.