Zong *et al.*
European Journal of Medical Research (2025) 30:230
https://doi.org/10.1186/s40001-025-02461-2

European Journal of Medical Research

REVIEW

Open Access

Meta-analysis of altered gray matter volume in acute lymphoblastic leukemia patients' postchemotherapy via the AES–SDM

Xuelian Zong[1†], Huiping Liu[2†] and Xiaoyun Zhao[2*]

Abstract

Background Voxel-based morphometry (VBM) reveals diverse alterations in gray matter volume in acute lymphoblastic leukemia (ALL) patients after chemotherapy. However, the reported results are inconsistent. Therefore, our objective was to conduct a meta-analysis to synthesize findings from existing VBM studies and identify consistent patterns of altered gray matter volume in ALL patients post-chemotherapy.

Materials and methods A systematic search was conducted across PubMed, Web of Knowledge, Embase, Google Scholar, and CNKI for VBM studies that compared ALL patients post-chemotherapy with healthy controls (HCs) up to April 1, 2024. Significant cluster coordinates were extracted for comprehensive analysis.

Results We included 7 studies involving 143 ALL patients post-chemotherapy and 140 HCs. ALL patients who underwent chemotherapy presented decreased gray matter volume in the left caudate nucleus, left calcarine fissure/surrounding cortex, left precentral gyrus and right anterior thalamic projections. Jackknife sensitivity analysis validated the robustness of these findings.

Conclusions This meta-analysis revealed consistent gray matter volume alterations in ALL patients post-chemotherapy, emphasizing the need to explore their underlying mechanisms and long-term effects on cognitive and neurological health.

Keywords Acute lymphoblastic leukemia, Voxel-based morphometry, AES–SDM, Meta-analysis

Introduction

Acute lymphoblastic leukemia (ALL) is a hematological malignancy characterized by the proliferation of immature lymphocytes in the bone marrow. It is the most common type of cancer in children, accounting for approximately 25% of all cancer diagnoses among individuals aged 0–14 years [1, 2]. Although the 5-year overall survival rate for ALL patients has surpassed 90%, both domestically and internationally [3, 4], modern therapeutic approaches aim to not only maintain high cure rates but also minimize the sequelae of treatment. Increasing evidence suggests that chemotherapy-related cognitive impairments (CRCIs) significantly affect the long-term quality of life of survivors. Krull et al.'s study indicated that children treated for ALL can experience persistent neurocognitive damage for decades post-recovery, with impairments in attention and executive functions being predominant, affecting up to 58.9% of individuals, and these impairments tend to worsen by approximately 5% annually [5, 6]. This underscores the necessity for

†Xuelian Zong and Huiping Liu—Co-first authors.

*Correspondence:
Xiaoyun Zhao
m15693916663_1@163.com
[1] Department of Hematology, The 940th Hospital of Joint Logistics Support Force of Chinese People'S Liberation Army, Lanzhou, China
[2] Department of Pediatrics, The 940th Hospital of Joint Logistics Support Force of Chinese People'S Liberation Army, No. 333 Nanbinhe Road, Qilihe District, Lanzhou 730050, Gansu, China

ongoing brain health monitoring and early intervention to address premature brain aging and structural changes.

Neuroimaging studies on cerebral gray matter thickness, volume, and density, as well as white matter fiber structure changes in ALL patients, suggest that these alterations are likely linked to the long-term cognitive processes associated with radiotherapy and chemotherapy [7–9]. Researchers have utilized voxel-based morphometry (VBM), a technique that quantifies volumetric changes in brain gray and white matter, to reveal the impacts of treatment on ALL patients worldwide. VBM allows for precise visualization of subtle structural changes in the brain caused by different diseases or treatments and has opened new avenues for identifying central biomarkers in ALL patients. However, findings vary [10–16], and discrepancies may be related to the duration of chemotherapy, disease progression, and severity.

Given the variations in VBM results and the need for more consistent and integrative data analysis methods, this study employs the anisotropy effect size signed differential mapping (AES–SDM) method. AES–SDM provides a more robust framework for combining probability maps from different studies, potentially offering clearer insights into the common patterns of brain alterations across ALL patients treated with chemotherapy. By conducting a meta-analysis using AES–SDM, this study aimed to characterize the specific features of chemotherapy-induced cerebral gray matter volume changes and explore the underlying neurological mechanisms.

Methods and analysis

Literature search

Study selection was conducted in accordance with the PRISMA guidelines [17]. This review was registered with PROSPERO (ID: CRD42024543479). A systematic search was conducted for relevant studies in the PubMed (http://www.pubmed.gov), Web of Knowledge (http://apps.webofknowledge.com), Embase (https://www.embase.com), and CNKI (https://www.cnki.net) databases up to April .1, 2024. The following keywords were employed for the identification of candidate structural magnetic resonance imaging (sMRI) studies: ("acute lymphoblastic leukemia OR leukemia OR ALL") AND (brain structure OR structural MRI OR sMRI OR voxel-based morphometry OR VBM OR voxel-based OR gray matter*). Manual examination of the bibliographies from the collected studies and pertinent review articles was performed.

The eligibility of studies was determined based on several criteria: (1) diagnosis confirmed via clinical symptoms, peripheral blood testing, and bone marrow analysis; (2) publication in a peer-reviewed scientific journal; (3) utilization of voxel-based morphometry (VBM) for comparing brain structures between ALL patients post-chemotherapy and healthy controls (HCs); and (4) inclusion of comprehensive brain results mapped in stereotactic coordinates. The exclusion criteria were as follows: (1) editorial letters, case reports, systematic reviews, meta-analyses, and other review articles; (2) studies focused on interventions; (3) studies lacking coordinates in a standard reference space; and (4) studies omitting full-brain analysis. In cases where studies presented multiple independent samples from patients, each set of coordinates was considered individually. We contacted the primary authors via email to request any supplementary data not mentioned in the original papers. Each study was meticulously reviewed and approved for inclusion based on these criteria by two independent researchers, ZXL and LHP, through a consensus approach.

Data extraction

Data were extracted by two independent investigators (ZXL and LHP). The extracted data included the first author's name, publication year, patient and control demographics (age, sex, number of subjects), and peak stereotactic coordinates (x, y, z) reported either in Talairach or Montreal Neurological Institute (MNI) space. The coordinates reported in Talairach space were converted to MNI space for consistent analysis. These coordinates were subsequently utilized for the AES–SDM meta-analysis. In instances where a study did not explicitly report the coordinates of the activation maxima, the authors were directly contacted to provide this essential information.

AES–SDM meta-analysis

AES–SDM software was used to analyze differences in gray matter volume between ALL patients post-chemotherapy and HCs [18]. The peak coordinates in Talairach space were converted to MNI space (http://www.brainmap.org/icbm-2tal/). If the results were presented as z values, they were converted to t values for use in the analysis (www.sdmproject.com/utilities/?show=Statistics). AES–SDM reconstructed effect sizes and statistical parameter maps of increased and decreased gray matter volumes from individual studies. The Monte Carlo random effects model used in AES–SDM integrated these statistical maps with a significance threshold set at FWHM = 20 mm, uncorrected voxel $p < 0.005$, and cluster extent ≥ 20 voxels [19]. Cluster coordinate reconstruction involves converting peak t values to Hedges' g, followed by the application of a Gaussian kernel for nonuniform smoothing of adjacent peak coordinate voxels. Volume rendering of cortical clusters with significant

differences was performed in MNI standard space using Mango software.

Jackknife sensitivity analysis was performed to evaluate the robustness of the results by repeating the meta-analysis 7 times, excluding one of the 7 studies in each iteration [20].

Results

Literature search and data extraction

A systematic search resulted in the identification of 550 studies, which were subsequently assessed based on predefined inclusion and exclusion criteria. After 173 duplicates were removed, 300 irrelevant studies, 15 reviews, 8 case reports, 8 abstracts, 10 rs-fMRI studies, 6 t-fMRI studies, and filtering 1 negative result, 6 studies without reported coordinates, and 16 studies lacking HC groups, 7 studies qualified for inclusion in this meta-analysis (Fig. 1). These studies included 143 ALL patients post-chemotherapy and 140 HCs, with 37 brain regions analyzed across the studies (Table 1).

AES–SDM meta-analysis results

Compared with HCs, ALL patients post-chemotherapy showed reduced gray matter volume in four significant clusters (Table 2). These regions included the left caudate nucleus, left calcarine fissure and surrounding cortex, left precentral gyrus, and right anterior thalamic projections (Fig. 2). No increases in gray matter volume were observed in any of the brain regions.

Sensitivity analysis results

The sensitivity analysis, which involved repeating the meta-analysis while systematically excluding one study at a time, confirmed the robustness of the findings. The left caudate nucleus showed consistent reduction across all seven analyses; the left calcarine fissure and surrounding cortex and the left precentral gyrus showed decreases in

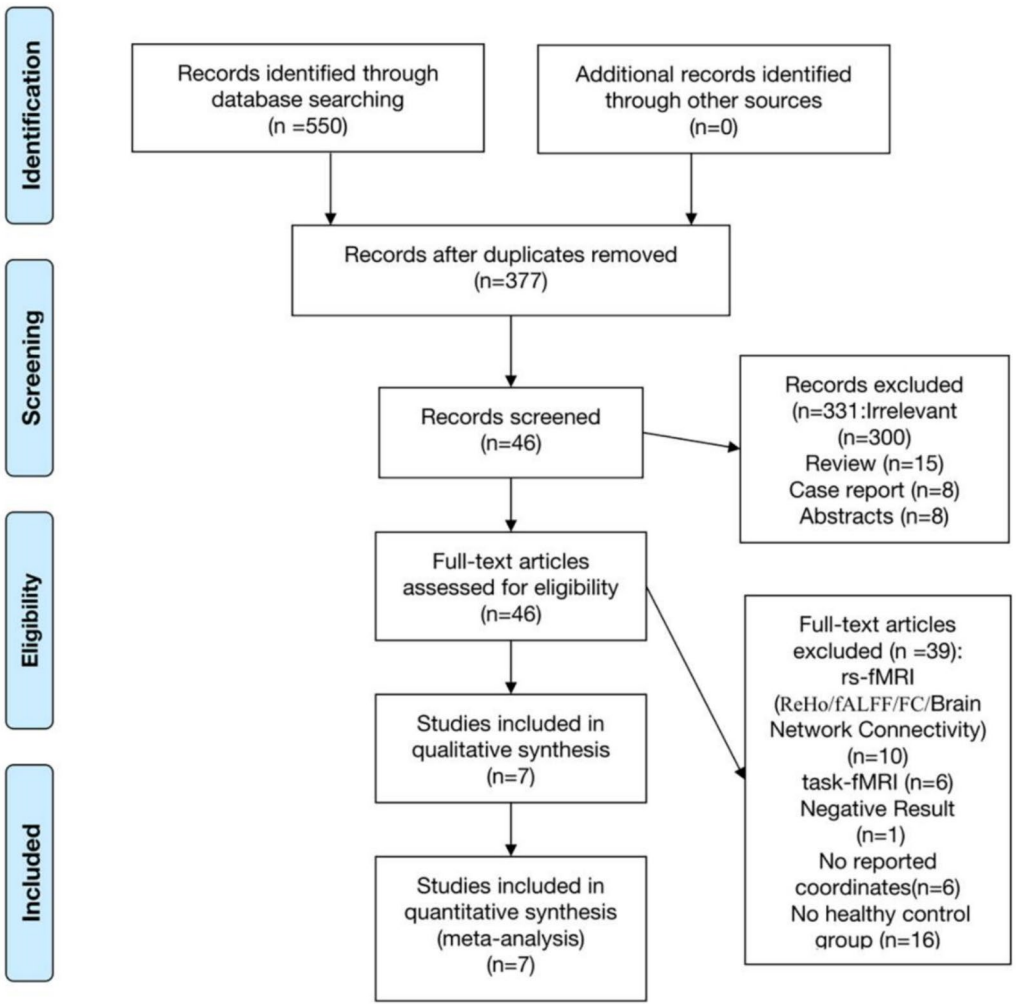

Fig. 1 Flow chart of the study selection strategy

Table 1 Characteristics of the included studies

Author, year	Sample size		Age ($X \pm S$)		Man/Female		MRI equipment	Method	Differential brain region	Corrective methods	Quality
	Patient	HCs	Patient	HCs	Patient	HCs					
Carey, 2008 [10]	9	14	15.17 ± 5.48	15.22 ± 3.78	3/6	7/7	1.5 T GE	GM	2	Puncorr < 0.001	4/1/1
Porto, 2008 [11]	20	20	8.1 ± 3.8	8.1 ± 3.8	10/10	10/10	3.0 T Siemens	GM	11	Puncorr < 0.001	4/1/1
Genschaft, 2013 [12]	27	27	15–21	15–21	14/13	14/13	3.0 T Siemens	GM	6	Puncorr < 0.001	4/1/1
Zou, 2017 [13]	28	20	40.71 ± 8.58	42.95 ± 6.39	14/14	8/12	3.0 T Siemens	GM	5	FWE p < 0.05)	4/1/1
Cahaney, 2020 [14]	15	15	15.12 ± 5.98	15.13 ± 4.21	——	——	3 T Siemens Biograph MR	GM	3	FDR p < 0.05	4/1/1
Yiwen, 2021 [15]	24	24	6.69 ± 3.55	6.93 ± 3.07	11/13	11/13	Siemens Skyra3.0 T	GM	2	Puncorr < 0.001	4/1/1
Fangling, 2023 [16]	20	20	10.72 ± 2.91	10.26 ± 2.43	11/9	11/10	signa HDxt 3.0 T	GM	8	FDR < 0.05	4/1/1

HCs healthy controls, *VBM* voxel-based morphometry, *MNI* Montreal Neurological Institute

six out of seven analyses; and the right anterior thalamic projections were noted in four analyses (Table 3).

Discussion

This AES–SDM meta-analysis confirmed consistent reductions in gray matter volume in key brain regions—namely, the left caudate nucleus, left calcarine fissure and surrounding cortex, left precentral gyrus, and right anterior thalamic projections—in post-chemotherapy ALL patients, highlighting critical neurostructural areas affected by chemotherapy. These findings suggest that chemotherapy induces widespread changes in brain areas related to motor control, sensory processing, and cognitive functions. These alterations align with the neurocognitive symptoms often reported by ALL patients post-chemotherapy, such as memory impairments, attention deficits, and motor dysfunctions. This finding is consistent with previous findings [21, 22], further indicating

Table 2 Applying the AES–SDM method to study changes in the gray matter volume in acute lymphoblastic leukemia patients post-chemotherapy

Research methods	Anatomical label Brodmann area (BA)	Peak MNI coordinate			SDM-Z	*P* value	Volume (mm^3)
		X	Y	Z			
Decrease	Left caudate nucleus	−12	16	10	−2.047	0.020326734	166
	Left calcarine fissure/surrounding cortex, BA 17	−2	−86	−4	−2.130	0.016573370	49
	Left precentral gyrus, BA 6	−24	−12	64	−1.937	0.026390970	33
	Right anterior thalamic projections	18	14	14	−1.832	0.033442497	8

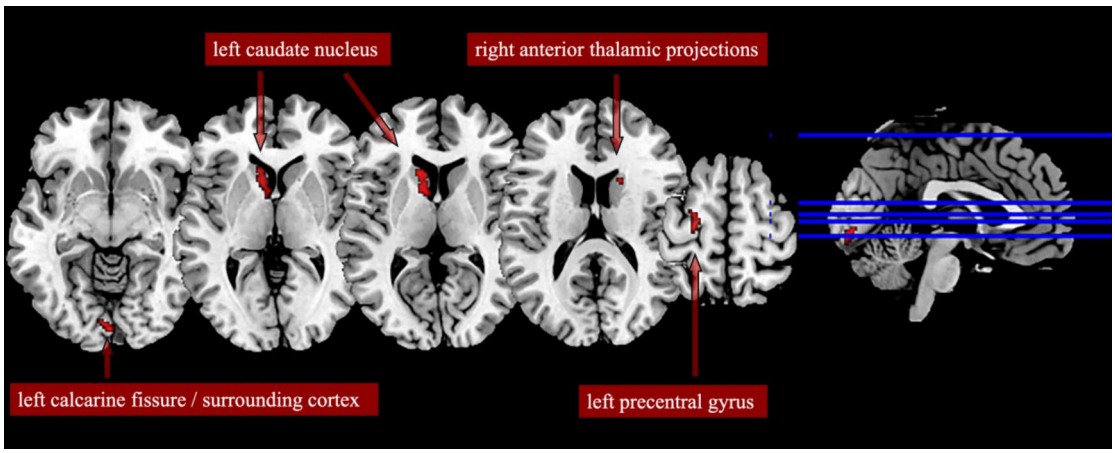

Fig. 2 Abnormal regions identified in an AES–SDM meta-analysis in acute lymphoblastic leukemia (ALL) patients post-chemotherapy. Regions showing decreased activation in ALL patients post-chemotherapy compared with healthy controls (HCs) are highlighted in red

Table 3 Results of sensitivity analysis

Discarded article	Left caudate nucleus	Left calcarine fissure/surrounding cortex	Left precentral gyrus	Right anterior thalamic projections
Carey [10]	Y	Y	Y	N
Porto [11]	Y	N	Y	Y
Genschaft [12]	Y	Y	Y	Y
Zou [13]	Y	Y	Y	Y
Cahaney [14]	Y	Y	Y	N
Yiwen [15]	Y	Y	Y	Y
Fangling [16]	Y	Y	N	N

Y: YES, N: NO

that ALL patients may experience varying degrees of damage to their gray matter volume after chemotherapy due to the direct or indirect neurotoxic effects of chemotherapy drugs. Diffusion tensor imaging studies have also confirmed white matter microstructural damage in ALL patients who receive chemotherapy, both before and after treatment [23, 24], which aligns with the neuropathological mechanisms described above. Understanding these changes in the context of chemotherapy-induced brain injury provides valuable insights into the neurobiological underpinnings of chemo brain and its long-term impact on ALL survivors.

Brain regions with decreased gray matter in ALL patients post-chemotherapy

The AES–SDM meta-analysis revealed significant reductions in gray matter volume in ALL patients post-chemotherapy, particularly in the left caudate nucleus, left calcarine fissure and surrounding cortex, left precentral gyrus, and right anterior thalamic projections. The caudate nucleus, a part of the striatum, is critical in supporting the executive function of the frontostriatal circuit. Damage to this area has been linked to impairments in attention, learning, memory, and language fluency. The calcarine fissure and surrounding cortex, located in the occipital lobe, serve as the primary visual processing region of the brain. The precentral gyrus, on the left side, is the primary motor cortex responsible for planning, controlling, and executing voluntary movements. Anterior thalamic projections are crucial for memory formation and spatial navigation and play a key role in transmitting information from the hippocampus to the cerebral cortex, which is essential for cognition and memory processing. Zou et al. [13] found gray matter shrinkage in ALL patients who had been treated for more than 3 years, with reductions in regions including the lingual gyrus, middle occipital gyrus, middle temporal gyrus, postcentral gyrus, inferior parietal lobule, precentral gyrus, and superior frontal gyrus. Zeller et al. [25] reported significant reductions in gray and white matter volumes, including those in the amygdala, caudate, hippocampus, and thalamus, through VBM analysis, although these reductions did not correspond with IQ differences between the treated patients and controls but were associated with deficits in processing speed and executive functions, which were related mainly to decreases in the volume of the gray matter, caudate, and thalamus in the brain. Furthermore, Van der Plas et al. [26] observed reductions in bilateral frontal white matter, right parietal white matter, right temporal gray matter, bilateral occipital gray matter, amygdala, thalamus, striatum, and corpus callosum volumes in ALL patients post-treatment. The decrease in frontal white matter volume was associated with impaired response inhibition, whereas reductions in the volume of the amygdala, thalamus, striatum, and corpus callosum were linked to working memory deficits. Further studies indicated that ALL patients' post-chemotherapy exhibited poorer performance in working memory and response inhibition than control patients did. Genschaft et al. [12] conducted VBM studies on pediatric ALL patients post-chemotherapy, revealing reductions in the volumes of the left calcarine gyrus, left cingulum, and anterior cingulate white matter, as well as in the amygdala, hippocampus, and thalamic gray matter, with the hippocampus showing the most significant decrease. Neurocognitive assessments demonstrated impairments in memory, attention, and learning capabilities. Comparative analysis indicated that reductions in hippocampal volume were correlated with declines in memory function. Furthermore, volume decreases in the amygdala and thalamic gray matter were associated with diminished stress-coping capacities and an increased propensity for depression. Notably, overall brain volume reductions were more significant in female patients than in their male counterparts, suggesting that females may be particularly susceptible to the cognitive risks associated with chemotherapy in ALL patients. In addition, research by Li and colleagues revealed that reductions in gray matter volume in pediatric ALL patients who had undergone chemotherapy were consistent with previous studies utilizing VBM techniques [16]. This consistency indicates that both during childhood and later in adulthood, chemotherapy-induced neurotoxic effects—either direct or indirect—result in varying degrees of gray matter volume loss. Overall, these findings suggest that chemotherapy can lead to structural changes in different brain regions, illustrating the diverse impacts of chemotherapy on brain architecture.

In our AES–SDM meta-analysis, we did not observe any regions with increased gray matter volume in ALL patients post-chemotherapy compared with HCs. A possible explanation for this finding is that there may be no regions of increased gray matter volume during treatment or that such regions are few, and the direct or indirect neurotoxic effects of chemotherapy cause varying degrees of gray matter volume reduction in ALL patients. Intriguingly, this study indicates that systemic and central nervous system-directed chemotherapy may affect gray matter, potentially leading to neurocognitive deficits associated with pathological gray matter patterns.

Changes in gray matter volume in ALL patients post-chemotherapy and their significance

Chemotherapy has a significant impact on the brain structure of ALL patients, particularly in terms of gray

matter volume. These changes are crucial for understanding how chemotherapy alters the biological basis of the brain. Traditionally, CNS prophylaxis for childhood ALL has included cranial irradiation and intrathecal chemotherapy. Since the 1980s, the neurotoxic effects of prophylactic cranial irradiation have led to its gradual replacement by intrathecal/intravenous chemotherapy [27], which presents lower neurotoxicity but still has lifelong impacts on brain development in children. Meta-analyses and large clinical data sets indicate that long-term survivors of ALL experience significant neurocognitive impairments, particularly in attention and executive functions, largely attributed to the neurotoxicity of MTX [28, 29]. MTX can cause transient or permanent neurotoxic damage via mechanisms including direct disruption of CNS folate homeostasis, direct neuronal damage, subsequent immune responses, inflammatory reactions, and microvascular injury [30]. Furthermore, evidence suggests that chemotherapy can disrupt critical periods of brain development, particularly in children with rapidly developing brains [31, 32]. Long-term follow-up studies have shown that even years after chemotherapy, the brain structure and function of these children may differ from those of healthy, untreated peers [33]. A study using VBM to analyze brain volumes 2 years post-chemotherapy in children and adolescents with ALL revealed reductions in temporal and occipital gray matter volumes [26]. In addition, reductions in subcortical gray matter structures, including the amygdala, thalamus, septal nuclei, caudate, pallidum, and striatum, have been observed [12, 26]. These findings suggest that the neurotoxic effects of chemotherapy might have lasting impacts, necessitating further research and monitoring. Overall, the changes in brain gray matter volume in ALL patients after chemotherapy illustrate the complex effects of treatment and highlight the challenges for future therapeutic strategies. Moreover, the impact of chemotherapy on brain white matter appears to be more pronounced than that on gray matter. One study revealed that white matter damage is a primary cause of neurocognitive late effects following childhood leukemia treatment [34]. Together, these structural changes in both gray and white matter emphasize the need for continued research to better understand their long-term impact on cognitive function in ALL survivors. Long-term neuropsychological and neuroimaging monitoring of these patients is essential. By gaining a deeper understanding of the effects of chemotherapy on the brain and cognitive functions of children, medical practitioners and researchers can better optimize treatment protocols, mitigate potential side effects, and ultimately improve the quality of life for these patients.

Limitations

The current study had several limitations. First, this study employed stringent exclusion criteria and analyzed published coordinates with significant differences rather than raw data, which may limit the generalizability of the findings [35]. Second, a conservative approach to multiple comparisons correction was used when analyzing the included literature data, suggesting a need for incorporating more studies and employing stricter correction methods in future observations. Third, because the original studies included in this meta-analysis did not compare chemotherapy-treated patients with non-chemotherapy-treated ALL patients, this study was unable to differentiate the specific effects of chemotherapy from those of the disease itself or other treatments. Therefore, to draw more robust and clinically actionable conclusions, future studies should include a control group that compares chemotherapy-treated and non-chemotherapy-treated patients. However, the fact that the results reached statistical significance despite these limitations suggests that the findings are robust.

Conclusion

This study, which utilized AES–SDM meta-analysis, identified consistent reductions in gray matter volume in key regions involved in executive control, sensory processing, motor function, and memory, including the left caudate nucleus, left calcarine fissure and surrounding cortex, left precentral gyrus, and right anterior thalamic projections. These changes may underlie neurocognitive impairments in ALL patients after chemotherapy and warrant further investigation. Future studies should use the most sensitive neuroimaging techniques to explore the effects of chemotherapy on ALL patients.

Author contributions

ZXL conceptualized and designed the research framework. ZXL and LHP were responsible for conducting the literature search, carrying out the initial screening, extracting relevant data, and performing the analytical computations. ZXY contributed to critical revisions that significantly improved the intellectual content of the manuscript.

Funding

The project was supported by the clinical nursing application of mesenchymal stem cell culture supernatant on oral mucosal injury (2021yxky077).

Availability of data and materials

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Competing interests
The authors declare no competing interests.

Received: 14 November 2024 Accepted: 13 March 2025
Published online: 02 April 2025

References

1. Inaba H, Pui CH. Advances in the diagnosis and treatment of pediatric acute lymphoblastic leukemia. J Clin Med. 2021;10(9):1926. https://doi.org/10.3390/jcm10091926.
2. Snodgrass R, Nguyen LT, Guo M, Vaska M, Naugler C, Rashid-Kolvear F. Incidence of acute lymphocytic leukemia in Calgary, Alberta, Canada: a retrospective cohort study. BMC Res Notes. 2018;11(1):104. https://doi.org/10.1186/s13104-018-3225-9.
3. Tang J, Yu J, Cai J, et al. Prognostic factors for CNS control in children with acute lymphoblastic leukemia treated without cranial irradiation. Blood. 2021;138(4):331–43. https://doi.org/10.1182/blood.2020010438.
4. Jeha S, Pei D, Choi J, et al. Improved CNS control of childhood acute lymphoblastic leukemia without cranial irradiation: St Jude total therapy study 16. J Clin Oncol. 2019;37(35):3377–91. https://doi.org/10.1200/JCO.19.01692.
5. Krull KR, Brinkman TM, Li C, et al. Neurocognitive outcomes decades after treatment for childhood acute lymphoblastic leukemia: a report from the St Jude lifetime cohort study. J Clin Oncol. 2013;31(35):4407–15. https://doi.org/10.1200/JCO.2012.48.2315.
6. Krull KR, Bhojwani D, Conklin HM, et al. Genetic mediators of neurocognitive outcomes in survivors of childhood acute lymphoblastic leukemia. J Clin Oncol. 2013;31(17):2182–8. https://doi.org/10.1200/JCO.2012.46.7944.
7. Mazio F, Aloj G, Pastorino GMG, et al. Default-mode network connectivity changes correlate with attention deficits in ALL long-term survivors treated with radio- and/or chemotherapy. Biology (Basel). 2022;11(4):499. https://doi.org/10.3390/biology11040499.
8. Zając-Spychała O, Pawlak MA, Karmelita-Katulska K, et al. Long-term brain status and cognitive impairment in children treated for high-risk acute lymphoblastic leukemia with and without allogeneic hematopoietic stem cell transplantation: a single-center study. Pediatr Blood Cancer. 2020;67(6): e28224. https://doi.org/10.1002/pbc.28224.
9. Ramli N, Lim CH, Rajagopal R, Tan LK, Seow P, Ariffin H. Assessing changes in microstructural integrity of white matter tracts in children with leukaemia following exposure to chemotherapy. Pediatr Radiol. 2020;50(9):1277–83. https://doi.org/10.1007/s00247-020-04717-x.
10. Carey ME, Haut MW, Reminger SL, Hutter JJ, Theilmann R, Kaemingk KL. Reduced frontal white matter volume in long-term childhood leukemia survivors: a voxel-based morphometry study. AJNR Am J Neuroradiol. 2008;29(4):792–7. https://doi.org/10.3174/ajnr.A0904.
11. Porto L, Preibisch C, Hattingen E, et al. Voxel-based morphometry and diffusion-tensor MR imaging of the brain in long-term survivors of childhood leukemia. Eur Radiol. 2008;18(11):2691–700. https://doi.org/10.1007/s00330-008-1038-2.
12. Genschaft M, Huebner T, Plessow F, et al. Impact of chemotherapy for childhood leukemia on brain morphology and function. PLoS ONE. 2013;8(11): e78599. https://doi.org/10.1371/journal.pone.0078599. (**Published 2013 Nov 12**).
13. Zou L, Su L, Xu J, et al. Structural brain alteration in survivors of acute lymphoblastic leukemia with chemotherapy treatment: a voxel-based morphometry and diffusion tensor imaging study. Brain Res. 2017;1658:68–72. https://doi.org/10.1016/j.brainres.2017.01.017.
14. Cahaney C, Stefancin P, Coulehan K, et al. Anatomical brain MRI study of pediatric cancer survivors treated with chemotherapy: correlation with behavioral measures. Magn Reson Imaging. 2020;72:8–13. https://doi.org/10.1016/j.mri.2020.05.007.
15. Yiwen L. The study of brain structural changes in children with acute lymphoblastic leukemia based on multimodal MRI. China Medical University; 2021.
16. Fangling L, Yimin G, Gaoqiang X, et al. Correlation between changes of gray matter volume and cognitive function in acute lymphoblastic leukemia children after chemotherapy based on VBM analysis. Magn Resonan Imaging. 2023;14(01):72–6.
17. Radua J, Rubia K, Canales-Rodriguez EJ. Anisotropic kernels for coordinate-based meta-analyses of neuroimaging studies. Front Psychol. 2014;5:13. https://doi.org/10.3389/fpsyt.2014.00013.
18. Nortje G, Stein DJ, Radua J, Mataix-Cols D, Horn N. Systematic review and voxelbased meta-analysis of diffusion tensor imaging studies in bipolar disorder. J Affect Disord. 2013;150:192–200. https://doi.org/10.1016/j.jad.2013.05.034.
19. Radua J, Van Den Heuvel OA, Surguladze SA. Metaanalytical comparison of voxelbased morphometry studies in obsessive-compulsive disorder vs other anxiety disorders. Arch Gen Psychiatry. 2010;67:701–11. https://doi.org/10.1001/archgenpsychiatry.2010.70.
20. Naewla S, Prajit R, Sritawan N, et al. Hesperidin ameliorates impairment in hippocampal neural stem cells related to apoptosis induced by methotrexate in adult rats. Biomed Pharmacother. 2023;166: 115329. https://doi.org/10.1016/j.biopha.2023.115329.
21. Sleurs C, Blommaert J, Batalle D, et al. Cortical thinning and altered functional brain coherence in survivors of childhood sarcoma. Brain Imaging Behav. 2021;15(2):677–88. https://doi.org/10.1007/s11682-020-00276-9.
22. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7): e1000097. https://doi.org/10.1371/journal.pmed.1000097.
23. Xi YL, Wang RZ, Xu HF, et al. Evaluation of cognitive function before and after chemotherapy in children with acute lymphoblastic leukemia using 3.0 T MR diffusion tensor imaging. J Clin Radiol. 2021;40(4):783–9. https://doi.org/10.13437/j.cnki.jcr.2021.04.035.
24. Cao WG, Gan YG, Zhao CL, et al. Diffusion tensor MR imaging in the evaluation of brain in children with acute lymphoblastic leukemia. J Clin Radiol. 2017;36(7):1019–23. https://doi.org/10.13437/j.cnki.jcr.2017.07.027.
25. Zeller B, Tamnes CK, Kanellopoulos A, et al. Reduced neuroanatomic volumes in long-term survivors of childhood acute lymphoblastic leukemia. J Clin Oncol. 2013;31(17):2078–85. https://doi.org/10.1200/JCO.2012.47.4031.
26. Van der Plas E, Schachar RJ, Hitzler J, et al. Brain structure, working memory and response inhibition in childhood leukemia survivors. Brain Behav. 2016;7(2): e00621. https://doi.org/10.1002/brb3.621.
27. Murillo LC, Sutachan JJ, Albarracín SL. An update on neurobiological mechanisms involved in the development of chemotherapy-induced cognitive impairment (CICI). Toxicol Rep. 2023;10:544–53. https://doi.org/10.1016/j.toxrep.2023.04.015.
28. Zhou C, Zhuang Y, Lin X, et al. Changes in neurocognitive function and central nervous system structure in childhood acute lymphoblastic leukaemia survivors after treatment: a meta-analysis. Br J Haematol. 2020;188(6):945–61. https://doi.org/10.1111/bjh.16279.
29. Mateos MK, Marshall GM, Barbaro PM, et al. Methotrexate-related central neurotoxicity: clinical characteristics, risk factors and genome-wide association study in children treated for acute lymphoblastic leukemia. Haematologica. 2022;107(3):635–43. https://doi.org/10.3324/haematol.2020.268565. (**Published 2022 Mar 1**).
30. Dias-Carvalho A, Ferreira M, Ferreira R, et al. Four decades of chemotherapy-induced cognitive dysfunction: comprehensive review of clinical, animal and in vitro studies, and insights of key initiating events. Arch Toxicol. 2022;96(1):11–78. https://doi.org/10.1007/s00204-021-03171-4.
31. Winocur G, Henkelman M, Wojtowicz JM, et al. The effects of chemotherapy on cognitive function in a mouse model: a prospective study. Clin Cancer Res. 2012;18(11):3112–21. https://doi.org/10.1158/1078-0432.CCR-12-0060.
32. Abalı ZY, Öztürk AP, Baş F, et al. Long-term endocrinologic follow-up of children with brain tumors and comparison of growth hormone therapy outcomes: a single-center experience. Turk Arch Pediatr. 2023;58(3):308. https://doi.org/10.5152/TurkArchPediatr.2023.22147.
33. Gandy K, Scoggins MA, Jacola LM, et al. Structural and functional brain imaging in long-term survivors of childhood acute lymphoblastic leukemia treated with chemotherapy: a systematic review. JNCI Cancer Spectr. 2021;5(5):pkab069. https://doi.org/10.1093/jncics/pkab069.
34. Anderson FS, Kunin-Batson AS, Perkins JL, et al. White versus gray matter function as seen on neuropsychological testing following bone marrow transplant for acute leukemia in childhood. Neuropsychiatr Dis Treat. 2008;4(1):283–8. https://doi.org/10.2147/ndt.s2361.

35. Ma T, Li ZY, Yu Y, et al. Gray and white matter abnormality in patients with T2DM-related cognitive dysfunction: a systemic review and meta-analysis. Nutr Diabetes. 2022;12(1):39. https://doi.org/10.1038/s41387-022-00214-2. (**Published 2022 Aug 15**).

Publisher's Note