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Central nervous system involvement in patients with Richter transformation of chronic lymphocytic leukemia (CLL): the Mayo Clinic experience

Blood Cancer Journal (2026)16:7 ; https://doi.org/10.1038/s41408-025-01446-y

To the Editor:

Richter transformation (RT) is the transformation of chronic lymphocytic leukemia (CLL) into an aggressive lymphoma, most commonly diffuse large B-cell lymphoma (DLBCL). RT involving the central nervous system (RT-CNS) is rare with existing knowledge largely limited to case reports and small series, leaving major gaps in understanding its clinicopathologic features, prognostic markers, and optimal management [1–5]. In the absence of established guidelines, most clinicians rely on treatment strategies extrapolated from primary CNS lymphoma (PCNSL) and secondary CNS DLBCL (SCNS-DLBCL) [6–9]. Given the limited data in this setting, we conducted a retrospective study to describe the clinical features, molecular profile, treatment strategies, survival outcomes and prognostic factors for patients with RT-CNS.

This study was approved by the Mayo Clinic Institutional Review Board. Patients with biopsy-confirmed RT to DLBCL or high-grade B-cell lymphoma (HGBCL) diagnosed between 01/2005 and 08/2024 and documented CNS involvement by aggressive lymphoma (biopsy- or imaging-confirmed) were identified. Clinical, pathological, molecular, and treatment data were abstracted. Overall survival (OS) was defined as time from CNS involvement to death from any cause and analyzed with the Kaplan–Meier method. Statistical analyses were performed using SPSS v28.0 and BlueSky v10.3.4.

Thirty-six patients with RT-CNS were identified. Baseline characteristics are summarized in Table 1. The median age at CLL diagnosis was 63 years (range 34–78) and 58.3% were male. High-risk disease features at CLL phase included *TP53* alteration (mutation and/or del(17p)) in 12 of 25 (48.0%) and unmutated *IGHV* in 8 of 15 (53.3%). Of the 36 patients, 24 (67.0%) were treatment-naïve for CLL at the time of RT diagnosis. The median time from CLL to RT diagnosis in these patients was 3.1 months (range 0–124.5). Among the 12 patients (33.0%) previously treated for CLL, the median number of CLL treatment lines prior to RT was 1.5 (range 1–5) and the median time from CLL to RT diagnosis was 75.9 months (range 0.3–277.4).

The median age at RT diagnosis was 69 years (range 46–79). RT histology was DLBCL in 33 patients and HGBCL in 3 (including two MYC/BCL2 double-hit and one HGBCL-NOS). Elevated LDH was noted in 33 patients (91.7%). Median Ki-67 was 90% (range 25–100%; $n = 16$). Clonal relatedness between CLL and RT based on B-cell gene (i.e., *IGHV*) rearrangement (BCGR) was related in 12 (75.0%) and unrelated in 4 (25.0%).

The median age at CNS involvement was 69 years (range 46–80). CNS involvement was parenchymal in 12 (33.3%), non-parenchymal in 13 (36.1%), and mixed in 11 (30.6%). Nineteen (52.8%) had isolated CNS disease, while 17 (47.2%) also had systemic involvement. CNS involvement occurred at RT diagnosis in 22 patients and at RT progression in 14. Among the latter, the median interval from RT diagnosis to CNS involvement was 11.1 months (range 1–41.6) and median line of prior RT therapy was 1 (range 1–5). Prior RT treatments included R-CHOP-based frontline only in 8 (22.9%), R-CHOP plus salvage in 5 (14.3%), and obinutuzumab plus high-dose methylprednisolone in 1 (2.9%) (Supplemental Table 1).

Treatments for RT-CNS are summarized in Supplemental Tables 1, 2. Among 19 patients with isolated CNS disease, 15 received high dose (HD) methotrexate (MTX)-based therapy (1 HD-MTX alone, 8 HD-MTX+ rituximab [MR], 5 HD-MTX + rituximab + temozolomide [MRT], 1 MATRix), 2 received other regimens (1 steroids only; 1 rituximab + temozolomide), 1 was untreated (early death), and treatment was unknown for one. Six underwent autologous stem cell transplant (ASCT) consolidation. Among the 17 patients with concurrent systemic and CNS disease, 6 received MTX-based therapy (3 HD-MTX, 2 MR, 1 MRT), 8 received anthracycline-based regimens plus CNS-directed therapy (5 MR-CHOP, 1 R-mini-CHOP + intrathecal MTX, 1 R-CHOP + whole brain radiotherapy, 1 hyper-CVAD), 1 received steroids/obinutuzumab/venetoclax, and 2 were untreated (early deaths). Two underwent ASCT consolidation.

After a median follow-up of 62.7 months (95% CI 45.9–79.5), the median OS following CNS involvement was 13.0 months (95% CI 1.4–24.6) (Fig. 1A, Supplemental Fig. 1). There was no statistically significant difference in OS between patients with different sites of CNS involvement (Supplemental Fig. 2A). Patients with isolated CNS involvement had a longer OS compared to those with concurrent systemic and CNS disease (median OS 34.7 vs 3.1; $P < 0.001$) (Fig. 1B). CLL treatment-naïve patients ($n = 24$) demonstrated significantly longer OS compared with those who had received prior CLL therapy (median OS 32.0 vs 1.8 months; $P < 0.001$) (Fig. 1C, Supplemental Fig. 2B).

In patients with isolated CNS disease ($n = 19$), those treated with MTX-based regimens ($n = 15$) had a median OS of 34.7 months (Supplemental Fig. 2C). Among patients with concurrent systemic and CNS involvement ($n = 17$), there was no significant difference in OS between MTX-based regimens ($n = 6$) and other treatments (anthracycline-based plus CNS-directed treatments, or other regimens; $n = 9$) as first-line management ($P = 0.492$) (Supplemental Fig. 2D).

Clonal relatedness by BCGR was not associated with OS ($P = 0.127$) but favored patients with clonally unrelated RT (Fig. 1D). Most long-term survivors (>5 years) had unrelated CLL and RT clones. *IGHV* mutation status showed no association with OS ($P = 0.19$) (Fig. 1E). In contrast, *TP53* alterations correlated with significantly shorter OS (3.2 vs 17.8 months; $P = 0.0198$) (Fig. 1F).

Received: 3 October 2025 Revised: 11 November 2025 Accepted: 12 December 2025
Published online: 07 January 2026

Table 1. Patient and disease characteristics of the study population.

Phase of disease	Number ($N = 36$)		%
Chronic lymphocytic leukemia	Sex		
	Male	21	58.3
	Female	15	41.7
	Age at diagnosis (years)		
	Median (range)	63 (34–78)	
	IGHV		
	Mutated	7	46.7
	Unmutated	8	53.3
	Missing	21	
	CLL *FISH* by Dohner hierarchy		
	Del(17p)	9	34.6
	Del(11q)	0	0
	Trisomy 12	6	23.1
	Negative	7	26.9
	Del(13q)	4	15.4
	Missing	10	
	TP53 somatic mutation		
	Negative	7	63.6
	Positive	4	36.4
	Missing	25	
	TP53 alteration (Del(17p) and/or *TP53* somatic mutation)		
	Negative	13	52.0
	Positive	12	48.0
	Missing	11	
	CLL treatment status prior to RT		
	Untreated	24	66.7
	Treated	12	33.3
	Lines of CLL treatment prior to RT		
	Median (range) in all	0 (0–5)	
	Median (range) in treated ($n = 12$)	1.5 (1–5)	
Richter transformation	Time to transformation (months)		
	Median (range)	17.3 (0–277.4)	
	Age at RT diagnosis (years)		
	Median (range)	69 (46–79)	
	Pathology at RT		
	DLBCL	33	91.7
	HGBCL	3	8.3
	Cell of origin		
	GCB	13	61.9
	Non-GCB	8	38.1
	Missing	15	
	MYC IHC		
	Negative	4	20.0
	Positive (≥40%)	16	80.0
	Missing	16	
	BCL2 IHC		
	Negative	5	20.0
	Positive (≥50%)	20	80.0
	Missing	11	
	MYC/BCL2 double expressor		
	Positive	10	27.8
	MYC FISH		
	Negative	13	61.9
	Positive	8	38.1
	Missing	15	
	BCL2 FISH		
	Negative	13	81.2
	Positive	3	18.8
	Missing	20	
	BCL6 FISH		
	Negative	16	100.0
	Positive	0	0
	Missing	20	
	Double-/triple-hit		
	MYC/BCL2 Double-hit	2	5.6
	PD-1 IHC		
	Negative	9	52.9
	Positive	8	47.1
	Missing	19	
	EBV IHC		
	Negative	15	93.7
	Positive	1	6.3
	Missing	20	
	MYD88 mutation		
	Negative	4	66.6
	Positive	2	33.3
	Missing	30	
	Ki-67 ($n = 16$)		
	Median (range)	90% (25–100%)	
	LDH		
	Elevated	33	91.7
	Normal	3	8.3
	Lines of treatment for RT before CNS involvement		
	Median (range) in all	0 (1–5)	
	Median (range) in treated (n = 15)	1 (1–5)	
	Clonal relatedness with CLL		
	Related	12	75.0
	Unrelated	4	25.0
	Missing	20	
CNS involvement of Richter transformation	Time from RT diagnosis to CNS involvement of RT (months)		
	Median (range) in all	0 (0–41.6)	
	Median (range) in those with CNS involvement at RT progression ($n = 14$)	11.1 (1–41.6)	
	Age at CNS RT diagnosis		
	Median (range)	69 (46–80)	
	CNS biopsy or imaging confirmation		
	Tissue biopsy	16	44.4
	CSF	5	13.9
	Vitreous fluid	3	8.3
	Imaging	12	33.3
	Timing of CNS involvement		
	At RT diagnosis	22	61.1
	At RT progression	14	38.9
	Extent of CNS involvement		
	Isolated CNS involvement	19	52.8
	CNS and systemic involvement	17	47.2
	Site of CNS involvement		
	Parenchymal only	12	33.3
	Parenchymal + others[a]	11	30.6
	Others[b]	13	36.1

[a]Parenchymal + others: parenchymal + leptomeningeal, cranial nerve roots, or ocular disease.
[b]Others: leptomeningeal, ocular, cranial or spinal nerve roots, and skull base lesions.

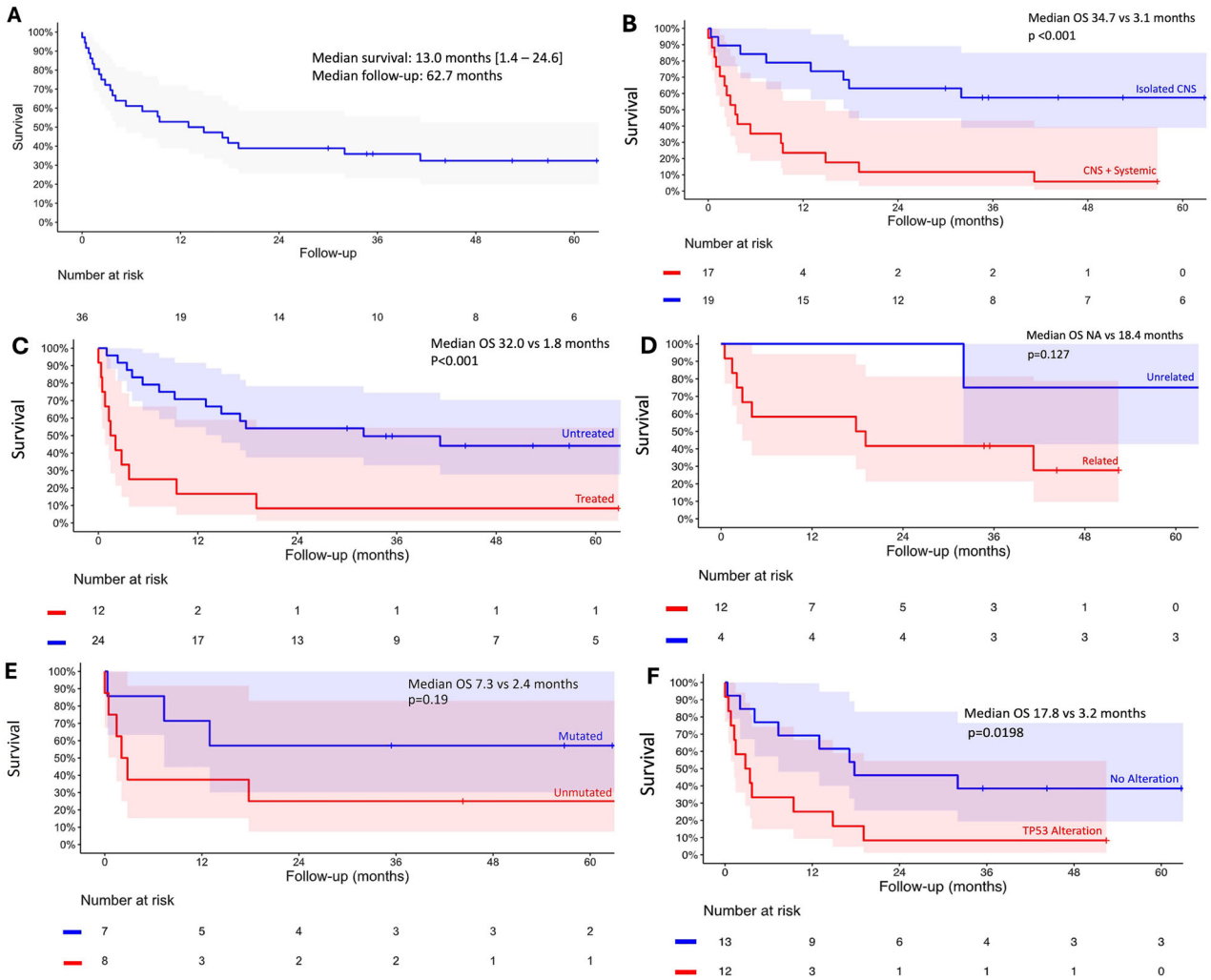

Fig. 1 Overall survival (OS) after confirmed CNS involvement of RT. A OS after CNS involvement of RT ($n = 36$). **B** OS after CNS involvement of RT, stratified by isolated CNS versus concurrent systemic and CNS involvement. **C** OS stratified by prior CLL treatment (untreated vs treated). **D** OS by clonal relatedness (clonally unrelated vs. related). **E** OS by *IGHV* mutational status (mutated vs. unmutated). **F** OS by *TP53* alteration status (altered vs. wild-type).

Our study represents the largest retrospective analysis to date evaluating the characteristics and outcomes of patients with RT-CNS. We found that RT-CNS is clinically heterogeneous, occurring either in isolation or in conjunction with systemic disease. The overall prognosis is poor, with a median OS of 13 months. However, patients with isolated CNS involvement had significantly better survival compared to those with concurrent systemic disease. This observation is consistent with prior studies in SCNS-DLBCL, where systemic disease is associated with worse outcomes and presents challenges in delivering therapies that effectively target both compartments [6, 8, 9]. In addition, prior CLL-directed therapy and *TP53* alterations were associated with inferior survival. These findings align with broader RT data from our group and others, suggesting that prior CLL therapy may be associated with or select for biologically high-risk disease leading to an aggressive disease presentation at the time of RT and CNS disease [10–13]. The association of *TP53* alterations with worse prognosis of RT-CNS is consistent with their well-established role as adverse prognostic factors in both CLL and RT.

Given the rarity of RT-CNS, formal treatment guidelines are lacking. Our study offers several treatment-related observations that may help guide therapeutic decisions. Despite the overall poor prognosis, patients with isolated RT-CNS who were treated with HD MTX-based regimens had more favorable outcomes, with a median OS of 34.7 months. This suggests that HD MTX-based therapy may be effective in this subgroup, and that treatment strategies used in PCNSL where HD MTX is a central component may be appropriate in RT cases with isolated CNS disease [7, 9]. Although data were limited by the small number of patients who underwent ASCT consolidation, this approach may be considered in patients with isolated CNS disease and those with clonally unrelated disease, since these may clinically and biologically behave similar to de novo PCNSL, where ASCT has shown survival benefit in fit patients achieving disease control post-induction therapy [14, 15]. We noted that patients with concurrent systemic disease represent a particularly challenging subgroup to manage, similar to those with SCNS-DLBCL accompanied by systemic disease [7, 9]. In our study, outcomes were poor in this group regardless of whether treatment started with CNS-directed HD MTX-based regimens alone or combined approaches targeting both CNS and systemic compartments. These findings highlight both the suboptimal effectiveness of current treatment strategies in patients with concurrent systemic disease and the lack of clarity around the optimal timing for addressing systemic versus CNS disease.

Limitations of this study include its retrospective design, modest sample size, heterogeneity in treatment approaches, and incomplete clonality and molecular data due to the long

span of study. These factors may limit the generalizability of our findings, reduce the power of subgroup analyses, and potentially underestimate the prevalence of high-risk alterations such as *TP53* mutations. Additionally, our series did not include patients treated with novel therapies, such as CAR T-cells, which have shown anti-lymphoma efficacy in the CNS, limiting our ability to evaluate the efficacy of these emerging modalities in the setting of RT-CNS. Despite these limitations, this study represents the largest reported and most comprehensive characterization and outcome analysis of RT-CNS to date and may help guide future therapeutic decision-making in this rare and clinically challenging population.

In conclusion, RT-CNS represents a rare entity with poor overall outcomes, especially in patients with concurrent systemic disease. Many of the adverse prognostic features we identified in RT-CNS, including prior CLL treatment and *TP53* alterations, parallel those seen in RT more broadly. RT with isolated CNS disease may represent a more favorable subgroup, potentially responsive to conventional CNS-directed therapies such as HD MTX. Prospective and larger studies, which would be facilitated by multicenter collaborations, are needed to validate these observations and guide optimal and novel treatment strategies for this challenging population.

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DATA AVAILABILITY

Data is available upon reasonable request.

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ACKNOWLEDGEMENTS

We thank the clinical teams and healthcare providers who provided care to the patients included in this study.

AUTHOR CONTRIBUTIONS

YW came up with conception. DB and SAAY collected and assembled the data. DB and YW performed statistical analyses. DB, SAAY and YW wrote the manuscript. DB, SAAY, PJH, LER, SSK, EM, NEK, ABK, ALB, CCW, PBJ, GSN, TMH, TH, MT, JFL, ACR, RDP, HWT, MS, RLK, RH, SAP, and YW reviewed the manuscript, provided expert opinion, and approved the final version of the manuscript.

COMPETING INTERESTS

DB: declares no conflicts of interest. PJH: *Research funding* (to institution): BeOne, AstraZeneca. *Consultancy and Honorarium* (compensation to the institution): AbbVie. LER: *Consulting*: AbbVie, Ascentage, AstraZeneca, Beigene, Janssen, Loxo Oncology, Pharmacyclics; *Data safety monitoring committee (DSMC) member*: Ascentage; CME speaker: DAVA, Curio, Medscape, and PeerView; *Minority ownership interest*: Abbott Laboratories; Travel support: LOXO oncology, *Research funding* (to institution): Adaptive Biotechnologies, AstraZeneca, Genentech, AbbVie, Pfizer, Loxo Oncology, Aptose Biosciences, Dren Bio, and Qilu Puget Sound Biotherapeutics. NEK: *Advisory Board for*: AbbVie, Astra Zeneca, Beigene, Janssen, Pharmacyclics, *DSMC* (Data Safety Monitoring Committee) for: AstraZeneca, BMS-Celgene, Dren Bio, *Research funding*: AbbVie, Acerta Pharma, Astra Zeneca, Pharmacyclics/Jannsen, Merck. TH: *Research funding* (to institution): BeiGene, BMS; Advisory Board: BeiGene. SAP: *Research funding*: Janssen, AstraZeneca, Merck, and Genentech for clinical studies in which Sameer A. Parikh is a principal investigator. *Honoraria*: Pharmacyclics, Merck, AstraZeneca, Janssen, BeiGene, Genentech, SoBi, MingSight Pharmaceuticals, Novalgen Limited, Kite Pharma, and AbbVie for Sameer A. Parikh's participation in consulting activities/advisory board meetings. YW: *Research funding* (to institution): Incyte, InnoCare, LOXO Oncology, Eli Lilly, MorphoSys, Novartis, Genentech, Genmab, AbbVie, BeiGene, Merck; *Advisory board* (compensation to institution): Eli Lilly, LOXO Oncology, TG Therapeutics, Incyte, InnoCare, Kite, Jansen, BeiGene, AstraZeneca, Genmab, AbbVie; *Consultancy* (compensation to institution): InnoCare, AbbVie; Honorarium (to institution): Kite.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Mayo Clinic Institutional Review Board. The study was conducted in compliance with the Declaration of Helsinki. Given the retrospective nature of the study, a waiver of consent was obtained.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41408-025-01446-y.

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