THYMIC REGRESSION AND LEUKEMIC INFILTRATION DYNAMICS IN ACUTE LYMPHOBLASTIC LEUKEMIA: PROSPECTIVE EVALUATION BY 18F-FDG PET/CT AND DIFFUSION-WEIGHTED MRI WITH CLINICO-MORPHOLOGICAL AND PROGNOSTIC CORRELATION

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ABSTRACT

Purpose: To quantitatively evaluate the dynamics of thymic involution and residual leukemic infiltration in T-lineage and B-lineage acute lymphoblastic leukemia (ALL) using multimodal imaging (18F-FDG PET/CT and diffusion-weighted MRI) and to determine their predictive value for early therapeutic response and long-term outcome. Materials and Methods: Prospective cohort of 46 patients (27 T-ALL, 19 B-ALL; age 3–42 years, median 14.8) diagnosed 2022–2025. All patients underwent baseline and day 22–28 18F-FDG PET/CT and 3T thoracic MRI (DWI b=0-1000 s/mm², ADC mapping). Thymic volume (3D volumetric segmentation), SUVmax, TLG, ADCmean, and ADCmin were measured. Thymic biopsies/resections (n=18) were analyzed by H&E and IHC (TdT, CD1a, CD3, CD99, Ki-67). MRD was assessed by 8-color flow cytometry (10^{-4} sensitivity). Results: At diagnosis, median thymic

volume in T-ALL was 48.7 cm³ (range 9.2–112.4) vs 8.4 cm³ in B-ALL ($p<0.001$); SUVmax 9.8 ± 3.4 vs 2.1 ± 0.9 ($p<0.001$). After induction, thymic volume decreased by 64.2 ± 14.8 % in T-ALL and 81.7 ± 11.2 % in B-ALL. ADCmean increased from 0.74 ± 0.12 to 1.41 ± 0.18 × 10^{-3} mm²/s ($p<0.001$). Thymic volume reduction ≥58 % and ADCmean ≥1.18 × 10^{-3} mm²/s predicted MRD negativity with 91 % sensitivity and 88 % specificity (AUC=0.94). Combined criterion (baseline SUVmax ≥8.5 + ADCmean ≤0.82) identified a high-risk group with 2-year overall survival of 61 % vs 92 % in the low-risk group (log-rank $p=0.012$). Histopathological correlation revealed 89.4 ± 7.2 % blast infiltration in T-ALL with strong inverse correlation to ADCmean ($r=-0.86$, $p<0.001$). Conclusion: The thymus represents the primary leukemic reservoir in T-ALL. Multimodal PET/CT and DWI-MRI accurately monitor thymic regression kinetics and serve as powerful, non-invasive early response and prognostic biomarkers superior to conventional morphology. These parameters enable risk-stratified therapy adaptation, potentially improving outcomes in high-burden disease.

KEYWORDS: leukemia, T-ALL, thymic involution, leukemic infiltration, 18F-FDG PET/CT, diffusion-weighted MRI, apparent diffusion coefficient (ADC), minimal residual disease, prognostic imaging biomarker, mediastinal mass, therapeutic response assessment, histopathological correlation

INTRODUCTION

T-cell acute lymphoblastic leukemia (T-ALL) constitutes 15 % of pediatric and 25–30 % of adult ALL cases and is distinguished by massive thymic infiltration in >80 % of patients, frequently manifesting as a bulky anterior mediastinal mass that may cause superior vena cava syndrome, tracheal compression, or cardiac tamponade. Beyond serving as the primary leukemic reservoir, the thymus provides a protective microenvironment through stromal factors (CXCL12, SCF, IL-7), fostering

chemoresistance and relapse. Consequently, rapid and complete thymic regression during induction is a pivotal therapeutic objective.

Current response assessment relies predominantly on invasive bone marrow MRD measurement (flow cytometry or NGS), which neglects the thymic sanctuary site and is costly and unavailable in many settings. Recent COG, AIEOP-BFM 2024–2025, and International BFM guidelines have begun incorporating imaging-based criteria to overcome these limitations.

This prospective study evaluates combined 18F-FDG PET/CT and diffusion-weighted MRI as non-invasive, quantitative, and reproducible tools for monitoring thymic involution. By integrating metabolic (SUVmax, TLG), volumetric, and microstructural (ADC) parameters, and correlating them with histopathology, MRD, and survival outcomes, we tested the hypothesis that a ≥58 % thymic volume reduction plus ADCmean ≥1.18 × 10^{-3} mm^2/s at the end of induction predicts MRD negativity with >90 % accuracy. These biomarkers have the potential to enable early risk-adapted intensification (e.g., blinatumomab, nelarabine) or de-escalation, thereby reducing relapse rates that remain 20–40 % despite modern immunotherapy.

AIM

To determine the diagnostic and predictive value of thymic volume, metabolic (PET/CT), and microstructural (DWI-MRI) parameters in T-ALL and B-ALL and to establish clinically applicable imaging response criteria for integration into risk-adapted protocols.

MATERIALS AND METHODS

This prospective single-center observational cohort study (January 2022 – October 2025) enrolled 46 consecutive newly diagnosed ALL patients (27 T-ALL, 19 B-ALL; median age 14.8 years, range 3–42; 32 males) at a tertiary hematology-oncology center. Diagnosis followed WHO/ICC 2022/2024 criteria with standard

immunophenotyping. Exclusion criteria: CNS involvement (n=2), PET/CT contraindications, or incomplete follow-up.

All patients received uniform induction therapy according to COG AALL1732 or AIEOP-BFM 2017 protocols (vincristine, daunorubicin, prednisone, PEG-asparaginase, intrathecal methotrexate; blinatumomab escalation in high-risk T-ALL if MRD >0.01 % on day 15).

Imaging was performed at baseline (within 48 h of diagnosis) and post-induction (days 22–28):

- **18F-FDG PET/CT** (GE Discovery MI): 5 MBq/kg, 60-min uptake; SUVmax, SUVmean, MTV, and TLG calculated using 40–50 % isocontour threshold (PERCIST 1.0, MIM Software v7.1).
- **3T MRI** (Siemens Magnetom Skyra): axial T1WI, T2WI, STIR, and multi-b DWI (b = 0, 50, 400, 800, 1000 s/mm²). ADC maps generated monoexponentially. Thymic 3D volumetry and ROI placement performed semi-automatically (ITK-SNAP 4.0 & 3D-Slicer 5.2) by two blinded radiologists (inter-observer ICC = 0.94).

Thymic biopsy/resection (n=18) underwent H&E and IHC (TdT, CD1a, CD3, CD4, CD8, CD99, Ki-67, CD34). MRD was assessed by 8-color flow cytometry (sensitivity 10^{-4}) on day 29 bone marrow aspirates. Follow-up reached 24 months (median 18.5 months); OS and EFS analyzed by Kaplan-Meier.

Statistical analysis: SPSS 27.0 and R 4.3; non-parametric tests, Spearman correlation, ROC-derived cut-offs (Youden index), log-rank, and multivariate Cox regression. Study powered to detect ≥20 % difference in OS (80 % power, α=0.05). Ethical approval (IRB #2021-045) and written informed consent were obtained from all patients/guardians.

The standardized, reproducible protocol ensures high-quality validation of imaging biomarkers in T-ALL.

RESULTS

Baseline characteristics confirmed T-ALL predominance in adolescents (median age 16.2 vs 12.1 years in B-ALL; $p=0.03$), higher WBC (45 vs 18 × 10^9/L; $p<0.001$) and LDH (1200 vs 650 U/L; $p<0.001$).

At diagnosis, T-ALL showed markedly larger thymic volumes (48.7 ± 21.3 cm^3 vs 8.4 ± 4.1 cm^3; $p<0.001$), intense hypermetabolism (SUVmax 9.8 ± 3.4 vs 2.1 ± 0.9; TLG 428.6 ± 312.4 g vs 24.1 ± 18.7 g; $p<0.001$), and restricted diffusion (ADCmean 0.74 ± 0.12 vs 1.23 ± 0.15 × 10^{-3} mm^2/s; $p<0.001$). Heterogeneous T2 signal with cystic/necrotic areas was seen in 74 % of T-ALL cases.

Post-induction (day 24.6 ± 2.1), thymic volume decreased by 64.2 ± 14.8 % in T-ALL (to 17.4 ± 8.2 cm^3) and 81.7 ± 11.2 % in B-ALL (to 1.5 ± 0.9 cm^3), with complete involution (<5 cm^3) in 22 % vs 68 %, respectively. Metabolic activity normalized (SUVmax 3.1 ± 1.4; Deauville 3–4 in 89 %) and diffusion restriction resolved (ADCmean 1.41 ± 0.18 × 10^{-3} mm^2/s; +91 %; $p<0.001$).

Optimal response thresholds for MRD negativity (<0.01 %):

- Thymic volume reduction ≥58 % → 91 % sensitivity, 88 % specificity (AUC 0.94)
- ADCmean ≥1.18 × 10^{-3} mm^2/s → 89 % sensitivity, 85 % specificity (AUC 0.92)
- Combined criteria → 95 % overall accuracy

Histopathology (n=18) confirmed 89.4 ± 7.2 % blasts, Ki-67 92.8 %, near-absent Hassall's corpuscles, and strong inverse correlation between blast percentage and ADCmean ($r=-0.86$; $p<0.001$).

ETP-ALL subgroup (n=5) displayed inferior regression (48.3 % volume reduction) and higher relapse rate (40 %). Two-year overall survival was 94 % in patients with ≥58 % volume reduction vs 43 % in those with <50 % (log-rank $p<0.001$).

Multivariate analysis confirmed imaging response as an independent prognostic factor (HR 4.2; p=0.001).

Multimodal PET/CT and DWI-MRI provided superior sensitivity and prognostic precision compared with single-modality or conventional morphological assessment.

DISCUSSION

Our findings align with and extend recent landmark studies, confirming the thymus as the dominant sanctuary in T-ALL and highlighting multimodal imaging's superiority in response assessment. Baseline hypermetabolism (SUVmax >9) and restricted diffusion (ADC $<0.8 \times 10^{-3}$ mm²/s) reflect dense blast infiltration, consistent with histopathological Ki-67 >90 %, underscoring PET/CT's role in tumor burden quantification akin to TLG in DLBCL. The 64 % volume regression post-induction exceeds CT-based benchmarks (40–50 % in prior reports), likely due to asparaginase's thymic-specific cytotoxicity, while ADC normalization signals apoptosis/necrosis, preceding MRD clearance by 1–2 weeks. ROC-derived ≥58 % reduction threshold outperforms EORTC visual criteria (AUC 0.94 vs 0.76), echoing COG 2024 imaging guidelines and AIEOP-BFM's emphasis on functional metrics. In ETP-ALL subsets, blunted response predicts 4-fold relapse risk, supporting nelarabine intensification. Compared to B-ALL, T-ALL's persistent thymic signal post-therapy (22 % incomplete involution) explains higher sanctuary relapses (15–20 % mediastinal), advocating PET/MRI surveillance over CT alone. Limitations include single-center design (n=46), potential selection bias (exclusion of sedated infants), and short follow-up (median 18 months), though power was adequate for primary endpoints. Future multicenter trials (e.g., COG AALL1931 addendum) should validate in diverse ethnicities and integrate AI for automated segmentation (reducing inter-observer variability <5 %). Therapeutically, high-risk signatures (SUVmax ≥8.5 + low ADC) identify candidates for CAR-T or HSCT escalation, potentially boosting 5-year EFS from 70 % to >85 %. By bridging imaging, pathology, and genomics, this framework transforms T-ALL

management from reactive to predictive, minimizing toxicity in responders and salvaging high-burden cases early.

CONCLUSIONS

The thymus is the dominant leukemic sanctuary site in T-ALL, with baseline volume >48 cm^3, SUVmax >9, and ADC <0.8 × 10^{-3} mm^2/s signifying high-risk disease amenable to targeted intensification. 2. Combined 18F-FDG PET/CT and DWI-MRI provide accurate, quantitative monitoring of thymic regression, with post-induction changes (volume ≥58 % reduction, ADC ≥1.18 × 10^{-3} mm^2/s) predicting MRD negativity in 95 % of cases. 3. These non-invasive biomarkers correlate robustly with histopathology (blast % r=−0.86) and outcomes (2-year OS HR 4.2), outperforming morphology and enabling risk-adapted therapy. 4. Integration into protocols like COG/AIEOP-BFM could reduce relapses by 20–30 %, with prospective validation needed for global adoption.

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