

OUTCOMES OF CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA TREATED ON A NATIONAL PROTOCOL IN PAKISTAN: A MULTICENTER PROSPECTIVE STUDY

A Pakistan Society of Pediatric Oncology (PSPO) Multicenter Prospective Study – PSPO ALL-2020-01

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INTRODUCTION

Childhood acute lymphoblastic leukemia (ALL) is highly curable in high-income countries (HICs), with survival approaching 85–90%. Outcomes in low- and middle-income countries (LMICs) remain substantially inferior, reflecting disparities in early diagnosis, access to standardized treatment, supportive-care infrastructure, and treatment adherence. Most LMIC data derive from single-center series that cannot capture national-level disease patterns or health-system challenges. To address this gap, the Pakistan Society of Pediatric Oncology (PSPO) developed a national, standardized, risk-adapted treatment protocol (PSPO ALL-2020-01) in 2021, enabling harmonized care and prospective multicenter data collection across the country, with post-induction therapy adapted to each center’s minimal residual disease (MRD) testing capacity. We report the clinical characteristics, treatment course, and survival outcomes of the total (all-phenotype) prospective cohort treated under this protocol — the first national, multicenter, prospective benchmark for pediatric ALL outcomes in Pakistan.

METHODS

Design: Prospective, multicenter cohort study under the PSPO national childhood ALL protocol (PSPO ALL-2020-01). **Setting:** Five tertiary pediatric oncology centers across Pakistan, participating in a coordinated national network. **Population:** Children aged 1–18 years with newly diagnosed ALL (immunophenotyping by flow cytometry / IHC), enrolled June 2021–February 2025. Previously treated patients were excluded. **Risk stratification:** NCI criteria, immunophenotype, CNS status, cytogenetics (where available), and response to a 7-day prednisolone prophase (Day-8 peripheral blast count). **Treatment:** 3-drug induction (standard risk) or 4-drug induction (high risk), risk-adapted post-induction therapy by MRD ($\geq 0.01\%$ = positive) or morphology per institutional capacity (Figure 1). **Outcomes:** Overall survival (OS) and event-free survival (EFS); EFS events = induction failure, relapse, death, and treatment abandonment. **Statistical analysis:** Kaplan–Meier survival estimation; group comparisons by appropriate tests; two-sided $p < 0.05$ considered significant.

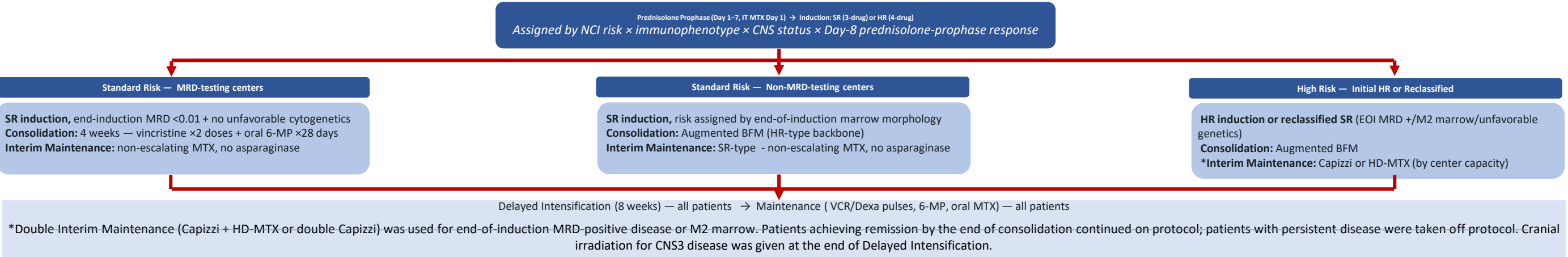


Figure 1. PSPO ALL-2020-01 Risk-Adapted Treatment Schema

RESULTS

Cohort characteristics and enrollment: The updated analytic cohort included 1,534 children with ALL, with enrollment distributed across five treating centers and concentrated at the largest-volume center. Patients were predominantly male, with a median age of 6 years. B-ALL accounted for about four-fifths of the cohort, while T-ALL represented 19.3%; nearly one-third presented with WBC $\geq 50 \times 10^9/L$. Baseline demographic, disease, and cytogenetic characteristics are summarized in Table 1, and center-wise enrollment is shown in Figure 2. **Treatment course and induction response:** Of 1,660 records collected, 1,534 were retained after verification and data cleaning. Most patients completed induction (82.3%), whereas 17.7% did not, primarily due to early mortality. Among patients who completed induction, 96.6% achieved complete remission. Subsequent treatment completion and the overall treatment pathway are summarized in Figure 3. **MRD response:** End-induction MRD was available in 866 patients, with approximately 30% remaining MRD-positive. Among 240 end-induction MRD-positive patients with an interpretable post-consolidation assessment, 157 (65.4%) converted to MRD negativity, demonstrating substantial further disease clearance during consolidation. MRD response patterns are shown in Figure 4A and 4B. **Factors associated with mortality:** In a univariate analysis, mortality differed significantly by presenting WBC, NCI risk, cytogenetic variables, induction regimen, end-of-induction remission, MRD status, and treating center; a smaller difference was also observed by sex. In contrast, age group, immunophenotype, CNS status, and prednisolone response were not significantly associated with mortality. See Table 2. **Events and survival:** Death was the leading adverse outcome, followed by treatment abandonment and relapse, with infection accounting for most classified deaths. At a median follow-up of approximately 1.4 years, estimated 3-year OS was 66.6% and 3-year EFS was 47.2% when abandonment was included as an event, increasing to approximately 55% when abandonment was censored. See Figures 5 and 6.

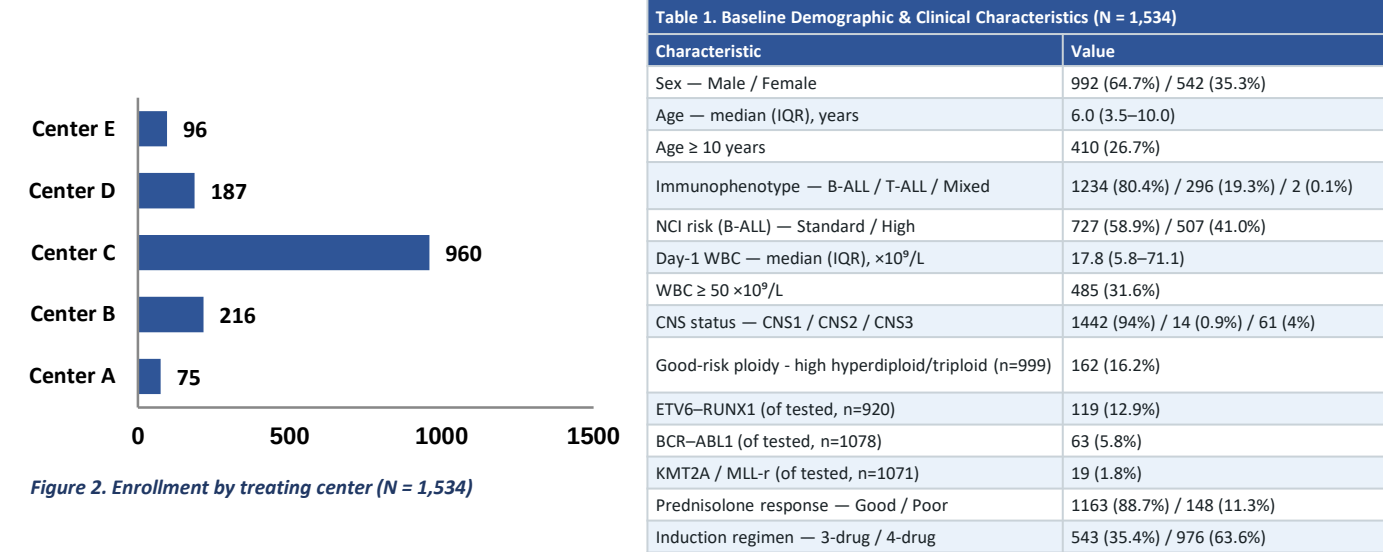


Figure 2. Enrollment by treating center (N = 1,534)

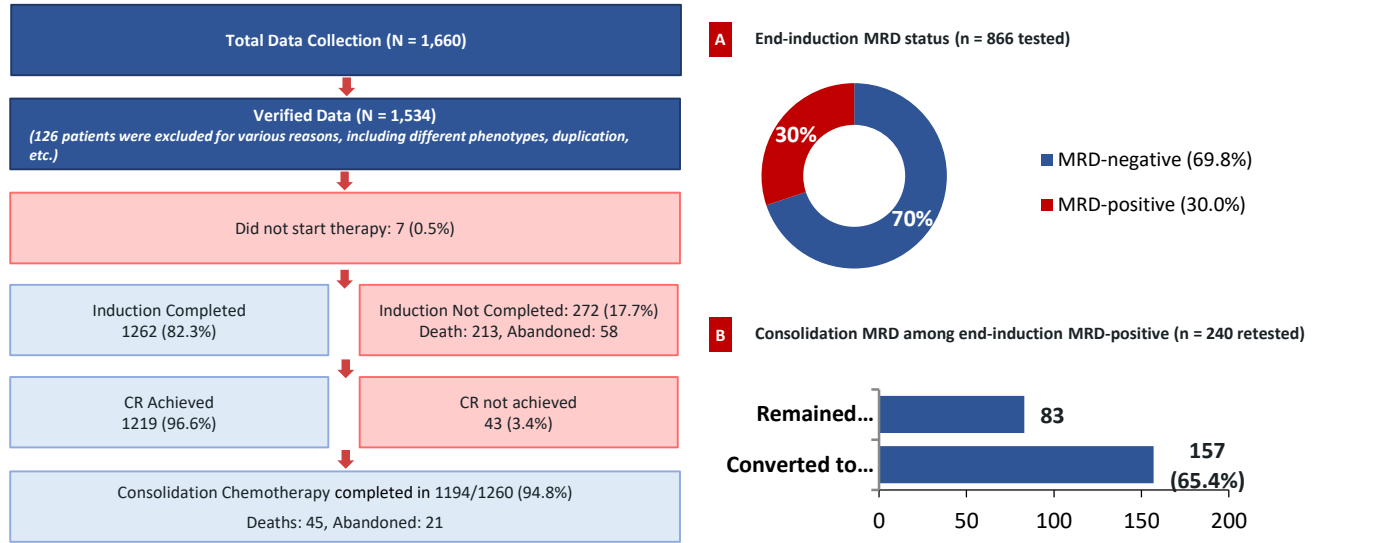


Figure 3. Treatment Course – Total Cohort

Figure 4. End-Induction MRD status & consolidation dynamics

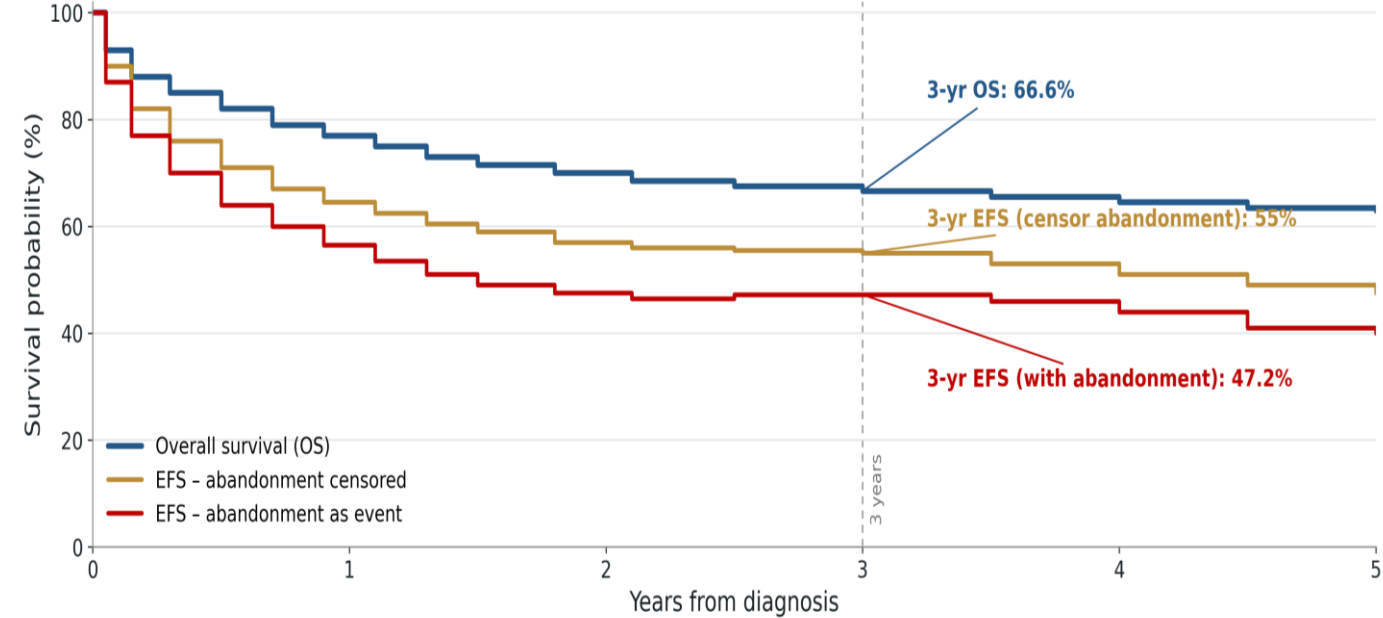


Figure 5. Kaplan–Meier Overall and Event-Free Survival

Table 2. Outcome Comparison by baseline characteristics and treatment factors (Univariate)				
Variable	Category	Alive	Dead	p-value
Sex	Male / Female	709 / 357	283 / 185	0.023
Age group	0–9.99y / 10–18y	786 / 280	338 / 130	0.54
Day-1 WBC	<50 / 50–100 / $\geq 100 (\times 10^9/L)$	764 / 124 / 177	284 / 78 / 106	<0.001
NCI risk	Standard / High	543 / 321	184 / 186	<0.001
Immunophenotype	B-ALL / T-ALL	864 / 200	370 / 96	0.46
CNS status	CNS1 / CNS2 / CNS3	1007 / 11 / 39	435 / 3 / 22	0.47
Ploidy	Good-risk / Not good-risk	170 / 538	50 / 179	<0.001
ETV6–RUNX1	Present / Absent / Not done	102 / 595 / 369	17 / 206 / 245	<0.001
BCR–ABL1	Present / Absent / Not done	39 / 776 / 251	24 / 239 / 205	<0.001
Prednisolone response	Good / Poor	816 / 103	347 / 45	0.671
Induction regimen	3-drug / 4-drug	427 / 631	116 / 345	<0.001
End-induction CR	Yes / No	979 / 30	239 / 13	<0.001
End-induction MRD	Negative / Positive	519 / 114	86 / 45	<0.001
Treating center	A / B / C / D / E	70 / 145 / 708 / 79 / 64	5 / 42 / 252 / 137 / 32	<0.001

DISCUSSION

- This updated cohort is one of the largest prospectively assembled childhood ALL datasets from a resource-constrained setting and demonstrates the feasibility of coordinated national protocol-based care with centralized outcome monitoring.
- The cohort carries a substantial high-risk burden, including frequent hyperleukocytosis, a relatively high T-ALL proportion, poor prednisolone response in 11.3% of evaluable patients, and end-induction MRD positivity in approximately 30% of tested patients.
- Disease control among children able to complete induction was strong: 96.6% achieved CR. However, 17.7% of the cohort did not complete induction, predominantly because of death, substantially lowering population-level remission and survival.
- Deaths represented more than half of all first events, and treatment abandonment accounted for a further 22%, indicating that non-relapse events are major drivers of the survival gap.
- The difference between EFS with abandonment included (47.2%) and with abandonment censored (55%) quantifies the additional impact of treatment discontinuation on outcome.
- Significant variation by treatment center highlights the need for minimum supportive-care standards, standardized diagnostics/MRD access, and cross-center quality-improvement strategies in addition to a shared chemotherapy backbone.

CONCLUSION

PSPO ALL-2020-01 provides a prospective national benchmark for childhood ALL outcomes in Pakistan. High remission rates among induction completers demonstrate that effective leukemia control is achievable within the protocol; however, overall survival remains constrained by early mortality, treatment abandonment, persistent MRD in a substantial subset, and inter-center variability. Improving outcomes will require strengthened infection prevention and supportive care, broader standardized MRD assessment, structured abandonment-mitigation strategies, and coordinated cross-center quality improvement.

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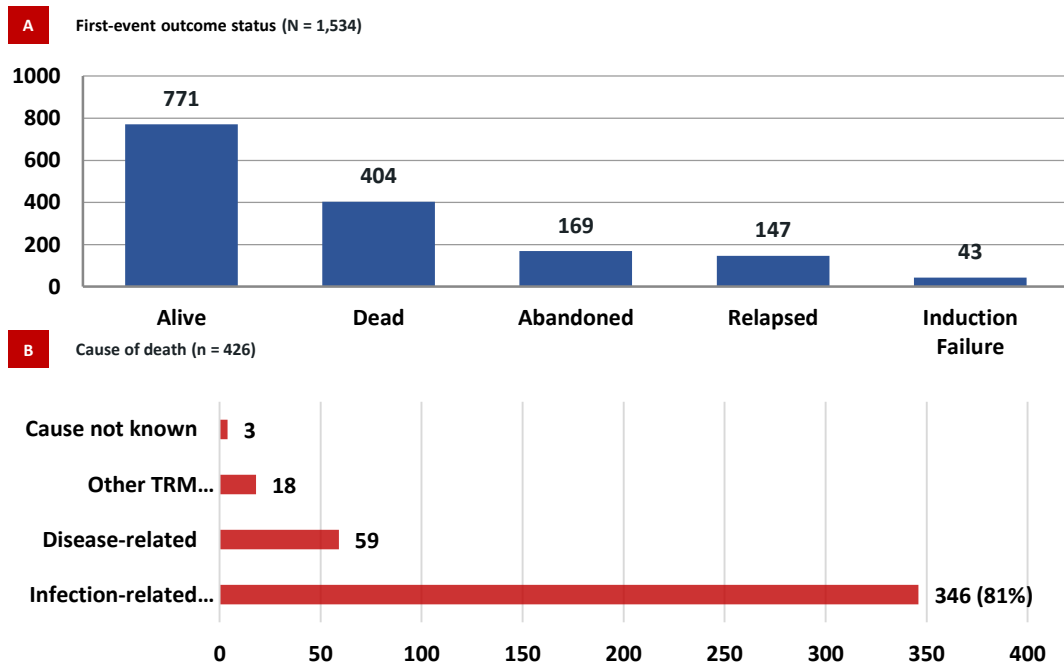


Figure 6. Outcome events & cause of death