

Infection-Related Mortality in Children with Acute Lymphoblastic Leukemia

A National, Prospective, Multicenter Cohort Study from Pakistan (PSPO ALL-2020-01)

Naeem Jabbar, Mohiba Ali Khowaja, Nuzhat Yasmeen, Sadia Imran, Uzma Imam, Zehra Fadoo, Zulfiqar Ali, Asim Belgaumi

Pakistan Society of Pediatric Oncology

I INTRODUCTION

Childhood acute lymphoblastic leukemia (ALL) has survival rates approaching 90% in high-income countries; however, outcomes remain substantially poorer in low- and middle-income countries (LMICs). This disparity is driven in part by high treatment-related mortality, particularly infection-related deaths during neutropenic phases of therapy.

The Pakistan Society of Pediatric Oncology (PSPO) established a national, multicenter, prospective standard-of-care protocol to standardize treatment for childhood ALL and enable systematic data collection. This national dataset offers a valuable opportunity to examine infection-related mortality in a large, prospectively followed cohort.

STUDY AIM

To characterize the burden, timing, and determinants of infection-related mortality in the PSPO ALL cohort and identify actionable priorities to strengthen supportive care and inform national infection-prevention strategies.

M METHODS

Prospective multicenter cohort study conducted within the PSPO ALL-2020-01 standard-of-care protocol across five pediatric oncology centers in Pakistan. Children aged 1–16 years with newly diagnosed ALL were enrolled from August 2021 to March 2025. Core clinical data, treatment outcomes, and cause of death were collected prospectively in the centralized study database. Additional infection-specific details for patients who died were subsequently abstracted retrospectively from available clinical records. Associations with infection-related mortality were assessed using Fisher’s exact test and univariate and multivariable logistic regression, with statistical significance set at $p<0.05$.



R RESULTS

Among 1,536 children, 426 (27.7%) died. Infection accounted for 346 deaths, representing 81.2% of all deaths and 22.5% of the overall cohort (Figure 1). Most infection-related deaths occurred early: 265 (76.6%) occurred during the first 6–8 months of intensive therapy and 81 (23.4%) during maintenance (Figure 2a). Induction accounted for 147 deaths (42.5%), with a peak during days 22–28 (Figure 2b).

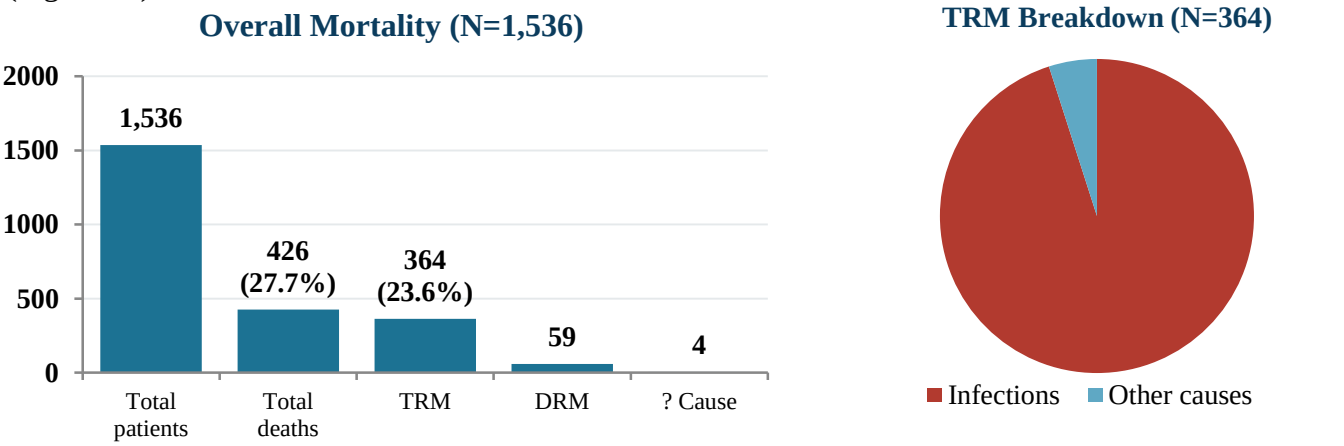


Figure 1. Overall mortality outcomes and breakdown of treatment-related mortality (TRM) by cause. DRM = disease-related mortality.

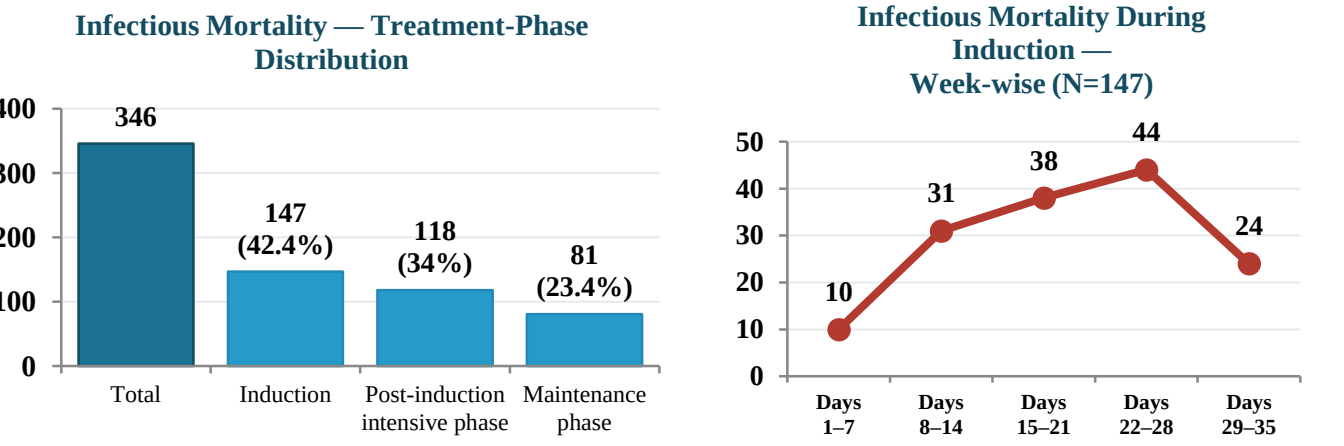


Figure 2. (a) Distribution of infection-related deaths across treatment phases, (b) Weekly distribution of infection-related deaths during induction

Age and presenting WBC were examined both as continuous and categorical variables in univariate analyses (age: 1–<10 vs ≥ 10 years; WBC: <50 vs $\geq 50 \times 10^9/L$). Younger age, higher presenting WBC, high-risk disease, and anthracycline-containing induction were associated with infection-related mortality. In the multivariable model, age and WBC were entered as continuous variables. Each additional year of age was associated with lower odds of infection-related death (adjusted OR 0.912, 95% CI 0.879–0.947; $p<0.001$), while anthracycline-containing induction remained independently associated with higher odds of infection-related mortality (adjusted OR 2.235, 95% CI 1.577–3.168; $p<0.001$).

Table 1. Univariate and multivariable logistic regression analysis of factors associated with infection-related mortality.

Variable	Crude OR (95% CI)	P	Adjusted OR (95% CI)	P
Age (per 1-year increase)	0.960 (0.930–0.991)	0.012*	0.912 (0.879–0.947)	<0.001*
Presenting WBC, continuous	1.001 (1.000–1.002)	0.046*	0.999 (0.980–1.001)	0.346
High-risk disease	1.475 (1.157–1.880)	0.002*	1.396 (0.959–2.033)	0.082
T-cell ALL	1.095 (0.806–1.487)	0.563	—	—
Anthracycline-containing induction	2.023 (1.541–2.656)	<0.001*	2.235 (1.577–3.168)	<0.001*

Marked inter-center variation was observed (Figure 3). Among deaths with available infection data, bloodstream bacterial infections were most frequent. Gram-negative organisms predominated, particularly *Escherichia coli* and *Klebsiella* spp. (See Tables 2 and 3)

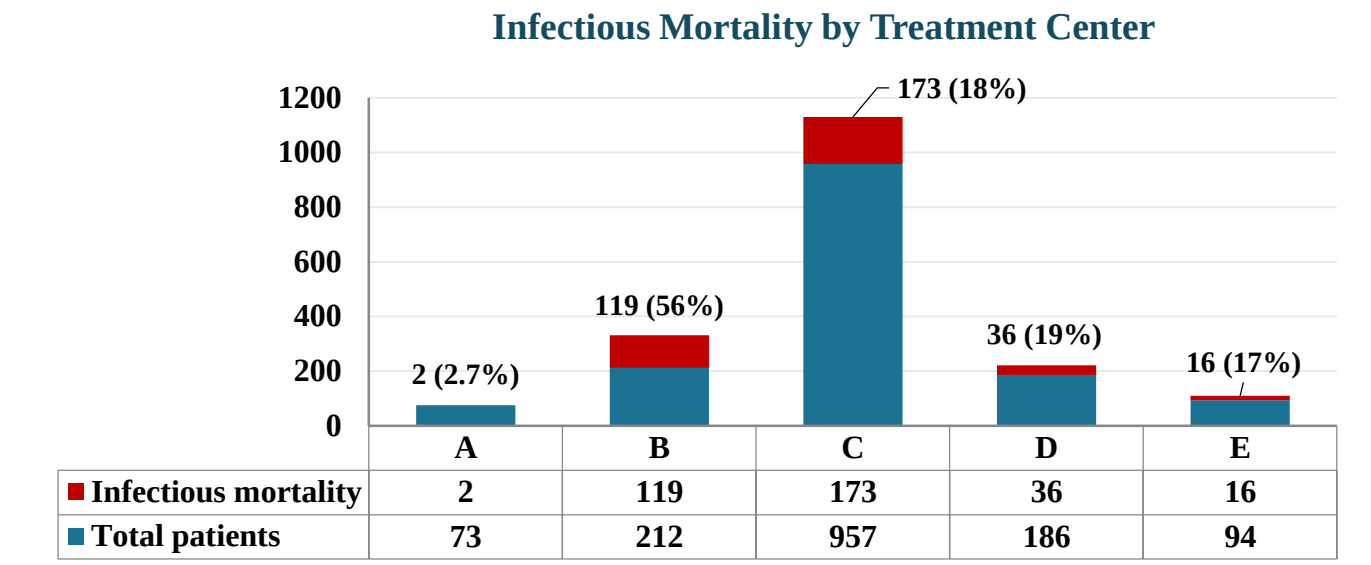


Figure 3. Infection-related mortality by treatment center (A–E). Center-level analysis includes 5/6 centers; retrospective infection-specific data were unavailable for reliable classification at one center.

Table 2. Infection etiology among deaths with available microbiological/clinical infection data (n=256).*	
Bloodstream infections	130 (38%)
Neutropenic colitis	33 (10%)
Other clinically convincing infections	24 (7%)
LRTI, probable bacterial	14 (4%)
Other viral (Dengue, CMV, COVID-19)	13 (4%)
Measles	12 (3%)
Varicella	9 (3%)
Urinary tract infection	9 (3%)
LRTI, probable fungal	6 (2%)
Probable meningoencephalitis	3 (1%)
Invasive fungal disease – mucormycosis	3 (1%)

*Infection-specific microbiological data were available from 4 participating centers; therefore, etiologic classification was possible for 256 of 346 infection-related deaths.

Table 3. Microbial organisms identified in bloodstream infection (N=130)	
E. coli	46 (35%)
Klebsiella spp.	23 (18%)
Candida spp.	18 (14%)
Pseudomonas spp.	20 (15%)
Enterococcus spp.	17 (13%)
Acinetobacter spp.	16 (12%)
Coagulase-negative staphylococci	16 (12%)
Staphylococcus aureus	6 (5%)

Organism categories are not mutually exclusive because individual isolates from polymicrobial bloodstream infections are included; therefore, percentages may exceed 100%. Polymicrobial infections occurred in 46/130 (35%) bloodstream infection episodes.

D DISCUSSION

Early vulnerability: Infection was the dominant cause of mortality, with deaths concentrated during intensive therapy, particularly during induction, identifying a critical period for enhanced monitoring, caregiver education, and rapid sepsis management.

Treatment and patient factors: Younger age and anthracycline-containing induction were independently associated with infection-related mortality, supporting risk-adapted monitoring and strengthening of supportive care during intensive therapy.

Microbiology and antimicrobial stewardship: Gram-negative predominance highlights the need for center-specific antibiograms, surveillance of antimicrobial resistance, and appropriate empiric antibiotic selection and de-escalation within antimicrobial-stewardship programs.

Center-level variation: Variation despite a shared treatment protocol suggests that supportive-care infrastructure, diagnostics, infection-control practices, antimicrobial use, staffing, and timely access to care may influence outcomes and represent targets for cross-center quality improvement.

LIMITATIONS: Many deaths lacked microbiological confirmation, and inter-center heterogeneity may limit the generalizability of findings.

C CONCLUSION

National febrile-neutropenia and sepsis-response pathways should prioritize rapid escalation during induction. Intensive regimens should be supported by structured infection-prevention and supportive-care bundles, with empiric antibiotic strategies guided by center-specific antibiograms and antimicrobial-stewardship principles. Cross-center quality-improvement initiatives and caregiver education are needed to reduce preventable mortality and variation in outcomes.

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Data Quality Officer: Muhammad Ali

Data Abstractors: Khushboo Asif, Mena Iqbal, Ghazal Fatima, Junaid Jamshed, Furqan Hussain