



Original Article



Treatment-Related Mortality in Pediatric Acute-Lymphoblastic and Myeloid Leukemia: Experience from A Low- and Middle-Income Setting

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ABSTRACT

Treatment-induced complications are challenging to manage in low-middle-income country (LMIC) settings, leading to higher mortality rates. **Objectives:** To ascertain the frequency, causes, and risk factors leading to treatment-related mortality (TRM) in children with acute leukemia (ALL and AML) in our setup. **Methods:** A Retrospective descriptive cohort study was done at the Hematology Oncology Department of the Children's Hospital, Lahore. Using non-probability consecutive sampling, data of pediatric acute leukemia patients (<16 years of age) who experienced TRM during the study period were recorded. **Results:** Among TRM 136 (75%) had Acute-Lymphoblastic-Leukemia, and 45 (25%) had Acute-Myeloid-Leukemia. Median age of expiry 7.0 years (1-15years) with a Male-to-Female ratio 1.5:1. Underlying causes of TRM were Infection-related mortality in 168 (93%), Hemorrhage in 10 (5.5%), and Drug toxicity in 3 (1.5%). Under-nutrition (<10th centile) was found in 111 (61%) and 120 (67.4%) patients who were on active chemotherapy. Median hospital stays 10 days (1-45days) and median distance of residence to medical facility 222km (41-995km). Median values of hematological parameters at death: hemoglobin 8.0g/dl (2.6-14.7g/dl), WBC 0.57x10³/mm³ (0.0-500), platelets 15x10³/mm³ (0-503), and CRP 149mg/L (0.1-193mg/L). Significant factors associated were platelet counts (p=0.009), hemoglobin (p=0.001), and CRP (p=0.017). **Conclusions:** The Major cause of TRM in children with acute leukemia is infection. Noteworthy factors were male gender, residents of rural areas, cytopenia, high CRP, under-nutrition, and ongoing chemotherapy sessions. The majority of deaths occurred during Induction chemotherapy. Infection prevention/control and enhanced supportive care can result in decreasing TRM in acute leukemia.

INTRODUCTION

Despite significant progress in pediatric oncology, cancer remains the leading cause of death among children globally and the second most common cause in high-income countries (HICs) [1]. Approximately 90% of the 400,000 annual pediatric cancer cases occur in low- and middle-income countries (LMICs), where five-year survival rates are markedly lower as compared to more developed areas or the world, estimating it less than 10% in low-income countries and around 50-60% in upper-middle-income countries (UMICs) [2-5]. In contrast, survival rates in HICs exceed 80% [2]. This striking disparity in outcomes can be attributed to numerous factors, including limited access to

specialized pediatric oncology centers, inadequate diagnostic services, insufficient availability of essential medicines and treatment supplies, a shortage of trained healthcare professionals, weak social support systems, delayed presentation, and high rates of treatment abandonment in LMICs [6]. As a result, the burden of pediatric cancer is disproportionately borne by resource-limited countries, which face significant challenges in providing optimal supportive care [7]. Many pediatric cancer units in LMICs lack the infrastructure and supportive care available in HICs, affecting outcomes when applying standardized/high-intensity regimens developed



in high-resource settings. As a result, the risks and benefits of these treatments often differ significantly between the two settings and are often associated with increased treatment-related toxicity and mortality in LMICs due to a lack of required supportive care [8]. Infections, particularly sepsis, remain a leading cause of death among children undergoing cancer treatment in these regions [9, 10]. Although treatment-related mortality (TRM) has declined over time in some UMICs, it continues to be a major contributor to poor outcomes in many LMICs. Enhancing the quality of care for pediatric cancer patients in these settings is essential to address the global survival gap [7]. However, a major barrier to progress is the lack of robust data on the causes and risk factors for TRM in LMICs, limiting the development of targeted, context-specific interventions.

Treatment-related mortality (TRM) remains a major barrier to improving survival in children with acute leukemia in low- and middle-income countries, where limited supportive care and high infection burden contribute substantially to poor outcomes. Despite advances in chemotherapy protocols, there is insufficient local evidence from Pakistan regarding the frequency, major causes, and contributing risk factors of TRM in pediatric ALL and AML patients. This study addresses this critical gap by evaluating the burden of TRM, identifying predominant causes such as infection and sepsis, and assessing demographic, nutritional, and clinical factors associated with mortality. This study aims to determine the rate and underlying causes of treatment-related mortality in pediatric patients with acute leukemia and to explore associated demographic and disease-related factors.

METHODS

This retrospective descriptive study was conducted in the Pediatric Hematology-Oncology and Bone Marrow Transplant Department at The Children's Hospital Lahore, Pakistan. The study duration was one year, and the data were collected from 1st January 2023 to 30th December 2023 after taking an Institutional Review Board approval (IRB No. 818/CH-UCHS). All pediatric acute leukemia patients who expired during the treatment and the study period and fulfilled the criteria of the study were recorded. The Non-probability consecutive sampling technique was used for the recruitment of the sample. Previous literature from similar low- and middle-income settings has reported TRM rates between 15–30%, particularly during induction chemotherapy [7]. Based on a total of 706 new leukemia cases in the study period, the observed TRM frequency of 181 (25.6%) was consistent with this expected range, supporting the relevance and adequacy of the sample size for descriptive analysis. The clinical course of the patient in each group was recorded on a pre-designed proforma. The

data obtained included demographic information (name, age, sex, and address), complete history, physical examination, subtype, laboratory, and radiological investigation that were done during hospital stay to determine the cause of the presenting illness and death. Patients were put in groups according to the type of leukemia. Inclusion criteria: All children diagnosed as having pediatric acute leukemia (ALL and AML) with an age range of 01 to 16 years, who were started on treatment and died before completing treatment due to any treatment-related complications. Exclusion criteria were children less than one year and more than 16 years of age, relapsed disease, expired before treatment started, treatment started/taken at other hospitals, malignancies other than acute leukemia, on Palliative treatment, and any cause of death other than treatment-related. All patients of ALL were treated according to the UKALL 2011 Interim Guidelines [11], and all patients of AML were treated according to the COG AAML 0531 protocol [12]. For the current study, operational definitions were formulated as follows: TRM was defined as any death during remission induction chemotherapy or any death occurring on treatment after remission induction chemotherapy with documented complete remission [13]. Under-nutrition was defined as less than the 10th centile weight-for-age (WFA) plotted on the CDC WFA centile growth charts. Death due to haemorrhage was defined as death due to intracranial bleeding or cerebral thrombosis evident on neuroimaging, viz, CT or magnetic resonance imaging (MRI). Death due to drug toxicity was defined as any drug-related complication suggested by the laboratory and/ or radiological findings. Sepsis was defined as clinical or laboratory evidence of infection with multiple organ dysfunction syndrome (MODS). The principal outcome measure of my study was to determine the causes of TRM. Further, they were divided into sepsis, drug toxicity, and hemorrhagic complications. The data were analyzed using SPSS version 24.0. Quantitative variables such as age, duration of illness, duration of treatment after diagnosis of malignancy, and hospital stay were summarized using medians and ranges due to non-normal distribution, as confirmed by the Shapiro-Wilk test. Categorical variables such as gender, clinical symptoms, and signs were described using frequencies and percentages. The Mann-Whitney U test was used to compare continuous variables between two independent groups, while the Pearson Chi-square test was applied to compare categorical variables. A p-value of <0.050 was considered statistically significant. Effect modifiers were controlled through stratification.

RESULTS

The total number of newly registered cases of acute leukemia in the duration of study period was 706, while the

total number of TRM of acute leukemia was 181 (25.6%) (Figure 1).

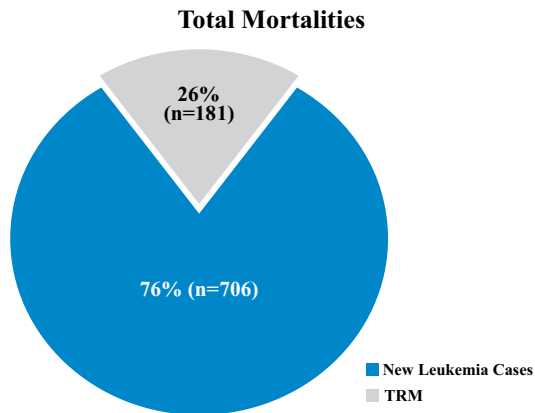


Figure 1: Total New Acute Leukemia Cases Vs TRM

Among the patients with TRM, 136 (75%) had Acute Lymphoblastic Leukemia, and 45 (25%) had Acute Myeloid Leukemia. Median age at expiry 7.0 years (1.0–15.0 years) with a Male-to-Female ratio of 1.5:1. The underlying causes of TRM were Infection-related mortality in 168 (93%), Hemorrhage in 10 (5.5%), and Drug toxicity in 3 (1.5%) (Table 1).

Table 1: Causes of Treatment-Related Mortality (TRM) (n=181)

Causes of TRM	Types	n (%)
Infection Related	Total	168 (92.8%)
	Sepsis	94 (51.4%)
	Fungal Pneumonia	34 (18.5%)
	Lower Respiratory Tract Infection	19 (10.5%)
	Central Nervous System (CNS) Infection	21 (11.6%)
Haemorrhagic	Intra-Cranial Bleed	10 (5.5%)
Drug Toxicity	Total	03 (1.7%)
	Peg Asparaginase-Associated Pancreatitis	01 (0.6%)
	Hepatic Failure	02 (1.1%)

The Mann-Whitney U test revealed significant differences in key hematological and inflammatory parameters at death. Platelet counts had a median of $15 \times 10^3/\text{mm}^3$ (range: 0–503; $p=0.009$) indicating a statistically significant reduction. Hemoglobin levels were also significantly low, with a median of 8.0 g/dL (range: 2.6–14.7; $p=0.001$). While WBC counts had a wide range (0–500 $\times 10^3/\text{mm}^3$) and a median of 0.57, the difference was not statistically significant ($p=0.096$). C-reactive protein (CRP) levels were markedly elevated median 149 mg/L (range: 0.1–193) showing a significant inflammatory response ($p=0.017$) (Table 2).

Table 2: Hematological Parameters Studied for Treatment-Related Mortality (TRM)

Factors	Parameter	Median (Range)	p-value (Mann-Whitney U test)
Hematological Parameters	Platelets ($\times 10^3/\text{mm}^3$)	15 (0–503)	0.009
	Hemoglobin (g/dL)	8.0 (2.6–14.7)	0.001
	WBC ($\times 10^3/\text{mm}^3$)	0.57 (0–500)	0.096
Inflammatory Marker	CRP (mg/L)	149 (0.1–193)	0.017

Undernutrition (<10th centile) was found in 111 (61%). Median stay at the hospital was 10 days (1–45 days), and median distance to travel to the medical facility was 222 km (41–995 km). Factors were studied concerning the cause of death (TRM), but no factor was found significant (Table 3).

Table 3: Factor Studied for Treatment-Related Mortality (TRM)

Factors	Groups	n (%)	p-Value
Age Groups	<1	0	0.190
	1–5	78 (43%)	
	5–10	62 (34.3%)	
	>10	41 (22.7%)	
Gender	Male	107 (59%)	0.530
	Female	74 (41%)	
Under-Nutrition	Yes	111 (61.3%)	0.740
	No	70 (38.7%)	
WFA (Centile)	<3	83 (45.9%)	0.930
	3–10	31 (17.1%)	
	11–25	23 (27.7%)	
	26–50	19 (10.5%)	
	51–75	13 (7.5%)	
	76–90	5 (2.8%)	
	91–97	1 (0.6%)	
	>97	6 (3.3%)	
Leukemia Type	ALL	136 (75%)	0.480
	Pre B	50 (27.6%)	
	Pre T	21 (11.6%)	
	Philadelphia +ve	5 (2.7%)	
AML	ALL	45 (25%)	0.090
	SR	16 (8.8%)	
ALL Risk Category	HR	65 (36%)	0.820
	SR	16 (8.8%)	
	SR	16 (8.8%)	
Last Chemo (Weeks Before Expiry)	<1	120 (66.3%)	0.820
	1–2	40 (22.1%)	
	>2	21 (11.6%)	
Expire During Chemo Session	Yes	122 (67.4%)	0.460
	No	59 (32.6%)	
Residence	Rural	135 (74.6%)	0.992
	Urban	40 (22%)	
	Afghanistan	6 (3.4%)	

(Data analysed using the Pearson chi-square test)

Blood culture results were available in only 14 (10.3%) cases of infection-related mortality with Pseudomonas (n=2), Klebsiella (n=1), MRSA (n=1), and no growth in 10 cases. Among the 168 infection-related treatment-related mortality (TRM) cases, 4 were culture-positive and 10

culture-negative. Median age was similar in both groups (7.5 vs. 6.5 years; $p=0.780$), with a comparable male predominance (75% vs. 60%; $p=0.620$). Rates of under-nutrition (75% vs. 70%), elevated CRP (median 162 vs. 141 mg/L), low platelets (median 12 vs. $16 \times 10^3/\text{mm}^3$), and anemia (median Hb 7.2 vs. 8.5 g/dL) were not significantly different (all $p>0.050$). Recent chemotherapy (<1 week) was more common in culture-positive cases (100% vs. 60%), though not statistically significant ($p=0.110$) (Table 4).

Table 4: Association of Culture Status with Clinical Variables among Infection-Related TRM Cases ($n=168$)

Variables	Culture-Positive (n=4)	Culture-Negative (n=10)	p-Value
Median Age (Years)	7.5 (3-12)	6.5 (1-14)	0.780
Gender (Male)	3 (75%)	6 (60%)	0.620
Under-nutrition (<10th centile)	3 (75%)	7 (70%)	0.840
Median CRP (mg/L)	162 (134-193)	141 (119-185)	0.210
Median Platelets ($\times 10^3/\text{mm}^3$)	12 (8-18)	16 (5-41)	0.390
Median Hemoglobin (g/dL)	7.2 (5.6-9.0)	8.5 (6.4-11.2)	0.160
Chemotherapy within <1 Week	4 (100%)	6 (60%)	0.110
Expired During Induction Phase	3 (75%)	6 (60%)	0.620

(Data analysed using the Pearson chi-square test)

Out of the total 181 TRMs, 118 (65%) were deaths during induction remission, and 17 (9.4%) during maintenance.

DISCUSSION

Roughly one in 15 children who are on active cancer treatment in LMICs die of treatment-related complications [7]. Chemotherapy-related febrile neutropenia (FN) exposes cancer patients to several treatment-related toxicities, making infectious complications the major cause of mortality among pediatric oncology patients [10]. Specific cancers have concomitant immune deficiencies, e.g, lymphocytic leukemia patients commonly have hypogammaglobulinemia, which predisposes them to an increased possibility of encapsulated organisms. They might have repeated chest infections and bacteremia [14]. Children with cancer also have an increased risk of opportunistic viral-like fungal and protozoal infections, which are otherwise mild and rare in healthy people, but may lead to life-threatening complications in cancer patients [15]. Acute lymphoblastic leukemia ranks number one among childhood cancers having approximately 30% rate of incidence worldwide [16]. The overall 5-year survival of acute leukemia patients in High-income countries (HIC) like Sweden improved from 5% to more than 90% over the past 30 years [17]. But there is a significant disparity in the survival rate of childhood cancers in HICs and LMICs, attributed to several factors, including huge differences in the economy and infrastructure of health in these

countries [18]. Because there is scarce quality supportive care in LMIC, even more crucial than recurrence in cancer is treatment-related mortality [19]. Moreover, malnutrition always poses challenges in pediatric oncological patients with concurrent chemotherapy-related complications. This is a known fact that malnutrition has a noteworthy impact in multiple ways on the management of patients with pediatric acute leukemia [13]. A study conducted by Farrag *et al.* on pediatric cancer mortality in 2024 showed that the primary cause of mortality among hematological malignancies was TRM (66% of all cancer deaths), and among TRM main causes of death were infection-related (60%), hemorrhage (7.1%), and chemotherapy-toxicity (4.2%) [20]. Another study conducted by Rahat-Ul-Ain *et al.* on TRM in children with Acute lymphoblastic leukemia showed sepsis (87.5%) as a major cause of TRM, with malnutrition (p -value=0.007), reason for admission (p -value=<0.001), immunophenotype (p -value=0.032) and ANC on death (p -value=<0.001) being the significant factors associated with TRM [13]. This study identified sepsis and infection-related complications (93%) as the leading causes of treatment-related mortality (TRM). Additional factors significantly associated with TRM included thrombocytopenia, anemia, and elevated CRP levels at the time of death (p -value=0.009, 0.001 and 0.017, respectively). A considerable proportion of TRM cases were also found to have underlying undernutrition (61%), and a notable percentage of deaths occurred during the induction phase of remission (65%). Importantly, these contributing factors are largely preventable. Although statistically non-significant, a large proportion of deaths occurred during induction and within one week of the last chemotherapy session, highlighting a clinically relevant trend. This suggests the induction phase is a high-risk period, warranting enhanced supportive care and close monitoring to prevent TRM. Therefore, TRM can potentially be reduced through improved supportive care, like strengthening infection control, prophylactic antibiotics use, nutritional support, and the use of appropriate chemotherapy protocols. Enhancing these aspects could significantly improve outcomes for pediatric oncology patients in low- and lower-middle-income countries. The Children's Hospital, University of Child Health Sciences Lahore, is the largest public sector pediatric hematology-oncology center in Pakistan, serving around 150 inpatients daily. This is the first study conducted from our center on factors associated with TRM in all types of acute leukemia. As the study highlights infection-related deaths as a major cause of death so it may serve as baseline assessment data for quality improvement projects in the future. This study was limited by its retrospective single-center design, which may reduce generalizability to other

healthcare settings, and incomplete microbiological data, particularly low blood culture availability, which restricted detailed pathogen-specific analysis. The use of non-probability sampling and reliance on medical records may also introduce selection and documentation bias. Future multicenter prospective studies are recommended to validate these findings, improve infection surveillance, and evaluate the effectiveness of enhanced supportive care measures such as nutritional rehabilitation, early sepsis management, and strengthened infection prevention protocols to reduce TRM in pediatric leukemia patients.

CONCLUSIONS

The major reason for TRM in childhood acute leukemia cases in our resource-limited setting is infection. Noteworthy factors seem to be related to TRM were male sex, residents of rural areas, cytopenia, high CRP, under-nutrition, and ongoing chemotherapy sessions. The majority of the deaths due to treatment occurred during the Induction phase of chemotherapy in all types of acute leukemia. Infection prevention and control, and the provision of enhanced supportive care, can result in decreasing TRM in all types of childhood acute leukemia cases.

Authors' Contribution

Conceptualization: SG

Methodology: SG, AA, LI, RUA

Formal analysis: LI, RUA

Writing and Drafting: SG, WM, MF, AA, LI, RUA

Review and Editing: SG, WM, MF, AA, LI, RUA

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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