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ORIGINAL ARTICLE

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Predictors of Mortality in Pediatric Acute Lymphoblastic Leukemia & Lymphoblastic Lymphoma: Analysis of 1004 Cases

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ABSTRACT

OBJECTIVE: To assess the predictors of treatment-related mortality (TRM) among pediatric acute lymphoblastic leukemia (ALL) and Lymphoblastic lymphoma (LBL) cases in Pakistan.

METHODOLOGY: This retrospective study was conducted in the Pediatric Oncology department at Combined Military Hospital Rawalpindi, Pakistan. All newly diagnosed ALL and LBL cases between the ages of one and 18 years from 1st January 2013, to 31st December 2022 were included in the study. Physical and demographic data of all subjects were obtained and treatment outcome in terms of any complications or mortality were recorded during the above mentioned period. All data were analyzed using SPSS software.

RESULTS: Among 1004 cases of ALL 636(63.3%) were males and 368(36.7%) were females. The mean age during the diagnosis was 5.76±3.60 years. Overall Mortality was 295 (29.4%) including 191/295(64.7%) TRM and 104(35.3%) relapse-related mortality. Among the TRM cases, 124/191(64.9%) expired during induction. The usual complication during induction was Neutropenic fever. In univariate analysis, malnutrition (P=0.043), high WBC count (P=0.011), reduced hemoglobin level (P=0.005), low platelet count (P=0.002), neutropenic sepsis (P=0.001), and hepatotoxicity (P=0.001), were found to be related to high induction mortality. On multivariate analysis, infection was the most significant predictor of mortality during the induction and post-induction period. Infection followed by bleeding was the most common cause of mortality. After a median follow-up of 49.94+34.04 months, the overall Survival and Disease-Free Survival rates at five years were 70.6% and 68.4% respectively.

CONCLUSION: The main causes of TRM in pediatric ALL are Neutropenic fever and bleeding. Malnutrition, high WBC count, neutropenic sepsis, and hepatotoxicity are the main predictors of high TRM.

KEY WORDS: Pediatric, Acute Lymphoblastic Leukemia, Mortality, Treatment Related Mortality.

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INTRODUCTION

Pediatric Acute Lymphoblastic Leukemia (ALL) is the most common type of cancer in children, accounting for approximately one-third of all pediatric malignancies.

Despite significant advancements in treatment approaches, mortality due to pediatric ALL remains a significant concern. Identifying predictors of mortality in this population is crucial for tailoring therapeutic strategies, improving outcomes, and optimizing patient care. In developed countries, the 5-year overall survival in ALL has exceeded 90%.[1] However 5-year overall survival rate of ALL in developing countries is 81.6%.[2] Children with cancer make up about 80% of the population in low-and middle-income countries (LMICs) and the treatment outcomes in LMICs are suboptimal.[3–6]

Pediatric ALL treatment-related mortality (TRM) in developed countries ranges from 1% to 3%. Whereas, in LMICs reported TRM is 11% to 21%.[7,8] The major causes of high TRM in LMICs are infection and bleeding.[9] Late presentation, malnutrition, and inadequate supportive and critical care facilities are additional variables that contribute to these lower survival rates.[10] A combination of these factors along with high-dose steroids and intensive chemotherapy during the induction phase of ALL results in a high prevalence of bacterial and fungal infections leading to high mortality in these children. Furthermore, the treatment regime is similar for both ALL and LBL and therefore

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both cases are studied together. Fewer data has been published on mortality in pediatric ALL in LMICs like Pakistan.

The current study has documented and analyzed the reasons for mortality in pediatric ALL and LBL during the ten years in a single tertiary care center. The aim of study is to describe the predictors of treatment-related mortality (TRM) among pediatric ALL and LBL cases in a single tertiary care center of Pakistan.

METHODOLOGY

This Retrospective study was conducted at the Combined Military Hospital (CMH) Rawalpindi, in the Pediatric Oncology department. All the newly diagnosed ALL/LBL cases between the ages of one and 18 years undergoing the treatment throughout ten years, from 1st January 2013, to 31st December 2022 were included. Cases with mixed phenotypic and undifferentiated leukemia, BCR: ABL1 fusion, abandoning before completion of treatment, and unwillingness to participate were excluded. Informed consent from the patient's parents and guardians was sought, as well as approval from the Institutional Review Board of CMH Rawalpindi (IRB# 352) was acquired.

The data at the time of admission, including medical history and clinical examinations were retrieved. The basic demographic and clinical information including age, sex, weight, pallor, temperature, bruising, bleeding, bone pains, respiratory symptoms, lymphadenopathy, and visceromegaly was documented in the excel sheet. Other important parameters like reporting time, nutritional status, prior treatment details, and socioeconomic status were also recorded. Furthermore, the treatment outcome whether remission or any complications and mortality related to treatment were recorded during the above mentioned period from all the included participants.

Using the statistical analysis program SPSS 25.0, the t-test and chi-square tests were employed to compare continuous and categorical variables. For the categorical variables, the frequencies and percentages were calculated. Kaplan---Meier survival curves estimated the event free survival (EFS) and overall survival (OS). The log-rank test was used to compare the EFS and OS. The Cox proportional-hazard regression model was used for univariate and multivariate analysis of prognostic factors with 95% confidence intervals (95% CIs). P-values less than 0.05 were regarded as significant.

RESULTS

Demographics and clinical characteristics

9A total of 1026 new cases of ALL/LBL were reported throughout the study period. Twenty-two cases, abandoned the treatment, including nine cases during induction and 13 post-induction. These cases were not included in the study. Data of 1004 cases, with 636 males (63.3%) and 368 females (36.7%), were analyzed. For analysis purposes the cases were divided into two time periods of five years each: 1st half from January 2013 to December 2017 and the later half from January 2018 to December 2022. At diagnosis, the mean age was 5.76±3.60 years (ranging from one to 18 years). The mean time to reach the pediatric oncologist was 52.10±56.82 days (ranging from 2 to 535 days). Pallor was the most typical presenting symptom in 957 (95.3%) followed by fever in 847 (84.4%) and

Variable	2013- 2017	2018-2022	Total	p-value
	Number (%)	Number (%)	Number (%)	
Total number	428 (42.6)	576 (57.4%)	1004 (100%)	
Sex				0.908
Male	272 (63.6)	364 (63.2)	636 (63.3)	
Female	156 (36.4)	212 (36.8)	368 (36.7)	
Age (Years)	5.55 ± 3.42	5.91 ± 3.72	5.76 ± 3.60	0.035
Age groups				0.096
Less than 10 years	356 (83.2)	455 (79.0)	811 (80.8)	
More than 10 years	72 (16.8)	121 (21.0)	193 (19.2)	
Nutritional Status				0.432
Normally Nourished	309 (72.2)	436 (75.7)	745 (74.2)	
Moderately Malnourished	75 (17.5)	91 (15.8)	166 (16.5)	
Severely Malnourished	44 (10.3)	49 (8.5)	93 (9.3)	
Blood Counts at Presentation (Mean + SD)				
WBC count (x109/L)	55.16 ± 102.6	53.21± 96.04	54.04 ± 98.87	0.457
Haemoglobin (g/dl)	7.27 ± 2.53	7.63 ± 2.57	7.48 ± 2.56	0.964
Platelets (x109/L)	64.85 ± 91.62	78.69 ± 109.1	72.79± 102.2	0.024
Immunophenotype				0.93
B-Cell	331 (77.3)	451 (78.3)	782 (77.9)	
T-Cell	62 (14.5)	79 (13.7)	141 (14.0)	
Inconclusive	35 (8.2)	46 (8.1)	81 (8.1)	
ALL Classification				0.965
Pre-B-ALL	332 (77.6)	451 (78.3)	783 (78.0)	
T-ALL	50 (11.7)	65 (11.3)	115 (11.5)	
ALL (based on morphology)	34 (7.9)	42 (7.3)	76 (7.6)	
Lymphoblastic Lymphoma (LBL)	12 (2.8)	18 (3.1)	30 (3.0)	
Risk Group				0.741
Standard Risk (Regimen A)	220 (51.4)	290 (50.3)	510 (50.8)	
High Risk (Regimen B)	208 (48.6)	286 (49.7)	494 (49.2)	

Table 1: Demographic characteristics of the patients (n=1004)

Table 2 –Predictors of Induction and all Phases Treatment-Related Mortality in Pediatric ALL Cases (n=1004). *p0.05 is considered significant.

Variable		TRM Induction			TRM All Phases of Treatment		
	Number (%)	Rate (Number %)	HR (95% CI)	P-Value	Rate (Number %)	HR (95% CI)	P-Value
Whole Cohort	1004 (100)	124 (12.3%)			191 (19.0%)		
Sex							
• Male	636 (63.3)	70 (11.0)	1	0.090	118 (18.6)	1	0.618
• Female	368 (36.7)	54 (14.7)	1.4 (.95-2.03)		73 (19.8)	1.09 (.78-1.50)	
Age							
• < 10 years	811 (80.8)	103 (12.7)	1	0.490	159 (19.6)	1	0.336
• ≥ 10 years	193 (19.2)	21 (10.9)	.84 (.51-1.4)		32 (16.6)	.82 (.53-1.23)	
Reporting time to the oncologist							
• < 6 months	953 (94.9)	116 (12.2)	1	0.459	178 (18.7)	1	0.230
• > 6 months	51(5.1)	8 (15.7)	1.34 (.62-2.92)		13 (25.5)	1.49 (.78-2.85)	
Nutritional Status							
• Well-nourished	745 (74.2)	88 (11.8)	1	.043*	131 (17.6)	1	.004
• Moderately malnourished	166 (16.5)	17 (10.2)	1.92 (1.10-3.33)	.021*	30 (18.1)	2.23 (1.40-3.58)	<.001
• Severely malnourished	93 (9.3)	19 (20.4)	2.25 (1.10-4.58)	.025*	30 (32.3)	2.16 (1.20-3.88)	.010
WBC count at presentation							
• < 50 x 10^9/L	706 (70.3)	73 (10.3)	1	.011	119 (16.9)	1	.026
• 50-100 x 10^9/L	142 (14.1)	26 (18.3)	1.65 (1.01-2.71)	.045	33 (23.2)	1.64 (1.08-2.48)	.018
• > 100 x 10^9/L	156 (15.5)	25 (16.0)	.85 (.47-1.56)	.601	39 (25.0)	1.10 (.65-1.87)	.018
Hemoglobin at presentation g/L							
• < 7	457 (45.5)	72 (15.8)	1	.005*	101 (22.1)	1	.077
• 7-10	389 (38.7)	42 (10.8)	.36 (.18-.72)	.004*	64 (16.5)	.69 (.43-1.12)	.132
• > 10	158 (15.7)	10 (6.3)	.56 (.273-1.14)	.111	26 (16.5)	1.00 (.61-1.65)	.999
Platelet count at presentation							
• < 50 x 10^9/L	606 (60.4)	92 (15.2)	1	.002*	128 (21.1)	1	.099
• 50-150 x 10^9/L	272 (27.1)	26 (9.6)	1.69 (1.07-2.69)	.025*	45 (16.5)	.62 (.36-1.06)	.083
• > 150 x 10^9/L	126 (12.5)	6 (4.8)	3.58 (1.53-8.37)	.003*	18 (14.3)	.84 (.46-1.52)	.566

The treatment used before Induction							
• No treatment	933 (92.9)	115 (12.3)	1	.625	177 (19.0)	1	.973
• Steroids	29 (2.9)	5 (17.2)	.67 (.25-1.80)	.433	6(20.7)	.89 (.36-2.23)	.816
• Chemotherapy	42 (4.2)	4 (9.5)	1.34 (.47-3.81)	.589	8 (19.0)	.99 (.45-2.18)	.990
Immunophenotype							
• B-Cell	782 (77.9)	98 (12.5)	1	.539	141 (18.0)	1	.313
• T-Cell	141 (14.0)	14 (9.9)	1.30 (.72-2.35)	.385	31 (22.0)	.78 (.50-1.21)	.268
• Inconclusive	81 (8.1)	12 (14.8)	.82 (.43-1.58)	.558	19 (23.5)	.72 (.42-1.24)	.233
Treatment Group							
• Regimen A	510 (50.8)	53 (10.4)	1	.056	84 (16.5)	1	.037
• Regimen B	494 (49.2)	71 (14.4)	1.45 (.99-2.11)		107 (21.7)	1.40(1.02-1.93)	
Neutropenic Sepsis							
• No	181 (18.0)	4 (2.2)	1	<.001*	15 (8.4)	1	<.001
• Yes	823 (82.0)	120 (14.6)	7.55 (2.75-20.7)		176 (21.4)	3.0(1.73-5.24)	
Fungal Infection							
• No	961 (95.7)	111 (11.6)	1	.001*	175 (18.2)	1	<.003
• Yes	43 (4.3)	13 (30.2)	3.32 (1.68-6.55)		16 (38.1)	2.66 (1.40-5.05)	
Hepatotoxicity							
• No	953 (95.1)	108 (11.3)	1	<.001*	170 (17.9)	1	<.001
• Yes	49 (4.9)	16 (32.7)	3.80 (2.03-7.14)		170 (17.9)	3.46 (1.92-6.24)	

Table 3: Causes of Mortality in Pediatric ALL (n=295)

Phase of therapy	n (%)	Infection n (%)	Bleeding n (%)	Hepatic Failure n (%)	Cardiac Failure n (%)	Encephalitis n (%)	Tumor Lysis Syndrome n (%)	Relapse	Total n (%)
Induction	124 (42.0)	98 (79.0)	15 (12.1)	7 (5.6)	1 (0.8)	2 (1.6)	1 (0.8)	0	124 (100)
Post-remission chemotherapy	67 (22.7)	53 (79.1)	8 (11.9)	2 (3.0)	2 (3.0)	2 (3.0)	0	0	67 (100)
Relapse	104 (35.3)	0	0	0	0	0	0	104	104
Total	295	151	23	9	3	4	1	104	295

bruising/bleeding in 414 (41.2%). Visceromegaly was documented in 823 (82.0%) cases. The mean white blood cell count was 54.05±98.87x109/L (ranging from 0.40 to 996 x109/L). The mean hemoglobin was 7.48±2.56 g/dl, and the mean platelets count was 72.79±102.19x109/L. Pre-B ALL was the most common subtype of ALL documented in 778 (77.5%) cases followed by T-ALL in 115 (11.5%) cases. Based on morphology, eighty-one (8.1%) cases were diagnosed as ALL because immunophenotyping was missing or inconclusive. There were 30 (3.0%) cases of LBL including 26 (86.7%) T-LBL and 4 (13.3%) B-LBL. Seventeen (1.7%) cases had central nervous system (CNS) disease. Only 2 (0.2%) boys had testicular disease. As per National Cancer Institute (NCI) criteria, 510 (50.8%) cases categorized as standard risk and received Regimen A induction. About 494 (49.2%) cases categorized as high-risk, received Regimen B induction. (Table 1)

The most frequent complications during induction were neutropenic fever and steroids-induced proximal myopathy which were documented in 822 (81.9%) and 674 (67.1%) cases, respectively. Induction mortality was 124 (12.4%) and out of the remaining 880 cases, 866/880 (98.4%) achieved morphological Complete Remission (CR), 12/880 (1.4%) had Bone Marrow Examination (BME) with M2 (i.e. 5-25% blasts) and only 2/880 (0.2%) had the refractory disease (>25% blasts).

Treatment-related mortality (TRM)

During the study period, 295 (29.4%) cases expired including 191/295 (64.7%) TRM and 104/295 (35.3%) relapse-related mortality (RRM). Among the TRM cases 124/191 (64.9%) expired during induction and 67/191 (35.1%) during various phases of post-induction chemotherapy, (15 during consolidation, 5 during interim maintenance, 21 during delayed intensification, and 26 during maintenance chemotherapy). Out of 124 induction mortality, 53 (42.7%) were in the standard risk group and 71 (57.3%) in the high-risk group (P =0.056).

Predictors of Induction and all Phases Treatment-Related given below in table-2. Age, sex, subtype of ALL, intensity of chemotherapy, and delay in starting chemotherapy had no statistically significant effect on induction mortality (Table-2).

Neutropenic sepsis and hepatic failure were the main causes of induction mortality. Causes of mortality are given in table-3.11During induction and post-induction period infection was the most significant predictor of mortality in multivariate analysis. Overall TRM rates during 2018 to 2022 improved significantly from 22.9% to 16.1% (P=0.007). TRM in the last year of the study (2022) was only 8.3%. (Table-4). Out of 813 cases, (excluding 191 TRM cases) 125/813 (15.4%) cases relapsed, including 50 (11.7%) in the standard risk group and 75 (19.4%) in a high-risk group (P=0.003). Factors associated with

Variable	2013- 2017	2018-2022	Total	p-value
	Number (%)	Number (%)	Number (%)	
Total number	428 (42.6)	576 (57.4%)	1004 (100%)	
Risk Group				
Standard Risk (Regimen A)	220 (51.4)	290 (50.3)	510 (50.8)	0.741
High Risk (Regimen B)	208 (48.6)	286 (49.7)	494 (49.2)	
Complications and Outcome				
Neutropenic Infection	347 (81.1)	475 (82.9)	822 (82.1)	0.457
Fungal Infection	25 (5.8)	17 (3.0)	42 (4.2)	0.025
Induction TRM	61 (14.3)	63 (10.9)	124 (12.4)	0.114
Total TRM	98 (22.9)	93 (16.1)	191 (19.0)	0.007
Relapse	67 (15.7)	58 (10.1)	125 (12.5)	0.008
Disease free Survival (DFS)	263 (61.4)	424 (73.6)	687 (68.4)	<0.001
Overall Survival (OS)	268 (62.6)	441 (76.6)	709 (70.6)	<0.001

Table 4: Induction Complications and Treatment-Related Mortality (n=1004) Relapse and Relapse Related Mortality (RRM). *p0.05 is considered significant.

high relapse rate were older age (23.0% in age >10 years and 13.5% in age <10 years (P=0.003), high WBC count (13.1% in WBC <50x109/L, 18.3% in WBC 50-100x109/L and 23.9% in WBC >100x109/L (P=0.003), slow early response to induction chemotherapy (20.7% in slow early responder and 14.6% in rapid early responder cases (P=0.132). Out of the 125 relapse cases, 93 (74.4%)

were offered palliative care due to very early/early relapse. Thirty-two cases (25.6%) were treated with a curative intention on the UKALLR3 protocol. Two cases underwent bone marrow transplant (BMT) with HLA-matched siblings and one case, being a foreign national had successful CAR-T cell therapy in the UK. Twenty of the 32 (62.5%) cases treated on UKALLR3 also expired. Total mortality in relapsed cases was 104/125 (83.2%). After a median follow-up of 49.94+34.04 months, Overall Survival (OS) was 70.8%; OS was 75.6% in the standard risk and 65.8% in the high-risk group. Disease-Free Survival (DFS) was 68.5%; DFS was 73.6% in the standard risk and 63.3% in the high-risk group.

DISCUSSION

The pediatric oncology department of Combined Military Hospital Rawalpindi is the 4th largest pediatric oncology unit in the country treating around 350 new cases of pediatric cancer annually.[11] Throughout the past few decades, high-income countries have seen significant drops in childhood cancer

mortality, and to a lesser extent in middle-income countries.11 In LMICs, high induction mortality is a major reason for poor outcomes and has been reported from 11% to 23%.[7,8]

In the present study, induction mortality was 12.4%. Two other studies from Pakistan have reported similar induction mortality. Fadoo et al in 2015 have reported 11.5% and 12.9% induction mortality from Karachi and Lahore respectively.[9,12] However, a recent study by Ain et al in 2021 from Lahore has reported induction mortality of 19.4%.7 Malnutrition was associated with high induction and post-induction mortality in our study. Children who are already undernourished are worsened nutritionally as a result of cancer and its treatment because of anorexia, inflammation, and an elevated metabolic rate. Increased morbidity and mortality in pediatric leukemia in malnourished children have been reported by various studies from LMICs.[12–15]

In a recent study, neutropenic sepsis followed by bleeding were the main causes of TRM. This is comparable to other studies from LMIC.[6,8,12] The main reason for high induction mortality in our setup was the limited availability of intensive care facilities. Infection was also the leading cause of death during the post-induction period, mainly due to delays in commencing appropriate broad-spectrum antibiotics. Many cases belong to rural areas with very meager healthcare facilities, limited availability of broad-spectrum antibiotics, and inadequate transport services to reach tertiary care hospitals for optimal care.

It is quite challenging to treat relapse cases ALL because of the high treatment intensity which is required to induce and sustain a second remission. Treatment-related toxicity impacts survival, especially in countries with scarce resources, relapsed disease is a major cause of poor survival.[8] LBL although is type of lymphoma, and the data was very limited due to small number of cases in this study. However, we have included the data as the treatment regime for LBL and ALL are similar and the outcomes have almost similar impact on the patients.14However, the study has certain limitations as it includes the patients from a single Centre in Pakistan which limits the generalizability of the results to other regions and settings.

Retrospective data was extracted from the hospital records and therefore systematic collection of data was not possible.

CONCLUSION

Treatment-related mortality in pediatric ALL is this study was 12.4%. Malnutrition, high WBC count, low hemoglobin level, low platelet count, neutropenic sepsis, and hepatotoxicity are main reasons associated with high induction mortality.

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CONFLICT OF INTEREST

The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

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CONFLICT OF INTEREST

Author declared no conflict of interest

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AU: Conception, Design of the work, Data collection, and Drafting, Reviewed, Final approval, Agreement to be accountable.

TG: Conception, Design of the work, Acquistion, Data Analysis, and Drafting, Reviewed, Final approval, Agreement to be accountable.

IA: Conception, Design of the work, Interpretation of data for the work, and Drafting, Reviewed, Final approval, Agreement to be accountable.

SA: Conception, Design of the work, Data collection, and Drafting, Reviewed, Final approval, Agreement to be accountable .

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