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Research Article

Navigating the Complexity- Complications in Pediatric Acute Lymphoblastic Leukemia Intensive Chemotherapy Treatment At A Tertiary Care Center in Central India

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Abstract

Objective: *In the realm of childhood acute lymphoblastic leukemia (ALL), where recent treatment strategies have ushered in promising results, this study aims to shed light on the persistent challenge of acute complications during treatment, remaining pivotal contributors to mortality and morbidity in a resource limited setting.*

Methods: *A comprehensive retrospective analysis was conducted on the medical records of 44 patients who underwent treatment following the Indian Collaborative Childhood Leukemia (ICiCle-ALL-14) protocol between 2018 and 2023, with a specific focus on acute complications arising during the intensive chemotherapy phase that includes the induction, consolidation, interim maintenance and delayed intensification.*

Results: *Among the 44 patients, 19 (43.19%) were male, and 25 (56.81%) were female, with a median age at diagnosis of 5.5(3.25- 7.5) years. Pre-B cell ALL dominated the landscape in 95.45% of cases, while pre-T cell ALL accounted for 4.55%. ICiCle risk stratification revealed 7 patients (15.9%) in the high-risk category,22 (61.4%) in the intermediate risk, and 10 (22.7%) in the standard risk. Acute complications manifested in 84.1% of cases, with infectious complications leading the fray, trailed by gastrointestinal, drug-related, neurological, amongst others.*

Conclusion: *This study highlights the significance of a holistic approach to the complexities of childhood ALL treatment. Particularly complications arising during the intensive chemotherapy phase. It is imperative to manage these complications aggressively, especially in resource-limited settings, is paramount to improving patient outcomes.*

Keywords: *Pediatric ALL, Intensive chemotherapy, Treatment-related complications, Resource-limited settings.*

Abbreviations

- ALL- Acute lymphoblastic leukemia
- ICiCle- Indian Collaborative Childhood Leukemia (ICiCle-ALL-14)
- TRC- Treatment related complications
- TRM- Treatment related mortality
- CTCAE- Common terminology criteria for adverse effects
- SR- Standard risk
- IR- Intermediate risk
- HR- High risk
- 6 MP- 6 Mercaptopurine
- MTX- Methotrexate
- E Coli Asp/L asp - E coli asparaginase
- EOI MRD- End of induction minimal residual disease
- NCI- National Cancer Institute

Introduction

Acute lymphoblastic leukemia (ALL) stands as the most prevalent pediatric malignancy, constituting 75-80% of pediatric leukemia cases. The incidence in India exhibits regional variation, with age-adjusted rates reported as high as 101.4 per million for boys and 62.3 per million for girls (1)(2) Predominantly affecting boys, with a peak incidence in the 2-5 age group, T cell ALL represents 15-20% of pediatric ALL cases (2). Advancements in understanding pathogenesis, molecular genetics, and the adoption of risk-stratified therapy, along with the introduction of novel therapeutic agents, have significantly improved the survival rates of children with ALL. The five-year overall survival (OS) rate has soared to 89%(3).In India, estimated OS rates range from 45% to 81%(4)

Despite remarkable advancements, ALL remains a significant contributor to childhood mortality, and

treatment-related complications (TRC) represent a notable cause. TRCs, which may be life-threatening, can lead to disruptions in the treatment protocol, cancellations, or dose reductions in medications. Such interruptions may compromise the effectiveness of treatment and potentially increase the risk of relapses. TRCs encompass a spectrum of issues, including infections, bleeding or thrombosis, endocrine and metabolic complications, gastrointestinal challenges, and drug toxicities. Additionally, rarer complications may also manifest (5)

In the Indian context, an enhanced understanding of TRCs holds particular significance, as advancements in supportive care have the potential to positively impact disease outcomes.

While both disease-related and treatment-related complications may emerge during the early treatment period, TRCs tend to be more prevalent in the later stages of treatment (6). This study aims to investigate TRCs resulting from chemotherapy in patients undergoing treatment for ALL.

Methodology

The medical records of children between 1-18 years diagnosed with Acute Lymphoblastic Leukemia (ALL)who had consented for treatment between the years 2018 and 2023 underwent a retrospective review. Patients with incomplete clinical records, individuals who underwent induction therapy before referral to our center, and those lost to follow-up before reaching day 60 post the completion of the intensive phase of treatment were excluded. The assessment focused on complications that arose during the intensive chemotherapy of 44 ALL patients. Treatment and subsequent monitoring followed the ICiCle 2014 treatment protocol (7) Additionally, for patients exhibiting t (9; 22) positivity, tyrosine kinase inhibitors were incorporated into the same treatment protocol. The evaluation encompassed complications that surfaced during the course of intensive chemotherapy. The study specifically considered Grade 3 and 4 toxicities in alignment with the common terminology criteria for adverse events v5.0.

Diagnosis:

The diagnosis of Acute Lymphoblastic Leukemia (ALL) was established through the identification of ≥25% lymphoblasts on bone marrow smears, assessed morphologically. Additionally, subtype analysis was conducted through flow cytometric immunophenotyping of bone marrow aspiration or peripheral blood samples. Cytogenetic assessment included karyotype analysis, and translocations such as t (12:21), t (4:11),

t (1:19) and t (9:22) were identified using fluorescence in situ hybridization and polymerase chain reaction techniques.

Risk Stratification: The classification of patients into standard-risk (SR), intermediate-risk (IR), and high-risk (HR) categories was determined based on the risk stratification protocol established by the ICiCle group, as outlined in Table 1. Treatment as outlined in Table 2,3,4 and 5.

Characteristics	Standard risk	Intermediate risk	High risk
Age at diagnosis	>1 years and <10 years	>10 years	
Bulk of disease		bulky lymph nodes (≥5 cm in peripheral region and in chest >5 cm on CT scan or occupying ≥1/3rd diameter on chest x-ray) and/or bulky liver/spleen reaching beyond midway to umbilicus and/or presence of testicular disease	
Leucocyte at diagnosis	<50,000/cumm	>=50,000/cumm	
Response to steroid at day 8			Poor response (Presence of ≥1000 blasts/μl)
End of induction MRD			>0.01%
Cytogenetics	High hyperdiploidy (modal chromosome number 51 – 67) ETV6/RUNX1 fusion translocation [t(12;21)(p13; q22)		BCR-ABL/MLL re arrangements Hypodiploidy (less than 45 chromosomes)
Immunophenotype			T ALL
CNS Disease	Absent	Absent	Present

Table 1 ICiCLE Risk Stratification

All patients underwent classification into standard, intermediate, or high risk groups following the risk classification system outlined in the protocol.

	STANDARD RISK		
INDUCTION	Drug	Dose	Day
	Prednisolone	60mg/m2	1-28 then taper over 1 week
	Vincristine	1.5mg/m2	8,15,22,29
	IT MTX	<2 yrs-8mg 2-<3 yrs -10mg >=3 yrs-12 mg	8,15,35
	E.coli ASP Cotrimoxazole	10000 IU/m2 As per BSA	16,18,21,24,27 1,8,15,22,29
CONSOLIDATION	IT MTX	<2 yrs-8mg 2-<3 yrs -10mg >=3 yrs-12 mg	8,15
	6MP	60mg/m2	1—21
	Cotrimoxazole	Asper BSA	1,8,15
INTERIM MAINTENANCE	Dexamethasone	6mg/m2	1-5 29-33
	Vincristine	1.5mg/m2	1,29
	IT MTX	<2 yrs-8mg 2-<3 yrs -10mg >=3 yrs-12 mg	15,43
	Oral MTX	20mg/m2 weekly	1st week 2nd week 4th,5th,6th week 8th,9th week
	6 MP	60mg/m2	1-49
	Cotrimoxazole	As per BSA	1,8,15,22,29,36,43,50,56
DELAYED INTENSIFICATION	Dexamethasone	10mg/m2	1-5 15-19
	Vincristine	1.5mg/m2	1,8,15
	IT MTX	<2 yrs-8mg 2-<3 yrs -10mg >=3 yrs-12 mg	1,15
	E Coli Asp	10000 IU/m2	4,7,10,13
	Doxorubicin	25mg/m2	1,8,15
	Cyclophosphamide	1000mg/m2	29
	Cytarabine	75mg/m2/day	30-40
	6MP	60mg/m2/day	29-42
	Cotrimoxazole	As per BSA	1,8,15,22,29,36,43

Table 2: Treatment Protocol for standard risk patients

	INTERMEDIATE RISK		
INDUCTION	Drug	Dose	Day
	Prednisolone	60mg/m2	1-28 then taper over 1 week (adolescent- 1-14 then 22-28)
	Vincristine	1.5mg/m2	8,15,22,29
	IT MTX	<2 yrs-8mg 2-<3 yrs -10mg >=3 yrs-12 mg	8,15,35
	E.coli ASP Daunorubicin Cotrimoxazole	10000 IU/m2 25mg/m2 As per BSA	9,12,15,18,21,24,27,30 8,15 1,8,15,22,29
CONSOLIDATION	IT MTX Cyclophosphamide Cytarabine	<2 yrs-8mg 2-<3 yrs -10mg >=3 yrs-12 mg 1000mg/m2 75mg/m2/day	8,15 1,5 2-5 9-12 16-19 23-26
	6MP	60mg/m2	1—28
	Cotrimoxazole	As per BSA	1,8,15,22,29
INTERIM MAINTENANCE (Capizzi)	IV MTX	Initial 100mg/m2 on day 2 then escalating dose by 50 mg/m2 as tolerated	2,12,22,32,42
	Vincristine	1.5mg/m2	2,12,22,32,42
	IT MTX	<2 yrs-8mg 2-<3 yrs -10mg >=3 yrs-12 mg	1,31
	Cotrimoxazole	As per BSA	1,8,15,22,29,36,43,50,56
DELAYED INTENSIFICATION	Dexamethasone	10mg/m2	1-5 15-19
	Vincristine	1.5mg/m2	1,8,15
	IT MTX	<2 yrs-8mg 2-<3 yrs -10mg >=3 yrs-12 mg	1,15
	E Coli Asp	10000 IU/m2	4,7,10,13
	Doxorubicin	25mg/m2	1,8,15
	Cyclophosphamide	1000mg/m2	29
	Cytarabine	75mg/m2/day	30-40
	6MP	60mg/m2/day	29-42
	Cotrimoxazole	As per BSA	1,8,15,22,29,36,43

Table 3: Treatment protocol for intermediate risk patients

	HIGH RISK		
INDUCTION	Drug	Dose	Day
	Prednisolone	60mg/m2	1-28 then taper over 1 week
	Vincristine	1.5mg/m2	8,15,22,29
	IT MTX	<2 yrs-8mg 2-<3 yrs -10mg >=3 yrs-12 mg	8,15,35
	E.coli ASP	10000 IU/m2	9,12,15,18,21,24,27,30
	Daunorubicin	25mg/m2	8,15,22,29
	Cotrimoxazole	As per BSA	1,8,15,22,29
CONSOLIDATION	IT MTX	<2 yrs-8mg 2-<3 yrs -10mg >=3 yrs-12 mg	1,8,29
	Vincristine	1.5mg/m2	16,23,44,51
	Cyclophosphamide	1000mg/m2	1,29
	Cytarabine	75mg/m2/day	2-5, 9-12, 16-19, 23-26
	L asp	10000 IU/m2	15,18,21,24,43,46,49,52
	6MP	60mg/m2	1—14, 29-42
	Cotrimoxazole	Asper BSA	1,8,15,22,29,36,43,50,57
INTERIM MAINTENANCE	IV High dose MTX	B ALL- @3g/m2 T ALL- @5g/m2	1,15,29,43
	Folinic acid rescue	15mg/m2	42,48 and 54 hours from HDMTX
	IT MTX	<2 yrs-8mg 2-<3 yrs -10mg >=3 yrs-12 mg	1,15,29,43
	6 MP	@25mg/m2	1-49
DELAYED INTENSIFICATION	Dexamethasone	10mg/m2	1-5, 15-19
	Vincristine	1.5mg/m2	1,8,15
	IT MTX	<2 yrs-8mg 2-<3 yrs -10mg >=3 yrs-12 mg	1,15,19
	E Coli Asp	10000 IU/m2	4,7,10,13
	Doxorubicin	25mg/m2	1,8,15
	Cyclophosphamide	1000mg/m2	29
	Cytarabine	75mg/m2/day	30-33, 37-40
	6MP	60mg/m2/day	29-42
	Cotrimoxazole	As per BSA	1,8,15,22,29,36,43

Table 4: Treatment protocol for high risk B ALL

	HIGH RISK T CELL ALL		
INDUCTION	Drug	Dose	Day
	Prednisolone Dexamethasone	60mg/m2 10mg/m2	1-8 8-14 22-28
	Vincristine	1.5mg/m2	8,15,22,29
	IT MTX	<2 yrs-8mg 2-<3 yrs -10mg >=3 yrs-12 mg	8,15,35
	E.coli ASP Daunorubicin Cotrimoxazole	10000 IU/m2 25mg/m2 As per BSA	9,12,15,18,21,24,27,30 8,15,22,29 1,8,15,22,29
CONSOLIDATION	IT MTX Vincristine Cyclophosphamide Cytarabine L asp	<2 yrs-8mg 2-<3 yrs -10mg >=3 yrs-12 mg 1.5mg/m2 1000mg/m2 75mg/m2/day 10000 IU/m2	1,8,29 16,23,44,51 1,29 2-5, 9-12, 16-19, 23-26 15,18,21,24,43,46,49,52
	6MP	60mg/m2	1—14 29-42
	Cotrimoxazole	Asper BSA	1,8,15,22,29,36,43,50,57
INTERIM MAINTENANCE	IV High dose MTX Folinic acid rescue	B ALL- @3g/m2 T ALL- @5g/m2 15mg/m2	1,15,29,43 42,48 and 54 hours from HDMTX
	IT MTX	<2 yrs-8mg 2-<3 yrs -10mg >=3 yrs-12 mg	1,15,29,43
	6 MP	@25mg/m2	1-49
DELAYED INTENSIFICATION	Dexamethasone	10mg/m2	1-5 15-19
	Vincristine	1.5mg/m2	1,8,15
	IT MTX	<2 yrs-8mg 2-<3 yrs -10mg >=3 yrs-12 mg	1,15
	E Coli Asp	10000 IU/m2	4,7,10,13
	Doxorubicin	25mg/m2	1,8,15
	Cyclophosphamide	1000mg/m2	29
	Cytarabine	75mg/m2/day	30-33 37-40
	6MP	60mg/m2/day	29-42
	Cotrimoxazole	As per BSA	1,8,15,22,29,36,43

Table 5: Treatment protocol for T ALL

Results

A total of 44 patients were included in the study. The median age of the cohort was 5.5 years (3.25-7.5) The most common type of complication observed in our study was infections. Infectious complications occurred in 37 of 44 patients (84.1%). Febrile neutropenia was the most common infection-related complication observed in 30 patients (85.7%). urinary tract infection in (n=3, 8.5%), neutropenic enterocolitis (n=2, 37.1%), respectively. Galactomannan positivity with imaging findings suggestive of fungal pneumonia were seen in 9 patients (24.3%). Culture positive blood stream infections were seen in 5 patients (13.5%) of which a bacterial isolate was obtained in 80% (N=4) of cases, most of which were gram-negative rods (N=3) followed by gram-positive cocci (N=1) and Invasive fungal infections (IFIs) represented only 1 case of non albicans candida sp.

Viral hepatitis was seen in 1 patient, while HSV infection was seen in 2 patients. 15.9% patients had non-infectious complications. In 26 (59%) patients, drug related complications were seen during intensive phase of chemotherapy. 12 patients (46.1%) had 6MP related cytopenias, requiring either drug dose modifications or withholding and 1 patient had rash post high dose methotrexate infusion, mainly seen during interim maintenance phase of chemotherapy, E.Coli LASP related grade 3 CTCAE hypersensitivity reactions were seen in 3 patients during induction, which was subsequently rechallenged in the delayed intensification phase with pre medications which was tolerated well. LASP related Drug induced liver injury was seen in 1 patient which was successfully treated with L carnitine and N acetylcystine infusion. L asp associated pancreatitis was seen in 1 patient during induction (CTCAE grade 3) and subsequent doses were omitted. Vincristine associated SIADH was seen in 1 patient, during induction which was managed with fluid restriction and reducing the subsequent dose of vincristine by 25%. Steroid induced PRESS seen in induction in 1 patient, Cyclophosphamide induced haemorrhagic cystitis requiring hyperhydration and diuresis was seen in 1 patient.

Overall TRM is 15.9% of which infection related causes were 77.7% and in majority it was related to sepsis.

Patient characteristics and complications are outlined in table 6 and 7.

Patient characteristics	n=44 (%)
Males	19 (43.1)
Females	2 (56.8)
Median Age	5.5 years (3.25- 7.5)
Phenotype B-ALL T-ALL Ph + B ALL	 42(95.4) 1 (2.3) 1 (2.3)
WBC Count <50000 >50000	 35(79.5) 9 (20.5)
No CNS/mediastinal involvement	-
Testicular involvement	1 (2.3)
Prednisolone response Good Bad	 41(93.2) 3 (6.8)
NCI Risk SR HR	 31 (70.5) 13 (29.5)
Initial ICICLE risk SR IR HR	 10 (22.7) 27 (61.4) 7 (15.9)
Final risk (based on EOI MRD) SR IR HR	 5 (11.4) 21(47.7) 19 (43.2)
Cytogenetics Normal ETV 6-RUNX1 BCR ABL MLL rearrangements TCF 3-PBX1	 33(75) 4 (9) 2 (4.5) 1 (2.3) 4 (9)
Karyotype Normal Not available Hyperdiploid Hypodiploid	 6 (13.6) 35 (79.5) 2 (4.5) 1 (2.3)
Post Induction MRD Positive Negative	 15 (34.1) 29 (65.9)

Table 6- Patient characteristics

Complications	n (%)
Febrile Neutropenia	30 (68.2)
UTI	3 (6.8)
LRTI	13(29.5)
Fungal Pneumonia (galactomannan positive with imaging findings)	9 (20.4)
Varicella	1 (2.3)
Culture positive sepsis	5 (11.4) Kleibella-2 E. Coli-1 Pseudomonas-1 Non-Candida albicans- 1
NEC	2 (4.5)
HSV infection	1 (2.3)
Viral Hepatitis	1 (2.3)
PRES	1 (2.3)
Convulsions	1 (2.3)
AKI	1 (2.3)
Others (Otitis externa, Submandibular abscess, Otitis media, Abscess on cheek)	1 each (2.3)
No infectious complications	7 (15.9)
Drug related complications	
MTX induced rash	1 (2.3)
6MP related Cytopenia	12 (27.3)
L-Asp related hypersensitivity (CTCAE grade 3)	3 (6.8)
L-asp pancreatitis	1 (2.3)
L asp liver injury	2 (4.5)
Cytarabine related extravasation	1 (2.3)
Cytarabine related Hypersensitivity (CTCAE grade 3)	1 (2.3)
Vincristine extravasation injury	1 (2.3)
Vincristine constipation	1 (2.3)
Vincristine SIADH	1 (2.3)
Cyclophosphamide Haemorrhagic cystitis	1 (2.3)
Steroid related PRESS	1 (2.3)

Table 7: Complications

Discussion

Despite advancements in supportive care services, favorable outcomes for Acute Lymphoblastic Leukemia (ALL) remain modest in a resource limited setting, with Treatment-Related Mortality (TRM), primarily attributed to infections, standing out as a significant factor influencing outcomes.

The median age of our patient cohort was 5.5 years (range: 3.25-7.5 years). Our findings align with similar studies; Khan et al(8) reported a mean age of 6.6 ± 2.67 years, and Makieieva et al(9)observed a median age of 5 years. This consistency underscores the prevalence of ALL within this age group.

In our study, there is a notable female predominance (56.81% vs. 43.19%). This contrasts with findings from Wali et al(10), Rubnitz et al(11)., and Makieieva et al(8)., where a male predominance was reported. Variations in gender distribution may be attributed to differences in patient availability during enrollment.

The majority of cases in our study presented with Pre-B-cell ALL (95.45%), aligning with Wali et al(10)Khan et al(8). and Makieieva et al(8)studies, where Pre-B-Cell ALL was predominant.

ICiCle risk stratification revealed that 15.9% of our patients were in High-risk, 61.4% in intermediate risk, and 22.7% in standard risk. This contrasts with Wali et al(10), who reported low risk in 77% and high risk in 23%. Makieieva et al(9) observed 75.7% with standard risk and 24.3% with high risk. This could be attributed to the differences in the protocols and risk stratification.

Infectious complications were prevalent in 84.1% of our cases, with febrile neutropenia being the most common (85.7%). Urinary tract infections and neutropenic enterocolitis occurred in 8.5% and 37.1% of cases, respectively. Galactomannan positivity, suggestive of fungal pneumonia, was noted in 24.3%. The majority of culture-positive bloodstream infections involved gram-negative rods (N=3), followed by gram-positive cocci (N=1). This aligns with the challenges posed by infectious complications in children with ALL, as seen in other studies. (Wali et al(10))

The overall treatment-related mortality in our study is 15.9%, (depicted in figure 1) predominantly attributed to infection-related causes (77.7%), with sepsis being a major contributor. This mortality rate is higher compared to some previous studies, such as Wali et al(10)(10%) and Rubnitz et al. (2.9% ± 5.3%), but comparable to Khan et al(8)(20.8%).

Drug-related complications were observed in 26 patients, with 6MP-related complications being the most

common (46.2%). L-Asp-related hypersensitivity (CTCAE grade 3) (11.5%) and L-Asp-related liver injury (7.7%) were also significant. Our findings are consistent with Yildrim et al(12), where 25.5% of patients experienced drug-related complications, mainly L-asparaginase-related reactions.

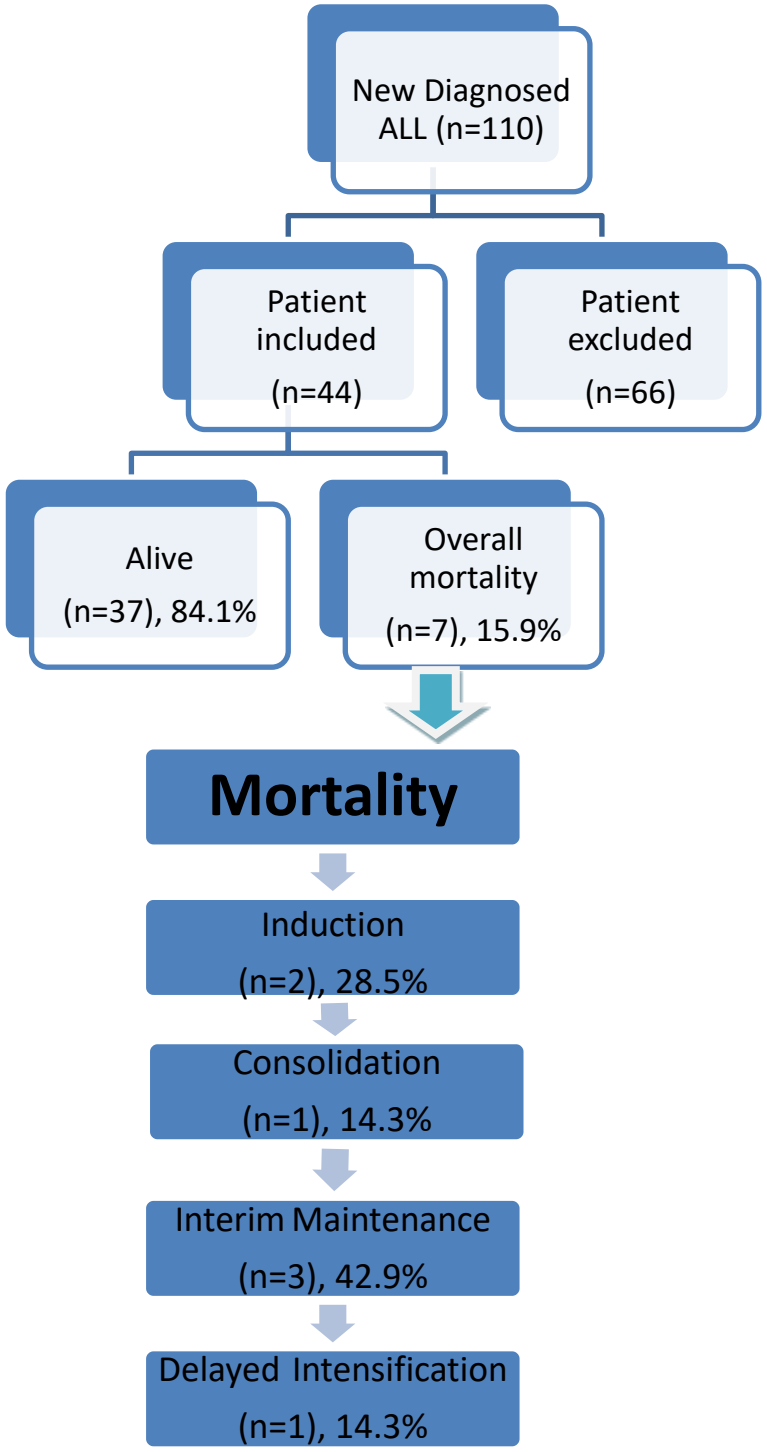

Figure 1: Depiction of Phase related mortality

Conclusion

This retrospective study highlights the critical importance of addressing the multifaceted challenges inherent in the treatment of pediatric acute lymphoblastic leukemia (ALL), particularly during the intensive chemotherapy phase in resource limited settings. With acute complications affecting a significant majority of patients, predominantly in the form of infectious complications, there is a pressing need for vigilant management strategies, especially within resource-limited settings, to enhance patient outcomes. The observed treatment-related mortality rate of 15.9 % primarily attributed to infection-related causes, highlights the urgency of proactive measures to mitigate these risks. Moving forward, a comprehensive approach to managing both infectious and non-infectious complications is paramount to improving the overall efficacy and safety of ALL treatment protocols. This study serves as a clarion call for continued research and the implementation of targeted interventions aimed at reducing the burden of treatment-related complications in pediatric ALL patients.

Limitations

The limitations of the study were it was a retrospective study, relying on existing data. The quality and completeness of the available data can vary, which might affect the accuracy and reliability of the study findings.

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