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Corresponding Author: Abdulaziz Wannas Abd

Affiliation: Almojtaba Hematology and Bone Marrow Transplant Center

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ABSTRACT

Background: Numerous international studies of Acute Lymphoblastic Leukemia (ALL) published in recent years have conclusively demonstrated that minimal residual disease (MRD) during the induction phase is the most reliable prognostic indicator in newly diagnosed ALL.

Methodology: This study included 53 newly diagnosed children with ALL who received chemotherapy at Almojtaba (BMTC) from August 1, 2023, to December 30, 2024. During the induction phase, patients were treated according to the Total XV protocol. Statistical analysis was performed using SPSS version 2022.

Results: Of the 53 participants, 29 were female (54.7%) and 24 were male (45.3%). T-cell ALL was diagnosed in 14 patients (26%), with 4 of them (7.5%) remaining MRD-positive at day 42. In comparison, only 3 patients (5.6%) with B-cell ALL were MRD-positive at day 42.The most common complication observed during induction was adjustment disorder, affecting 9 participants (15.7%), followed by local skin infection (cellulitis) in 5 patients (9.4%), and pneumonia in 4 (7%). Acute renal failure with tumor lysis syndrome, sepsis, and cardiac dysfunction were each observed in 1 patient (1.7%).

There was no significant association between MRD status at day 42 and the presence of underlying comorbidities. Additionally, no statistically significant association was found between sex and MRD outcomes at day 15 and day 42 (p-values 0.5 and 0.09, respectively), as determined by Fisher's exact test. The induction mortality rate was 1.7%.

Conclusion: Most complications encountered during the induction phase of pediatric ALL treatment are manageable and typically arise due to the aggressive nature of the disease, the intensity of chemotherapy, or the presence of pre-existing comorbidities. While these complications may cause temporary treatment interruptions, they generally do not affect overall induction outcomes. The majority of patients achieve remission by the end of induction.

INTRODUCTION

Pediatric leukemia is the single most common malignancy affecting children, representing up to 30% of all pediatric cancers. Dramatic improvements in survival for acute lymphoblastic leukemia (ALL) have occurred over the past four decades, with outcomes approaching 90% in the latest studies. However, progress has been slower for myeloid leukemia and certain subgroups like infant ALL, adolescent/young adult ALL, and relapsed ALL. Recent advances include the recognition of molecularly defined subgroups, which have ushered in precision medicine approaches[1,2].

Current treatment protocols for childhood ALL focus on achieving complete remission during the induction phase, typically within 4 to 6 weeks. This is accomplished in over 95% of cases through the systematic use of multi-agent chemotherapy, commonly including a glucocorticoid, vincristine, L-asparaginase, and in some cases, an anthracycline[3,4].

However, treatment-related complications, such as infections, metabolic disturbances, and organ toxicity, can pose significant challenges during induction, requiring prompt recognition and management. A key determinant of prognosis in pediatric ALL is the level of measurable residual disease (MRD) at the end of induction therapy. Numerous studies have shown that MRD levels $\geq 10^{-4}$ (0.01%) are associated with a significantly increased risk of relapse. Emerging technologies, such as next-generation sequencing (NGS) and next-generation flow (NGF) cytometry, offer even greater sensitivity, yet the clinical significance of MRD levels below 10^{-4} remains under investigation.

While large multi-center trials have provided valuable insights into induction therapy and MRD stratification, there is a need for more detailed data from real-world, single-center experiences, especially from advanced centers that may encounter complex patient populations and unique complication patterns[5,6,7,8].

METHODOLOGY

This retrospective observational study included 53 newly diagnosed children aged 1-14 years with acute lymphoblastic leukemia who received induction Almojtaba Hematology and Bone Marrow Transplant Center (BMTC), Health Authority and Medical Education, Holy Shrine of Hussain, Karbala, between August 1, 2023, and December 30, 2024. Inclusion criteria were newly diagnosed ALL cases within the specified age group who completed induction therapy and had available MRD data, while patients with relapsed disease, mixed phenotypes, AML, or incomplete records were excluded.

During the induction phase, patients were treated according to the St. Jude Children's Research Hospital protocol, which included seven chemotherapy drugs: vincristine (VCR), Asparaginase, Daunorubicin, prednisolone, cyclophosphamide, 6-mercaptopurine (6-MP), and Cytarabine (Ara-C), along with intrathecal therapy. Intermediate- and high-risk patients received additional doses of Asparaginase or single-dose peg-Asparaginase after day 15 of induction. The induction period lasted six weeks, and MRD assessments were performed on Day 15 and between Days 38-42. Data collected included demographics, clinical characteristics, comorbidities, laboratory findings, and treatment-related complications, recorded using the Certacure system and patient progress notes from the pediatric hematology-oncology ward.

The diagnosis was confirmed by CBC, bone marrow aspiration, peripheral blood film, immunophenotyping, and cytogenetic/karyotype studies. Statistical analysis was conducted using SPSS version 27. Categorical variables were compared using Chi-square or Fisher's exact test as appropriate. For MRD outcome analysis, binary logistic regression was used to assess predictors such as age, sex, immunophenotype, and presence of complications. Results were expressed as odds ratios (OR) with 95% confidence intervals (CI), and a p-value <0.05 was considered statistically significant.

This study was approved by the Ethics Board of the Health Authority and the Medical Education, Holy Shrine of Hussain, Karbala.

RESULTS

Out of the 53 participants enrolled in the study, 29 were female (54.7%) and 24 were male (45.3%). The majority of patients (73.6%) were diagnosed with B-cell acute lymphoblastic leukemia (B-ALL), while the remaining 26.4% had T-cell ALL. Children under the age of 10 were the most commonly affected age group.

At day 42 of induction therapy, 4 out of 14 patients (28.6%) with T-cell ALL remained MRD-positive (7.5% of the total cohort), compared to only 3 patients (5.6%) with B-cell ALL. No statistically significant associations were found between MRD status at day 42 and the presence of underlying comorbidities such as hypothyroidism, agammaglobulinemia, Gracile syndrome, congenital heart disease, or other conditions. Similarly, there was no significant relationship between sex and MRD outcomes at day 15 or day 42, with p-values of 0.3 and 0.5, respectively, based on Fisher's exact test. Additionally, there was no sig-

nificant association between gender and MRD status at the end of induction (day 42), with p-values of 0.5 and 0.09, respectively.

The most frequently observed complication was adjustment disorder, affecting 9 participants (15.7%). Other complications included local skin infections (cellulitis) in 5 patients (9.4%), pneumonia in 4 (7.5%), hyperglycemia and hypertension in 3 patients each (5.6%), and systemic infections in 2 (3.5%). Acute renal failure with tumor lysis syndrome, sepsis, and cardiac dysfunction were each observed in 1 patient (1.7%). The induction mortality rate was 1.7%.

A total of 53 participants enrolled in the study, 29 were female (54.7%) and 24 were male (45.3%). The majority of patients (73.6%) were diagnosed with B-cell acute lymphoblastic leukemia (B-ALL), while the remaining 26.4% had T-cell ALL. Children under the age of 10 were the most commonly affected age group.

The most common complication observed during induction was adjustment disorder, affecting 9 participants (15.7%), followed by local skin infection (cellulitis) in 5 patients (9.4%), pneumonia in 4 (7%), hyperglycemia in 3 (5.2%), hypertension in 3 (5.2%), and systemic infections in 2 (3.5%). Acute renal failure with tumor lysis syndrome, sepsis, and cardiac dysfunction were each observed in 1 patient (1.7%).

There was no significant relationship between age, gender, and MRD outcomes at day 42, with p-values of 0.3 and 0.09, respectively, based on Fisher's exact test. At day 42 of induction therapy, 4 out of 14 patients (28.6%) with T-cell ALL remained MRD-positive (7.5% of the total cohort), compared to only 3 patients (5.6%) with B-cell ALL.

Table 1. Frequency of sex and age distribution of pediatric acute lymphoblastic leukemia

Demographic data of ALL		Frequency	Percent
Gender	Female	29	54.7
	Male	24	45.3
Age	< 10 years	40	75.5
	≥ 10 years	13	24.5

Table 2. Frequency distribution of complication during induction

Complication	Frequency	Each percent from total number of patients (53)
Acute renal failure	1	1.80%
Adjustment disorder	9	16.90%
Cellulitis	5	9.40%
Chicken pox	1	1.80%
Hyperglycemia	3	5.60%
Hypertension	3	5.60%
Systemic infection	2	3.70%
Cardiac dysfunction	1	1.80%
Sepsis	1	2%
Pneumonia	4	8%

Table 3. Frequency distribution of gender, age and MRD day 42 during induction therapy

ALL Data		MRD 42 DAY			Frequency	P- value
		Positive	Negative	Not done		
Gender	female	5	21	4	29	0.5
	male	2	18	3	24	
Age	< 10 years	3	31	6	40	0.09
	≥ 10 years	4	8	1	13	

Table 4. Frequency distribution of MRD day 15 and MRD day 42 results according types of leukemia

MRD evaluation		Type			p-value
		B cell	T cell	Total	
MRD 15 days	Positive	6	5	11	0.1
	Negative	26	5	31	
	Not done	7	4	11	
MRD 42 days	Positive	3	4	7	0.01
	Negative	33	6	39	
	Not done	3	4	7	

Table 5. Frequency distribution of underlying comorbidity in pediatric acute lymphoblastic leukemia patients

Comorbidity	Frequency	Percent (%)
Down syndrome	2	3.70%
Gracile syndrome	1	1.80%
Agamma globulinemic	1	1.80%
Cardiac Problem VSD	1	1.80%
Asthma	1	1.80%
Autism	1	1.80%
Hypothyroidism	1	1.80%
Epilepsy	1	1.80%
None	44	83%
Total	53	100%

DISCUSSION

This descriptive study aimed to assess the frequency and nature of complications, both chemotherapy-related and disease-related, during induction in pediatric patients with acute lymphoblastic leukemia, as well as to evaluate their early treatment response through measurable residual disease (MRD) outcomes. We found that 75.5% of ALL cases occurred in children aged ten years or younger Table 1-A. Our findings are consistent with these observations and may partially explain the low induction mortality (1.7%) and favorable MRD clearance rates in this cohort.

While previous studies have suggested that boys with ALL may have inferior outcomes compared to girls[9], our results showed no statistically significant difference in MRD status by sex at either day 15 or day 42. This finding may reflect improvements in standardized treatment protocols that have reduced historical sex-based disparities[10]. However, the relatively small sample size in our study limits the ability to draw definitive conclusions. The peak incidence of

ALL in early childhood supports prior evidence that children aged 1-9 years typically have a better prognosis and higher remission rates[11,12].

MRD remains the most powerful prognostic factor in childhood ALL, providing early insights into treatment response and relapse risk[13,14]. In our center, MRD was monitored using flow cytometry in line with standard practice[15,16]. Consistent with previous literature, our results confirmed that patients with T-cell ALL were more likely to remain MRD-positive at day 42 compared to those with B-cell ALL. (Please give references.) This supports the well-documented observation that T-cell disease is often associated with slower early clearance and a higher risk of relapse[17].

In our study, MRD status at the end of induction was significantly associated with both patient age and leukemia cell type. These findings reinforce the role of MRD as a critical prognostic tool in pediatric ALL. The St. Jude Total Therapy Study XV was the first to prospectively use MRD during and after remission induction to guide risk-directed therapy[18].

Similarly, the Children's Oncology Group (COG) demonstrated that MRD ≥0.01% at day 42 (or day 29 in newer protocols) is a strong predictor of poor outcomes[19]. Other studies have proposed alternative thresholds and time points; Cave et al. suggested that a cut-off of 0.1% post-induction was particularly informative[20], while the BFM Study Group reported a high relapse risk in patients with MRD ≥0.1% on days 33 and 78[21].

Despite improvements in survival, now exceeding 90% with risk-adapted protocols and enhanced supportive care[22], intensified chemotherapy regimens carry a significant risk of treatment-related complications, particularly infections[23]. This is comparable to rates reported in other contemporary ALL trials, which range from 2% to 4%, with infections being the primary cause[24].

Among high-risk cytogenetic features observed in our cohort were hypodiploidy and tetrasomy of chromosome 21. Although our sample size was limited, further analysis, these abnormalities is well recognized as adverse prognostic markers in pediatric ALL.

This study was approved by the Ethics Board of the Health Authority and the Medical Education, Holy Shrine of Hussain, Karbala.

Endocrine complications are increasingly observed due to improved ALL survival rates and prolonged chemotherapy exposure[25]. In particular, hyperglycemia may result from the combined effects of corticosteroids and L-asparaginase. Glucocorticoids induce insulin resistance, asparaginase reduces insulin secretion and may impair insulin receptor function[26,27]. In our study, 3 patients (5.6%) developed hyperglycemia requiring insulin therapy, and all responded well. This incidence is slightly higher than earlier reports, suggesting a 1% rate[26,27], possibly reflecting closer monitoring or patient-specific risk factors. While some studies found no significant association between hyperglycemia and treatment outcomes[28], more recent evidence suggests that patients who develop diabetes induced by dexamethasone (DIDM) during induction face higher rates of ICU admission, serious infections, relapse, and overall healthcare burden[29].

This underscores the need for vigilant metabolic monitoring during induction. Hypertension was noted in 3 patients (5.6%) during induction. In pediatric ALL patients, hypertension increasingly recognized as a common, often transient complication. Previous studies have reported that 12–45% of normotensive children develop elevated blood pressure during induction[30], and up to 14.7% receive antihypertensive medications during hospitalization[31]. Although often asymptomatic and self-limiting, its occurrence may reflect early renal or cardiovascular stress, meriting routine blood pressure monitoring during therapy.

Our study examined how pre-existing comorbidities and treatment-related complications affected early outcomes in pediatric ALL patients. We found that underlying conditions such as Gracile Syndrome and agammaglobulinemia did not significantly impact MRD status at the end of induction. In these cases, dose-modified chemotherapy was used, similar to approaches reported at other centers, despite patients being treated under a high-risk protocol[32]. Likewise, the presence of Down syndrome in two patients (3.7%) had no observed effect on MRD outcomes. These patients were treated according to standard risk stratification protocols, in line with Children's Oncology Group (COG) guidelines[33].

Psychosocial complications were also observed, with 9 patients (16.9%) showing clear signs of adjustment disorder during the induction period. This aligns with earlier research reporting psychiatric disorders in 10-30% of pediatric ALL patients[34,35], although some studies have found emotional difficulties in ALL patients comparable to those of their peers[36]. Psychological distress may arise both during treatment and persist long after it ends[37]. While our study included a broad age range, the limited sample size restricts our ability to draw developmental conclusions about psychological impact. Delays in chemotherapy were common and primarily due to treatment-related toxicities and infectious complications, particularly febrile neutropenia. These delays ranged from several days to a few weeks. In our study, such interruptions did not appear to affect MRD clearance at the end of induction. However, emerging literature suggests that while short-term safety is

improved with chemotherapy delays, the long-term impact on survival outcomes remains uncertain[38,39].

We also observed induction failure in 3 patients (5.6%), all of whom had adverse clinical and cytogenetic features, including T-cell phenotype, hyperleukocytosis, hypo-diploidy, and tetrasomy of chromosome 21. These findings are consistent with prior studies showing that induction failure, although rare (2–3% incidence), is associated with poor outcomes, particularly in patients with high-risk features such as older age, high leukocyte count, BCR-ABL1 positivity, and T-cell lineage[40,41].

Induction mortality occurred in one patient (1.8%), a female with febrile neutropenia and rapid clinical decline. While some studies report higher treatment-related mortality in female patients[42], the reasons remain unclear. In another study, researchers also showed that the females were significantly more likely due to treatment-related causes in immune response or chemotherapy-related toxicity that may contribute to increased vulnerability and prolonged neutropenia in girls[43]. Infections remain the leading cause of induction-phase mortality, and in some settings, particularly in developing countries, induction-related deaths due to infections have been reported in up to 64.7% of cases[44]. Our findings underscore the ongoing need for aggressive supportive care and infection control during induction.

CONCLUSION

This study documented the range and frequency of complications experienced during induction therapy in pediatric patients with acute lymphoblastic leukemia (ALL). The most common complications included hypertension, hyperglycemia, acute renal failure, and infections. While these adverse events led to temporary treatment delays, they did not significantly affect remission rates or minimal residual disease outcomes at the end of induction. Despite the presence of comorbidities or the need to modify treatment protocols due to toxicity or infection, most patients in this cohort achieved MRD negativity by day 42. Importantly, the type of leukemia-T-cell versus B-cell-was the only variable that significantly influenced MRD response, consistent with established literature on ALL prognostics. Clinicians should maintain vigilant supportive care during induction to manage predictable toxicities such as hyperglycemia and hypertension. The dose modifications, when necessary, should be made promptly to prevent long-term complications while preserving MRD response. MRD monitoring should remain central to risk stratification, especially in patients with T-cell ALL who are at higher risk of delayed clearance. Larger, multicenter studies are needed to further evaluate the long-term impact of treatment delays and comorbidities on survival outcomes and to better understand the psychosocial needs of this population.

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REFERENCES

1. Madhusoodhan PP, Carroll WL, Bhatla T. Progress and prospects in pediatric leukemia. *Curr Probl Pediatr Adolesc Health Care*. 2016 Jul;46(7):229-41.

2. Jabbour E, Pui CH, Kantarjian H. Progress and innovations in the management of adult acute lymphoblastic leukemia. *JAMA Oncol*. 2018 Oct 1;4(10):1413-20.

3. Pui CH, Evans WE. Treatment of acute lymphoblastic leukemia. *N Engl J Med*. 2006 Jan 12;354(2):166-78.

4. Aricò M, Valsecchi MG, Rizzari C, et al. Long-term results of the AIEOP-ALL-95 trial for childhood acute lymphoblastic leukemia: insight on the prognostic value of DNA index in the framework of Berlin-Frankfurt-Muenster based chemotherapy. *J Clin Oncol*. 2008 Jan 10;26(2):283-9.

5. Akabane H, Logan A. Clinical significance and management of MRD in adults with acute lymphoblastic leukemia. *Clin Adv Hematol Oncol*. 2020 Jul;18(7):413-22.

6. Brown PA, Shah B, Advani A, et al. Acute lymphoblastic leukemia, version 2.2021, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw*. 2021 Sep 20;19(9):1079-109.

7. Brüggemann M, Raff T, Flohr T, et al. Clinical significance of minimal residual disease quantification in adult patients with standard-risk acute lymphoblastic leukemia. *Blood*. 2006 Feb 1;107(3):1116-23.

8. Berry DA, Zhou S, Higley H, et al. Association of minimal residual disease with clinical outcome in pediatric and adult acute lymphoblastic leukemia: a meta-analysis. *JAMA Oncol*. 2017 Jul 13;3(7):e170580.

9. Gupta S, Teachey DT, Chen Z, et al. Sex-based disparities in outcome in pediatric acute lymphoblastic leukemia: a Children's Oncology Group report. *Cancer*. 2022 May 1;128(9):1863-70.

10. Erdmann F, Kaatsch P, Zeeb H, et al. Survival from childhood acute lymphoblastic leukaemia in West Germany: does socio-demographic background matter? *Eur J Cancer*. 2014 May;50(7):1345-53.

11. Pullen J, Shuster JJ, Link M, et al. Significance of commonly used prognostic factors differs for children with T cell acute lymphocytic leukemia (ALL), as compared to those with B-precursor ALL: a Pediatric Oncology Group (POG) study. *Leukemia*. 1999 Nov;13(11):1696-707.

12. Creutzig U, Büchner T, Sauerland MC, et al. Significance of age in acute myeloid leukemia patients younger than 30 years: a common analysis of the pediatric trials AML-BFM 93/98 and the adult trials AMLCG 92/99 and AMLSG HD93/98A. *Cancer*. 2008 Feb 1;112(3):562-71.

13. Schwartz MS, Muffly LS. Predicting relapse in acute lymphoblastic leukemia. *Leuk Lymphoma*. 2024 Dec;65(13):1934-40.

14. Chandhok NS, Sekeres MA. Measurable residual disease in hematologic malignancies: a biomarker in search of a standard. *EClinicalMedicine*. 2025 Jul 10;86:103348.

15. van der Velden VH, Cazzaniga G, Schrauder A, et al. Analysis of minimal residual disease by Ig/TCR gene rearrangements: guidelines for interpretation of real-time quantitative PCR data. *Leukemia*. 2007 Apr;21(4):604-11.

16. Theunissen P, Mejstrikova E, Sedek L, et al. Standardized flow cytometry for highly sensitive MRD measurements in B-cell acute lymphoblastic leukemia. *Blood*. 2017 Jan 19;129(3):347-57.

17. van Dongen JJ, Seriu T, Panzer-Grümayer ER, et al. Prognostic value of minimal residual disease in acute lymphoblastic leukaemia in childhood. *Lancet*. 1998 Nov 28;352(9142):1731-8.

18. Yilmaz B, Koc A, Dogru O, et al. The results of the modified St Jude Total Therapy XV protocol in the treatment of low- and middle-income children with acute lymphoblastic leukemia. *Leuk Lymphoma*. 2023 Jul–Aug;64(7):1304-14.

19. Dworzak MN, Fröschl G, Printz D, et al. Prognostic significance and modalities of flow cytometric minimal residual disease detection in childhood acute lymphoblastic leukemia. *Blood*. 2002 Mar 15;99(6):1952-8.

20. Campana D. Minimal residual disease in acute lymphoblastic leukemia. *Semin Hematol*. 2009 Jan;46(1):100-6.

21. Flohr T, Schrauder A, Cazzaniga G, et al. Minimal residual disease-directed risk stratification using real-time quantitative PCR analysis of immunoglobulin and T-cell receptor gene rearrangements in the international multicenter trial AIEOP-BFM ALL 2000 for childhood acute lymphoblastic leukemia. *Leukemia*. 2008 Apr;22(4):771-82.

22. Inaba H, Greaves M, Mullighan CG. Acute lymphoblastic leukaemia. *Lancet*. 2013 Jun 1;381(9881):1943-55.

23. Afzal S, Ethier MC, Dupuis LL, et al. Risk factors for infection-related outcomes during induction therapy for childhood acute lymphoblastic leukemia. *Pediatr Infect Dis J*. 2009 Dec;28(12):1064-8.

24. O'Connor D, Bate J, Wade R, et al. Infection-related mortality in children with acute lymphoblastic leukemia: an analysis of infectious deaths on UKALL2003. *Blood*. 2014 Aug 14;124(7):1056-61.

25. Silverman LB, Gelber RD, Dalton VK, et al. Improved outcome for children with acute lymphoblastic leukemia: results of Dana-Farber Consortium Protocol 91-01. *Blood*. 2001 Mar 1;97(5):1211-8.

26. Tosur M, Viau-Colindres J, Astudillo M, et al. Medication-induced hyperglycemia: pediatric perspective. *BMJ Open Diabetes Res Care*. 2020 Jan;8(1):e000801.

27. Howard SC, Pui CH. Endocrine complications in pediatric patients with acute lymphoblastic leukemia. *Blood Rev*. 2002 Dec;16(4):225-43.

28. Handattu K, Sharma LK, Vijayasekharan K, et al. Drug induced diabetes mellitus in pediatric acute lymphoblastic leukemia: approach to diagnosis and management. *J Pediatr Hematol Oncol*. 2022 Aug 1;44(6):273-9.

29. McCormick MC, Sharp E, Kalpatthi R, et al. Hyperglycemia requiring insulin during acute lymphoblastic leukemia induction chemotherapy is associated with increased adverse outcomes and healthcare costs. *Pediatr Blood Cancer*. 2020 Sep;67(9):e28475.

30. Bakk I, Koch T, Stanek J, et al. Steroid-induced hypertension during induction chemotherapy for acute lymphoblastic leukemia in US children's hospitals. *J Pediatr Hematol Oncol*. 2018 Jan;40(1):27-30.

31. Malhotra P, Kapoor G, Jain S, et al. Incidence and risk factors for hypertension during childhood acute lymphoblastic leukemia therapy. *Indian Pediatr*. 2018 Oct 15;55(10):877-9.

32. Hoshino A, Okuno Y, Migita M, et al. X-linked agammaglobulinemia associated with B-precursor acute lymphoblastic leukemia. *J Clin Immunol*. 2015 Feb;35(2):108-11.

33. Michels N, Boer JM, Enshaei A, et al. Minimal residual disease, long-term outcome, and IKZF1 deletions in children and adolescents with Down syndrome and acute lymphocytic leukaemia: a matched cohort study. *Lancet Haematol*. 2021 Oct;8(10):e700-10.

34. Anestin AS, Lippé S, Robaey P, et al. Psychological risk in long-term survivors of childhood acute lymphoblastic leukemia and its association with functional health status: a PETALE cohort study. *Pediatr Blood Cancer*. 2018 Nov;65(11):e27356.

35. Mertens AC, Gilleland Marchak J. Mental health status of adolescent cancer survivors. *Clinical Oncology in Adolescents and Young Adults (COAYA)*. 2015;5:87-95.

36. Marcoux S, Robaey P, Krajinovic M, et al. Predictive factors of internalized and externalized behavioral problems in children treated for acute lymphoblastic leukemia. *Pediatr Blood Cancer*. 2012 Jun;58(6):971-7.

37. Furlong W, Rae C, Feeny D, et al. Health-related quality of life among children with acute lymphoblastic leukemia. *Pediatr Blood Cancer*. 2012 Oct;59(4):717-24.

38. Agrawal V, Kayal S, Ganesan P, et al. Chemotherapy delays are associated with inferior outcome in acute lymphoblastic leukemia: a retrospective study from a tertiary cancer center in South India. *Indian J Med Paediatr Oncol*. 2021;42:5-60.

39. Yeoh A, Collins A, Fox K, et al. Treatment delay and the risk of relapse in pediatric acute lymphoblastic leukemia. *Pediatr Hematol Oncol*. 2017 Feb;34(1):38-42.

40. Conter V, Aricò M, Basso G, et al. Long-term results of the Italian Association of Pediatric Hematology and Oncology (AIEOP) studies 82, 87, 88, 91 and 95 for childhood acute lymphoblastic leukemia. *Leukemia*. 2010 Feb;24(2):255-64.

41. Schrappe M, Hunger SP, Pui CH, et al. Outcomes after induction failure in childhood acute lymphoblastic leukemia. *N Engl J Med*. 2012 Apr 12;366(15):1371-81.

42. Christensen MS, Heyman M, Möttönen M, et al. Treatment-related death in childhood acute lymphoblastic leukaemia in the Nordic countries: 1992-2001. *Br J Haematol*. 2005 Oct;131(1):50-8.

43. Meeske KA, Ji L, Freyer DR, et al. Comparative toxicity by sex among children treated for acute lymphoblastic leukemia: a report from the Children's Oncology Group. *Pediatr Blood Cancer*. 2015 Dec;62(12):2140-9.

44. Hafez HA, Soliaman RM, Bilal D, et al. Early deaths in pediatric acute leukemia: a major challenge in developing countries. *J Pediatr Hematol Oncol*. 2019 May;41(4):261-6.