Evaluation of Prognostic Factors in Children with Acute Lymphoblastic Leukemia

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Abstract

Background: Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy. Despite major therapeutic advancements, relapse and treatment failure continue to be serious challenges, particularly in low- and middle-income countries. While several well-established prognostic factors such as age, white blood cell (WBC) count, cytogenetic abnormalities, minimal residual disease (MRD), and socioeconomic status (SES) have been validated in high-income regions, limited evidence is available from developing countries. Therefore, this study aimed to investigate the prognostic factors associated with relapse and mortality in children diagnosed with ALL in a developing country setting.

Materials and Methods: This prospective cohort study included 130 children younger than 15 years with confirmed ALL admitted to a tertiary referral center from 2014 to 2020. Demographic, clinical, laboratory, MRD, genetic, and socioeconomic data were collected from the patients, and they were followed for up to 48 months after achieving remission. Univariate and multivariate Cox regression models were used to identify the independent predictors of relapse and mortality (significance threshold: $p < 0.05$).

Results: The mean age of the participants was 4.76 ± 3.36 years, and relapse or death occurred in 31 (23.8%) of them. The univariate analysis showed that older age, MRD > 0.1% on day 33, and higher hemoglobin level were associated with relapse. The multivariate analysis identified MRD > 0.1% on day 33 as the only significant independent predictor of relapse. A survival analysis via a multivariate Cox-regression model also showed a lower income level (HR = 2.150, $p = 0.033$) associated with a higher mortality.

Conclusion: This study reveals MRD on day 33 as the strongest determinant of relapse and highlights the critical role of socioeconomic disparities in mortality among children with ALL in developing countries. Early MRD-based risk stratification and policies aimed at bridging socioeconomic gaps may contribute to improved survival outcomes. Larger multicenter studies and extended molecular profiling are recommended.

Keywords: Acute lymphoblastic leukemia, Genetic predisposition to disease, Minimal residual disease

Introduction

Acute lymphoblastic leukemia (ALL) is the most common malignancy in children, accounting for one-third of all childhood cancers (1). The incidence of childhood ALL varies in different countries (2); in the United States, an incidence of 3.4 cases per 100,000 was reported (1). From 2006 to 2014, studies in Iran revealed that the average annual incidence of this disease was 2.25 per 100,000 children under 15, with a cumulative incidence rate of 21.31 per 100,000 in the same age group (2).

The incidence of ALL amongst children appears to be increasing (3), but this may be due to more accurate reporting. The outcome of childhood ALL has improved in recent years such that the five-year overall survival (OS) reaches ninety percent in developed countries (4).

Certain clinical and laboratory features at diagnosis are considered as prognostic factors, being of great importance in the design of therapeutic trials as well as stratification of treatment. Such stratification enables achieving better outcomes and reduction of treatment-related toxicity as well (5). The initial white blood cell (WBC) count, age at diagnosis, sex, cytogenetics, immunophenotyping, central nervous system (CNS) involvement at diagnosis, minimal residual disease (MRD) and presence of hematogones are the known prognostic factors of pediatric ALL (6). As of now, MRD remains the strongest independent prognostic factor in childhood ALL (7); nevertheless, characteristic factors such as age and sex also have an impact on prognosis. It has been shown that age of ≥ 10 years or ≤ 1 year has less favorable outcomes (8). Moreover, in most studies, females have better outcomes (9).

It is of note that almost all the studies evaluating prognostic factors have been conducted in western/developed countries (10). Hence, it is necessary to evaluate the prognostic features in developing countries so as to understand the validity of the established factors and find other setting-specific variables possibly affecting the outcomes. For instance, it has been shown that low socioeconomic status (SES) is associated with a number of unfavorable prognostic factors (11). Thus, the goal of the current study was to evaluate the impacts of patients' characteristics, socioeconomic status and laboratory findings on the relapse and mortality rate of the disease.

The evaluation of prognostic factors in children with acute lymphoblastic leukemia is imperative for enhancing treatment efficacy and patient survival. Ongoing research and technological advancements continue to refine our understanding of these factors, paving the way for more personalized and effective therapeutic approaches.

Material and Methods

Study design and population

This is a prospective cohort study conducted on children with ALL admitted to Omid Hospital (a tertiary referral hospital affiliated to Isfahan University of Medical Sciences). The patients had a definite diagnosis of ALL during 2014-2020. The study protocol was approved by the university ethics committee (ethical code: IR.ARI.mui.rec.1400.117). Written informed consent was also provided by the parents, and oral assent of the children was received where applicable. Those included in the study were all <15 years of age with a definite diagnosis of ALL. Children with incomplete medical records and those not accessible for correction of the missing data were excluded from the study. After a full explanation of the study, written consent was obtained from the children's parents.

Variables and measurements

The participants' electronic records, gathered at the time of diagnosis via semi-structured medical interviews, physical examination and laboratory tests, were extracted anonymously for analysis at the end of the study. Also, their demographic data (sex and age), anthropometric data (weight, height, body surface area or BSA, and birth weight), clinical data and laboratory testing results (complete blood count results, ALL subtype, genetic abnormalities, minimal residual disease or MRD on the 33rd day of treatment initiation, disease relapse and mortality) were also extracted. The studied genetic abnormalities included t (12; 21) ETV6-RUNX1, t (1; 19) TCF3-PBX1, t (9; 22) BCR-ABL1 and t (v; 11q23.3) KMT2A-rearranged. The MRD was evaluated via 4-color

flow cytometry using the European BIOMED-1 standardized technique for the detection of MRD (12). The subjects' socioeconomic status including income level and maternal occupation status at the time of diagnosis was also extracted from the records. The income levels were categorized based on the income percentiles defined by the Iranian Welfare Information Technology Services Company (13). The treatment strategy and the relapse/remission assessment were carried out in accordance with the International Berlin-Frankfurt-Münster Study Group (ALL IC-BFM 2009) protocol (14), and all the procedures were done in accordance with the Declaration of Helsinki. The subjects were followed up for 48 months after complete remission, and the decisions on the outcome were based on CNS, bone marrow, relapse or death.

Statistical analysis

The analyses were performed using the IBM SPSS software (Version 25.0. IBM Corp). The frequencies of the qualitative variables data were presented as percentages, and those of the quantitative variables data were reported as mean ± SD (standard deviation). The normality of different variables was assessed by the Kolmogorov-Smirnov test. The categorical variables were compared by the chi-square analysis and Student's t test, Fisher's exact test or Mann-Whitney's U test were used to compare the continuous variables. Univariate and multivariate cox-regression survival analyses were also conducted to evaluate the potential prognostic factor. A P-value of less than 0.05 was considered to be statistically significant.

Results

Of the 130 children studied, 74 (56.9%) were male and 56 (43.1%) were female with the mean age of 4.76 ± 3.36 years. There were no significant differences in terms of birth weight (p = 0.837), body weight (p = 0.599), height (p = 0.636), BSA (p = 0.706), and distribution of feeding type (p = 0.874) during infancy. The most common ALL subtypes were pro-B/early pre-B (n = 57, 43.8%) and pre-B ALL (n = 57, 43.8%). During the follow-up period, 31 (23.8%) of the participants

had a relapse and/or died. Among the 24 patients with a relapse, 10 had a CNS relapse, 10 had a bone marrow relapse, and 4 had simultaneous CNS and bone marrow relapses with an overall mortality rate of 86.5%. More subjects without a relapse/death had a genetic abnormality (15.1% vs. 12.9%) but with no statistically significant difference (p = 0.671). In terms of genetic abnormalities, 13 (10%) had ETV6-RUNX1, 5 (3.8%) had TCF3-PBX1, and 1 child (0.8%) had BCR-ABL1. Both groups were comparable in terms of maternal occupation rate (93.9% and 90.3% housewives in those without and with relapse/death, respectively; p = 0.445). They were also similar in terms of income level (52.5% vs 48.4%) without any significant difference (p = 0.316). Further details on the patient characteristics, socioeconomic status, and disease outcomes are presented in Table I.

The participants who had a relapse or died had a significantly higher mean hemoglobin at 8.43 ± 2.68 vs. 7.27 ± 0.72 g/dL (p = 0.040). They also had a lower platelet count (65290 ± 78006 per µL) and a higher WBC count (52770 ± 76193 per µL), neither of which was significantly different. Those with and without a relapse/death had rates of 45.2% and 34.3% for MRD ≥ 0.1 on the 33rd day, respectively, which was not a statistically significant difference (p = 0.528). More data on the blood and bone marrow (BM) analysis results are provided in Table II.

In the univariate analysis, higher age (HR = 1.119, p = 0.032), MRD > 0.1% on the 33rd day (HR = 1.408, p = 0.041), and higher hemoglobin (HR = 1.186, p = 0.022) were found to be the risk factors associated with relapse. Through the multivariate cox-regression analysis, MRD > 0.1% on the 33rd (HR = 1.394, p = 0.043) day was found to be a significant prognostic factor for relapse. In terms of mortality, as the univariate analysis showed, higher age (HR = 1.111, p = 0.062) and lower income level (HR = 4.648, p = 0.023) were associated with a higher risk of death. A survival analysis via a multivariate Cox-regression model also showed a lower income level (HR = 2.150, p = 0.033) associated with a higher mortality. The detailed results of the Cox-regression analysis of the prognostic factors for relapse and death are presented in Table III.

Table I: (A) Patient and disease characteristics, (B) outcomes

	Total N = 130	No relapse/death N = 99	Relapse or death N = 31	P-value
A. Patient and disease characteristics				
Sex Male, N (%)	74 (56.9%)	54 (54.5%)	20 (64.5%)	0.407*
Female n, (%)	56 (43.1%)	45 (45.5%)	11 (35.5%)	0.407
Age (year) Mean ± SD Median	4.76 ± 3.36 4.00	4.47 ± 3.06 4.00	5.65 ± 4.09 4.00	0.280**
Weight (Kg)	19.84 ± 15.20	19.12 ± 12.27	22.14 ± 13.74	0.599**
Birth weight (gr)	3062 ± 588	3073 ± 599	3028 ± 559	0.837
Height (CM)	109.72 ± 24.25	108.43 ± 22.71	113.83 ± 28.66	0.636**
BSA (m^2)	0.76 ± 0.31	0.74 ± 0.29	0.82 ± 0.35	0.706**
Feeding type (first year) Breast milk Formula milk Both Missing	109 (83.8%) 3 (2.3%) 15 (11.5%) 3 (2.3%)	83 (83.8%) 2 (2.0%) 12 (12.1%) 2 (2.0%)	26 (83.9%) 1 (3.2%) 3 (9.7%) 1 (3.2%)	0.874*
Genetic abnormalities ETV6-RUNX1 TCF3-PBX1 BCR-ABL1	13 (10.0%) 5 (3.8%) 1 (0.8%)	11 (11.1%) 3 (3.0%) 1 (1.0%)	2 (6.5%) 2 (6.5%) 0 (0%)	0.671*
Subtypes of ALL Pro-B/early pre-B Pre-B T-cell	57 (43.8%) 57 (43.8%) 16 (12.3%)	47 (47.5%) 42 (42.4%) 10 (10.1%)	10 (32.3%) 15 (48.4%) 6 (19.4%)	0.218*
B. Socioeconomic status				
Income level, N (%) Low Middle High Missing	55 (42.3%) 67 (51.5%) 6 (4.6%) 2 (1.5%)	42 (42.4%) 52 (52.5%) 3 (3.0%) 2 (2.0%)	13 (41.9%) 15 (48.4%) 3 (9.7%) 0 (0%)	0.316*
Maternal occupation, N (%) Homemaker Worker	121 (93.1%) 9 (6.9%)	93 (93.9%) 6 (6.1%)	28 (90.3%) 3 (9.7%)	0.445
C. Outcomes				
Relapse, N (%)	24 (18.5%)			
Relapse site CNS Bone marrow CNS + Bone	10 (7.7%) 10 (7.7%) 4 (3.1%)			
Mortality n, (%)	21 (16.2%)			

SD: standard deviation, Kg: kilogram, gr: gram, CM: centimeter, N: number
*. Chi-Square, **. T-Test

Table II: Blood and BM analysis

	Total N = 130	No relapse/death N = 99	Relapse or death N = 31	P-value
WBC **Total (per µL), Mean** **≥ 50000, N (%)**	33782 ± 52903 26 (20%)	27776 ± 41785 18 (18.18%)	52770 ± 76193 8 (25.80%)	0.112** 0.440
Platelets (per µL), Mean ± SD	91463 ± 106546	99742 ± 113181	65290 ± 78006	0.074** (t-test)
Hemoglobin (g/dL), Mean ± SD	7.55 ± 2.63	7.27 ± 0.72	8.43 ± 2.68	0.040*
MRD (33rd day) **≥ 0.1 %, N (%)**	48 (36.9%)	34 (34.3%)	14 (45.2%)	0.528*

WBC: white blood cell, SD: standard deviation, MRD: Minimal Residual Disease
**. T-test, *(Fisher's exact test)

Table III: Adjusted and unadjusted Cox-regression analyses of prognostic factors for relapse and death

Prognostic factor of relapse	Univariate analysis HR (95.0% CI), P-value	Multivariate analysis HR (95.0% CI), P-value (Cox Proportional Hazards Regression)
Sex (male)	2.45 (0.976-6.192), 0.057	2.008 (0.777-5.189), 0.150
Age	1.119 (1.010-1.240), 0.032	1.088 (0.977-1.212), 0.126
MRD 33rd day > 0.1%	1.408 (1.030-3.199), 0.041	1.394 (1.060-3.186), 0.043
Hemoglobin (g/dL)	1.186 (1.025-1.372), 0.022	1.084 (0.930-1.265), 0.302
Weight	1.021 (0.997-1.046), 0.085	
Height	1.012 (0.998-1.027), 0.099	
Birth weight	1.00 (0.999-1.001), 0.975	
Feeding (breast = ref) **formula**	1.049 (0.313-3.518), 0.938	
Income level (middle = ref) **Low** **high**	1.265 (0.167-9.577), 0.820 0.833 (0.104-6.663), 0.863	
Mother's occupation (worker)	0.548 (0.163-1.839), 0.330	
Platelets (per µL)	1.000 (1.000-1.000), 0.121	
WBC	1.35 (0.537-3.406), 0.523	
Prognostic factor of death	**Univariate analysis HR (95.0% CI), P-value**	**Multivariate analysis HR (95.0% CI), P-value**
Age	1.111 (0.995-1.241), 0.062	1.116 (0.0998-1.249), 0.053
Income level (middle = ref) **Low** **high**	4.648 (1.233-17.527), 0.023 1.638 (0.646-4.152), 0.298	2.150 (1.064-4.347), 0.033
Gender (male)	1.313 (0.544-3.170), 0.545	
MRD 33rd day > 0.1%	1.046 (0.432-2.531), 0.921	
Hemoglobin (g/dL)	1.116 (0.957-1.300), 0.160	
Weight	1.024 (0.997-1.051), 0.079	
Height	1.013 (0.997-1.029), 0.125	
Birth weight	1.000 (0.999-1.001), 0.807	
Feeding (breast-feeding = ref) **formula**	2.514 (0.335-18.861), 0.370	
Mother's occupation (worker)	2.095 (0.617-7.114), 0.236	
Platelets (per µL)	1.000 (1.000-1.000), 0.283	
WBC	1.119 (0.439-3.275), 0.723	

Kg: kilogram, gr: gram, CM: centimeter, N: number, WBC: white blood cell, SD: standard deviation, MRD: Minimal Residual Disease, µL: micro liter, dl: deciliter

Discussion

Despite the high incidence of ALL in children and the significant impact of prognostic factors on treatment planning and follow-up strategies, research on this topic remains insufficient, especially in developing countries. Our study aimed to evaluate the prognostic factors associated with relapse and mortality in children with ALL, considering both clinical and socioeconomic variables.

One of the most critical prognostic factors identified in our study was MRD > 0.1% on the 33rd day of the treatment initiation (15). It was significantly associated with an increased risk of relapse in both univariate and multivariate analyses (16). This finding aligns with the other reports in the literature emphasizing MRD as the strongest independent predictor of relapse and treatment response in pediatric ALL. MRD assessment has been incorporated into risk stratification models, guiding therapeutic decisions and intensity of treatment (17). Various studies have demonstrated that MRD positivity at early treatment time points correlates with poor survival outcomes, reinforcing the necessity of MRD monitoring to optimize treatment strategies.

Another significant factor influencing prognosis was age at diagnosis. Higher age was found to be a predictor of both relapse (in univariate analysis) and mortality (in both univariate and multivariate analyses) (18). These results are consistent with the existing studies, which have shown that older children, particularly those above 10 years of age, have a poorer prognosis due to increased resistance to treatment and a higher likelihood of adverse genetic profiles. Similarly, infants (< 1 year) also experience unfavorable outcomes, primarily due to the high prevalence of MLL gene rearrangements in this subgroup (19).

Our findings also highlight the potential impact of hemoglobin levels on the risk of relapse; the patients experiencing relapse had significantly higher baseline hemoglobin levels compared to those who remained in remission. While the exact mechanism remains unclear, previous research has suggested that elevated hemoglobin levels may be associated with a more aggressive disease phenotype or an underlying biological factor that affects disease progression (20).

Importantly, our study sheds light on the role of SES in determining treatment outcomes. We found that lower income level was an independent predictor of mortality, increasing the risk by more than twice, as shown in the multivariate analysis. This aligns with studies from other developing countries that emphasize the adverse effects of financial constraints on treatment adherence, timely access to care, and overall survival. Patients from lower-income backgrounds may face delays in diagnosis, interruptions in therapy, and limited access to advanced treatment options, all of which contribute to poorer outcomes (21). Future research should explore targeted interventions by taking disparities into account and addressing financial support programs and healthcare accessibility.

Although WBC count at diagnosis has been widely regarded as an essential prognostic factor in risk stratification, our study did not find a statistically significant association between WBC count and relapse or mortality. This discrepancy could be attributed to sample size limitations or differences in population characteristics. However, previous research suggests that a WBC count of >50,000/µL at diagnosis generally correlates with a higher risk of relapse and poorer survival (22).

Our study has several strengths, including its prospective design and comprehensive analysis of both clinical and socioeconomic variables. However, there are notable limitations, such as potential selection bias (due to recruitment from a single institution), limited follow-up duration, and the lack of certain molecular markers that could further refine risk assessment. Future studies should aim at larger, multi-center cohorts with extended follow-up periods to validate these findings and incorporate next-generation sequencing techniques to identify novel genetic predictors of treatment response.

Beyond the identified prognostic indicators, our findings highlight the importance of integrating both clinical and socioeconomic parameters into comprehensive risk stratification models. The lack of significant association between genetic

abnormalities and clinical outcomes in our study may reflect either limited sample size or variability in access to advanced molecular diagnostic tools, which remain less available in resource-limited settings. Additionally, higher hemoglobin levels correlate with relapse, as observed in the univariate analysis, although not sustained in the multivariate model, suggests that traditional laboratory markers alone may not adequately predict the disease behavior; they should be interpreted within a broader clinical context. These results emphasize that treatment outcomes in developing countries are impacted not only by biological disease factors but also by contextual determinants such as financial capacity, treatment adherence, availability of supportive care, and timely access to specialized oncology services. Therefore, improving outcomes may require health-system-level strategies such as subsidized treatment programs, improved referral pathways, MRD-based national treatment algorithms, and family-centered supportive interventions.

This study provides valuable insights into the prognostic factors affecting relapse and mortality in children with ALL within a developing country setting. We confirmed that MRD > 0.1% on day 33 remains a critical determinant of relapse, while higher age and lower income level significantly impact the risk of mortality. These findings underscore the importance of early risk stratification, tailored treatment approaches, and socioeconomic support systems to improve the outcomes in children with ALL. Further research is warranted to explore additional prognostic markers and implement strategies to mitigate socioeconomic disparities in ALL treatment outcomes.

Conclusion

Overall, the prognostic factors for children with ALL in the setting of a developing country were found to be higher age, MRD > 0.1%, and higher hemoglobin. These factors were associated with more relapse, and higher age and lower income were associated with a higher risk of mortality. Also, MRD and lower income were found to be independent prognostic factors for

predicting relapse and death, respectively.

Availability of Data

The data that support this study are available, but there are restrictions to their availability of these data; they were used under license just for the current study, thus not publicly available. The data are, however, available from the authors upon reasonable request and with permission of Maryam Manoochehri.

Ethical Considerations

All the procedures in this study were conducted in accordance with ethical standards. The research received approval from the ethics committee of Isfahan University of Medical Science (ethical code: IR.ARI.mui.rec.1400.117). Moreover, informed consent was obtained from all the participants. The study ensured the confidentiality and anonymity of all the participants and followed ethical guidelines regarding data handling, privacy, and reporting of the results.

Authors' Contributions

S.Y performed article structure, references, data analysis, editing, formatting guidelines, peer review.

M.M performed data analysis, editing, formatting guidelines, peer review, and figures and tables.

Conflict of Interest

The authors declare no conflict of interests regarding this study.

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