Original Article
Middle East Journal of Cancer; January 2023; 14(1): 92-101

Evaluation and Diagnosis of Prognostic Factors Affecting the Survival of Leukemia Patients Using Cumulative Incidence Function

Hamid Reza Khalkhali*, PhD, Mehran Noroozi **, MD, Robabeh Bahadori*, MD, Tahereh Omidi****, PhD, Farid Ghazizadeh**, MD, Sasan Hejazi**, MD, Masoumeh Mahdi-Akhgar*****♦, MSc, Rohollah Valizadeh******, PhD**

*Patient Safety Research Center, Department of Biostatistics and Epidemiology, Urmia University of Medical Sciences, Urmia, Iran
**Department of Pediatric Hematology, Motahari Hospital, Urmia University of Medical Sciences, Urmia, Iran
***Department of Pediatrics, Urmia University of Medical Sciences, Urmia, Iran
****Department of Biostatistics, Hamadan University of Medical Sciences, Hamadan, Iran
*****Solid Tumor Research Center, Urmia University of Medical Sciences, Urmia, Iran
******Urmia University of Medical Sciences, Urmia, Iran

Please cite this article as: Khalkhali HR, Noroozi M, Bahadori R, Omidi T, Ghazizadeh F, Hejazi S, et al. Evaluation and diagnosis of prognostic factors affecting the survival of leukemia patients using cumulative incidence function. Middle East J Cancer. 2023;14(1):92-101. doi: 10.30476/ mejc.2022. 89478.1528.

♦Corresponding Author:
Masoumeh Mahdi-Akhgar, MSc
Solid Tumor Research center, Urmia University of Medical Sciences, Urmia, Iran
Email: maasoumehakhghar@gmail.com

Abstract

Background: Acute lymphoblastic leukemia (ALL) accounts for 25% of cancers among children less than 15 years of age. This study aimed to evaluate and determine the prognostic factors affecting the survival of leukemia patients using cumulative incidence function.

Method: This was a retrospective study done on 176 children under 15 who had ALL between 2011 and 2019. Overall survival, event-free survival, disease-free survival (DFS), and non-relapse mortality served as the study's endpoints. Using the Fine-Gray model, the Kaplan-Meier, single-variable, and multivariable analyses were conducted. Schwenfeld weighted residuals were used to test the proportional hazard hypothesis. SAS was used to conduct the analysis.

Results: The hazard ratio (HR) of DFS for effective variables was calculated (girls compared to boys: 0.37 [95% confidence interval (CI): 0.15-0.91], positive testis test: 10.34 [95% CI: 4.44-24.05], children with central nervous system involvement: 2.95 [95% CI: 1.36-6.40], testicular swelling in children: 11.54 [95% CI: 4.21-31.59], children with hepatosplenomegaly larger than 2 cm: 0.30 [95% CI: 0.10-0.88], high risk of disease compared to low risk: 4.76 [95% CI: 1.12-20.22], children with complete remission in 28th day compared with no complete remission: 0.10 [95% CI: 0.04-0.25]. Only hemoglobin was substantially linked with DFS in the multivariate DFS HR. Children who got radiation had a 77% reduced risk of non-recurrence death than those who did not (HR: 0.23, 95% CI: 0.08-0.60).

Conclusion: Being a girl, having family history, and not having radiotherapy were the main factors to develop death before the first recurrence in children.

Keywords: Leukemia, Neoplasms, Child, Survival

Received: December 25, 2020; Accepted: June 29, 2022

Introduction

One of the main causes of mortality and a significant global public health issue is cancer. The most prevalent malignancy among children under the age of 14 is leukemia.[1-4] Leukemia is regarded as the second most common cause of mortality in children under the age of 15.[5] Among kids under the age of 15, acute lymphoblastic leukemia (ALL) makes about 25% of all cancer cases.[6] In recent decades, there was a significant improvement to treat children with leukemia, but now a large proportion of children with cancer relapse after the disease.[7] Despite advances in treating this disease, about 20% of patients experience recurrence.[8]

ALL in children is a heterogeneous disease, and various factors, such as age at diagnosis, gender, lymph node enlargement, white blood cell count, immune phenotype, central nervous system (CNS) disease, and response to initial treatment are important to determine the prognosis of the disease.[9, 10] Therefore, sufficient information on the factors affecting the survival of the patients with leukemia can prevent premature death of patients with timely treatment. As a result, it is important to examine it as a public health issue. One of the types of research used to assess the state of the illness and its contributing elements is the survival of cancer patients. A statistical technique known as survival analysis is used to simulate the time to event and investigate the impact of auxiliary factors on survival time.[11] When analyzing survival data, an event might happen for a variety of reasons, and when one of those reasons occurs, it precludes the occurrence of other reasons, which is known as competing risk.[12] Thus, in competing hazard data, there are at least two reasons for failure that compete for occurrence. When recurrence of leukemia is an event of interest, death without recurrence is a competing risk that any individual may experience the event.[13] Therefore, to achieve accurate patient

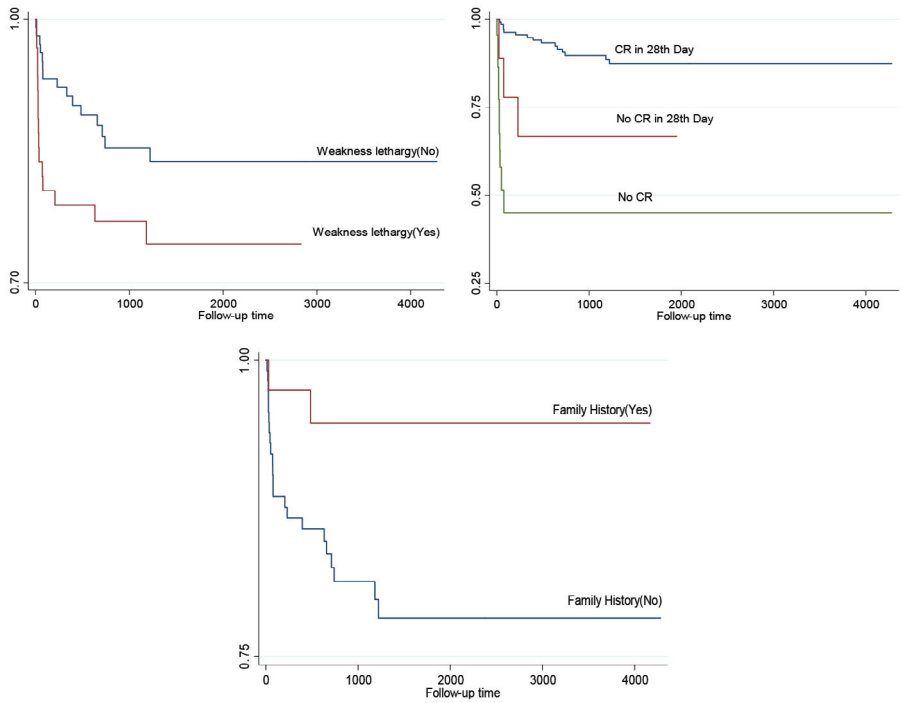

Figure 1. Kaplan Meier curves for the cumulative survival free from leukemia events (Horizontal: Time; Vertical axis: Survival probability, %). The HR of NRM among children with/without a family history of the disease was significantly different. There was a statistically significant difference in the likelihood of NRM for the children with complete remission in 28th day compared with no complete remission. There was a significant difference among three groups regarding free of NRM survival. The group with no complete remission had the lowest free of NRM survival.

CR: Complete remission; NRM: Non-relapse mortality; HR: Hazard ratio

Table 1. Baseline characteristics of the participants

Age group	
≤10 Years	150 (85.7)
>10 Years	25 (14.3)
Sex	
Girl	81 (46.0)
Boy	95 (54.0)
Residential area	
Urban	88 (50.3)
Rural	87 (49.7)
Blood group	
A	58 (40.8)
B	20 (14.1)
AB	10 (7.0)
O	54 (38.0)
Family history	
Yes	40 (25.3)
No	118 (74.7)
WBC group	
>50000	46 (26.1)
≤50000	130 (73.9)
T (9.22)	
Positive	4 (2.3)
Negative	172 (97.7)
T (1.19)	
Positive	1(0.6)
Negative	175 (99.4)
Risk of disease	
High	92 (53.2)
Standard	54 (31.2)
Low	27 (15.6)
Immunophenotyping	
Mature B-cells	6 (4.8)
Precursor B-cells	100 (80.6)
Precursor T-cells	18 (14.5)
Reply to treatment	
Complete remission in 28th day	138 (81.7)
No complete remission in 28th day	9 (5.3)
No complete remission	22 (13.0)
Rheumatoid signs	
Yes	0 (0)
No	170 (100)
Hepatosplenomegalia ≥2 cm	
Yes	64 (37.6)
No	106 (62.4)
Lymphadenopathy ≥2 cm	
Yes	33 (19.4)
No	137 (80.6)
Fever, cough and diarrhea	
Yes	52 (30.6)
No	118 (69.4)
Weakness and loss of anorexia	
Yes	63 (37.1)
No	107 (62.9)
Testicular swelling	
Yes	5 (2.9)
No	165 (97.1)
Bleeding	
Yes	36 (21.2)
No	134 (78.8)
Lower extremity pain/Abdominal pain	
Yes	44 (25.9)
No	126 (74.1)
CNS	
Positive	45 (26.8)
Negative	123 (73.2)
Testis	
Positive	8 (4.8)
Negative	160 (95.2)
Radiotherapy	
Yes	71 (42.3)
No	97 (57.7)
Status of patients	
First recurrence	28 (15.9)
Death	49 (27.9)
Alive	99 (56.2)
BMI (kg/m^2)	15.72.5
Platelet (mcL)	40000(18000-101000)
Hemoglobin (g/dl)	7.32.8
LDH (U/l)	843.5(585.7-1831.7)

WBC: White blood count; BMI: Body mass index; LDH: Lactate dehydrogenase; CNS: Central nervous system

estimates as well as factors affecting patients' survival time, competitive risks must be considered in the analysis.[14]

The case-specific model is one of several techniques for interpreting competitive risk data. The cumulative probability of the period of the event for the event as a cause-specific and other risks are considered as censoring in the cumulative incidence function (CIF) utilized for competitive risk data. This model requires the assumption of proportional hazards and is often presented as a semi-parametric.[15-18] Furthermore, in different studies, the competitive risk regression model was an efficient model compared with standard survival models, such as Cox, which is used in the presence of competing risks.[13, 19, 20] This study aimed to investigate the prognostic factors affecting the survival of leukemia using cumulative incidence functions competing.

Methods

In this retrospective study, the medical record of 176 children under 15 years of age with ALL from April 2011 to March 2019, who were referred to Motahari hospital in West Azerbaijan province, was studied. Motahari hospital is the only cancer referral center for pediatric leukemia in West Azerbaijan province. Present data were taken from patients' medical records and in the event that the records were insufficient, phone calls

Table 2. Univariate and multivariate HRs of the cox regression models for disease-free survival cause (continued)

	Univariate		Multivariate	
Variables	**HR (%95 CI)**	***P*-value**	**HR (%95 CI)**	***P*-value**
BMI	1.13 (0.98-1.30)	0.096		
Platelet	1.00 (1.00-1.00)	0.271		
Hemoglobin	1.17 (1.03-1.34)	0.017	0.86 (0.71-1.03)	0.097
LDH	1.00 (1.00-1.00)	0.790		
Age				
≤10 years	0.94 (033-2.72)	0.912		
>10 years	1			
Sex				
Female	0.37 (0.15-0.91)	0.031	0.43 (0.15-1.25)	0.121
Male	1	1		
Residential area				
Urban	1.20 (0.57-2.53)	0.631		
Rural	1			
Blood group				
A	0.63 (0.26-1.55)	0.316		
B	0.88 (0.25-3.15)	0.847		
AB	0.46 (0.06-3.55)	0.455		
O	1			
Family history				
Yes	1.09 (0.47-2.53)	0.845		
No	1			
WBC				
>50000	1.80 (0.83-3.91)	0.138		
≤50000	1			
T (9.22)				
Positive	3.35 (0.45-25.17)	0.240		
Negative	1			
T (1.19)				
Positive	16.615 (2.10-131.21)	0.008		
Negative	1			
Risk of disease				
High	4.76 (1.12-20.22)	0.034	11.25 (2.02-62.7)	0.006
Standard	0.48 (0.07-3.38)	0.458	1.01 (0.13-8.01)	0.992
Low	1			
Immune phenotype				
Mature B-cells	2.43 (0.33-17.86)	0.383		
Precursor B-cells	0.91 (0.20-4.15)	0.905		
Precursor T-cells	1			
Reply to treatment				
Complete remission in 28th day	0.10 (0.04-0.25)	<0.001		
No complete remission in 28th day	0.16 (0.02-1.32)	0.090		
No complete remission	1			
Hepatosplenomegalia ≥2 cm				
Yes	0.30 (0.10-0.88)	0.029	0.21 (0.06-0.67)	0.009
No	1			
Lymphadenopathy ≥2 cm				
Yes	0.53 (0.16-1.78)	0.305		
No	1			
Fever, cough, diarrhea				
Yes	0.66 (0.25-1.76)	0.403		
No	1			
Weakness, loss of appetite				
Yes	0.40 (0.15-1.08)	0.071		
No	1			
Testicular swelling				
Yes	11.54 (4.21-31.59)	<0.001		
No	1			
Bleeding				
Yes	0.54 (0.16-1.81)	0.318		

Table 2. Univariate and multivariate HRs of the cox regression models for disease-free survival cause (continued)

	Univariate		Multivariate	
Variables	**HR (%95 CI)**	***P*-value**	**HR (%95 CI)**	***P*-value**
No	1			
Pain				
Yes	0.65 (0.25-1.74)	0.397		
No	1			
CNS				
Positive	2.95 (1.36-6.40)	0.006		
Negative	1			
Testis				
Positive	10.34 (4.44-24.05)	<0.001	8.02 (2.5-25.3)	<0.001
Negative	1		1	
Radiotherapy				
Yes	0.91(0.40-2.05)	0.814		
No	1			

HR: Hazard ratio; CI: Confidence interval; BMI: Body mass index; LDH: Lactate dehydrogenase; WBC: White blood cell; CNS: Central nervous system

and interviews with the patient's family were conducted. The names of the people were hidden and the information was only accessible to study researchers. The requirement for inclusion was to have an eight-year medical history (2011-2019). People who were not native to the province of West Azerbaijan were not included in the research. Patients' characteristics were descriptively reported. Prognostic factors considered in the analysis included age, gender, place of residence, body mass index, platelet, hemoglobin, low-density lipoprotein (LDL), blood type, family history, white blood cell, cytogenetic disorders, risk of disease, immune phenotype, response to treatment, clinical signs consisting of rheumatoid symptoms, hepatosplenomegaly ≥ 2 cm, lymphadenopathy ≥ 2 cm, fever, cough, diarrhea, weakness, loss of appetite, testicular swelling-bleeding, abdominal pain, pain in lower extremities, CNS involvement, testicular involvement, and radiotherapy. Overall survival, event-free survival, disease-free survival (DFS), and non-relapse mortality (NRM) served as the study's endpoints (NRM). The period of time from diagnosis to death from any cause or recurrence was used to determine overall survival and DFS. The time between the diagnosis date and the last follow-up before the first incident was used to compute the event-free survival period. All deaths without recurrence were counted as mortality without recurrence. This study was approved by ethical committee of Urmia University of Medical Sciences (#IR.UMSU.REC.1397.151).

Statistical analysis

Continuous variables with normal and skewed distributions were expressed as mean ±SD and median (IQR, 25th and 75th percentile), respectively. Baseline data regarding the categorical variables are presented as frequency (percentages). At first, based on previous studies, predictor variables were selected as important clinical onset leukemia variables. Cox proportional hazard regression model was used to investigate the hazard ratio (HR) of each risk factor. Time to event was defined as time of censoring or having event, whichever came first. To detect the most important risk factors of leukemia, a forward stepwise approach was used ($P < 0.2$ for entry and $P > 0.1$ for removal). The proportional hazards assumption in the Cox model was checked graphically, using the Schoenfeld's test of residuals; all proportionality assumptions were generally appropriate. All analyses were carried out using STATA version 14 SE (Stata Corp LP, TX, USA), with two-tailed *P*-values 0.05 being considered as significant.

Results

A total of 176 children with ALL (46% girl) were included in the analysis: the patients (85.7% less than 10 years old) with a mean age of 5.61 ± 3.56 years and a mean body mass index (BMI) of 15.7 ± 2.5 kg/m^2 with median follow-up time of 1195 days (25th 75th interquartile: 485-2013 days).Other baseline characteristics can be found

Table 3. Univariate and multivariate HRs of the cox regression models for non-relapse mortality cause (continued)

	Univariate		Multivariate	
Variables	**HR (%95 CI)**	***P*-value**	**HR (%95 CI)**	***P*-value**
BMI	1.05(0.91-1.21)	0.525		
Platelet	1.00 (1.00-1.00)	0.484		
Hemoglobin	1.00 (0.88-1.14)	0.981		
LDH	1.00 (1.00-1.00)	0.277		
Age				
≤10 years	0.83(0.32-2.16)	0.698		
>10 years	1			
Sex				
Female	1.60(0.787-3.29)	0.203		
Male	1			
Residential area				
Urban	1.32(0.64-2.73)	0.446		
Rural	1			
Blood group				
A	0.84 (0.33-2.11)	0.709		
B	1.87 (0.66-5.25)	0.236		
AB	0.51 (0.06-4.06)	0.528		
O	1			
Family history				
Yes	0.23 (0.05-0.97)	0.046	0.19(0.04-0.85)	0.030
No	1			
WBC group				
>50000	1.05 (0.47-2.35)	0.911		
≤50000	1			
T (9.22)				
Positive	1.55 (0.21-11.38)	0.66		
Negative	1			
Risk of disease				
High	1.45 (0.49-4.28)	0.504		
Standard	0.97 (0.29-3.24)	0.967		
Low	1			
immune phenotype				
Mature B-cells	0.49 (0.06-4.20)	0.515		
Precursor B-cells	0.59 (0.22-1.60)	0.305		
Precursor T-cells	1			
Reply to treatment				
Complete remission in 28th day	0.10(0.05-0.23)	<0.001	0.04(0.01-0.13)	< 0.001
No complete remission in 28th day	0.40(0.11-1.43)	0.159	0.55 (0.14-2.21)	0.399
No complete remission	1			
Hepatosplenomegalia ≥2 cm				
Yes	0.69(0.32-1.51)	0.359		
No	1			
Lymphadenopathy ≥2 cm				
Yes	0.59 (0.20-1.68)	0.319		
No	1			
Fever, cough, diarrhea				
Yes	1.58 (0.76-3.28)	0.221		
No	1			
Weakness, loss of appetite				
Yes	1.86 (0.91-3.81)	0.089	4.44 (1.67-11.85)	0.003
No	1			
Testicular swelling				
Yes	0.05 (0.00–442.28)	0.513		
No	1			
Bleeding				
Yes	0.60 (0.21-1.71)	0.337		
No	1			
Pain				
Yes	0.97 (0.43-2.18)	0.940		
No	1			

Table 3. Univariate and multivariate HRs of the cox regression models for non-recurrent mortality cause (continued)

	Univariate		Multivariate	
Variables	**HR (%95 CI)**	***P*-value**	**HR (%95 CI)**	***P*-value**
CNS				
Positive	0.86 (0.37-2.02)	0.735		
Negative	1			
Testis				
Positive	0.05 (0.00–83.05)	0.421		
Negative	1			
Radiotherapy				
Yes	0.23 (0.08-0.60)	0.003		
No	1			

HR: Hazard ratio; CI: Confidence interval; BMI: Body mass index; LDH: Lactate dehydrogenase; WBC: White blood cell; CNS: Central nervous system

in (Table 1).

Tables 2 and 3 summarize the risks associated with the presence of DFS and NRM. The HR of DFS for effective variables was calculated (girls compared with boys: 0.37 [95% confidence interval (CI): 0.15-0.91], t(1.19): 16.61 [95% CI: 2.10-131.2], positive testis test: 10.34 [95% CI: 4.44-24.05], children with CNS involvement: 2.95 [95% CI: 1.36-6.40], testicular swelling in children: 11.54 [95% CI: 4.21-31.59], children with hepatosplenomegaly larger than 2 cm: 0.30 [95% CI: 0.10-0.88], high risk of disease compared with low risk: 4.76 [95%CI: 1.12-20.22], children with complete remission in 28th day compared with no complete remission: 0.10 [95%CI: 0.04-0.25].

In the multivariate HR for DFS, only hemoglobin, sex, risk of disease, hepatosplenomegalia ≥2 cm and testis remained in which only hemoglobin was significantly associated with DFS. The HR of NRM among children with a family history of disease was 0.23 (95%CI: 0.05-0.97). There was a statistically significant difference in the likelihood of NRM for children with complete remission in 28th day compared with no complete remission (HR: 0.10, 95%CI: 0.05-0.23). Only family history, radiotherapy, weakness, loss of appetite, and response to treatment remained in the multivariate NRM and only radiotherapy was substantially linked with NRM in children (HR: 0.23, 95 percent CI: 0.08-0.60). According to Kaplan-Meier curves, there was a substantial difference between the three groups in terms of survival free of NRM (Figure 1). The group without a full remission had the lowest free of NRM survival as a result.

Discussion

In summary, our results out of 176 children with ALL showed that the HR of DFS for the effective variables was 0.37 for gender variable (girls vs. boys); 10.34 for positive testis test, 2.95 for children with CNS involvement], 11.54 for testicular swelling in children, 0.30 for children with hepatosplenomegaly larger than 2 cm, 4.76 for high risk of disease compared with low risk and 0.10 for children with complete remission in 28th day compared with no complete remission. Moreover, in the multivariate HR for DFS, only hemoglobin, sex, risk of disease, hepatosplenomegalia ≥2 cm and testis remained in which only hemoglobin was significantly associated with DFS. Children with a family history of the illness had a 0.23 HR of NRM. With an HR of 0.10, there was a statistically significant difference between children who had full remission in their 28th day and those who had none. Only family history, radiation, weakness, lack of appetite, and response to treatment were left in the multivariate HR for NRM, and only radiotherapy-received children were substantially linked with NRM. There was a significant difference between the three groups regarding free of NRM survival. Moreover, the group with no complete remission had the lowest free of NRM survival.

Leukemia is the most common malignancy of childhood that causes bone marrow failure with clonal proliferation of cells and it is divided into acute and chronic types.[21] The one-year survival rate in children is lower than adults, but the

survival rate of 2 to 3 years in children is higher than adults.[22-25] One of the reasons for the higher survival rate of ALL than other types of leukemia is that ALL occurs more in higher socioeconomic classes and in children and young adults.[26] Thus, Bhatia et al. stated in their study that the outcome of ALL leukemia in adults was worse than the outcome of ALL leukemia in children.[27]

This type of leukemia has a greater survival rate in children than in adults, which may be a result of the disease's molecular and clinical features as well as the better response to therapy in children than in adults.[27] Data from 310 individuals with leukemia in children and adults in the Kurdistan Province were retrieved from their medical records for a retrospective analysis by Moradi et al. 201 adults with a mean age of 50.8 years and 109 children with a mean age of 5.2 years were studied. The prevalence of AML type leukemia was higher in adults (30.8%) but the frequency of ALL cases was higher in children (86.2%). Survival rates of 1 and 5 years in adults were 94.4% and 49.5%, respectively, and survival rates of 1 and 5 years in children were 92.6% and 83%, respectively. HR in adults according to the type of thalassemia with ALL (HR = 5.18, 95% CI: 2.60-13) and in the people with AML type (HR = 4.11, 95% CI: 1.55-10.4) were different.[28]

In a study by Zareifar et al., the cumulative 5-year survival rate of leukemia was 53.3 %. Cox regression model showed that there is a significant relationship among the platelet variables and the number of relapses with cancer survival. The platelet count and frequency of disease recurrence were identified as effective factors in the patient survival, so considering these factors can help further survival of these patients.[28] Less than 10,000 WBCs often had a better prognosis, according to studies of various organizations, which typically demonstrate the importance of WBC in the survival rate of patients with leukemia, particularly ALL.[29, 30] We found that a number of variables, including testicular edema, radiation, gender, family history, t (1, 19), response to treatment, fever and coughing, diarrhea, weakness, and lack of appetite, were significantly associated with mortality before the first recurrence in children. Then, death or survival can be affected by the above-mentioned factors. The risk of death without recurrence in girls was 2.94 times higher than boys and children with a family history of the disease had a good prognosis for NRM. Another finding of our study was the preventive effect of radiotherapy in which children who received radiotherapy had a 77% lower risk of NRM than children who did not. In order to identify the risk factors for all causes of mortality for patients with leukemia, it is crucial to employ robust statistical methods to uncover probable relationships. One example of this is the use of competing risk models.[31, 32]

Cumulative incidence function as an advanced research was used for competitive risk data in our study. Considering the strength point of analysis used, we had just a total of 176 children with ALL in which are small and it is beneficial to have larger sample size to run statistical modeling.

Conclusion

Female gender, having family history, and not having radiotherapy were main factors to develop death before the first recurrence in children. In total, the risk of death without recurrence in girls was 2.94 times higher than boys and children who received radiotherapy had a 77% lower risk of NRM than children who did not.

Conflict of Interest

None declared.

References

1. Azeem S, Gillani SW, Siddiqui A, Jandrajupalli SB, Poh V, Syed Sulaiman SA. Diet and colorectal cancer risk in Asia--a systematic review. *Asian Pac J Cancer Prev.* 2015;16(13):5389-96. doi: 10.7314/apjcp.2015.16.13.5389.
2. Mousavi SM, Gouya MM, Ramazani R, Davanlou M, Hajsadeghi N, Seddighi Z. Cancer incidence and mortality in Iran. *Ann Oncol.* 2009;20(3):556-63. doi: 10.1093/annonc/mdn642.
3. Moradi A, Semnani S, Roshandel G, Mirbehbehani N, Keshtkar A, Aarabi M, et al. Incidence of childhood cancers in golestan province of iran. *Iran J Pediatr.*

2010;20(3):335-42.
4. Yang L, Fujimoto J, Qiu D, Sakamoto N. Childhood cancer in Japan: focusing on trend in mortality from 1970 to 2006. *Ann Oncol.* 2009;20(1):166-74. doi: 10.1093/annonc/mdn562.
5. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. *CA Cancer J Clin.* 2009;59(4): 225-49. doi: 10.3322/caac.20006.
6. Hunger SP, Lu X, Devidas M, Camitta BM, Gaynon PS, Winick NJ. Improved survival for children and adolescents with acute lymphoblastic leukemia between 1990 and 2005: a report from the children's oncology group. *J Clin Oncol.* 2012;30(14):1663-9. doi: 10.1200/JCO.2011.37.8018.
7. Malempati S, Gaynon PS, Sather H, La MK, Stork LC; Children's Oncology Group. Outcome after relapse among children with standard-risk acute lymphoblastic leukemia: Children's Oncology Group study CCG-1952. *J Clin Oncol.* 2007;25(36):5800-7. doi: 10.1200/JCO.2007.10.7508.
8. Lugthart S, Cheok MH, den Boer ML, Yang W, Holleman A, Cheng C, et al. Identification of genes associated with chemotherapy crossresistance and treatment response in childhood acute lymphoblastic leukemia. *Cancer Cell.* 2005;7(4):375-86. doi: 10.1016/j.ccr.2005.03.002.
9. Pui CH, Pei D, Sandlund JT, Ribeiro RC, Rubnitz JE, Raimondi SC, et al. Long-term results of St Jude total therapy studies 11, 12, 13A, 13B, and 14 for childhood acute lymphoblastic leukemia. *Leukemia*. 2010;24(2):371-82. doi: 10.1038/leu.2009.252.
10. Möricke A, Zimmermann M, Reiter A, Henze G, Schrauder A, Gadner H, et al. Long-term results of five consecutive trials in childhood acute lymphoblastic leukemia performed by the ALL-BFM study group from 1981 to 2000. *Leukemia.* 2010;24(2):265-84. doi: 10.1038/leu.2009.257.
11. Klein P, Moeschberger L. Survival analysis: techniques for censored and truncated data. New York: Springer; 2003.p.26-60.
12. Kleinbaum G, Klein M. Survival analysis: a self-learning text. Gail M, Krickeberg K, Samet JA, et al, editors. 3rd ed. New York: Springer Science and Business Media; 2006.p.11-17.
13. Abadi A, Dehghani-Arani M, Yavari P, Alavi-Majd H, Bajik K. Application of the competing risk models for the analysis of risk factors in patients with breast cancer. *Feyz J.* 2013;16:546-52.
14. Pintilie M. Competing risks: a practical perspective. Ontario Cancer Institute, Canada: John Wiley & Sons, Ltd; 2006.
15. He P, Eriksson F, Scheike TH, Zhang MJ. A Proportional hazards regression model for the sub-distribution with covariates adjusted censoring weight for competing risks data. *Scand Stat Theory Appl.* 2016;43(1):103-22. doi: 10.1111/sjos.12167.
16. Satagopan JM, Ben-Porat L, Berwick M, Robson M, Kutler D, Auerbach AD. A note on competing risks in survival data analysis. *Br J Cancer.* 2004;91(7):1229-35. doi: 10.1038/sj.bjc.6602102.
17. Prentice RL, Kalbfleisch JD, Peterson AV Jr, Flournoy N, Farewell VT, Breslow NE. The analysis of failure times in the presence of competing risks. *Biometrics.* 1978;34(4):541-54.
18. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc.* 1999;94(446):496-509. doi: 10.1080/01621459.1999.10474144.
19. Fürstová J, Valenta Z. Statistical analysis of competing risks: overall survival in a group of chronic myeloid leukemia patients. *J Biomed Inform.* 2011;7(1).
20. Shin A, Joo J, Yang HR, Bak J, Park Y, Kim J, et al. Risk prediction model for colorectal cancer: National Health Insurance Corporation study, Korea. *PLoS One.* 2014;9(2):e88079. doi: 10.1371/journal.pone.0088079.
21. Pizzo P, Pollock DG. Principles and practice of pediatric oncology. 4th ed. Philadelphia: Lippincott Williams & Wilkins;2002.p.1091-105.
22. Ziaei JE. High frequency of acute promyelocytic leukemia in northwest Iran. *Asian Pac J Cancer Prev.* 2004;5:188-9.
23. AkbarzadehBaghban A, Hosseinifard H, Baghestani AR, Ahmadi S, Rezaei Tavirani M. Factors that affecting survival of patients with acute myeloid leukemia. [In Persian] *Koomesh.* 2016;17: 596-602.
24. Abdali F, Taghavi S, Vazifekhah S, Naghavi Behzad M, Mirza Aghazadeh Attari M. Effect of progesterone on latent phase prolongation in patients with preterm premature rupture of membranes. *Acta Med Iran.* 2017;55(12):772-8.
25. Rauscher GH, Sandler DP, Poole C, Pankow J, Mitchell B, Bloomfield CD, et al. Family history of cancer and incidence of acute leukemia in adults. *Am J Epidemiol.* 2002;156:517-26. doi: 10.1093/aje/kwf075.
26. Kleinbaum G, Klein M. Survival analysis: a self-learning text. New York: Springer; 2012. p.52-124.
27. Bhatia S, Sather HN, Heerema NA, Trigg ME, Gaynon PS, Robison LL. Racial and ethnic differences in survival of children with acute lymphoblastic leukemia. *Blood.* 2002;100(6):1957-64. doi: 10.1182/blood-2002-02-0395.
28. Zareifar S, Almasi-Hashiani A, Karimi M, Tabatabaee S H, Ghiasvand R. Five-year survival rate of pediatric leukemia and its determinants. [In Persian] *Koomesh*. 2012;14(1):13-9.
29. Hazar V, Karasu GT, Uygun V, Akcan M, Küpesiz A, Yesilipek A. Childhood acute lymphoblastic leukemia in turkey: factors influencing treatment and outcome a single center experience. *J Pediatr Hematol Oncol*. 2010;32(8):e317-22. doi: 10.1097/MPH.0b013e3181ed163c.
30. Hussein H, Sidhom I, Naga SA, Amin M, Ebied E,

Khairy A, et al. Outcome and prognostic factors of acute lymphoblastic leukemia in children at the National Cancer Institute, Egypt. *J Pediatr Hematol Oncol.* 2004;26(8):507-14. doi: 10.1097/01.mph.0000132735.93396.92.

31. Khalkhali HR, Gharaaghaji R, Valizadeh R, Kousehlou Z, Ayatollahi H. Ten years' survival in patients with cervical cancer and related factors in West Azerbaijan Province: Using of cox proportion hazard model. *Asian Pac J Cancer Prev.* 2019;20(5):1345.doi: 10.31557/APJCP.2019.20.5.1345.
32. Noroozi M, Khalkhali HR, Bahadori R, Omidi T, Ghazizadeh F, Hejazi S, et al. The survival of childhood acute lymphoblastic leukemia and its related factors using competing risks model: A retrospective study from 2011 to 2019 in northwestern Iran. *Middle East J Cancer.* 2022:13(3):531-42. doi: 10.30476/mejc.2022.88069.1455.