Middle East Special Report
Middle East Journal of Cancer; July 2020; 11(3): 351-359

Determining the Survival Rate in Children with ALL in the Northeast of Iran via Competing Risks Approach

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Abstract

Background: We designed this study to assess the significant prognostic factors of both recurrence and death in patients with acute lymphoblastic leukemia in a university-based hospital using a parametric competing risks model.

Methods: In this retrospective study, we included 417 patients with acute lymphoblastic leukemia. Staining of bone marrow smears with Giemsa method confirmed the diagnosis, justifying at least 25% lymphoblast. Treatment of patients was based on the Berlin-Frankfurt-Münster (BFM) protocol. We considered the first recurrence of cancer as the event of interest and non-relapse mortality as a competing risk. The employed two-parameter Weibull model accounted for both the interest and the competing events.

Results: The relapse-free survival and the five-year overall mortality rates of patients were 85.9% and 74%, respectively. The majority of the patients (72.7%) did not experience any event during the study period. We explained these events as first recurrence and non-relapse mortality, which occurred in 44 (10.6%) and 70 (16.8%) of the patients in the given order. The cumulative incident probability of the first recurrence and non-relapse mortality, were 13.43% and 18.61%, respectively.

Conclusion: Based on the model, we identified white blood cell count and central nervous system involvement as important prognostic factors in determining the incidence rate. Therefore, they must be considered in the selection of treatment plan and risk stratification.

Keywords: Survival analysis, Acute lymphoblastic leukemia, Parametric competing risks model, Cumulative incidence probability

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Middle East Journal of Cancer

Received: March 30, 2019; Accepted: January 04, 2020

Introduction

Acute lymphoblastic leukemia (ALL) is a type of cancer with the highest incidence rate among children. Nearly 70% of the cases are patients younger than 20 years old.[1] The occurrence of ALL is five times more than acute myeloid leukemia (AML) in children.[2] However, AML occurs mostly in patients older than 20.[3]

The improvement in the survival of children with ALL has become notable since 1940s.[4] The surveillance, epidemiology, and end results (SEER) program has reported that five-year survival for pediatric ALL has increased over the past two decades.[5] The survival rate of pediatric ALL has also been enhanced to approximately 90% in recent years.[6] The highest survival rate belongs to individuals diagnosed between 15-19 years old and infants have the lowest survival rate. These rates have increased from 80 to 90% since the beginning of the 21st century.[7] The incidence of ALL is about three new cases each year in 100,000 children younger than 15 years. The incidence peaks at 2-5 years of age.[2,8,9] According to a study on childhood ALL in the United States during 2001-2014, the overall incidence of ALL was 34.0 cases per one million. The rate was higher in boys (38.0) compared to girls (29.7), varying from 1-4 years old.[10] However, compared to boys, girls had a 23% higher incidence of ALL, during the first two years of life and 60% higher incidence of AML, for the first year of life.[2]

Age at diagnosis and sex are among the important factors affecting the survival of ALL.[11] Clinical and biological features, such as white blood cell (WBC) count, immunophenotype, and cytogenetic abnormalities have further been recognized as important prognostic factors for both incidence and survival rates among patients with ALL.[12] Success in the treatment of ALL patients is dependent on early diagnosis, progress in chemotherapy methods and protocols, and advancement in supportive care.[13] An effective method for treating ALL patients is risk-adapted chemotherapy. However, certain patients are not considered 'high-risk' and treated accordingly; they experience a bone marrow relapse following the initial successful treatment with an approximate mortality rate of 60%.[14] Despite improvements in treatment strategies over the past decades, relapse in ALL is still a serious problem.[7] Most of the anthracyclin-antibiotic-treated patients with childhood leukemia are long-term survivors; however, many of these cases experience serious treatment-related side-effects such as congestive heart failure.[15] Today, more than 80% of the children with ALL are treated and they rarely experience recurrence. Therefore, long-term follow-up is an important factor in this study.[16]

In the present research, the survival of an ALL patient was considered as the period between diagnosis and cancer-associated death. The identification of prognostic factors and survival analysis have made it possible to differentiate the presenting features of the disease.

The purpose of this study was to describe the clinical features of children with ALL treated at a university-based hospital. Moreover, we evaluated the prognostic factors for survival using a competing risks approach.

Materials and Methods

This retrospective study included patients under the age of 15 with ALL; subjects were treated at Sheikh Hospital in Mashhad, Iran, from March 2007 to February 2016. Sheikh Hospital is a university-based teaching hospital in the northeast of Iran. During the mentioned period, we originally reviewed a total of 600 cases; due to duplicate or incomplete clinical records, we excluded 183 cases for the final analysis. The Ethics Committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran confirmed the study. The approval code is Ir.sbmu.retech.rec.1397.652.

Staining of bone marrow smears with Giemsa method confirmed the diagnosis of ALL in children, justifying at least 25% lymphoblasts. Using flow cytometry, we differentiated ALL with B cell origins (positive CD20, CD19, CD10, and CD22 markers) and ALL with T cell origins

(positive CD3, CD5, and CD7 markers). Complete remission could be achieved with the absence of blast cells in cerebrospinal fluid (CSF), existence of lower than 5% of lymphoblasts in bone marrow, and a complete progression of clinical symptoms. The assessment method for complete remission was microscopic.

In this center, the treatment of patients with ALL is based on the BFM protocol. However, physicians could modify the treatment based on the patients' physical condition and response to treatment. Medical records provided demographics, laboratory results, and information on treatment methods in a hard copy format. We utilized the patients' clinical characteristics as prognostic variables in the analysis. We further obtained the cut-point value for platelet count (PLT) from the normal range based on the study performed by Daly.[17]

Survival analysis is a statistical procedure, in which the outcome variable of interest is time until an event occurs.[18] There are situations where the subject under study can experience more than one event. A competing risk is an event whose occurrence either precludes that of another event under study or changes the occurrence probability of this other event. Under such conditions, the most optimal approach to analyze the survival time is to employ the competing risks models.[19] When there are multivariable competing events, using Kaplan Meier either underestimates or overestimates the probability of survival, yielding biased results. Therefore, in the presence of competing risks, we use other methods for estimating the survival function. Cumulative incidence function (CIF) is one of these methods.[20] It provides the estimates pertaining to the marginal probabilities of an event in the presence of competing events.[20]

Because they require fewer assumptions, semi-parametric models are preferred over parametric ones.[21] However, parametric models are based on fewer parameters; therefore, they provide a good fit to the data and result in more accurate parameter estimation.[19] The two-parameter Weibull model by simultaneous modeling of the two competing causes is a more appropriate model among all the popular models employed in competing risk studies.

We analyzed the data using a parametric competing risks model; owing to the flexibility of the Weibull distribution, we used the two-parameter Weibull model that allows for both interest and competing events, simultaneously.

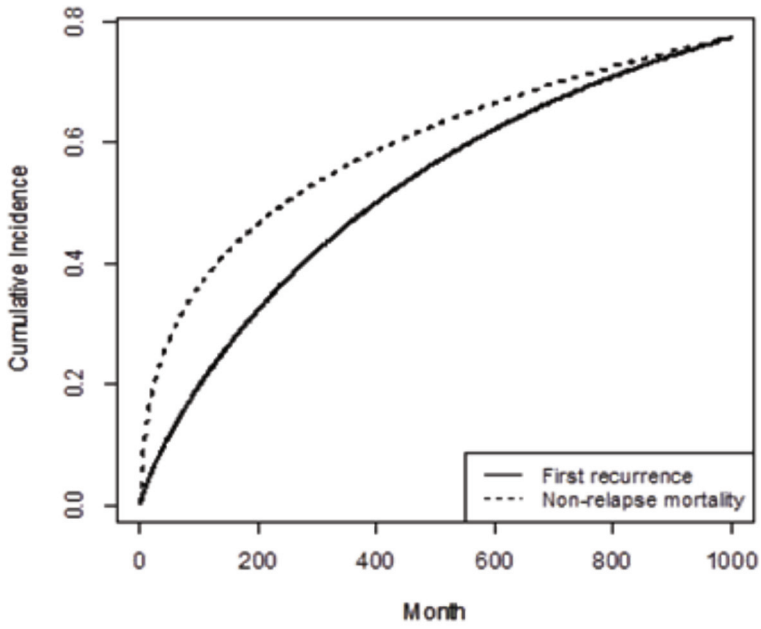

Figure 1. Cumulative incidence curve of both interest and competing events. The cumulative incidence probability for non-relapse mortality was higher than the first recurrence.

In this model, we considered the first recurrence of cancer as the event of interest. We also considered non-relapse mortality as a competing risk and censored all other events. Our primary outcome measure was whether the independent prognostic variables affected the survival of the ALL patients.

R programming language version 3.0.2 and SPSS software version 22 carried out the statistical analysis. We set the level of statistical significance for univariable and multivariable analyses at 25% and 5%, respectively.

Results

A total of 417 patients with ALL participated in the study. The ages varied from nine months to 15 years at the time of diagnosis. The mean ±SD age for men and women were 5.5±3.7 and 5.63±3.9 years, respectively. The preponderance of the patients (72.7%) did not experience any event (death or recurrence), during the study period. 70 (16.8%) patients died prior to the first recurrence. Among the survivors, the first recurrence occurred in 44 (10.6%) patients. The disease-free survival (DFS) and the five-year overall survival (OS) were 85.9% and 74%, respectively. We treated the majority of the patients based on the BFM protocol. Table 1 shows the demographic and prognostic factors of the patients. We classified the patients into subgroups according to cut-off values of different factors. A large number of patients (77.2%) were aged between 1-10 years. As observed, 331 (79.4%) of patients had platelet counts lower than 150000 cells/mL, and 254 (60.9%) had WBCs of lower than 10000 cells/mL.

We plotted the cumulative incidence curve for the interest and competing events. Table 2 shows the one-year, five-year, and eight-year cumulative incidence probabilities. Regarding the first recurrence, the five-year cumulative incidence probability was 13.43; therefore, the cumulative risk (marginal probability) for the recurrence of leukemia in five years was 13.43% in the presence of non-relapse mortality (Figure 1). Concerning non-relapse mortality, the five-year cumulative

Table 1. Demographic and prognostic factors of the study population

Characteristics	Mean SD - Frequency (%)
Age	
<1	35(8.4%)
1-10	322(77.2%)
>10	60(14.4%)
Gender	
Male	169(40.5%)
Female	248(59.5%)
WBC (cells/mL)	
<10000	254(60.9%)
10000-49999	101(24.2%)
50000-99999	27(6.5%)
≥100000	35(8.4%)
Hemoglobin (g/dL)	
—	7.92.57
PLT (cells/mL)	
<150000	331(79.4%)
150000-400000	71(17%)
>400000	15(3.6%)
Cell Lineage	
T cell	29(7%)
B cell	388(93%)
CNS	
Yes	13(3.1%)
No	404(96.9%)
Hemorrhage	
Yes	58(13.9%)
No	359(86.1%)
Mediastinal Mass	
Yes	2(0.5%)
No	415(99.5%)
Rheumatoid Signs	
Yes	130(31.2%)
No	287(68.8%)
Tumor Lysis Syndrome	
Yes	21(5%)
No	396(95%)
Hepatosplenomegaly	
Yes	175(42%)
No	242(58%)
Lymphadenopathy	
Yes	86(20.6%)
No	331(79.4%)

WBC: White blood cell; SD: Standard deviation; CNS: Central nervous system; PLT: platelet

Table 2. Cumulative incidence of probabilities of events

	Event of interest (%)	Competing event (%)
One-year cumulative incidence	3.7	11.46
Five-year cumulative incidence	13.43	18.61
Eight-year cumulative incidence	19.18	21.34

incidence probability was 18.61; therefore, the cumulative risk (marginal probability) for non-relapse mortality in five years, in the presence of first recurrence, was 18.61%. As shown in figure 2, the patients with WBC≥100000 had a significantly higher incidence compared to other WBC groups.

We further conducted the univariable and multivariable analyses. Based on the univariable model, the effects of age at diagnosis (HR: 2.47, CI: (1.44, 4.22)) and central nervous system (CNS) (HR: 3.85, CI: (1.66, 8.91)) were significant for the competing event. WBC count (HR: 3.98, CI: (1.85, 8.56)) regarding the event of interest, and hemoglobin (HR: 1.12, CI: (0.99, 1.26); HR: 1.06 CI: (0.96, 1.16)) and PLT count (HR: 0.54, CI: (0.29, 1.02); HR: 1.67, CI: (0.85, 3.27)) concerning both interest and competing events significantly affected the survival time. Table 3 shows the multivariable model, which contains all the significant variables. As seen, WBC count, for the event of interest, and CNS for the competing event significantly affected the survival time of ALL patients. According to table 3, results are as follows:

The event of interest: The hazard of recurrence in patients with WBC counts between 50000-99000 (cells/mL) was 5.76 times higher than those with WBC counts lower than 10000 (cells/mL).

The competing event: The incidence of death in patients with CNS involvement was 4.25 times higher than those with no CNS involvement.

Discussion

The purpose of this study was to determine the influence of prognostic factors on the survival of ALL patients using a parametric competing risk model. In the Weibull model, the occurrence probabilities of the two competing causes are not

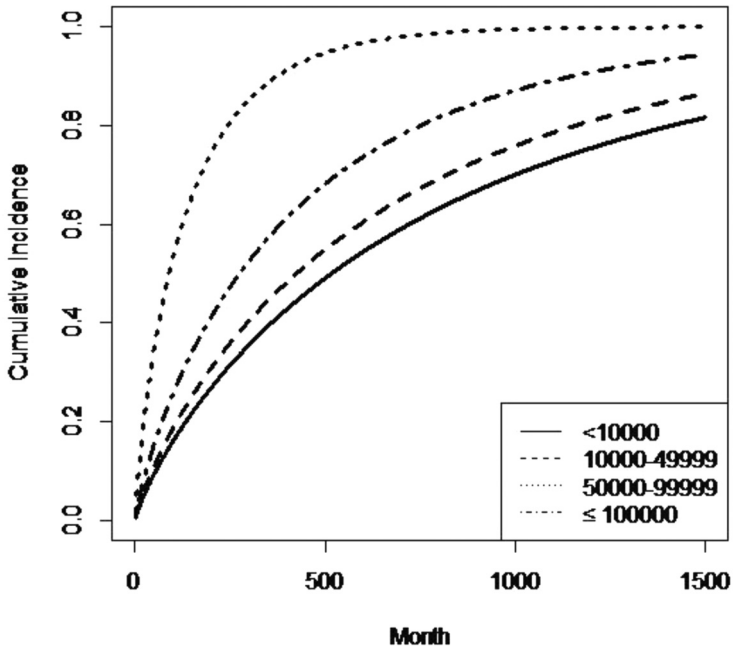

Figure 2. Cumulative incidence curve pertaining to the event of interest for WBC count (cells/mL). WBC counts higher than 100000 (cells/mL) had the highest incidence compared with other WBC groups.
WBC: White blood cell

Table 3. Competing risks model related to 417 cases of acute lymphoblastic leukemia

Variables	Adjusted Subhazard Ratio	95% CI	*P*-Value
Age (first recurrence)			
<1	_	-	-
1-10	0.97	(0.35 - 2.65)	0.95
>10	1.45	(0.46,4.59)	0.51
WBC count (cells/ml) (first recurrence)			
<10000	-	-	-
10000-49999	1.34	(0.62, 2.89)	0.45
50000-99999	5.76	(2.46, 13.49)	0.000*
≥100000	2.46	(0.76,7.98)	0.13
Hemoglobin(g/dL) (first recurrence)			
-	1.10	(0.97,1.25)	0.11
PLT Count(cells/ml) (first recurrence)			
150000-400000	-	-	-
<150000	0.48	(0.23,1.07)	0.05
>400000	1.31	(0.35,4.89)	0.67
CNS (first recurrence)			
No	-	-	-
Yes	1.17	(0.15,8.95)	0.87
Age (non-relapse mortality)			
<1	-	-	-
1-10	0.97	(0.40,2.37)	0.96
>10	2.21	(0.86,5.67)	0.09
WBC count(cells/ml) (non-relapse mortality)			
<10000	-		
10000-49999	0.74	(0.40,1.37)	0.34
50000-99999	0.94	(0.33,2.65)	0.91
≥100000	1.57	(0.72,3.42)	0.24
Hemoglobin(g/dl) (non-relapse mortality)			
-	1.05	(0.95,1.17)	0.30
PLT count(cells/ml) (non-relapse mortality)			
150000-400000	-	-	-
<150000	1.62	(0.79,3.31)	0.18
>400000	0.51	(0.06,4.11)	0.52
CNS (non-relapse mortality)			
No	-	-	-
Yes	4.25	(1.79,10.05)	0.000*

*: significant at alpha=0.05; WBC: White blood cell; PLT: platelet; CNS: Central nervous system;

independent. This indicates that simultaneous modeling of causes should be considered. The true effects of prognostic variables on these causes should be further examined.

Our study results showed that in the Weibull model, patients with WBC counts between 50000-99000 (cells/mL) had a higher recurrence rate compared to those with lower than 10000 (cells/mL) WBC counts. We obtained a shorter confidence interval for the hazard ratio based on

the Weibull model compared to the Fine and Gray model for WBC count. This shows that estimations based on the Weibull model are more accurate than the Fine and Gray model.[13] The present study considered univariable and multivariable models. In the univariable model, age and CNS for the competing event were statistically significant. However, for both events (competing event and event of interest), significant variables were WBC counts, hemoglobin, and PLT count. The other variables of the study, including gender, cell-lineage, hemorrhage, mediastinal mass, lymphadenopathy, hepatosplenomegaly, and rheumatoid signs did not show any statistically significant results. Therefore, based on our results, WBC of more than 10000 and CNS involvement are the most important factors for identifying the chances of recurrence and death. A higher WBC may augment the tissue infiltration, particularly in the immune privileged sites. These findings were also reported in previous studies. In a univariable analysis, Hazar et al. reported that significant variables were ages lower than 10 years, WBC count, hepatosplenomegaly, mediastinal mass, and immunophenotype.[12] In another study on leukemia relapse, Karimi et al. observed WBC count and age to be significantly correlated with the average survival rate; similarly, WBC count and age were significant in the present study.[22] Other variables, including mediastinal mass and CNS involvement, had no significant relationship with survival rate.[22] We assumed that most patients with CNS involvement were actually diagnosed in high stages; moreover, it is known that CNS is an immunologically privileged region isolated from the blood system by blood-brain barriers (BBB) and blood-CSF barriers. Accordingly, when lymphoblastic cells reside in the CNS, they escape from the effects of chemotherapy agents.

Similarly, our multivariable model assessment showed that WBC count and CNS involvement were significant; however, the other significant variables in the univariable model did not show significant results in this model. In a multivariable analysis by Baker et al., gender and time of treatment independently correlated with overall survival using a Cox proportional hazard.[23] In 2007, Moorman et al. used a Cox proportional hazards model to assess the relationship between the prognostic variables and the survival of ALL patients.[24] Sex, age, and T-cell status were significant predictors of the outcome for the EFS and OS.[24] In a study performed by Sousa et al. on patients with ALL in northern Brazil, the age at diagnosis had a relationship with prognosis.[6] The overall survival rate was significantly better in patients aged 9 years or younger and those with WBC counts lower than 50000 (cells/mL).[6] Based on our results, in contrast to the previous studies, age variable had no significant influence on the disease course. Such discrepancy might be ascribed to the differences in statistical analysis methods. Bonakchi et al. performed a study on childhood leukemia in Iran, using a proportional subdistribution hazard model.[13] The five-year cumulative incidence probabilities were 12% and 17% regarding the event of interest and competing event, respectively. Moreover, for the first recurrence, WBC and platelet counts were significant in the multivariable analysis.[13] These results are in line with our study regarding the first recurrence, but they are different in terms of non-relapse mortality. Hosseini et al. performed a Cox regression model on ALL patients and found out that age at diagnosis and WBC count were significant for the event of death.[25] According to the issues mentioned at the beginning of this discussion, more significant variables on survival rate were obtained in the Weibull model compared to subdistribution hazard model. The results of the multivariable Weibull model suggested that the mortality incidence in patients with CNS involvement was 4.25 times more than those without CNS involvement.

Our study carried some limitations. First, this study was performed in a specific geographic area of Iran. On the other hand, there might be some unknown genetic or environmental factors influencing the results; therefore, the findings might not be completely generalizable to other populations. Second, the data on diagnosis and treatment plans were based on the documentations done by multivariable providers; therefore, they

were subject to inconsistency in documentations, although death and cancer recurrence are objective measures. This was a relatively large study with dissent follow-up period and small attrition.

Collectively, we observed WBC count and CNS involvement as the most important prognostic markers in specifying relapse and death rates; therefore, these markers are to be considered when selecting a treatment plan or performing risk stratification. This study also showed that in regard to the assessment of true effects, Weibull model was more flexible than cause-specific and subdistribution models. In addition, it is more accurate in identifying significant prognostic factors when the competing events are not censored. Huang and Chen mentioned that considering these competing events as censors could lead to biased survival probabilities.[26,27] In a competing risks analysis, all the possible causes should be considered, because by focusing on only one cause, the risk of disregarding important factors increases, thereby affecting the analysis.

Acknowledgements

We would like to express our sincere gratitude to the Pediatric Hematology and Oncology Group of Mashhad University of Medical Sciences that provided the information required for this research.

Conflict of Interest

None declared.

References

1. Mohammadian M, Pakzad R, Mohammadian-Hafshejani A, Salehiniya H. A study on the incidence and mortality of leukemia and their association with the human development index (hdi) worldwide in 2012. *WCRJ*. 2018; 5 (2): e1080.
2. Gurney JG, Severson RK, Davis S, Robison LL. Incidence of cancer in children in the United States. Sex-, race-, and 1-year age-specific rates by histologic type. *Cancer.* 1995;75(8):2186-95.
3. Afridi JM, Amir S, Munir A, Rehman Y. Types and subtypes of leukaemia in newly diagnosed patients admitted in the department of child health in a tertiary care hospital. *J Med Sci.* 2018;26(2):99-101.
4. Hunger SP, Mullighan CG. Acute lymphoblastic leukemia in children. *N Engl J Med.* 2015;373(16):1541-52. doi: 10.1056/NEJMra1400972.
5. Pulte D, Gondos A, Brenner H. Trends in 5- and 10-year survival after diagnosis with childhood hematologic malignancies in the United States, 1990-2004. *J Natl Cancer Inst*. 2008;100(18):1301-9. doi: 10.1093/jnci/ djn276.
6. Sousa DWLd, Ferreira FVdA, Félix FHC, Lopes MVdO. Acute lymphoblastic leukemia in children and adolescents: prognostic factors and analysis of survival. *Rev Bras Hematol Hemoter.* 2015;37(4):223-9. doi: 10.1016/ j.bjhh.2015.03.009.
7. Hunger SP, Lu X, Devidas M, Camitta BM, Gaynon PS, Winick NJ, et al. 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. doi: 10.1200/JCO.2011.37.8018.
8. Ross JA, Davies SM, Potter JD, Robison LL. Epidemiology of childhood leukemia, with a focus on infants. *Epidemiol Rev.* 1994;16(2):243-72. doi:10.1093 /oxfordjournals.epirev.a036153.
9. Swensen AR, Ross JA, Severson RK, Pollock BH, Robison LL. The age peak in childhood acute lymphoblastic leukemia: exploring the potential relationship with socioeconomic status. *Cancer.* 1997;79(10):2045-51.
10. Siegel DA, Henley SJ, Li J, Pollack LA, Van Dyne EA, White A. Rates and trends of pediatric acute lymphoblastic leukemia-United States, 2001-2014. *MMWR Morb Mortal Wkly Rep.* 2017;66(36):950-954. doi: 10.15585/mmwr.mm6636a3.
11. Hossain MJ, Xie L, McCahan SM. Characterization of pediatric acute lymphoblastic leukemia survival patterns by age at diagnosis. *J Cancer Epidemiol.* 2014;2014:865979. doi: 10.1155/2014/865979.
12. 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-e22. doi:10.1097/MPH. 0b013e 3181ed163c.
13. Bonakchi H, Farhangi H, Esmaily H, Boosti H, Forouzannejhad M. Factors affecting survival of children with acute lymphoblastic leukemia using competing risks model. [Article in Persian] *J Adv Med Biomed Res.* 2017;25(110):123-36.
14. van Dongen JJ, Seriu T, Panzer-Grümayer ER, Biondi A, Pongers-Willemse MJ, Corral L, et al. Prognostic value of minimal residual disease in acute lymphoblastic leukaemia in childhood. *Lancet.* 1998;352(9142):1731-8.
15. Swain SM, Whaley FS, Ewer MS. Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials. *Cancer.* 2003;97(11):2869-79.
16. Baghestani AR, Moammer S, Pourhosseingholi MA,

Khadem Maboodi AA. The application of competing risk model in identifying the factors affecting the survival time of patients with colorectal cancer. [In Persian] *RJMS.* 2016;23: No. 151.
17. Daly ME. Determinants of platelet count in humans. *Haematologica.* 2011;96(1):10-3. doi: 10.3324/haematol.2010.035287.
18. Kleinbaum DG, Klein M. Evaluating the proportional hazards assumption. Survival analysis. Statistics for biology and health. New York, NY: Springer; 2012.
19. Baghestani AR, Hajizadeh E, Fatemi SR. Parametric model to analyse the survival of gastric cancer in the presence of interval censoring. *Tumori.* 2010;96(3):433-7.
20. Crowder MJ. Classical competing risks. London: Chapman and Hall/CRC Press; 2001.
21. Klein J, Moeschberger M. Survival analysis: statistical methods for censored and truncated data. New York, NY: Springer-Verlag; 2003.
22. Karimi M, Yarmohammadi H, Sabri MR. An analysis of prognostic factors and the five-year survival rate in childhood acute lymphoblastic leukemia. *Med Sci Monit.* 2002;8(12):CR792-6.
23. Baker JM, To T, Beyene J, Zagorski B, Greenberg ML, Sung L. Influence of length of time to diagnosis and treatment on the survival of children with acute lymphoblastic leukemia: A population-based study. *Leuk Res*. 2014;38(2):204-9. doi: 10.1016/j.leukres.2013.11.014.
24. Moorman AV, Harrison CJ, Buck GA, Richards SM, Secker-Walker LM, Martineau M, et al. Karyotype is an independent prognostic factor in adult acute lymphoblastic leukemia (ALL): analysis of cytogenetic data from patients treated on the Medical Research Council (MRC) UKALLXII/Eastern Cooperative Oncology Group (ECOG) 2993 trial. *Blood.* 2007;109(8):3189-97. doi: 10.1182/blood-2006-10-051912.
25. HosseiniTeshnizi S, Zare SH, Tazhibi M. The evaluation of Cox and Weibull proportional hazards models and their applications to identify factors influencing survival time in acute leukemia. [In Persian] *Hormozgan Med J.* 2012; 15(4):e88497.
26. Huang X, Zhang N. Regression survival analysis with an assumed copula for dependent censoring: a sensitivity analysis approach. *Biometrics.* 2008; 64(4): 1090-9. doi: 10.1111/j.1541-0420.2008.00986.x.
27. Chin CC, Wang JY, Yeh CY, Kuo YH, Huang WS, Yeh CH. Metastatic lymph node ratio is a more precise predictor of prognosis than number of lymph node metastases in stage III colon cancer. *Int J Colorectal Dis.* 2009;24(11):1297-302. doi: 10.1007/s00384-009-0738-7.