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Prognostic Factors and Survival Outcomes by Disease Subtypes in a Cohort of Iranian Patients with acute leukemia

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ABSTRACT

Introduction*:* Studying the survival factors of leukemia patients can lead to a reduction in healthcare costs. This study aimed to evaluate the survival rate and potential predictive factors in leukemia patients in northeast Iran.

Methods: Baseline demographic and clinical data of patients referred to Ghaem Hospital between 2014 and 2019 were extracted from their medical records. The survival rates were determined by gathering information from phone calls or archived files.

Results: This cohort study consisted of 302 patients with a mean age of 19.09±41.09 years. Among them, %43.3) 127) had acute lymphoid leukemia, while %56.7) 166) had myeloid leukemia. The mean overall survival time for all patients was 50.81 months. However, the mean overall survival time for patients with lymphoid leukemia (61.7 months) was significantly higher (P<0.001) than that for patients with myeloid leukemia (41.1 months). Moreover, lymphoid patients had significantly higher one-month and one-year survival rates (%93 and %72.8) than the myeloid group (%81 and %53.7) (P=0.002 and P=0.001). However, significant difference did not exist in the five-year survival rate between the lymphoid and myeloid groups (%26.2 vs %18.2, P=0.174). Cox regression analysis indicated that patient survival was correlated with the type of leukemia (%95 ,1.45CI=8.92-1.10, P=0.011), age, hemoglobin levels, as well as WBC, RBC, neutrophil, and platelet count.

Conclusion: Our findings indicated that patients with lymphoid leukemia exhibited a higher survival rate than those with myeloid leukemia. Survival outcomes were dependent on patient's age, leukemia type, and levels of WBC, RBC, neutrophil, platelet, and hemoglobin levels.

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Introduction

Hematologic malignancies represent a group of rare disorders originating from hematopoietic and lymphoid tissues, accounting for approximately 6.5% of all cancers worldwide (1, 2). The incidence of these malignancies depends on various factors, including age, geographical distribution, and genetic and molecular variation. Acute leukemia, a major subtype, is categorized into myeloid (AML) and lymphoid (ALL) leukemias (1,3) and both types are slightly more common in males than females.

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Patients with ALL have been found to have a higher recovery rate compared to those with AML (1). Previous meta-analysis has reported the five-year survival rates of ALL and AML in Iran to be 57% and 35.0%, respectively (4). Several factors have been related with overall and disease-free survival in leukemia patients, including genomic instability (such as RUNX1, ASXL1, and TP53 mutations), clinical factors (such as leukocyte counts, platelet counts, and comorbidity), patients' response to treatment (such as white and red blood cell count and mean corpuscular hemoglobin, sodium, potassium, and calcium), and demographic variables (such as age, gender, smoking, nutritional status, and ethnicity).

However, the contribution of each of these factors varies across different populations, ranging from 25% to 75%, highlighting the need for the identification of more specific prognostic factors with higher accuracy for different populations and based on the disease subtypes. In this context, evaluating survival rates and identifying related factors is critical for proper monitoring of each patient's prognosis, improving quality of life, comprehensive management of screening programs, and developing new effective treatment strategies (5). Therefore, the aim of the current study was to determine the survival rates and define the affecting factors of ALL and AML in an Iranian northeast population. By using this cohort, the study aimed to identify the factors associated with the different disease subtypes to improve the accuracy of patient prognosis, quality of life, and provide individualized treatment options. The results of the study may help provide information to optimize treatment strategies and develop more accurate prognostic models for patients with different disease subtypes. The findings of the study could also contribute to enhancing patient care and survival rates, ultimately leading to a decrease in the morbidity and mortality rates of this disease.

Materials and Methods

All patients hospitalized in Ghaem Hospital, Mashhad, Iran, and diagnosed with acute leukemia between 2014 and 2019 were enrolled in this retrospective cohort study. The files and archives of the patients were accessed to extract necessary information. Additional information was obtained through telephone interviews with the patients. In addition, a checklist was used to collect demographics data, including age, gender, occupation, educational level, a family history of primary leukemia, and any concomitant diseases. Furthermore, pertinent clinical information such as the type of acute leukemia, along with white blood cell (WBC), red blood cell (RBC), neutrophil and platelet counts, as well as hemoglobin levels at the time of diagnosis were meticulously documented. The primary outcomes that were evaluated included bone marrow transplantation, complete remission following chemotherapy, recurrence after achieving complete remission or bone marrow transplantation, as well as the overall survival rate during the first month, first year, and fifth year of treatment.

To illustrate the statistical findings, quantitative variables were reported as mean and standard deviation, while qualitative variables were presented as frequency and percentage. The t-test (Mann-Whitney) and chi-square test (Fisher's exact test) were used to compare variables between the two groups of patients for quantitative and qualitative variables, respectively. Kaplan-Meier curve was generated to illustrate the survival of all patients. Additionally, univariate and multivariate Cox models were employed to assess the effect of various factors on survival.

Results

A total of 302 subjects participated in this study (mean age: 41.09±19.09 years). The gender distribution was 175 (57.9%) males and 127 (42.9%) females. In terms of disease type, 127 patients (43.3%) had acute lymphoid leukemia and 166 patients (56.7%) had myeloid leukemia. Baseline characteristics of patients, based on disease subtype, are shown in Table 1.

Table 1. Mean and standard deviation and frequency of different variables studied

Variables	Type of leukemia		P-value
	Lymphoid n=127	Myeloid n=166	
Sex (Male %)	n=127	Myeloid	0.50*
Age	n=166	46.24±18.96	0.04**
WBC (×109 per liter)	23.37±49.75	32.7±54.49	0.13**
RBC (×106 per microliter)	3.08±0.82	2.87±0.79	0.02**
Platelet (×102 per microliter)	77.39±96.89	91.35±160.41	0.36**
Hemoglobin (gr/dl)	8.77±2.80	8.29±2.16	0.10**
Neutrophil (%)	49.24±30.97	39.36±29.74	0.02**
Lymphocyte (%)	27.32±23.35	26.76±23.04	0.86**

WBC: whith blood cell, RBC: red blood cell
*Q-square test was used to compare two groups
** Independent t-test was used to compare two groups

The mean age of acute lymphoid leukemia patients was significantly lower than patients with myeloid

leukemia (36.22 vs. 46.24 years) (p=0.04). Also, significant difference existed regarding RBC counts (p=0.02) between the two types, with higher RBC counts in the lymphoid type. However, there was no significant differences in sex, WBC counts, platelet counts, and lymphocyte or hemoglobin levels between lymphoid and myeloid leukemia.

In term of survival analyses, the mean survival time of all patients was 50.81 months. According to the age of diagnosis, patients were divided into two age groups. The mean survival time of patients aged 25 to 65 years was the highest (44 months) and the lowest was less than 25 years (28.76 months) (p=0.021) (Table 2).

Table 2. Mean and median survival of patients with acute leukemia based on age and leukemia type

Age (years)	Mean	95% CI	Median	95% CI	*P-value
16-25	28.76±4.91		24	8.78-15.21	
25-65	44±3.27	34.48-92.54	24	13.37-34.62	0.021
>65	29.55±6.68		11	14.57-17.42	
Total	41.73±3.47		15	11.3-18.69	
Type	**Mean**	**95% CI**	**Median**	**95% CI**	***P-value**
Lymphoid	61.8±70.64		24	11.36-85.14	
Myeloid	41.4±10.1	44.78-75.65	12	5.18-69.30	<0.001
Total	53.5±54.61		18	14.21-39.60	

CI: confidence interval,
*Log-rank test

With regard to the disease subtypes, the mean survival time of patients with lymphoid cancer was significantly longer than patients with myeloid cancer (61.7 vs. 41.1 months) (p<0.001) (Table 2). Kaplan–Meier analysis also revealed a significant difference for overall survival between the two disease subtypes (p=0.009) (Fig 1).

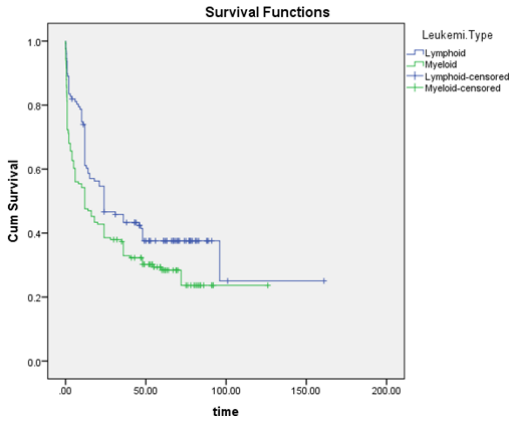

Figure 1. Kaplan-Meier analysis revealed that patients with myeloid cancer had a shorter OS than those with lymphoid cancer (P=0.009).

One-month and one-year survival of patients with lymphoid type were also significantly higher than those with myeloid type (p=0.002 and p=0.001, respectively). However, no significant difference was found in the five-year survival rate between these two groups (p>0.05).

In terms of recurrence rate of acute leukemia, our results revealed no significant difference between patients with lymphoid cancer and patients with myeloid cancer (p=0.174).

Table 3 shows the results of uni- and multivariate Cox regression analyses, which was applied to examine the effect of interfering factors on disease subtypes and overall survival (OS). Initial univariate analysis revealed that several factors including disease subtype (0.011), age (p=0.009), WBC (p=0.046), RBC (p=0.001), platelet count (p=0.002), hemoglobin level (p=0.013), and neutrophil count (p=0.001) were significantly associated with patient survival rates. However, after performing multivariate analysis, only age, leukemia type, and levels of WBC remained significantly associated with OS. This suggests that disease subtype may be an independent factor that contributes to a poor prognosis among leukemia patients.

Table 3. Univariate and multivariate analyses for variables associated with the overall survival of Leukemia patients

Variables	Univariate analysis		Multivariate analysis	
	HR (95 % CI)	*P-value	HR (95 % CI)	*P-value
Leukemia type	1.45 (1.10-1.93)	0.011	1.34 (1.10-1.98)	0.014
Age	1.01 (1.00-1.02)	0.009	1.01 (1.0-1.02)	0.026
WBC	1.01 (1.00-1.10)	0.004	1.006 (1.02-1.12)	0.006
RBC	0.75 (0.64-0.89)	0.001	0.78 (0.50-1.20)	0.261
Platelet	0.98 (0.97-0.99)	0.002	1.00 (0.99-1.10)	0.357
Hemoglobin	0.93 (0.88-0.98)	0.013	1.03 (0.91-1.16)	0.686
Neutrophil	0.98 (0.97-0.99)	0.001	0.99 (0.99-1.01)	0.430
Lymphocyte	0.99 (0.98-1.01)	0.387	-	-

CI: confidence interval, HR: Hazard ratio, WBC: white blood cell, RBC: red blood cell
*Cox regression analysis test

Discussion

This study found that patients with lymphoid leukemia had a higher survival rate compared to patients with myeloid leukemia. The mean overall survival time in the lymphoid group was significantly higher than the myeloid group (61.7 months vs. 41.1 months). Furthermore, the one-month and one-year survival rates in lymphoid patients were significantly higher than the myeloid group, while no significant difference was found in the five-year survival rate between the two groups. We also found that patient survival was dependent on patient's age, leukemia type, and levels of WBC, RBC, neutrophil, and platelet, as well as hemoglobin levels. The highest survival rate was observed in those between 25 to 65 years old, whereas the lowest survival rate was for patients under 25 years. The study results showed that late diagnosis has a poor prognosis for survival in all types of cancer. Additionally, the study found that high WBC counts were associated with higher survival rates.

The findings of the study regarding the five-year survival rate in leukemia patients (22%) varied from various parts of the world with a five-year survival rate of 36.5% in Turkey (6), 81.8% in China (7), 51% in India (8), and 69.9% in Korea (9). The varying results can be attributed to factors such as discrepancies in the method of sampling and sample size, as well as, the variables affecting patient survival, and the differences in the year of publication. In subgroup analysis based on the disease subtypes, ALL patients had a more favorable prognosis with a five-year survival rate of 26.2%, while AML patients had a rate of 18.2%. In one study, the five-year survival rates for AML patients were 65% for those under 15 years old, 60% for those aged 15-25, 40% for those aged 25-64, and only 5% for those over 65 (10).

However, the five-year survival rate for ALL patients was higher, generally at 70%, ranging from 90% for patients under 15 years of age to 15% for those over 65. One difference in our study was that patients aged between 25 and 65 years had the highest survival rate with an average of 44 months, while those under 25 years had the lowest survival rate with an average of 28.76 months. This variation may be attributed to several factors, such as the genetic differences among populations, variation in treatment modalities, or differences in the geographic regions where these studies were conducted. As a result, it is recommended that future investigations into leukemia focus on smaller geographic areas within Iran.

Several studies have investigated factors affecting survival rates in ALL patients. Younger age and WBC were associated with higher survival rates, while late diagnosis is linked to poor prognosis (4,11, 12). Another study found that increased WBC predicts improved survival (13). Additionally, two studies conducted on Iranian children with leukemia showed that age at diagnosis, type of leukemia, sex, WBC, platelet count, hemoglobin, and recurrence history, influenced patient survival rates (14, 15). Saffar et al. (2015), showed that age at diagnosis, marital status, smoking habit, history of bone marrow transplantation, specific disease background, region, treatment resistance, and various laboratory factors such as WBC, RBC, hemoglobin, salt, potassium, and calcium levels significantly effect patient survival (16). A retrospective cohort study focusing on pediatric patients with ALL and AML, identified a significant association between platelet count, disease relapse, and cancer survival, highlighting the significance of monitoring and managing thrombocytopenia to improve survival rates (17).

In a systematic study with 2517 acute leukemia patients, the five-year survival rate was found to be 56%, which was higher than those observed in our study. Consistent with our findings, they also observed that patients with ALL exhibited significantly higher survival rates than those with AML (4). In one study by José Carlos Jaime-Pérez et al., both event-free survival and overall survival were relatively low, at 23.4% and 31.1%, respectively. Furthermore, nearly half of the patients (45.7%) experienced a relapse, which usually occurred at the bone marrow site (48.8% of cases). Notably, the five-year survival rate was significantly lower than 16.4%. (18). These findings are consistent with those observed in our own study. In another study, the mean OS was found to be about 6.6 months, which was lower than the results obtained in our study (19). In this study, only patients diagnosed with AML were treated with a specific dietary intervention, whereas in our study, we examined all subjects with different types of acute leukemia at various stages and with a range of treatment regimens.

Our study faced some limitations. Firstly, we were unable to conduct long-term follow-ups with patients for a duration of 10 years or more. Therefore, more studies with an extended follow-up duration are needed to provide a comprehensive understanding. Additionally, we could not thoroughly examine other influential factors that may effect survival rates, such as underlying diseases, additional laboratory findings, different genotypes, and so on.

In conclusion, our results suggest that the survival rate for ALL patients is higher compared to AML patients. However, this result is significantly affected by numerous factors, including the patient's age, type of leukemia, and the levels of serum markers like WBC, RBC, platelets, and hemoglobin. Consequently, it is crucial to consider and evaluate multiple factors when assessing patient outcomes and highlight the potential significance of disease subtype in developing effective management strategies for leukemia.

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References

1. Hashemi AJEoP, JSSU PFiPALLPAtSSH. Manochehri naieni M, Eslami Z, Bahrami Ahmadi A, Kheirandish M, Rafieyan M. 2009;16:14-19.
2. Jaime-Pérez JC, Jiménez-Castillo RA, Herrera-Garza JL, Gutiérrez-Aguirre H, Marfil-Rivera LJ, Gómez-Almaguer DJCLM, et al. Survival rates of adults with acute lymphoblastic leukemia in a low-income population: a decade of experience at a single institution in Mexico. 2017;17:60-68.
3. Dores GM, Devesa SS, Curtis RE, Linet MS, Morton LMJB, The Journal of the American Society of Hematology. Acute leukemia incidence and patient survival among children and adults in the United States, 2001-2007. 2012;119(1):34-43.
4. Veisani Y, Khazaei S, Delpisheh A. 5-year survival rates based on the type of leukemia in Iran, a Meta-analysis. Caspian journal of internal medicine. 2018;9:316-324.
5. Mousavinasab SN, Yazdani Cherati J, Karami H, Khaksar SJJoMUoMS. Risk Factors influencing the survival of pediatric acute leukemia using competing risk model. 2015;24:31-38.
6. Pamuk ON, Pamuk GE, Soysal T, Ongören S, Başlar Z, Ferhanoğlu B, et al. Chronic lymphocytic leukemia in Turkey: experience of a single center in Istanbul. South Med J. 2004;97:240-245.
7. Wu T, Li Z-J, Wang Y-F, Zhao Y-Z, Qi J-Y, Qian L-S, et al. [Prognostic factor analysis in 203 patients with chronic lymphocytic leukaemia]. Zhonghua xue ye xue za zhi = Zhonghua xueyexue zazhi. 2009;30:435-439.
8. Gogia A, Raina V, Gupta R, Gajendra S, Kumar L, Sharma A, et al. Prognostic and predictive significance of smudge cell percentage on routine blood smear in chronic lymphocytic leukemia. Clin Lymphoma Myeloma Leuk. 2014;14:514-517.
9. Oh CM, Won YJ, Jung KW, Kong HJ, Cho H, Lee JK, et al. Cancer Statistics in Korea: Incidence, Mortality, Survival, and Prevalence in 2013. Cancer Res Treat. 2016;48(2):436-50.
10. 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;30:1663-1669.
11. Delpisheh A, Veisani Y, Sayehmiri K, Rahimi E. Esophageal carcinoma: long-term survival in consecutive series of patients through a retrospective cohort study. Gastroenterol Hepatol Bed Bench. 2014;7:101-107.
12. Veisani Y, Delpisheh A. Survival rate of gastric cancer in Iran; a systematic review and meta-analysis. Gastroenterol Hepatol Bed Bench. 2016;9:78-86.
13. Lee KM, Ward MH, Han S, Ahn HS, Kang HJ, Choi HS, et al. Paternal smoking, genetic polymorphisms in CYP1A1 and childhood leukemia risk. Leuk Res. 2009;33(2):250-8.
14. Mousavinasab SN, Yazdani Cherati J, Karami H, Khaksar S. Risk Factors Influencing the Survival of Pediatric Acute Leukemia Using Competing Risk Model. Journal of Mazandaran University of Medical Sciences. 2015;24:31-38.
15. Almasi-Hashiani A, Zareifar S, Hashemi-Teir A. Survival rate among children with acute lymphoblastic leukemia based on their relapse status in Shiraz Shahid Faghihi hospital during 2004-9. Feyz Journal of Kashan University of Medical Sciences. 2012;16:248-253.
16. SAFFAR A, RAHGOZAR M, SHAHI F, BIGLARIAN A. SURVIVAL ANALYSIS OF ACUTE MYELOID LEUKEMIA. RAZI JOURNAL OF MEDICAL SCIENCES (JOURNAL OF IRAN UNIVERSITY OF MEDICAL SCIENCES). 2015;22.
17. Moradi G, Rasouli MA, Fathi F, Ghaderi B, Nikkhoo B, Roshani D, et al. Evaluation of the survival rate and its related factors in patients with leukemia in Kurdistan Province. Scientific Journal of Kurdistan University of Medical Sciences. 2018;23:12-20.
18. Jaime-Pérez JC, Jiménez-Castillo RA, Herrera-Garza JL, Gutiérrez-Aguirre H, Marfil-Rivera LJ, Gómez-Almaguer D. Survival Rates of Adults With Acute Lymphoblastic Leukemia in a Low-Income Population: A Decade of Experience at a Single Institution in Mexico. Clin Lymphoma Myeloma Leuk. 2017;17:60-68.
19. Bouligny IM, Mehta V, Isom S, Ellis LR, Bhave RR, Howard DS, et al. Efficacy of 10-day decitabine in acute myeloid leukemia. Leukemia research. 2021;103:106524.