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Determination of Survival Rate and Its Effective Factors in Pediatric Leukemia in Hamadan Province During Years 2007 to 2016

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Abstract

Background: The most common type of childhood cancer is leukemia, therefore, the aim of this study was to evaluate the survival rate and its effective factors in patients with malignancies under the age of 18 years in Hamadan province, during the years 2007 to 2016.

Methods: In this historical cohort study, data were collected from the files of a hospital's archive of Hamadan province, and the log-rank test was used to compare the survival curves. Modeling of survival factors was done by using the Cox regression model.

Results: The most frequent age group was 5 to 9 years old and there were 53 (37.9%) males and 86 (61.4%) females. The risk ratio for people with white blood cell count above 50000 to that of under 10000 was 2.260 (P value = 0.035) and for those with platelet levels above 50000 compared with those, who had levels less than 50000 was 0.376 (P value < 0.001). For the relapse rate, the risk ratio for those, who had relapses was 0.407 (P value = 0.031) when compared with those, who did not relapse.

Conclusions: The results of this study were similar to that of similar studies in most of the examined cases, those with lower white blood count (WBC) count, and patients with high blood platelets had a higher survival rate than those with a lower risk profile. Regarding the variable relapse status, less survival was reported for those, who had relapses than those, who did not show relapse.

Keywords: Acute Leukemia, Survival, Children, Cox Mode

1. Background

The most common type of childhood cancer is leukemia, which accounts for more than 3000 new cases annually and 25% of all malignancies are diagnosed in young patients (less than 20 years old) in the united states. Among 75% of cases, subtypes and prevalence include acute lymphoblastic leukemia (ALL), while acute myelogenous leukemia (AML) is found in 20%, and chronic myelogenous leukemia (CML) in less than 5%. Other types of chronic leukemia are extremely rare during childhood and include those of lymphocytic and myelomonocytic cell lineages (1).

According to official reports, cancer is the third cause of death in Iran (2) and pediatric cancers are the sixth group of common malignancies in Iran (3). Cancer is one of the causes of death in industrialized countries and the second leading cause of death among children after unpremeditated injury (4, 5). Although the overall incidence of leukemia is low, this type of cancer is the most common cancer in children (6). Acute lymphoblastic leukemia and acute myeloblastic leukemia comprise 97% of all acute leukemia cases (7, 8). Leukemia makes up about 0.22% of childhood cancers and the most common leukemia among children is ALL (9, 10). In developed countries, approximately 80% of leukemia in children is ALL, however, AML is very rare in children. In European countries, the incidence is between four and nine per million individuals each year (11). Although the causes of leukemia have not been determined accurately, yet it could be suggested that age at diagnosis and the number of white blood cells are the causes of this disease (12, 13).

When dealing with analysis of survival data, there are two main goals, the first goal of the model is to find a suitable combination of explanatory variables that affect the survival and the next goal is to find reliable estimates for

the risk function in the subsets of the case. In general, there are two basic strategies in the analysis of survival data, including parametric and semi-parametric methods. When dealing with this perspective in the analysis of survival, with respect to each of the above goals, one of the solutions is more important than the other (14).

A cohort study by Parvareh and Khanjani was conducted on patients with ALL and AML. There were 219 cases, who were all younger than 15 years old, admitted to Afzalipour Hospital, Kerman, Iran, between 1998 and 2009. Survival rates were estimated by applying the Kaplan-Meier method. Log-rank test was used to estimate the statistical difference in survival probability and the effect of independent variables on survival was examined using Cox regression (15).

A retrospective study by Ismael and Hassan was conducted on children aged 15 years old or younger, who had suffered leukemia and were admitted and diagnosed at Basra Maternity and Children Hospital, from 1st of January 2004 to 31st of December 2008. Overall, 578 patients diagnosed with cancer were admitted to the pediatric oncology unit during this period (1).

Parvareh and Khanjani performed a cohort study on patients with ALL and AML. Cases' age was younger than 15 years in 217 patients, and they were admitted to Afzalipour Hospital, Kerman, Iran between 1998 and 2009. By applying the Kaplan-Meier method, survival rates were estimated. To estimate the statistical difference in survival probability and the effect of independent variables on survival, log-rank was used, and to examine the effect of independent variables on survival, Cox regression was used.

A retrospective cohort study by Zareifar et al. was conducted on 280 patients with ALL and AML cancers in order to calculate the survival rate. The Cox model showed that the platelet and the number of relapse of disease had a significant effect on survival rate of cancer (16). In the study of Bahrami et al., the results of Cox model demonstrated that the age at diagnosis and the number of white blood cells had a significant effect on survival of the patients (17).

Thus, various factors may be effective on survival of patients. Therefore, the aim of this study was to evaluate the survival and its effective factors in patients with malignancies under the age of 18 years old in Hamadan province during years 2007 to 2016, to identify the risk factors. The results could be effective in teaching the community, and allow prevention and early diagnosis.

2. Methods

In this historical cohort study, children with malignancy under 18 years old in Hamadan province were assessed from September 2007 to September 2016. Data were collected from the files of hospital's archive of Hamadan province. The collected data included age, gender, type of malignancy, familial cancer history, recurrence status, white blood cell count, blood platelet count, clinical signs, and survival time. Patients were followed up through periodical referrals and hospital visits and/or phone calls. The survival time was considered as the time period from diagnosis to either death or the end of the study. All malignancies under the age of 18 years old in Hamadan province were admitted to Hamadan Hospital and bone marrow transplant patients were transferred to Tehran hospitals. The information of these patients has not been analyzed in this study. The Kaplan-Meier survival rate was used to determine the survival rate and a log-rank test was used to compare the survival curves. Modeling of survival factors was done by using the Cox regression model. The assumption of the proportion of risk as one of the assumptions of the Cox model was also investigated using Shoenfeild's residuals. For the Cox regression model, variables that had a P value of less than 0.25 in the univariate analysis and assumed a constant risk ratio were eligible to enter this model. Data analysis was performed using the SPSS 23 software.

3. Results

In this study, 140 children with acute leukemia were analyzed during years 2007 to 2016. There were 111 children with type-II leukemia (79.3%) and the rest were AML. Up to the end of the study, 48 (38.1%) of the patients died, from whom 35 (74.47%) were ALL and 13 (25.53%) were AML. The mean (SD) age of ALL patients was 6.4 (3.87) years and that of AML patients was 8.87 (4.89) years. Furthermore, 86 (61.4%) patients were male. Table 1 shows the other characteristics of the patients.

The mean follow up period was 21.22 $\pm$ 13.6 months. The survival rate of 1, 3 and 5 years were 96%, 50% and 8%, respectively. The results of the log-rank test are shown in Table 2.

In the following, variables that were in a one-variable mode at 15% level influenced the survival of patients, in order to simultaneously evaluate the Cox multiple regression model. In this model, the Cox model for all patients and the type of leukemia were determined, the factors influencing survival were examined and the results are presented in Tables 3-5.

The results of multi-variable analysis using the Cox model for patients are shown in Table 3. For the total number of leukemia patients, the Cox model showed that there was a significant relationship between the variables of white blood cell count, platelet count, and relapse rate, so that the risk proportion of people with white blood cell

Table 1. Characteristic of Patients with Acute Leukemia in Hamadan

Parameter	No. (%)
Type of leukemia	
ALL	111 (79.3)
AML	29 (29.7)
Age category, y	
0 - 4	48 (34.3)
5 - 9	53 (37.9)
10 - 17	39 (27.9)
Gender	
Male	86 (61.4)
Female	54 (38.6)
Kind of birth	
Normal	99 (70.7)
Cesarean	41 (29.3)
The number of white blood cells	
< 10000	100 (71.4)
10000 - 30000	16 (11.4)
30000 - 50000	8 (5.7)
> 50000	16 (11.4)
The number of blood plate	
< 50000	53 (37.9)
> 50000	87 (62.1)
Recurrence status	
Had	12 (14.3)
Didn't have	72 (85.7)
Fever	
Had	68 (48.6)
Didn't have	72 (51.4)
Pale	
Had	42 (37.5)
Didn't have	70 (62.5)
Bleeding	
Had	30 (21.4)
Didn't have	100 (78.6)
Skeletal pain	
Had	36 (25.7)
Didn't have	104 (74.3)

count above 50000 was 260.2 times the number of people with a low white blood cell count of 10000 (P = 0.035, CI-060/822/82). Platelet surface (> 50000) was 3706 times the platelet (< 50000) (P = 0.001, CI = 0.212 - 0.667). For the relapse status variable, the risk ratio for those, who had relapse was 0.47 times more than those, who did not have so (P = 0.031, CI = 0.180 - 0.199).

The results of the analysis using the Cox model for people with ALL is shown in Table 4. The variables of blood platelet count and relapse status had a significant relationship with the survival rate of cancer. The risk profile for people with white blood cell levels of 10000 to 30000, 50000 to 30000, and 50000 in comparison with patients, who had white blood cells at the level of 1000 >, was 1.544 (P = 0.427 = P, CI = 0.529 - 4.508), 1.369 (P = 0.672, CI = 0.321 - 5.843), and 1.524 (P = 0.396, CI = 0.576 - 4.031), respectively. The risk profile in patients with platelet levels of > 50000 was 0.403 time more than patients with platelet levels < 50000 (P = 0.008, CI = 0.207 - 0.788) and the risk ratio in those, who did not relapse, was 0.237 times more than relapsed patients (P = 0.004, CI = 0.089 - 0.634).

The results of the analysis using Cox model for patients with AML are shown in Table 5. Two variables of white blood cell count and blood platelet count had a significant relationship with survival. In case of platelet count, the risk ratio for platelet levels (> 50000) was 0.368 times (< 50000) (P = 0.099, CI = 0.122 - 1.207). The risk ratio for people with white blood cell levels of 10000 to 30000, 50000 to 30000, and > 50000 compared to those with white blood cells at the level of < 1000 was 5.764 (P = 0.021, CI = 1.362 - 43.457), 7.693 (P = 0.021, CI = 1.362 - 43.457), and 5.203 (P = 0.021, CI = 1.283 - 21.107), respectively.

4. Discussion

Over the past decades, impressive progress has been made in the treatment of childhood cancers (16). However, childhood cancers, especially blood cancers, are known as an effective factor in child mortality (12).

In this study, factors affecting the survival of patients with leukemia have been investigated. The population of the study included 140 leukemic patients, most of whom had ALL-type leukemia (79.3%). Demographic variables, including age group, gender, order of birth, and history of disease in the family have been investigated. In the age group, the highest frequency belonged to the age group of five to nine years with a frequency of 37.9%. In the variable of gender, the male group had the highest frequency (61.4%). The type of birth was most commonly in the natural delivery group (70.7%). For the child's rank, the highest was single-child (42.5%) and the lowest frequency was 8.3 child (9.4%). Regarding family history, the disease had the highest frequency of 80%. In the study of Zareifar et al., with 243 patients, which was similar to results of the current study, in total there were 73.7% ALL patients and 26.3% AML patients (16).

In this study, a number of factors affected the prediction of ALL and AML patients, such as age, clinical signs of remission and bleeding, white blood cell count, blood platelet count, and relapse status of the disease.

Patients were divided to three age groups of zero to four, five to nine, and nine to seventeen years, based on their age. In this study, age group did not show a significant relationship with survival rate (P value = 0.106). For the age group of five to nine years old, the risk ratio was

Table 2. Evaluation of Factors Affecting the Survival of Patients According to the Type of Leukemia (Kaplan-Meier and Leg-Range Test)

Parameter	Median of Survival			P Value (of Log-Rang)		
	ALL	AML	Total	ALL	AML	Total
Age category, y[a]				0.155	0.766	0.106
0 - 4	40	24	40			
5 - 9	49	-[b]	49			
10 - 17	41	-	41			
Gender				0.867	0.557	0.788
Male	44	-	44			
Female	40	20	40			
Kind of birth				0.104	0.099	0.555
Normal	41	-	41			
Cesarean	-	8	-			
The number of white blood cells[c]				0.733	0.010	0.043
< 10000	44	-	44			
10000 - 30000	-	1	21			
30000 - 50000	-	3	19			
> 50000	46	6	24			
The number of blood plate[c]				0.006	0.082	< 0.001
< 50000	40	9	21			
> 50000	44	-	44			
Recurrence status[c]				0.002	-	0.023
Had	19	-	19			
Didn't have	46	24	44			
Fever				0.302	0.336	0.627
Had	44	20	41			
Didn't have	46	-	46			
Pale				0.111	0.260	0.473
Had	46	-	46			
Didn't have	41	24	41			
Bleeding[a]				0.166	0.551	0.123
Had	44	-	44			
Didn't have	46	24	46			
Skeletal pain[a]				0.093	0.793	0.090
Had	44	24	44			
Didn't have	41	20	41			

[a] Significant at 15%.
[b] Cannot be determined.
[c] Significant at the level of 5%.

0.56 times of the age range of zero to five years. In the study of Mousavinasab et al., the level of the age group of five to nine years old was 3.86 higher than the age range of zero to five years old (18).

The average follow-up period for patients in this study was 22.22 $\pm$ 13.6 (1.49) months. The cumulative probability of survival of one, three, and five years of cancer in this study were 0.96%, 0.50%, and 0.08% respectively. In the study of Mousavinasab et al., the mean survival time for 97 patients was 20.20 $\pm$ 17.17 months with a median of 14.83 months (the lowest survival time was 0.66 months and the highest one was 7.07 months) (18).

There was no significant relationship between the survival rate of the gender variable (P value = 0.788), indicating that the survival rate was fairly similar between males and females, which resulted in a similar result with that of Pastore et al. and the study of Zareifar et al. (16, 19). Also, in a study from India and Turkey, age and gender variables with a five-month survival rate did not indicate a significant relationship. The results of this study also confirmed other findings (20, 21).

In the current study on bone pain variability, for middle-aged individuals, the survival rate was 44 months, and for AML, the survival rate was 24 months. In all cases, those, who did not have bone pain survived 44 months longer than those, who had bone pain and had a significant relationship with bone pain. Blood variables did not indicate a significant relationship with survival (P value = 0.123).

Various studies have indicated the effective role of

Table 3. Evaluation of Survival Factors Using Cox Regression Model for All Individuals with Leukemia

Parameter	Risk Ratio	5% Confidence Interval for Risk Ratio	P Value
Age category, y			
0 - 4	1	-	
5 - 9	0.560	0.269 - 1.165	0.120
10 - 17	1.194	0.618 - 2.308	0.598
The number of white blood cells			
< 10000	1	-	
10000 - 30000	2.218	0.959 - 5.131	0.063
30000 - 50000	2.308	0.802 - 6.623	0.121
> 50000	2.260	1.060 - 4.822	0.035
The number of blood plate			
< 50000	1	-	
> 50000	0.376	0.212 - 0.667	0.001
Recurrence status			
Had	1	-	
Didn't have	0.407	0.180 - 0.919	0.031
Bleeding			
Had	1	-	
Didn't have	0.616	0.328 - 1.156	0.131
Skeletal pain			
Had	1	-	
Didn't have	1.901	0.885 - 4.080	0.099

Table 4. Evaluation of Survival Factors Using Cox Regression Model for ALL

Parameter	Risk Ratio	5% Confidence Interval for Risk Ratio	P Value
Age category, y			
0 - 4	-	-	
5 - 9	0.479	0.211 - 1.087	0.078
10 - 17	0.982	0.442 - 2.183	0.964
The number of white blood cells			
< 10000	-	-	
10000 - 30000	1.544	0.529 - 4.508	0.427
30000 - 50000	1.369	0.321 - 5.843	0.672
> 50000	1.524	0.576 - 4.031	0.396
The number of blood plate			
< 50000	-	-	-
> 50000	0.403	0.207 - 0.788	0.008
Recurrence status			
Had	-	-	-
Didn't have	0.237	0.089 - 0.634	0.004
Bleeding			
Had	-	-	-
Didn't have	0.587	0.227 - 1.266	0.174
Skeletal pain			
Had	-	-	-
Didn't have	2.206	0.850 - 5.724	0.104

white blood cell counts in the survival rate of leukemia patients, especially ALL. In the current study, patients with high levels of white blood cell count (WBC < 10000) had a median survival of 44 months, with the highest average survival rate and a statistically significant relationship between white blood cell count and survival (P = 0.043). In Hazar et al., Hashemi et al., and Hussein et al.'s studies, people with less than 10000 white blood cells had greater survival than other people, and there was a significant relationship between white blood cell count and survival rate of patients (20, 22, 23). In the study of Zarei et al., those with higher white blood cell levels had a lower survival rate (40.3 months compared to 49.1 months) than those with less white blood cell count, and there was a statistically significant difference in the survival of patients and the number of white blood cells, yet there was no signif-

Table 5. Evaluation of Survival Factors Using Cox Regression Model for AML

Parameter	Risk Ratio	5% Confidence Interval for Risk Ratio	P Value
Age category, y			
0 - 4	-	-	
5 - 9	1.261	0.210 - 7.568	0.800
10 - 17	1.688	0.355 - 8.032	0.511
The number of white blood cells			
< 10000	-	-	
10000 - 30000	5.764	1.280 - 25.959	0.023
30000 - 50000	7.693	1.362 - 43.457	0.021
> 50000	5.203	1.283 - 21.107	0.021
The number of blood plate			
< 50000	-	-	-
> 50000	0.368	0.112 - 1.207	0.099
Bleeding			
Had	-	-	-
Didn't have	0.709	0.224 - 2.240	0.558
Skeletal pain			
Had	-	-	-
Didn't have	1.187	0.324 - 4.356	0.796

icant relationship between WBC and survival rate of patients, which may be due to the results of WBC for patients during treatment and chemotherapy (16). In the study of Mousavinasab et al., a significant relationship was found between the number of white blood cells and the survival rate of patients (18).

In the study of Bajel et al. (24) from India, there was a significant relationship between WBC and survival rate of patients. Also, Miguel et al., in a study on 217 patients with leukemia, found a significant relationship between white blood cell count and survival. In case of white blood cell count, those with white blood cell of > 50000 had a risk ratio of 2.26 times more than that of patients with white blood cell count of < 10000. In the study of Mousavinasab et al., those with a blood white blood cell count of > 50000 had a risk ratio 2.83 times more than that of patients with white blood cell count of < 10000 (18).

In this study, records were collected from hospitals and a series of information, such as the exact status of recurrence of all patients was not recorded. In similar studies, the patient's metastasis status variable was effective on the survival rate of patients, yet in the current study, the patient's metastasis information was not complete in all of the patients, and, therefore it was not analyzed, so it is advisable to study this, if possible. In the future, it is suggested that due to the low prevalence of malignancy among children, studies should be conducted in several provinces or at the national level.

In the current study, all cases of recurrence of the disease were not investigated due to lack of accurate records in patient information, yet in the study of the relapse status, the median survival rate for those, who had recurrence was 19 months and the median survival rate for them was lower than those, who did not recur within 46 months and there was a significant relationship between relapse status and survival rate (P value = 0.023). In the study of Zareifar et al., the incidence of recurrence and its number were significantly associated with survival (16). In similar studies by Pui et al. (12), Tsurusawa et al. (25), and Arellano et al. (26), survival rates were reported to be lower in those, who had recurrence.

Also, in the present study, the number of blood platelets was a predictor of survival. In people with high blood platelet count of > 50000, their median survival was higher than those with low platelet count of > 50000 (44 months to 21 months), and platelet levels were significantly related to survival (P value < 0.001). For the blood platelet count variable, the risk ratio for individuals with a level of > 50000 was 0.37 times more than that of subjects with platelet levels of < 50000. In the study of Mousavinasab et al., for platelet variables, the risk ratio for individuals with a level of > 50000 was a risk ratio of 1.64 times more than that of subjects with platelet levels of < 50000 (18).

Also, in the study of Zareifar et al., platelet count in patients with ALL was obtained as a survival predictor (16). Zeidler et al. also performed a study on 256 children. Those with ALL, who had blood platelets less than the first one showed a significant difference in treatment outcomes (27). Also, in a study by Miguel et al., which examined 217 patients with leukemia, a significant relationship was found between blood platelets and survival rates. In the study of Mousavinasab et al., platelet variables had no significant correlation with survival rate of patients (P value = 48.4)

(18).

4.1. Conclusion

The results of this study were similar to that of similar studies and in most of the examined cases, those with lower white blood cell count and those with high blood platelets had a higher survival rate than those with a lower risk profile. Regarding the variable relapse status, less survival was reported for those who had relapses than those, who did not.

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Footnote

Conflict of Interests: No conflict of interest is declared.

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