Predictive Factors of Survival Time after Hematopoietic Stem Cell Transplant in Acute Myeloid Leukemia Patients who Received Allogeneic BMT from Matched Sibling Donors Using Generalized Gamma Models

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Abstract

Introduction: This paper used Generalized Gamma (GG) distribution to find the predictive factors of overall survival (OS) after haematopoietic stem cell transplant (HSCT) in acute myeloid leukemia patients.
Methods: Discrimination among the exponential, Weibull, GG, log-logistic, and lognormal distributions was done using maximum likelihood and Akaike information criteria.
Results: The 5-year OS in 301 patients was 65% (95%CI: 60.7-69.3). Peak mortality hazard occurred at months 6-7 after HSCT then, it was U Shape. The data was fitted by GG distribution better than other distributions. Univariate analysis using GG distribution showed a positive association between OS with dose of infused WBC (P=0.018), CD3 (p=0.001), no relapse (P<0.001), cGVHD (P<0.001), and platelet recovery (P<0.001). Multivariate analysis indicated that, OS has relationship with relapse (P<0.001), platelet recovery (P=0.004), disease status at transplant (P=0.036) and aGVHD (P=0.036).
Conclusion: We showed that GG distribution can be a useful tool for recognizing prognostic factors of OS in AML patients.
Keywords: acute myeloid leukaemia • prognostic factors •generalized gamma distribution• survival analysis

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Introduction

Historically, prognostic in acute myeloid leukemia (AML) was based on morphology and cytochemistry.(1) Several factors are known to predict long-term survival of acute leukemia patients, including age, cytogenetic, leukocyte count at presentation, previous hematologic disease and prior exposure to chemotherapy.(1-3)
Prognostic factors of AML after haematopoietic stem cell transplant (HSCT) are already identified by using nonparametric survival methods such as Kaplan-Meier and Cox Proportional Hazard (PH) in many studies.(4-9) In Kaplan-Meier method, we can not determine the simultaneously effects of covariates on outcome. The Cox Proportional Hazard (PH) regression model which is a model for hazard rate or instantaneous risk of a given event has been used extensively in previous studies.(10) However, this model is based on the PH assumption and this may not hold in some survival studies. However, as PH assumption is not met, using the standard Cox proportional hazard model is not suitable and it may entail serious bias and loss of power when estimating or making inference about the effect of a given prognostic factor on mortality.(10)
Due to availability of standard methods such as Maximum likelihood (ML) for parameter estimation and testing, and no requirement of PH assumption, AFT models, as parametric models, are attractive.(11) If survival time has a specific statistical distribution, the predictive power of parametric survival models is higher than nonparametric or semi-parametric survival models.(12) A parametric survival models is one in which survival time (the outcome) is assumed to follow a known distribution. The exponential, Weibull, log-logistic, lognormal and the generalized gamma (GG) are examples of parametric distributions commonly used for survival time.

Survival estimates obtained from parametric survival models typically yield plots that are more consistent with a theoretical survival curve.(13)
In parametric survival models, survival and hazard function can be specified completely as well as determining the effects of changing covariates on survival time. So, these characteristics are the main appeals of using a parametric approach.
Base on our knowledge, given the use of Accelerated failure time (AFT) models in several medical researches specially in kidney transplantation, it has not been used to recognize the prognostic factors of acute myeloid leukemia patients so far.(14-17) Thus, in this article we choose fitting distribution among AFT models and use it for recognizing prognostic factors survival after HSCT in acute leukemia patients.

Material and Method

Data Collection and Patient Selection

Data on patients who underwent bone marrow or peripheral-blood transportation from HLL identical siblings were obtained from the Hematology-Oncology and Stem Cell Transplantation Research Center at Shariati Hospital, Tehran, Iran. Transplantations were performed between Oct 17, 1993 and Jan 31, 2007.
All patients receive a BuCy regimen (busulfan 4mg /kg/day orally on days -6 to -3 and cyclophosphamide 60 mg/kg/day by intravenous infusion on days -2 to -1) for conditioning therapy with subsequent infusion of donor marrow cells on day 0. For graft-versus-host disease (GVHD) prophylaxis in all patients received conventional Protocol Cyclosporin 3 mg/kg/day IV from days -2 and methotrexate 10 mg/m^2 day +1 and 6 mg/m^2 days 3, 6 and 11. We changed Cyclosporin to oral formulation when oral intake was possible.
All patients' records were reviewed for the occurrence of adverse events including GVHD and regimen-related toxicities. There were two transplantations performed with cord-blood that were excluded from the data analysis of study. Eligible patients for the study were 301 AML patients. The included patients in this study ranged in age from 2 to 56 years, and had received a HLA-matched marrow transplant. The median follow up time after transplantation was about 17 months (range 3-143 months).

Definition of Endpoints

Platelet recovery was defined by a count of at least 20,000 platelets per micro liters, unsupported by transfusion for seven days.
Hematopoietic recovery: Neutrophil recovery was defined by an absolute neutrophil count of at least 500 cells per cubic millimeter in three consecutive

Table 1. Patients and Transplants Characteristic

Characteristic	Frequency (%)
Patients' sex	
Male	165(54.8)
Female	136(42.2)
Donor' sex	
Female	112(37.2)
Male	189(62.8)
Donor –recipient sex match	
Male-male	106(35.2)
Male-female	59(19.6)
Female-male	83(27.6)
Female-female	53(17.6)
Age Mean(SD)	27.4(11.64)
Age(years),Median(range)	27(2-55)
Donor age, Median(range)	25(1-54)
Age group	
<15 yr	49(16.3)
16-20 yr	55(18.3)
21-30 yr	76(25.2)
31-40 yr	72(23.9)
>40 yr	49(16.3)
Disease status	
CR1	218(74.7)
>CR1	57(19.5)
PIF	9(3.1)
Relapse 1,2,3,other	8(2.7)
FAB or immunophenotype classification	M0:4(1.3) M1:18(6) M2:131(43.5) M3:23(7.6) M4:78(25.2) M5:31(10.3) M6:7(2.3) Other,specify:3(1) Unspecified:3(1)
Conditioning regimen	
BuCy	247 (83.2)
BuFluATG	8(2.7)
Busulfan - Oral	294(99)
Stoposide	2(0.7)
Cyclophosphamide	250(84.2)
ALG/AIS/ATG	11(3.7)
Source of stem cells	
Bone marrow	23(7.8)
Peripheral blood	278(92.4)
Cell dose, Median(range)	
WBC	10.32(2.1-24.5)
CD3	25(0.2-74.6)
$CD34^+$cells($\times 10^6$/kg)	1.9(0.2-79.2)
MNC	6.95(1.04-17.6)
Outcomes	
Death	67(22.3)
Relapse	51(16.9)
aGVHD	188(71.8)
cGVHD	62(25.5)
Platelet recovery	224(80.0)
Neutrophil recovery	225(86.1)

Table 2. Prognostic Factors of OS in Univariate Analysis Using Generalized Gamma(GG) distribution in AML patients(n=301)

Characteristics	p-value	exp(b) (95% CI)
WBC	0.018	1.11 (1.02-1.21)
CD3	0.001	1.05 (1.03-1.05)
Donor age(years)	0.03	1.02 (1.01-1.03)
Relapse	<0.001	9.77 (4.85-19.49)
aGVHD	0.11	0.59 (0.31-1.2)
cGVHD	<0.001	3.66 (2.87-4.71)
Platelet recovery	<0.001	1.93 (1.1-3.84)
Neutrophil recovery	0.54	1.26 (0.59-2.6)
Disease statues at transplant	0.053	2 (1.01-4.35)

WBC;Cell dose of WBC, aGVHD; acute graft-versus-host disease, cGVHD; chronic graft-versus-host disease

days. The median time to recovery was calculated using the product-limit method.

GVHD: The incidence of acute GVHD (aGVHD) was determined in all patients. Acute GVHD was graded according to the Seattle criteria.(18) If the grade of aGVHD was 1,2,3,4, they were defined as having aGVHD. Chronic GVHD (cGVHD) was defined according to standard criteria.(19) The incidence of chronic GVHD (cGVHD) was determined in patients who survived for at least 90 days.(20, 21)

Relapse: Relapse was defined as a recurrence of leukemia confirmed by cytology.

Survival: Overall Survival (OS) was defined as the time interval between HSCT and death of any cause or censoring. Censoring was defined as being alive at the last follow-up.

Statistical Analysis

The cumulative incidence of platelet recovery, neutrophil recovery, aGVHD, cGVHD, death and relapse were calculated with the use of cumulative-incidence-function methods.(22) The probability of OS was estimated using Kaplan-Meier estimator.(22) Confidence intervals were calculated via Log transformation.

Table 3. Prognostic Factors of OS in the Final Model using Generalized Gamma in AML patients (Multivariate Analysis) (n=301)

Variables name	exp(b) (95% CI)	P
Disease status at transplant (CR1 vs. other)	2.1(1.05 3.84)	0.053
Relapse(no vs. yes)	8.93(4.39 17.28)	<0.001
Platelet recovery(yes vs. no)	2.45(1.13 5.3)	<0.022
aGVHD(yes vs. no)	2.83(1.26 6.29)	0.036

aGVHD; acute graft-versus-host disease, CR1; first complete remission,

The accelerated failure time (AFT) models such as the exponential Weibull, Log-Logistic, lognormal and Generalizes Gamma (GG) distributions were used for finding the best distribution fitted to time to event (death) after HSCT .Discrimination among the exponential Weibull, Log-Logistic, lognormal and GG distributions were done using Maximum likelihood (LL), Akaike information criteria(AIC) and graphical methods.(21) Conditional distributions of parametric and nonparametric survival time models were estimated by including different covariates in models.

GG distribution was used for finding prognostic factors of survival after HSCT. PH assumption was checked using graphical, the goodness-of-fit testing and the time-depended variables procedures.(22)

Smoothed hazard function was estimated using Kernel smoothing method.(23) P-value less than 0.05 was considered significant. Analyses were done using SPSS ver.16 and STATA ver.10.

Results

Table 1 shows the characteristics of 301 patients who were included in the study. The 5-yr survival rate based on Kaplan-Meir curve was 65% (95% CI: 60.7-69.3) (Figure 1). In CR1 disease stage, it was 84% (95% CI: 81.3 -86.7).

The shape of hazard function showed that peak mortality hazard occurred at months 6-7 after HSCT and then it has a U shape in a way that it decreased for about two years after transplant and then it increased afterwards (Figure 2).

Prognostic Factors of Survival after HSCT, Univariate Analysis

Maximum likelihood (ML) and Akaike criteria (AIC) showed that the GG fitted data better than other distributions. Therefore, all variables were evaluated using GG distribution as potential risk factors for OS.

Univariate analysis showed a significant association between OS with donor age, WBC, CD3, relapse, aGVHD, cGVHD, neutrophil recovery and platelet recovery (Table 2). There was no any significant association between other variables with OS.

Table 2 shows that patients' survival time can increase about 11%, with every 1000 unit's increment in WBC dose. A significant association was observed between OS and WBC dose (P=0.018, exp(b) =1.1). There was a significant association between CD3 dose and OS (P<0.001, exp(b) =1.05). It shows that with every unit incensement in CD3 cell dose, patients' survival time can increase about 5%.

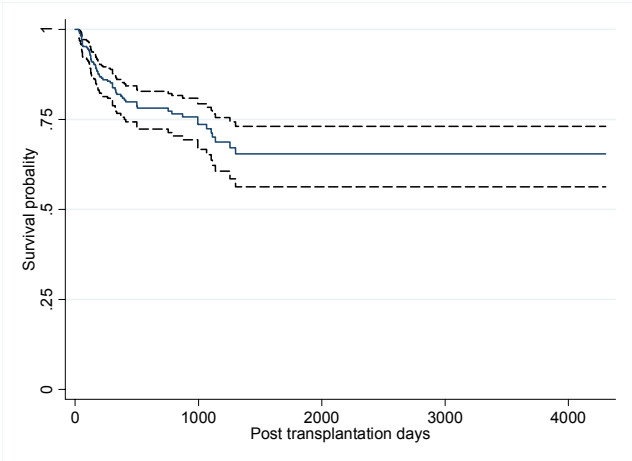

Figure 1. Kaplan-Meier estimated survival after transportation for patients diagnosed with acute myeloid leukemia.

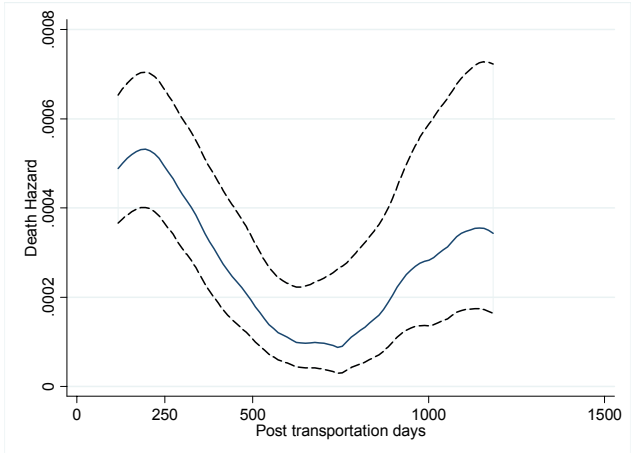

Figure 2. Smoothed death hazard in acute myeloid leukemia patients.

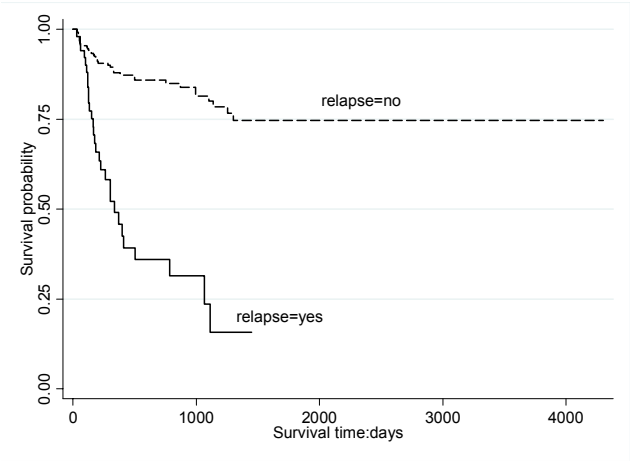

Figure 3. Kaplan-Meier estimated survival of acute myeloid leukemia patients after transplantation grouped according to relapse development.

Relapse

There was a strong correlation between OS and leukemia recurrence after transplantation (P<0.001, exp(b) =9.8). Those patients who have had relapse after transplantation; their OS was about 9.8 times shorter than other patients (Figure 3)

Acute GVHD

Occurring aGVHD had a negative effect on OS. But, its effect was not significant (P=0.11, exp(b) =0.59).

Chronic GVHD

There was a significant association between cGVHD and OS (P<0.001 exp(b)= 3.66). It indicates that OS was about 3.11 times longer in the patients with cGVHD compare to the patients without cGVHD. Incidence of cGVHD, among patients who survived for 90 days or longer after transplantation was 25.5%.

Platelet Recovery

There was a strong association between platelet recovery and OS (P<0.001, exp(b) =1.93), which is shown in table 2 and Figure 4. The OS in patients who had platelet recovery, was 1.93 time longer than the patients who did not have platelet recovery.

Neutrophil Recovery

There was not any significance association between neutrophill recovery and OS (P=0.54, exp(b) =1.26).

Prognostic Factors of Survival after HSCT, Multivariate Analysis

The variables that showed a significance level of less than 0.2 on univariate analysis were considered in the multivariate models. Also, the patients' age and sex were considered in the variable selection process.

The GG or/and Weibull distributions were seemed to be appropriate for data set. Therefore, all models were estimated using GG or Weibull distribution.

In a multivariate model, OS had a strong association with relapse (exp(b)=10.58, adjusted for dose cell (Adjusted for patients' sex and age) have

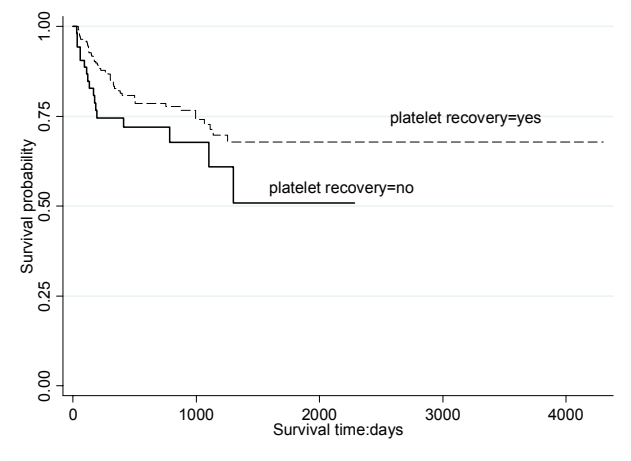

Figure 4 Kaplan-Meier estimated survival of acute myeloid leukemia patients after transplantation grouped according to platelet recovery development.

age and sex, CI 95% (5.4-20.7), P<0.001). WBC had significant association with OS (exp(b)=1.13, CI 95% (1.037-1.23), P=0.005), which meant that with every unit increment in WBC dose cell, OS of patients increased about 13% CI 95% (3.7% to 23%). Owing to convergence problem in the GG model, Weibull distribution was used to consider the relationship between OS and aGVHD, cGVHD, platelet recovery and patients' sex and age in a multivariate model. In this model, there was a significant association between platelet recovery and OS (HR=2.57, CI 95%: 1.7-3.9; P=0.004). Therefore, the death risk in patients with no platelet recovery was 2.57 times more than those patients who had platelet recovery.

Final Model

AIC information criteria(AIC) shows that a model including relapse, platelet recovery, disease status at transplant (CR1 vs. other) and aGVHD that has the smallest AIC, is the final model (Table 3). PH assumption was not met for this model (p<0.001). So, we can not use Cox PH model in the final model.

Discussion

Generalized Gamma model was used In order to identify predictive factors of OS and find hazard function shape in AML patients with HLA-matched HSCT. Hazard function had a decreasing rate in the first 7 months after transplantation then it had a decreasing rate for 2 years and then increased for next 2 years. Peak mortality hazard occurred at months 6-7. The reasons of the U shape hazard were not clear, but it seems that the hazard of death increased as a result of relapsed after two year. In univariate analysis GG distribution fitted to data better than other parametric survival models such as the exponential, Weibull, log-normal, log- logistic distribution. Hazard function in the GG distribution can take a wide variety of shapes.(23) To our knowledge, no other researches have considered GG distribution for finding hazard shape after HSCT or finding prognostic factors of OS in AML patients. GG distribution was used in several medical researches.(12-17) In AFT survival models such as GG distribution proportional hazard (PH) assumption is not required.(10) and also these models can specify a direct relation between the logarithm of survival time and the explanatory variables.(10) However, when PH assumption met, maybe the result of GG model and Cox model is different. In previous article we show predictive power AFT models is higher than Cox PH and Cox with time-varying coefficients.

In our study, based on Kaplan-Meier curves, five-year survival rates in AML patients at CR1 disease stage was 84% (CI 95%: 81.3 -86.7). The Center of International Blood and Marrow Transplant Research (CIBMTR) and the National Marrow Donor Program (NMPD) have reported 65% survival rates in AML patients.(27) Five-year survival rate in ALL patients was ranging from 11% for patients over 55 years to 71% in infants.(27-31) Among patients who were not transplanted in first remission, the five year survival rate was only 5% (CI 95%: 1-15%).(27) Thus, improvement in patients' survival seems to be associated with the increasing use of transplantation.

In this study, cGVHD developed in 24.1% of ALL patients. In adults, the reported incidence of cGVHD was ranging between 30% and 50% of HLA-identical sibling transplant recipients.(36) This study shows that developed cGVHD has had a good effect on prognosis of patients. There are some studies found that cGVHD was a prognostic factor for OS too.(37-38)

In summary, the results of current study suggest that in survival analysis studies in cancer research centers GG model maybe useful in recognizing prognosis factors in acute myeloid leukemia and they may be used as alternatives for Cox PH models. The choice of the appropriate model may lead to finding effective factors for OS of patients and also changing treatments.

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