

**RESEARCH
ARTICLE**

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Are the Conventional Risk Factors Still Valid for Acute Myeloid Leukemia Patients?

ABSTRACT

Objective: The aim of this study was to investigate the survival data of patients with acute myeloid leukemia (AML) and to determine the risk factors that can be easily evaluated.

Methods: A retrospective analysis was made of the AML patients admitted to our center between 2009 and 2018. Demographic and disease data were analyzed and response rates, overall survival (OS) and progression-free survival (PFS) rates were calculated. Factors affecting survival were determined using Cox-regression analysis.

Results: A total of 119 patients were included in the study during the 9-year study period. Of these, 21 patients had secondary AML and 11 had acute promyelocytic leukemia (AML-M3). The mean follow-up period was 12.43 ± 15.63 months. OS of all patients was 9.20 months and PFS was 7.23 months. Age and leukocyte count at the time of diagnosis were significantly found to have adverse effect on both OS and PFS (p <0.05).

Conclusions: In addition to genetic and molecular features, which are expensive and difficult to obtain, the age and leukocyte count of AML patients remain important as conventional prognostic factors.

Keywords: Leukemia, Survival, Age, Leukocyte

Akut Myeloid Lösemi'de Konvansiyonel Risk Faktörleri Önemi Koruyor mu?

ÖZET

Amaç: Bu çalışmanın amacı, merkezimize başvuran akut myeloid lösemi (AML) hastalarının sağkalım verilerini incelemek ve sağkalımı etkileyen kolay ve hızlı elde edilebilir faktörleri belirlemektir.

Gereç ve Yöntem: 2009-2018 yılları arasında merkezimize başvuran ve AML tanısı konulan 119 hasta retrospektif olarak incelendi. Demografik ve hastalık verileri incelenerek tedaviye yanıt oranları, genel ve hastalısız sağkalım oranları hesaplandı. Cox-regresyon analizi ile sağkalımı etkileyen faktörler belirlendi.

Bulgular: 9 yıllık çalışma süresi boyunca toplam 119 hasta çalışmaya dahil edildi. Hastaların 21'i sekonder AML ve 11'i akut promyelositer lösemi (AML-M3) idi. Ortalama takip süresi 12.43±15.63 ay olarak bulundu. Hastalarda genel sağkalım (OS) 9.20 ay, hastalısız sağkalım (PFS) 7.23 ay olarak bulundu. Hastaların tanı anındaki yaşı ve lökosit sayısının hem OS hem de PFS üzerine olumsuz etkisi olduğu görüldü (p<0.05).

Sonuç: Son yıllarda ilgi gören, geç elde edilebilen ve daha maliyetli olan genetik ve moleküler özelliklerinin yanında, AML hastalarında tanı anında yaş ve beyaz küre sayısı günümüzde halen prognostik önemini korumaktadır.

Anahtar Kelimeler: Lösemi, Sağkalım, Lökosit, Yaş

INTRODUCTION

Acute myeloid leukemia (AML) is a hematological malignant disease characterized by the uncontrolled proliferation of immature hematopoietic cells (1). It is the most common type of acute leukemia in adults, accounting for approximately 80 % of the cases in this group, and the incidence is approximately 2.7/100,000 (2). AML can develop at any age, but is more common in the >65 years age group (3). The clinical outcome is highly variable and overall survival (OS) ranges from a few days to several years, although survival is longer in patients who have allogeneic stem cell transplantation (HSCT) (3-5).

Since survival rates are so variable, the risk factors that predict both complete remission (CR) and survival have been the subject of research for many years. The most common factors include age, cytogenetic abnormalities, secondary leukemia, white blood cell count (WBC) and achieving CR after initial induction therapy (6). Age is considered to be the most significant patient-specific risk factor, while chromosomal abnormalities are the strongest disease-specific risk factor (7). Another strong determinant of the outcome, especially in elderly patients, is the performance status. The aim of this study was to investigate the effect of prognostic factors on the survival of AML patients treated in the Hematology Department of Diskapi Yildirim Beyazit Training and Research Hospital.

MATERIAL AND METHODS

Patients admitted to the hematology department of our tertiary referral training and research hospital between 2009 and 2018 were evaluated retrospectively. Patients who were diagnosed with AML, acute promyelocytic leukemia and AML secondary to myelodysplastic syndrome (MDS) were included. Demographic data, specific diagnosis, date of diagnosis, treatment regimen, treatment response and follow-up periods were recorded for all patients. Using these data, response rates, OS and progression-free survival (PFS) data were calculated. Analysis was made of the impact on OS and PFS of the patient hematological parameters at the time of diagnosis; hemoglobin (Hb) level, hematocrit (Hct) level, platelets count, WBC count, lactate dehydrogenase (LDH), ferritin and vitamin B12 levels.

Statistical Analysis: All statistical analyses were performed using SPSS statistics software (SPSS Inc, Chicago, IL). Descriptive data were stated as percentage values. The Kaplan-Meier method was used for survival analysis. OS was measured from the time of diagnosis to death or until the final visit. PFS was measured from diagnosis to death, disease progression or relapse,

whichever was earlier, or until the final visit. The Log-Rank test was applied in the comparisons between patient groups.

Compliance with Ethical Standards: All procedures performed in the current study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Approval for this study was granted by Local Ethics Committee (Number: 58/08 Date: 07.01.2019).

RESULTS

A total of 119 patients were included in the study. The demographic characteristics of the patients are shown in Table 1. OS for all patients was 9.20 months and PFS was 7.43 months (Figure 1). According to the Log Rank (Mantel-Cox) test for OS and PFS, there was no statistically significant difference between the diagnostic subgroups (denovo AML, APL, secondary AML) in terms of survival ($p>0.05$) (Table 2, Figure 2).

Table 1. Demographic and disease characteristics of the patients

(N=119)	
Age (mean±SD)(year)	61.50±16.48
Gender	
Male	70 (%58.8)
Female	49 (%41.2)
Diagnosis subtypes	
AML	87 (%73.1)
APL	11 (%9.2)
SAML	21 (%17.7)
Number of comorbidity (Median [Min-Max])	1.0 [0.0-4.0]
First line treatment	
Anthracycline + Cytarabine	61 (%51.3)
Hypomethylating agents	38 (%31.9)
Other	20 (%16.8)
Response to first line therapy	
Refractory	77 (%64.7)
Remission	42 (%35.3)
Final response status	
Refractory	83 (%69.7)
Remission	36 (%30.3)
Final status	
Exitus	85 (%71.4)
Survivor	34 (%28.6)
Total follow-up (mean±SD)(month)	12.43±15.63

AML: Acute myeloid leukemia, APL: Acute promyelocytic leukemia, SAML: Secondary AML, SD: Standard deviation

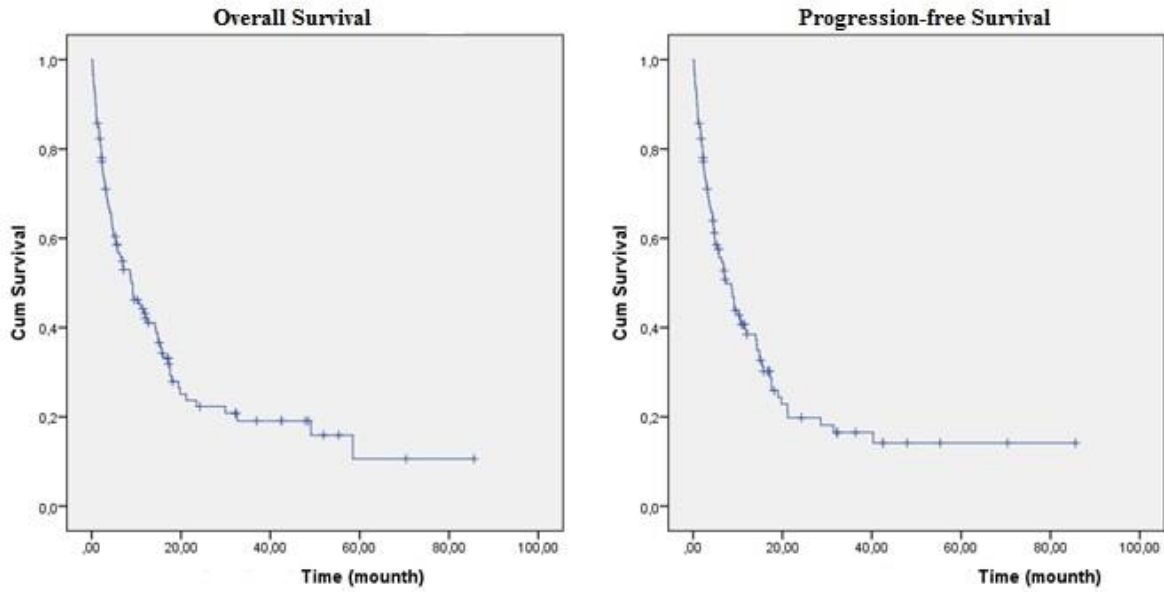


Figure 1. Overall and progression-free survival analysis of all patients.

Table 2. The survival rates according to disease subgroups

		χ^2	<i>p</i>	Survival (months)			
				AML	APL	SAML	Overall
Log-Rank	OS	5.199 (2)	0.074	8.77	8.65	9.20	9.20
	PFS	4.343 (2)	0.144	7.13	7.00	8.60	7.43

OS: Overall Survival, PFS: Progression-free survival, AML: Acute myeloid leukemia, APL: Acute promyelositic leukemia, SAML: Secondary AML

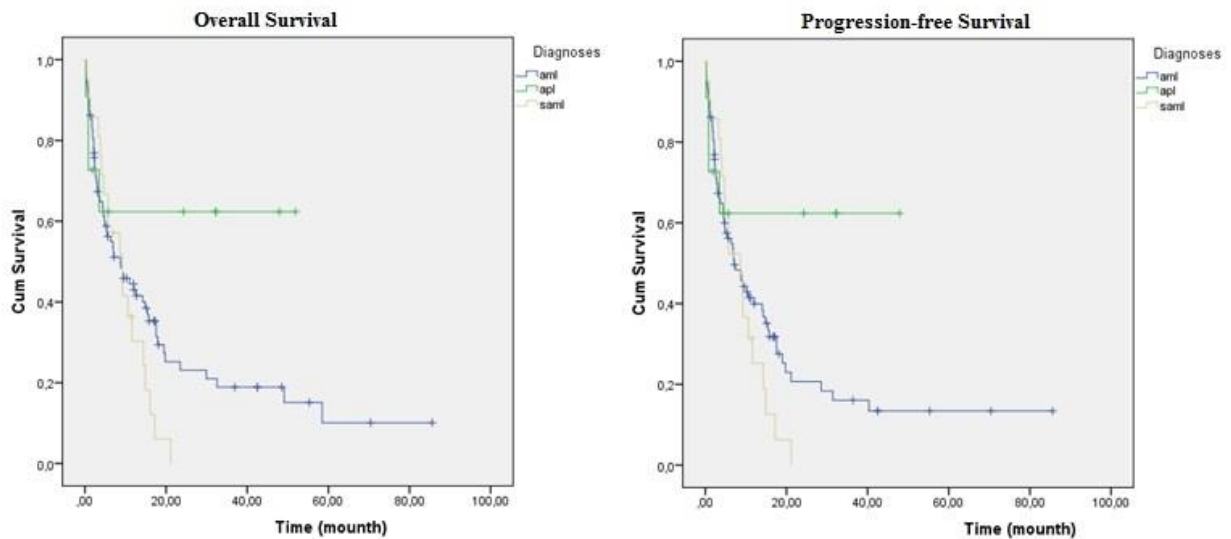


Figure 2. Overall and progression-free survival analysis according to disease subgroups.

Data were analyzed to determine the factors affecting survival rates. According to the Cox-Regression model, age and leukocyte count were found to be parameters with an effect on OS ($p < 0.05$). Mortality risk was determined to increase by 4.4% with a 1-year increase in age (OR=1.044;

CI=1.019-1.069). The mortality risk was determined to increase by 10% with an increase in leukocyte count of 10,000 (OR=1.100; CI=1.100-1.200). The effect of the parameters on OS was examined in the Cox-Regression model, as shown in Table 3.

Table 3. Analysis of the effect of parameters on overall survival with Cox-Regression model

	B	SE	Wald	p	95% CI for Exp(B)	
					Lower	Upper
Age	0,043	0,012	12,682	0,000	1,019	1,068
Gender	-0,041	0,313	0,017	0,896	0,520	1,774
Hemoglobin (gr/dl)	0,072	0,077	0,873	0,350	0,924	1,250
Platelet (/mm³)	0,000	0,000	0,031	0,861	1,000	1,000
Leukocyte(/mm³)	10000,0	5000,0	5,002	0,025	1,100	1,200
Ferritin	0,000	0,000	0,417	0,518	1,000	1,001
LDH	0,000	0,000	1,515	0,218	1,000	1,001

LDH: Lactate dehydrogenase, CI: Confidence interval

Age and leukocyte count were found to have a significant impact on PFS according to the Cox-Regression model ($p < 0.05$). The risk of progression was determined to increase by 4.2% with a 1-year increase in age (OR=1.042; CI=1.018-1.066) and

by 10% with an increase in leukocyte count of 10,000 (OR=1.100; CI=1.100-1.200). The Cox-Regression model of the effects of some parameters on PFS is shown in Table 4.

Table 4. Analysis of the effect of parameters on progression-free survival with Cox-Regression model

	B	SE	Wald	p	95% CI for Exp(B)	
					Lower	Upper
Age	0,041	0,012	12,019	0,001	1,018	1,066
Gender	-0,016	0,315	0,003	0,959	0,531	1,823
Hemoglobine (gr/dl)	0,088	0,077	1,306	0,253	0,939	1,269
Platelet (/mm³)	0,000	0,000	0,001	0,977	1,000	1,000
Leukocyte(/mm³)	10000,00	5000,00	5,021	0,025	1,100	1,200
Ferritin	0,000	0,000	0,900	0,343	1,000	1,001
LDH	0,000	0,000	1,041	0,308	1,000	1,001

LDH: Lactate dehydrogenase, CI: Confidence interval

DISCUSSION

Since AML is the most common type of acute leukemia in adult patients, prognostic or predictive factors are frequently investigated in these patients. In addition to patient-related factors such as age and performance, which have been previously reported, disease-related genetic and molecular risk factors have been emphasized more recently. However, as cytogenetic and molecular properties are expensive, cannot be easily obtained in every center and results are not immediately available, long-standing conventional risk factors remain important.

Age is one of the most important factors for AML patients. With aging, both the nature of the disease and the patient's health status change. Therefore, it has been known for many years that age has a negative effect on PFS and OS (2, 7-10). Increased age has been shown to be a negative prognostic factor even after adjustment of risk factors such as cytogenetics, molecular genetics, and AML type (eg, de novo AML, previously MDS or MDS/MPN history AML, therapy-related AML) (1). In the current study, the prognostic importance of conventional risk factors was investigated. The results demonstrated that age and leukocyte count

have adverse effect on OS (OR=1.044 vs OR=1.100, $p < 0.05$). Some authors have argued that calendar age alone should not be considered a reason for not giving intensive treatment to an elderly patient (11). In particular, it has been suggested that the performance status should be considered together with age (12).

Approximately 20% of AML patients are accompanied by a high leukocyte count at the time of diagnosis ($>50 \times 10^9/L$) (5, 13). Although the term hyperleukocytosis generally refers to conditions in which the WBC is $>100 \times 10^9/L$, many studies have shown leukocytosis to be an indicator of poor prognosis in AML patients (4, 5, 7, 14). Similarly, in the current study, the leukocyte count had a negative effect on both OS and PFS. In a study of 375 adult (non-M3) AML patients, it was seen that continuous analysis of leukocyte count as a variable was a better indicator of induction death and OS. In that patient cohort, WBC of $\geq 30 \times 10^9/L$ showed high sensitivity and specificity in the prediction of early death and predicted more accurately together with the performance score rather than age (15). Since an initial higher leukocyte count in AML is a serious condition, the

effects on survival of cytoreductive therapy to reduce the number of WBC before induction treatment have also been investigated. Mamez AC et al. showed that emergent cytoreductive treatment before induction therapy decreased hospital mortality in AML patients (13). However, in a retrospective cohort study conducted between 1998 and 2006, Kuo KH et al. showed that although a higher leukocyte count had an association with early mortality and lower OS, pre-induction cytoreductive treatment had no effect. Therefore, if appropriate, emergent induction therapy is recommended for AML patients with hyperleukocytosis (14). Similarly in another study, early deaths associated with hyperleukocytosis in AML were shown to be unaffected by leukopheresis or cytoreductive therapies (16). Based on the results of both the current and previous studies mentioned above, it can be considered that the increased WBC count is not only a laboratory finding, but also an indicator of a more aggressive course of the disease. Therefore, a reduction in leukocyte count without treating the underlying leukemia disease may not be adequate. In contrast to these results, a phase III study of 485 elderly patients with AML who received supportive therapy or hypomethylating agents showed no relationship between the leukocyte count at the time of diagnosis and response (17).

Following better identification of cytogenetic and molecular features, these characteristics are now frequently used in both classification and risk stratification (18). Of the 119 patients included in the current study, only 59 had complete genetic results. Therefore, these features could not be included in the analysis. Similar to the current study, one of the largest studies analyzing risk factors without including genetic features was the study published by the Swedish Leukemia Group (11). A total of 2767 AML patients (except APL) between 1997 and 2005 were examined, and from the results of the study, it was reported that the strongest determinants were age and performance score for CR and survival. In another study where cytogenetic features were not included, Zhao BB et al. applied multivariate and univariate analyses to the clinical data of 211 AML patients in respect of age, disease subtype, performance status, WBC, serum LDH and albumin levels, and treatment strategies (19). According to the results of the study, the significant parameters in the univariate analysis were found to be age, achieving CR, performance status, organ dysfunction, increased number of WBC, higher LDH, and lower albumin levels. Multivariate analysis showed that only failure to achieve CR, poor performance status and increased WBC were independent prognostic factors.

Table 5. 2017 European Leukemia Net risk stratification by genetics

Risk Category	Genetic abnormalities
Favorable	t(8;21)(q22;q22.1); RUNX1-RUNX1T1 inv(16)(p13.1;q22) or t(16;16)(p13.1;q22); CBFβ-MYH11 Mutated NPM1 without FLT3-ITD or with FLT3-ITD _{low} Biallelic mutated CEBPA
Intermediate	Mutated NPM1 and FLT3-ITD _{high} Wild type NPM1 without FLT3-ITD or with FLT3-ITD _{low} (w/o adverse risk genetic lesions) t(9;11)(p21.3;q23.3); MLLT3-KMT2A Cytogenetic abnormalities not classified as favorable or adverse
Adverse	t(6;9)(p23;q34.1); DEK-NUP214 t(v;11q23.3); KMT2A rearranged t(9;22)(q34.1;q11.2); BCR-ABL1 inv(3)(q21.3;q26.2) or t(3;3)(q21.3;q26.2); GATA2, MECOM(EVI1) -5 or del(5q); -7; -17/abn(17p) Complex karyotype, monosomal karyotype Wild type NPM1 and FLT3-ITD _{high} Mutated RUNX1 Mutated ASXL1 Mutated TP53

There are many studies in which both conventional risk factors and genetic properties have been analyzed together. In a recent study, the factors with an independent effect on survival were found to be age <60 years, good cytogenetic markers and leukocyte count <30 x 10⁹/L (4).

Similarly, in another study, age <60 years, favourable cytogenetics, de novo AML and leukocyte count at the time of diagnosis of <4 x 10⁹/L were shown to be associated with higher PFS and OS (20). In another retrospective study of 137 adult AML patients between 2010 and 2015,

predictive factors for OS and CR were shown to be age and the presence of monosomy (21). Analysis of survival data in two different studies revealed that age is a highly significant prognostic factor even in cytogenetic risk subgroups (22, 23). For the most recent genetic-based risk classification according to the European Leukemia Network published in 2017 (10), see Table 5.

The major limitation of this study is the retrospective design and lack of genetic risk stratification due to inadequate molecular analysis of all patients. Further large-scale, prospective clinical trials are needed to determine the effect of prognostic factors on the survival, especially for disease subtypes separately.

Conclusion

The prognostic factors in AML have a significant impact on the survival and treatment strategies of the patients. Age and performance

status are the most important patient-related risk factors, while cytogenetic and molecular genetics are the strongest disease-related prognostic factors. Age is still the most important predictive and prognostic feature whether or not cytogenetic features are included. In addition, the performance score and the leukocyte count are also effective factors. Consequently, besides to chromosomal and molecular characteristics, conventional risk factors continue to be an important tool for predicting outcome in AML. However, for clinicians there is the problem of answering the question of "Should we wait for the expensive and delayed cytogenetic results before making a treatment decision for AML patients, or should the induction be started as soon as possible by identifying risk factors that can be easily obtained at baseline?". The answer to this question is an important topic of current discussions and will have to be solved in the near future.

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