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The effect of bone marrow reticulin fibrosis on survival in acute myeloid leukemia patients

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Abstract

Although acute myeloid leukemia is a rare cancer, it is a disease that deserves attention because of its increasing incidence and high mortality. Many prognostic factors, in particular age and cytogenetic classification, are important in the management of AML. Identifying new prognostic factors will enhance our understanding of AML and contribute to improved survival.For the purpose of investigating the impact of bone marrow reticulin fibrosis on overall survival, a total of 121 patients with acute myeloid leukemia were included in the study. Out of these 121 patients, 70 (57.9%) were male and 51 (42.1%) were female. The mean age of all patients was 57.72±16.3 years.There was no bone marrow reticulin fibrosis in 56 patients (47.9%), first degree fibrosis in 47 patients (40.2%), second degree fibrosis in 13 patients (11.1%) and third degree fibrosis in 1 patient (0.9%). No correlation was found between bone marrow reticulin fibrosis and age, gender, FAB classification, or bone marrow blast rate at diagnosis. Patients in the unfavorable cytogenetic risk group had more bone marrow reticulin fibrosis. The mean overall survival was 17.4±1.9 months. In the group without bone marrow reticulin fibrosis, it was 18.87±2.77 months, while in the group with bone marrow reticulin fibrosis, it was 11.09±1.51 months. This observed difference was determined to be statistically significant. Therefore, the presence of bone marrow reticulin fibrosis was considered an important prognostic factor for overall survival.Scientific publications, which have increased significantly in recent years, have contributed to a better understanding of acute myeloid leukemia and thus to the development of new approaches. Pharmacological inhibition of bone marrow reticulin fibrosis could potentially offer clinical utility and extend patient survival. Further studies are needed to incorporate bone marrow reticulin fibrosis into prognostic risk classifications, to develop appropriate chemotherapy regimens, and to improve the clinical efficacy of treatment in AML patients.

Keywords: Acute Myeloid Leukemia, bone marrow fibrosis, prognostic factors

1. Introduction

AML is a clonal disorder of hematopoietic stem cells that causes impaired differentiation and excessive proliferation of hematopoietic stem or progenitor cells from the myeloid lineage. The accumulation of immature and undifferentiated myeloid progenitor cells (blasts) in the bone marrow and sometimes in surrounding tissues leads to life-threatening complications such as neutropenia, thrombocytopenia, and anemia (1). AML may develop due to various environmental or genetic factors, although the etiology is unknown in most cases.

AML is slightly more prevalent in men than women, but the lifetime risk of diagnosis averages at approximately 0.5% for both sexes (2). The incidence rate of AML rose by 2% per year from 2007 to 2016; however, the mortality rate has remained stagnant. Significant breakthroughs in treatment have substantially increased survival rates for most forms of leukemia (3). AML, a condition that rarely occurs before the age of 45 years, primarily affects the elderly population, with 60% of diagnosed patients being aged 65 and above. Mortality rates are known to increase with age. The 5-year survival rates are 25% across all age groups (4).

When acute leukemia is clinically suspected, it is necessary to evaluate the morphology (bone marrow smear) and perform flow cytometry analyses. Additionally, cytogenetic and genetic testing are mandatory to aid diagnosis, assess prognosis, and determine the most effective therapeutic approach. The French-American-British (FAB) classification system was developed in 1976 to differentiate between AML subtypes. With advancements in immune phenotyping and cytogenetics, which increased during the latter part of the 20th century, the World Health Organization (WHO) introduced a new classification in 1999 that was later updated in 2022 (7). The WHO classification for acute leukemia is centered on clinical, morphological, immunophenotypic, cytogenetic, and molecular characteristics. However, these classifications do not provide prognostic and survival data.

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In AML treatment, achieving a cure is possible with standard treatment regimens for some patients, but some patients are unresponsive to intensive treatment regimens. It is crucial to anticipate these differences in response to treatment at the time of diagnosis to inform a treatment plan. Age is one of the most crucial prognostic indicators in AML and other diseases. AML has a poor outcome for patients over 60 years old (8). Patients with a low Karnofsky performance status score or an unfavorable Eastern Cooperative Oncology Group performance score are likely to experience a reduction in overall survival (9). The presence of pulmonary complications, hyperleukocytosis, or the expression of CD34, CD56, or CD25 at the time of diagnosis are associated with poor prognostic factors (10-12). It has been observed that patients who achieve complete remission with induction treatment generally have a more positive prognosis (11). Abnormalities in the number or structure of chromosomes are found in up to 60% of patients with AML and are considered the most important prognostic factor (13). The European LeukemiaNet (ELN) has categorized patients into three prognostic risk groups based on cytogenetic and molecular abnormalities in AML. These groups are further divided according to complete remission, disease-free survival, and overall survival rates. For acute promyelocytic leukemia (APL), the risk classification utilized is based on GIMEMA and PATHEMA studies (14). The presence of eosinophils (FAB M2 and M4Eo) is considered a positive prognostic factor, whereas the presence of dysplasia indicates a poorer prognosis. Consequently, FAB subtypes M0, M5, M6, and M7 demonstrate a less favorable prognosis compared to other FAB subtypes.

Increased fibrosis in the bone marrow has been linked to various benign and malignant conditions, but the underlying pathophysiology remains unclear (15). While bone marrow fibrosis is commonly observed in hematological diseases, its impact on disease prognosis is not fully understood. In AML, bone marrow fibrosis has been identified as a secondary reaction to clonal proliferation of hematopoietic cells (16). Bone marrow fibrosis has been found to be a negative prognostic factor in myelodysplastic syndrome (17). However, its effect on prognosis and survival in AML patients has been limited to a few studies in the literature (18, 19). The current AML diagnosis, classification, and treatment guidelines of ELN and WHO do not include an evaluation of bone marrow fibrosis. The purpose of this study is to investigate the impact of bone marrow reticulin fibrosis on overall survival among AML patients.

2. Materıals and Methods

A total of 487 patients with AML were followed up and treated at the Ondokuz Mayıs University Faculty of Medicine Hospital, Department of Hematology, between 2008 and 2019. After receiving approval from the Ondokuz Mayıs University Clinical Research Ethics Committee on January 16, 2020, with the reference number B.30.2.ODM.0.20.08/17, 121 patients from this group, for whom genetic results could be obtained, were included in the study. Patient data at the time of diagnosis and during follow-up were retrospectively reviewed using the patient management information system. For the cytogenetic risk classification of the patients, ELN guidelines were applied to non-APL patients, while GIMEMA and PATHEMA guidelines were used for APL patients. The bone marrow reticulin fibrosis grade of 117 patients who underwent bone marrow biopsies upon admission was categorized into grades 0, 1, 2, and 3, following the WHO 2008 classification criteria.

SPSS 22.0 (Statistical Package for the Social Sciences) package program was used for data analysis. Kolmogorov-Smirnov and Shapiro Wilk normality tests were applied to determine which test to use from the comparison tests. Independent two-sample t-test was used for two-category variables with normal distribution, and Mann-Whitney U-test was used for two-category variables that did not show normal distribution. For variables with more than two categories, ANOVA test was used for normally distributed variables, and Kruskal Wallis H test was used for non-normally distributed variables. However, Chi-square and Fisher tests were used to determine the relationship between categorical variables. Kaplan-Meier survival method was used for the analysis of patients' survival.

3. Results

Among the 121 patients diagnosed with AML who were over the age of 18, males accounted for 70 (57.9%) and females accounted for 51 (42.1%) of the population. The youngest patient was 21 years old, while the oldest patient was 83 years old. The patients included in the study had a mean age of 57.72±16.3 years. Among the patients, 55 (45.5%) were 60 years of age or older. The mean bone marrow blast rate was 53±25.8%, where the lowest was 20% and the highest blast rate was 95%. Eighteen patients were unable to attain a FAB classification following their bone marrow assessment. Among the patients who were successfully classified, the most prevalent subgroup was M0 with 37 patients (30.6%) and M1 with 22 patients (18.2%). The subgroups M5, M6, and M7 were the least commonly observed. The details regarding patient characteristics have been provided in Table 1.

At the point of diagnosis, the pathology department assessed reticulin fibrosis in 117 patients' bone marrow biopsy samples using silver stain, following WHO 2008 criteria. Of those, 56 patients (47.9%) didn't present any fibrosis, whereas 47 patients (40.2%) had first degree fibrosis, 13 patients (11.1%) had second degree fibrosis, and only 1 patient (0.9%) showed third degree fibrosis. When the patients were assessed based on age, gender, blast rate and FAB group in relation to the presence or absence of fibrosis in the bone marrow, no significant statistical difference was discovered. However, when categorized by risk groups, the presence or absence of fibrosis between the favorable and intermediate risk groups was similar. In the adverse cytogenetic risk group, bone marrow reticulin fibrosis was absent in one patient (9.1%),

whereas 10 patients (90.9%) exhibited fibrosis, which was statistically significant (p:0.021) (Table 2).

Table 1. General characteristics of patients

	Parameters		Number Of Patients	Percent
Patient Characteristics	Gender	Male	70	57,9
		Woman	51	42,1
	Age	<60	66	54,5
		≥60	55	45,5
	Cytogenetic Risk Group	Favorable	30	24,8
		Intermediate	80	66,1
		Adverse	11	9,1
	FAB Group	M0	37	30,6
		M1	22	18,2
		M2	12	9,9
		M3	12	9,9
		M4	14	11,6
		M5	4	3,3
		M6	0	0
		M7	1	0,8
		Unclassified	19	15,7
	Bone Marrow Reticulin Fibrosis Grade	Grade 0	56	47,9
		Grade 1	47	40,2
		Grade 2	13	11,1
		Grade 3	1	0,9
Survival	Overall Survival		**Average**	**Median**
			17,4 ± 1,9	11,3 ± 3,7 ay
Blood Count Parameters	**Parameters**		**Median**	**Lowest - Highest**
	WBC (thousand/µL)		10,9	0,47-237
	Monocyte (thousand/µL)		1,95	0,01-170
	Lymphocyte (thousand/µL)		2,43	0,09-96,62
	Neutrophil (thousand/µL)		1,73	0-74,7
	Eosinophil (thousand/µL)		0,03	0-6,2
	Basophil (thousand/µL)		0,03	0-22,89
	Hemoglobin (gr/dL)		8,7	3,5-14,7
	MCV (fL)		91,6	60-111
	Platelets (thousand/µL)		54	3-1106
Biochemical Parameters	Total protein (g/dL)		6,82	5,1-9,4
	Albumin (g/dL)		3,8	1,61-4,88
	B2 Microglobulin (ng/mL)		2.419	1.894-8.518
	Vitamin B12 (pg/mL)		520	7,45-2355
	Folic Acid (ng/mL)		5,2	0,6-20
	Iron (µg/dL)		103	105-362
	Ferritin (ng/mL)		780	21,3-21.000
	LDH (U/L)		407	132-4.700
	Uric acid (mg/dL)		4,8	0,7-14
	CRP (mg/L)		29	0,15-436
	Sedimentation (mm/h)		70	1-156

Table 2. Evaluation of patient characteristics with the presence of bone marrow reticulin fibrosis

Parameters		**No bone marrow reticulin fibrosis (Grade 0)**		**Bone marrow reticulin fibrosis present (Grade 1-2 and 3)**		**p**
		n	**%**	**n**	**%**	
Gender	<60 yaş	30	46,9	34	53,1	0,814
	>60 yaş	26	49,1	27	50,9	
Age	Erkek	30	43,5	39	56,5	0,342
	Kadın	26	54,2	22	45,8	
Cytogenetic Risk Group	Favorable	15	51,7	14	48,3	**0,021***
	Intermediate	40	51,9	37	48,1	
	Adverse	1	9,1	10	90,9	
FAB Group	M0	18	51,4	17	48,6	0,441
	M1	11	50	11	50	
	M2	5	41,7	7	58,3	
	M3	2	18,2	9	81,8	
	M4	5	35,7	9	64,3	
	M5	3	75	1	25	
	M6	0	0	0	100	

	M7	0	0	1	100	
	Unclassified	12	70,6	5	29,4	
Blast median percentage		50 (20-90)		50 (20-95)		0,837
Overall survival		18,87 ± 2,77 month		11,09 ± 1,51 month		**0,041***

The mean overall survival time equated to 17.4±1.9 months, whereas the median overall survival time was 11.3±3.7 months. When analyzing the impact of reticulin fibrosis in the bone marrow on overall survival, the group without bone marrow reticulin fibrosis had a mean overall survival of 18.87±2.77 months, while the group with bone marrow reticulin fibrosis had a mean overall survival of 11.09±1.51 months. This difference was statistically significant (p: 0.041).

4. Discussion

Bone marrow reticulin fibrosis is present to varying degrees in one-third to one-half of patients with AML at the time of diagnosis. Increased reticulin fibers in the bone marrow of AML patients are due to cytokine overproduction, which increases with CD34 and HLA-DR expression on leukemic cells (20, 21). The local bone marrow renin-angiotensin system plays a significant role in the onset of leukemia. Renin-angiotensin system mediates numerous biological processes involved in the formation and functioning of blood cells, including fibrosis. The local renin-angiotensin system is one of the causes of cytokine overproduction (22).

In a study of 34 patients by Islam et al, no reticulin fibrosis was found in 65% of patients, whereas grade 1 reticulin fibrosis was found in 26% and grade 3 reticulin fibrosis in 9% (23). In a study of 183 patients by Tang et al, 54% of patients had no reticulin fibrosis, 27.8% of patients had 1st and 2nd grade reticulin fibrosis, and 18% of patients had 3rd and 4th grade reticulin fibrosis (24). In our study, similar to the literature, 56 patients (47.9%) had no reticulin fibrosis, 47 patients (40.2%) had grade 1 reticulin fibrosis, 13 patients (11.1%) had grade 2 reticulin fibrosis, and 1 patient (0.9%) had grade 3 reticulin fibrosis.

It has been reported in the literature that fibrosis varies significantly according to the subgroup of leukemia; increased fibrosis is observed in the M7 subgroup, whereas increased fibrosis is rarely observed in the M3 subgroup (20). In our study, when the relationship between the degree of bone marrow reticulin fibrosis and the FAB groups was evaluated, no statistically significant difference was found between them. Among 11 patients diagnosed with APL in whom bone marrow reticulin fibrosis evaluation was performed, no fibrosis was observed in 2 (18%) and grade 1 reticulin fibrosis was observed in 9 patients (81.8%). Grade 2 fibrosis was observed in one patient diagnosed with M7. The presence of bone marrow reticulin fibrosis in APL can be a diagnostic challenge for clinicians. It may erroneously lower the index of suspicion for leukemiaand possibly delay the administration of appropriate treatment. It is important to consider the potential for bone marrow reticulin fibrosis in APL. Early initiation of ATRA following a correct APL diagnosis could improve the chances of a cure.

In our study, we classified patients into two groups based on the severity of their bone marrow reticulin fibrosis: those without fibrosis (grade 0) and those with fibrosis (grades 1-2-3). Our findings indicate that age, gender, and blast rate at the time of diagnosis did not differ significantly between these two groups. To our knowledge, no previous studies have examined this relationship.

In our study, an objective analysis of cytogenetic risk groups revealed that the presence or absence of bone marrow reticulin fibrosis was comparable in both favorable and intermediate risk groups. Technical term abbreviations will be explained upon initial use. However, within the unfavorable cytogenetic risk group, one patient (9.1%) displayed no signs of fibrosis, while fibrosis was present in the remaining 10 patients (90.9%), resulting in a statistically significant correlation (p:0.021). This study examines the correlation between cytogenetic risk classification, a crucial factor in determining AML prognosis, and bone marrow reticulin fibrosis.

The results reveal that patients without bone marrow reticulin fibrosis had an overall survival of 18.84±2.77 months, whereas those with the condition only had a survival rate of 11.09±1.51 months, a statistically significant difference (p:0.041). Our study showed that the effect of the presence of bone marrow fibrosis on overall survival was statistically significant. Therefore, the presence of bone marrow reticulin fibrosis was considered an important prognostic factor for overall survival.

A study by Zhang et al. involving 190 patients reported that patients with bone marrow reticulin fibrosis had a shorter overall survival. Three-year overall survival was 35.4% in the group without bone marrow reticulin fibrosis and 9.6% in the group with bone marrow reticulin fibrosis (18). The study by Wu et al, which included 152 patients, showed that overall survival decreased in the group with bone marrow reticulin fibrosis (19). Both studies showed increased bone marrow reticulin fibrosis in patients in the unfavorable cytogenetic risk group. The effect of the presence of bone marrow reticulin fibrosis on overall survival in AML patients was limited to these two studies. The results of our study support these two studies. The pathophysiology of bone marrow reticulin fibrosis in AML needs to be better understood, and new therapeutic strategies targeting bone marrow reticulin fibrosis may be promising to improve clinical outcomes.

Our study indicates that bone marrow reticulin fibrosis is an adverse prognostic indicator for AML patients. Further

research is required to incorporate bone marrow reticulin fibrosis into prognostic risk classifications, formulate appropriate chemotherapy regimes, and enhance the clinical effectiveness of treatment for patients with AML.

Conflict of interest

The authors declared no conflict of interest.

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Authors' contributions

Concept: Ö.Y.Ç., E.K., Design: Ö.Y.Ç., Data Collection or Processing: Ö.Y.Ç., E.K., Analysis or Interpretation: Ö.Y.Ç., E.K., Literature Search: Ö.Y.Ç., E.K., Writing: Ö.Y.Ç., E.K.

Ethical Statement

Approval was obtained from Ondokuz Mayıs University Clinical Research Ethics Committee, the study started. The ethics committee decision date is 16/01/2020 and the number of ethical committee decisions is 2020/17.

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