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Original Article

Serum albumin and ferritin levels: a practical indicator of prognosis in acute myeloid leukemia over 50 years of age?

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Abstract: Background: Low albumin and high ferritin levels have negative effects on survival in acute myeloid leukemia (AML). In this study, the aim is to determine the role of these factors on survival in patients over 50 years of age with AML. Methods: Eighty patients followed up between January 2014 and July 2019 were included in the study. Patients were categorised into three subgroups: The favorable, intermediate and high-risk groups. Results: The overall survival of the favorable group was found to be longer in a statistically significant way. Conclusion: In this study, it has been shown that serum albumin and ferritin values are useful and simple laboratory values to show prognosis in AML over 50 years of age.

Keywords: AML, albumin, ferritin, prognosis

Introduction

Acute myeloid leukemia (AML) is a malignant clonal disease characterized by the proliferation and accumulation of myeloid precursor cells in the bone marrow, resulting in hematopoietic failure. It is the most common type of leukemia seen in adults [1, 2]. In the US, AML constitutes 1.1% of all newly diagnosed cancer cases [3].

Disease prognosis in hematological malignancies is shaped by the interaction of many positive or negative factors [4, 5]. Age has a very important place in prognosis, especially in AML, which is more common in older [6-8].

In addition to clinical, morphological and immunophenotyping evaluation, molecular cytogenetic methods are the main ones used in AML classification and predicting prognosis [2, 3]. The risk stratification of non-acute promyelocytic leukemia (non-APL) AML [3] consists of three separate layers, and this way, it predicts prognosis while guiding treatment: Favorable, intermediate, poor/adverse. In a retrospective review of adult patients with AML treated on Cancer and Leukemia Group B protocols, the 5-year survival rates for patients with favorable, intermediate, and poor-risk subgroups were 55%, 24%, and 5%, respectively [4]. The AML 11 trial had similar 5-year survival rates of the favorable, intermediate, and poor-risk subgroups of 34%, 13%, and 2%, respectively [5].

The main approach to treatment has not changed much over the years. An initial examination is important to reveal whether the patient is suitable for conventional chemotherapeutic agents [9]. At this stage, not only the age but also the comorbidities of the patient play a major role. Medically fit patients may benefit more from intensive therapies than non-intensive ones [9, 10]. Although intensive therapies such as “7+3” are essential for patients especially in the poor-risk subgroup, the risk-benefit assessment should be considered [10].

It has been shown in studies that low albumin and high ferritin levels have negative effects on survival cases with AML, which are examined in studies showing that they are good markers for

predicting survival. In these studies, the prognostic importance of the nutritional status of the patient at initial diagnosis is mentioned and it has been emphasized that hypoalbuminemia (serum albumin <3.5 g/dl) is an important prognostic factor that adversely affects survival in malignant myeloid diseases [11, 12].

Serum ferritin level is an examination used to detect iron accumulation especially in hematological malignancies receiving chemotherapy or where frequent blood transfusion is required. Lebon et al. reported for the first time that high serum ferritin levels are negative prognostic factors on OS and progression-free survival (PFS) in young patients with intermediate-risk karyotype [13].

In our study, the goal is to determine the place of these factors on survival by analyzing serum albumin and ferritin levels together in patients over 50 years of age with AML.

Material and methods

The study was planned as a single-center, retrospective, cross-sectional, case-control study. Eighty patients over the age of 50 who were followed up with the diagnosis of AML in Istanbul Training and Research Hospital, Department of Hematology between January 2014 and July 2019 were included in the study. The study was approved by Clinical Research Ethics Committee (Date: 20/03/2020 and Decision No: 2225).

Inclusion criteria

During the study, patient data were obtained by retrospective file review. Patients:

√ who were diagnosed with AML.

√ who had at least 1 value of serum albumin and ferritin at the time of diagnosis.

√ who were followed up and treated in our center were included in the study.

Exclusion criteria

Patients:

√ who had a chronic disease affecting serum levels of albumin and ferritin (liver cirrhosis, nephrotic syndrome, malnutrition, etc.).

√ who were diagnosed with AML-M3.

√ who had an initial iron therapy or acquired (hepatitis) or a genetic disease that can lead to iron accumulation (hemochromatosis etc.).

√ who need chronic blood transfusion due to any disease other than leukemia.

√ who received iron or albumin at the time of diagnosis or before diagnosis.

√ who had additional factors affecting serum albumin and ferritin levels, disease or drug use were excluded from the study.

Subgrouping of patients

Ferritin was measured by using immunoturbidimetry and albumin by colorimetric analysis. Cut-off values for albumin and ferritin were determined from reference studies of literature [11, 14, 15]. Considering the previous studies in this field, serum albumin and serum ferritin levels were divided into subgroups as good and poor risk factors:

-Serum albumin: ≥3.5 g/dl: good risk, <3.5 g/dl: poor risk factor.

-Serum ferritin: <500 ng/ml: good risk, ≥500 ng/ml: poor risk factor.

According to these risk factors, patients were categorised into three subgroups:

-Serum albumin and ferritin both as good risk factors (favorable risk group).

-One of serum albumin or ferritin as poor risk factors (intermediate-risk group).

-Serum albumin and ferritin both as poor risk factors (high-risk group).

The relationship of these 3 different risk groups with serum albumin and serum ferritin level subgroups and OS were evaluated statistically. In addition, the relationship of these risk groups with the favorable-intermediate-adverse cytogenetic risk groups according to the 2017 European LeukemiaNet (ELN) AML cytogenetic risk classification was statistically analyzed.

Table 1. Age and gender distribution of subgroups

		Favorable		Intermediate		High		p
Age		65,57±9,41		64,7±9,65		67,1±9,71		0.686*
Gender	Male	17	56,67%	12	40,00%	14	70,00%	0.105+
	Female	13	43,33%	18	60,00%	6	30,00%	

*One Way Variance Analysis, +Chi-square Test.

Table 2. Mean albumin, ferritin and follow up duration (months) of subgroups

	Favorable	Intermediate	High	p
Initial Albumin (g/dl)	4,05±0,36	3,55±0,42	2,89±0,32	0.0001*
Initial Ferritin (ng/ml)	267,9±143,03	641,27±350,31	1160,9±384,12	0.0001*
Follow Up (month)	41,64±46,48	17,29±25,27	24,02±31,89	0.033‡

*One Way Variance Analysis, ‡Kruskal Wallis Test.

Table 3. Multiple comparison analysis of subgroups

	Tukey		Dunn's
	Albumin	Ferritin	Follow Up
Favorable/Intermediate	0.0001	0.0001	0.029
Favorable/High	0.0001	0.0001	0.126
Intermediate/High	0.0001	0.0001	0.796

Statistical analysis

Statistical analysis in this study was performed using the Number Cruncher Statistical System (NCSS) 2007 Statistical Software (Utah, USA) package program. While evaluating the data, in addition to descriptive statistical methods (mean, standard deviation), one-way analysis of variance in the comparison of normally distributed variables between groups, Kruskal Wallis test for intergroup comparisons of variables not normally distributed, Tukey and Dunn's multiple comparison tests for subgroup comparisons, Chi-square for comparisons of qualitative data. Kaplan-Meier method for survival analysis and Log-Rank test for analysis of one-way variables were used. The results were evaluated at the significance level of $P<0.05$.

Results

Age and gender distribution of subgroups

The mean age of the patients was 65.6±9.49 (range: 50-87) years old; 43 of them were male (53.75%), 37 were female (46.25%). Favorable risk group consists of 30 people, intermediate-risk group consists of 30 people and the high-risk group consists of 20 people. There was no statistically significant difference observed between the age and gender distributions of the favorable, intermediate and high-risk groups (P=0.686 and P=0.105, respectively) (**Table 1**).

Mean albumin, ferritin and follow up duration (months) of subgroups

There were significant results obtained in the statistical analysis performed in terms of albumin and ferritin levels at the time of diagnosis and the duration of follow-up of the favorable risk, intermediate risk and high-risk groups (P=0.0001, P=0.0001, P=0.033, respectively). It was observed that there was a significant decrease in albumin levels and a statistically significant increase in ferritin levels (**Table 2**).

Multiple comparison analysis of subgroups

While the mean follow-up time of the favorable risk group was found to be statistically significantly higher than the intermediate-risk group (P=0.029), no statistically significant difference was observed between the mean of follow-up periods of the other risk groups (P>0.05) (**Table 3**).

Survival distribution in the 3rd and 6th month follow-up

When the survival differences of these 3 risk groups in the 3rd month and 6th month were examined; statistically significant differences were observed between the groups (P=0.022, P=0.007, respectively) (**Table 4**).

Table 4. Survival distribution in the 3rd and 6th month follow-up

		Favorable		Intermediate		High		p
3rd Month	Alive	24	80,00%	14	46,67%	14	70,00%	0.022+
	Exitus	6	20,00%	16	53,33%	6	30,00%	
6th Month	Alive	24	80,00%	12	40,00%	11	55,00%	0.007+
	Exitus	6	20,00%	18	60,00%	9	45,00%	

+Chi-square Test.

Table 5. Cytogenetic distribution of subgroups

		Favorable		Intermediate		High		p
Cytogenetic Risk Groups	Favorable	2	18,18%	2	18,18%	1	10,00%	0.842+
	Intermediate	8	72,73%	9	81,82%	8	80,00%	
	High	1	9,09%	0	0,00%	1	10,00%	

Patients whose cytogenetic analysis data were available were compared, +Chi-square Test.

Table 6. Survival analysis of subgroups

	Favorable	Intermediate	High
6th Month	0,958	0,947	0,923
1st Year	0,917	0,947	0,923
2nd Year	0,792	0,477	0,592
3rd Year	0,458	0,397	0,296
Median ± s.d. OS	166,87±15,08	47,05±12,42	78,14±16,63
%95 Confidence Interval	137,32-196,43	22,72-71,39	45,55-110,74

Log-Rank =9,03 P=0.011

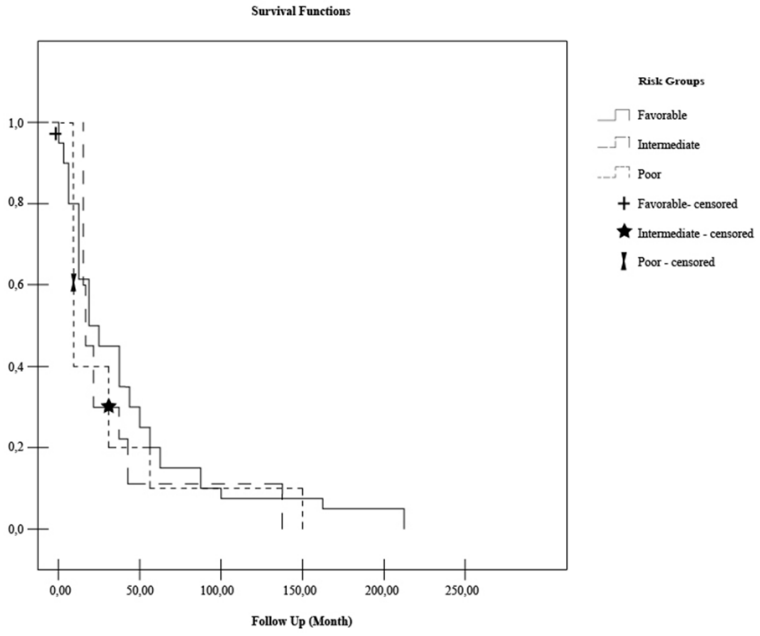

Figure 1. Overall survival curve of groups.

Cytogenetic distribution of subgroups

No statistically significant correlation or difference was observed between the favorable, intermediate and high risk and cytogenetic subgroups (P=0.842) (**Table 5**).

Survival analysis of subgroups

A statistically significant difference was observed between subgroups in survival analysis and the OS of the favorable risk group was found to be longer (Log-Rank: 9,03 P=0.011) (**Table 6**; **Figure 1**).

Discussion

AML is one of the hematological malignancies in which many risk factors play a role in prognosis. In these patients, treatment options are limited in the advanced age group. For this reason, many studies have been conducted in order to determine the factors predicting short- and long-term survival at the time of diagnosis in elderly patients. For this purpose, it seems to be a mean-

ingful, practical and important method to have an idea about the prognosis with the results of 2 easy-to-use tests such as serum albumin and ferritin levels during diagnosis, as in our study.

The severity of inflammation is one of the main factors determining the prognosis in malignancies. Specifically, in hematological malignancies, it is expected that there will be a decrease in serum albumin level and an increase in ferritin level as a result of increased cytokine-related catabolism and frequent infections. Low serum albumin has been defined as a negative prognostic factor in many hematological disorders such as leukemia, lymphoma, multiple myeloma and MDS [11].

In a study in which relapsed and refractory AML patients were evaluated in addition to newly diagnosed AML patients, it was shown that those with serum albumin <3.5 g/dl before salvage therapy were associated with low complete remission (CR) rate and shorter OS [16]. Similarly, in another study, serum albumin <3 g/dl was reported to be associated with a reduced rate of CR and lower 60-day survival [17]. A Chinese cohort, most recently published in 2020, shows that albumin can be used as a simple, inexpensive and objective prognostic factor in improving AML regimens [18]. In a study from 2021 [19], a lower baseline albumin was found to be independently associated with a higher number of grade ≥3 complications when adjusting for age, secondary AML, gender and intensive treatment. 30 day and 60-day mortality rates were significantly higher in the hypoalbuminemia group (24.0%) (Hypoalbuminemia <2.5 g/dl) and marked hypoalbuminemia group (45%) (Hypoalbuminemia 2.5-3.4 g/dl) compared with normal albumin group. Patients with lower baseline albumin levels had increased treatment-related morbidity and mortality. In our study, as mentioned in the results, in newly diagnosed AML patients with the age of 50 years and above, hypoalbuminemia at initial diagnosis (serum albumin <3.5 g/dl) was considered as a poor risk factor at 3rd and 6th months. It was determined that there was a statistically significant factor affecting survival negatively in follow-up period (P=0.022, P=0.007, P=0.011, respectively).

Although iron is indispensable for life, the excess level of it may damage tissues and cause oxidative damage and organ dysfunction [20, 21]. It has been stated that the increased serum ferritin level in AML patients is a parameter with an independent negative prognostic significance, which causes chemoresistance through most of the inflammation and has a negative effect on mortality [22, 23]. In our study, patients were divided into 3 subgroups (favorable, intermediate, high-risk group) according to the threshold values of serum albumin (<3.5 and ≥3.5) and ferritin (<500 and 500) at initial diagnosis. When the survival analyses were compared, it was found that the life expectancy of the favorable risk group was longer than the others and the life expectancy of the high-risk group was shorter than the others (P=0.011). In the light of all this data, it seems necessary to develop a new clinical scoring system that includes basal albumin-ferritin levels in AML. It is also possible to increase its effectiveness by combining it with cytogenetic classification.

In a multicenter retrospective analysis, it was stated that high ferritin level in AML patients is an indirect marker of tumor burden and may be a prognostic marker that provides a prediction of worse event-free survival in the high-risk group [24]. Specifically, in patients with AML whose ferritin level is ≥5000 ng/ml, this value has been reported to be significant for an increased risk of death [25]. In addition, there are studies showing that low albumin adversely affects overall survival in patients with AML and MDS who underwent bone marrow transplantation [26]. In our study, patients with ferritin levels ≥500 ng/ml were considered to have a negative risk factor. Patients with lower serum ferritin levels were compared in terms of survival, it was observed that survival was significantly lower in the group with high ferritin levels (3rd month P=0.022, 6 months P=0.007, OS P=0.011). Initial ferritin levels and the need for chelation therapy should be checked before starting induction therapy, especially in patients with a delayed diagnosis or a history of frequent transfusion. In another study on patients with MDS [27], a significant relationship was shown between iron overload and survival; elevated intracellular iron was found to be associated with acceleration of the abnormal proliferation of blasts. In another study from our clinic [28], iron overload was evaluated retrospectively and there were statistically more patients with serum ferritin >1000 in the AML

group compared to the ALL group at 6 months after beginning of induction therapy (P=0.011). When evaluated together with this study, both initial and pretransplant ferritin levels should be well considered, especially in patients with AML.

In some of the studies, the relationship of these biological markers with genetic risk factors has been partially shown [29]. In our study, it was found that there was no statistically significant relationship between the presence of both risk factors and cytogenetic risk categories of our patients.

Our study also had limitations. The most important limitation point is a smaller patient group compared to other studies. It may be thought that when divided into subgroups, it makes statistical analysis even more difficult. It is thought that parallel results will be obtained with cytogenetic risk factors when evaluated with a larger patient group.

Conclusion

In this study, it has been shown that serum albumin and ferritin values are useful, simple, and accessible laboratory values to show prognosis in AML patients over 50 years of age and their use together can be a prognostic marker in predicting survival and predicting clinical course. From this point of view, we believe that our study will inspire new prospective studies to be carried out on many cases in the field.

Acknowledgements

We respectfully remember all the colleagues we lost in the COVID-19 fight.

Ethical committee approval was received (20/03/2020 and Decision No: 2225) and the patients and control subjects gave informed consent before the beginning of the study. The experimental procedures were based on the Declaration of Helsinki and relevant institutional regulations.

Disclosure of conflict of interest

None.

Abbreviations

AML, Acute myeloid leukemia; Ph, Philadelphia; OS, Overall Survival; PFS, Progression free survival; NPM1, Nucleophosmin-1; CEBPA, CCAAT/enhancer binding protein alpha; MDS, Myelodysplastic syndrome; CR, Complete remission.

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