ORIGINAL ARTICLE

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Can Serum Albumin Level At Diagnosis Be A Guide for Clinical Features, Time to Treatment, and Response in Patients with Follicular Lymphoma?

Foliküler Lenfoma Hastalarında Tanı Anı Serum Albumin Düzeyi Klinik Özellikler, Tedaviye Kadar Geçen Süre ve Yanıt Hakkında Yol Gösterici Olabilir Mi?

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ABSTRACT

Aim: The aim of the present study was to determine the association between serum albumin level and treatment demand, time to treatment and treatment response in patients with follicular lymphoma (FL).

Materials and Methods: We retrospectively evaluated the data of 25 FL patients. The data comprised gender, age, lactate dehydrogenase (LDH) level, number of nodal sites, presence of extranodal involvement, B symptoms and bulky mass, presence of bone marrow, liver and spleen involvement, Follicular Lymphoma International Prognostic Index score, Eastern Cooperative Oncology Group (ECOG) performance score, tumor grade, albumin level, globulin level, white blood cell count, platelet count and hemoglobin level at diagnosis; treatment demand, time to treatment, and response to treatment.

Results: The median age of the patients was 53 years. The patients were divided into 2 groups according to the median albumin level as >4.4 gr/dL and <4.4 gr/dL. While 13 (52%) patients had an albumin level of ≤4.4 gr/dL, 12 (48%) patients had an albumin level of >4.4 gr/dL. Two groups were comparable in terms of treatment demand, time to treatment and treatment response in patients who were applied treatment (p>0.05). No correlation was found between the level of serum albumin and the need for treatment in patients with FL.

Conclusion: FL, constituting approximately 20% of all non-hodgkin lymphomas, is the second most common lymphoma in adults. The age, LDH and hemoglobin levels, ECOG performance score, stage, extranodal, involvement, number of nodal sites involved, β2 microglobulin level, bone marrow involvement, presence of B symptoms and bulky mass are the conventional risk factors used to determine prognosis in FL. Although we found that treatment requirement was higher and time to treatment was shorter in patients with low serum albumin levels, they did not reach a statistical significance.

Keywords: Follicular lymphoma, albumin, treatment demand

ÖZ

Amaç: Bu çalışmanın amacı foliküler lenfoma (FL) tanılı hastalarda serum albumin düzeyi ile tedavi ihtiyacı, tedaviye kadar geçen süre ve tedaviye yanıt arasındaki ilişkiyi belirlemektir.

Gereç ve Yöntem: Mart 2011 ile Mayıs 2017 tarihleri arasında Sağlık Bilimleri Üniversitesi İstanbul Eğitim ve Araştırma Hastanesi Hematoloji Bölümünde FL tanısıyla takip edilen 25 FL hastasının verileri retrospektif olarak değerlendirildi. Histopatolojik olarak doğrulanmış FL hastalarının verileri hematoloji bölümünün tıbbi kayıtlarından incelendi. Veriler cinsiyet, yaş, laktat dehidrogenaz (LDH) düzeyi, nodal bölge sayısı, ekstranodal tutulum varlığı, B semptomları ve büyük kitle, kemik iliği, karaciğer ve dalak tutulumu varlığı, Foliküler Lenfoma Uluslararası Prognostik İndeksi

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skoru, Doğu Kooperatif Onkoloji Grubu (ECOG) performans skoru, tümör derecesi, albumin düzeyi, globulin düzeyi, lökosit sayısı, beyaz kan hücresi, trombosit sayısı ve tanı anındaki hemoglobin düzeyini; tedavi gereksinimini, tedaviye kadar geçen süreyi ve tedaviye yanıtı içeriyordu.

Bulgular: Hastaların ortanca yaşı 53 (aralık 33-76) idi. 10 (%40) hasta kadın, 15 (%60) hasta erkekti. Hastalar albumin düzeyine göre >4,4 gr/dL ve <4,4 gr/dL olmak üzere 2 gruba ayrıldı. 13 (%52) hastanın albumin düzeyi ≤4,4 gr/dL iken, 12 (%48) hastanın albumin düzeyi >4,4 gr/dL idi. Tedavi uygulanan hastalarda tedavi gereksinimi, tedaviye kadar geçen süre ve tedaviye yanıt açısından iki grup benzerdi (p>0,05). FL'li hastalarda serum albumin düzeyi ile tedavi gereksinimi arasında bir korelasyon bulunmadı.

Sonuç: Tüm hodgkin dışı lenfomaların yaklaşık %20'sini oluşturan FL, yetişkinlerde en sık görülen ikinci lenfomadır. Yaş, LDH ve hemoglobin düzeyleri, ECOG performans skoru, evre, ekstranodal tutulum, tutulan nodal alan sayısı, β2 mikroglobulin düzeyi, kemik iliği tutulumu, B semptomlarının varlığı ve büyük kitle FL'de prognozu belirlemek için kullanılan risk faktörleridir. Serum albumin düzeyleri düşük olan hastalarda tedavi gereksiniminin daha yüksek ve tedaviye kadar geçen sürenin daha kısa olduğunu saptamamıza rağmen, bulgular istatistiksel olarak anlamlı değildi.

Anahtar Kelimeler: Foliküler lenfoma, albumin, tedavi gereksinimi

INTRODUCTION

Follicular lymphoma (FL) is an indolent type of lymphoma that develops from germinal center B cells. As the second most prevalent lymphoma in adults within Western nations, FL accounts for roughly 20% of all non-hodgkin lymphomas (NHL)[1,2]. Typically occurring around the age of 60 years, FL predominantly affects females. The most common initial presentation involves painless enlargement of peripheral lymph nodes at one or multiple sites. Furthermore, the bone marrow and spleen are commonly affected[2]. In the management of FL patients, determining the stage and assessing risk are crucial factors. Prognostic indicators commonly used for FL include the patient's age, levels of lactate dehydrogenase (LDH) and hemoglobin, Eastern Cooperative Oncology Group (ECOG) performance status, disease stage, involvement of extranodal sites, number of affected nodal areas, β2 microglobulin concentration, bone marrow infiltration, presence of B symptoms, and the existence of a bulky mass[1,3]. Researchers have examined the predictive value of serum albumin, a protein that decreases during inflammatory responses, in various solid tumor cancers. Studies have consistently demonstrated that higher albumin levels correlate with improved survival outcomes in these malignancies[4]. In the field of hematological malignancies, serum albumin levels have long been utilized as part of the International Staging System to assess prognosis in patients with multiple myeloma[5]. Furthermore, research has demonstrated that serum albumin levels serve as a prognostic indicator in various NHL, including diffuse large B cell lymphoma (DLBCL), localized aggressive NHL, and low-grade lymphomas[6,7,8]. This prognostic value extends to myelodysplastic syndrome as well[9]. In this study, we aimed to determine the association between serum albumin level and treatment demand, time to treatment and treatment response in patients with FL.

MATERIALS AND METHODS

We retrospectively evaluated the data of 25 FL patients, who were followed with the diagnosis of FL at University of Health Sciences, İstanbul Training and Research Hospital, Department of Hematology, between March 2011 and May 2017. The data of histopathologically verified FL patients were reviewed from the medical records of hematology department. The data comprised gender, age, LDH level, number of nodal sites, presence of extranodal involvement, B symptoms and bulky mass, presence of bone marrow, liver and spleen involvement, Follicular Lymphoma International Prognostic Index (FLIPI) score, ECOG score, tumor grade, albumin level, globulin level, white blood cell count (WBC), platelet count and hemoglobin level at diagnosis; treatment demand, time to treatment, and response to treatment. The patients were staged according to the Ann Arbor classification[10]. Staging procedure included physical examination, search for B symptoms, computed tomography (CT) scans or positron emission tomography-CT scans. The approval was obtained from the İstanbul Training and Research Hospital Ethics Committee of University of Health Sciences (decision no: 1085, date: 22.09.2017).

Statistical Analysis

Statistical evaluation was made by SPSS 24 program. Data were described as numbers and percentage or median and range, when appropriate. The x^2 Fisher's exact test was used for evaluating categorical values and the Mann-Whitney U test for continuous values in patient groups. All p values were 2-sided with statistical significance at 0.05 alpha levels.

RESULTS

The characteristics of 25 patients are summarized in Table 1. The median age of the patients was 53 years (range, 33-76). Ten (40%) patients were female and 15 (60%) were male. Four (16%) patients had hemoglobin level of <12 gr/dL and 21 (84%) patients had hemoglobin level of >12 gr/dL at the time of diagnosis. The median WBC was 8620/mm^3 (3930-16000/mm^3), platelet count was 246000/mm^3 (range, 32000-476000/mm^3), LDH was 198 IU/mL (range, 150-709), albumin was 4.4 gr/dL (range, 3.41-4.8) at the time of diagnosis. The number of nodal regions involved was median 5 (range, 1-9). Two (8%) patients had FLIPI score >4 and 23 (92%) patients had ≤4. Five (20%) patients were at stage I-II and 19 (76%) patients

Table 1. Patients' characteristics

Characteristic	n=25
Gender, n, (%)	
Female	10 (40%)
Male	15 (60 %)
Age, years, median (range)	53 (33-76)
Hemoglobin level, g/dL, n (%)	
<12	4 (16%)
>12	21 (84%)
WBC, $10^3/mm^3$, median (range)	8620 (3930-16000)
Platelet, $10^3/mm^3$, median (range)	246000 (32000-476000)
LDH level, U/dL, median (range)	198 (150-709)
Serum albumin level, g/dL, median (range)	4.4 (3.41- 4.8)
The number of nodal sites involved, median, (range)	5 (1-9)
FLIPI score, n (%)	
<=4	23 (92%)
>4	2 (8%)
Stage, n (%)	
Stage I-II	5 (20%)
Stage III-IV	19 (76%)
Unknown	1 (4%)
B symptom, n (%)	
Present	4 (16%)
Absent	11 (44%)
Unknown	10 (40%)
Bone marrow involvement, n (%)	
Present	11 (44%)
Absent	12 (48%)
Unknown	2 (8%)
Liver involvement, n (%)	
Present	0 (0%)
Absent	22 (88%)
Unknown	3 (12%)
Splenomegaly, n (%)	
Present	12 (48%)
Absent	13 (52%)
Unknown	
Bulky mass, n (%)	
Present	5 (20%)
Absent	19 (76%)
Unknown	1 (4%)
ECOG	0
Tumor grade, n (%)	
Grade 1-2	15 (60%)
Grade 3	10 (40%)
Time to treatment, months, median, (range)	2 (0-37)
Treatment demand, n, (%)	
Present	17 (68%)
Absent	8 (32%)
Response to treatment, n (%)	
Present	13 (76%)
Absent	2 (12%)
Unknown	2 (12%)

ECOG: Eastern Cooperative Oncology Group, FLIPI: Follicular Lymphoma International Prognostic Index, LDH: Lactate dehydrogenase, WBC: White blood cell count

at stage III-IV. Four (16%) patients had B symptoms, 11 (44%) patients had bone marrow involvement, 12 (48%) patients had splenomegaly and 5 (20%) patients had bulky mass. ECOG score of all patients included in the study was 0. Fifteen (60%) patients had histological grade 1 disease and 10 (40%) had grade 2. There were 17 (68%) patients who had treatment demand and 13 (76%) of them responded. The median duration between diagnosis and treatment was 2 (range: 0-37) months in patients requiring treatment.

The patients were divided into 2 groups according to the median albumin level as >4.4 gr/dL and <4.4 gr/dL. While 13 (52%) patients had an albumin level of ≤4.4 gr/dL, 12 (48%) patients had an albumin level of >4.4 gr/dL. Two groups were comparable in term of gender, age, hemoglobin level, WBC, platelet count, LDH level, FLIPI score stage, presence of B symptoms, bone marrow involvement, liver involvement and splenomegaly, and tumor grade at the time of diagnosis, treatment demand, time to treatment and treatment response in patients who were applied treatment (p>0.05) (Table 2). Bulky mass was present in 5 (42%) patients with albumin level <4.4 gr/dL and none of the patients had bulky mass with albumin >4.4 gr/dL (p=0.029) (Table 2).

DISCUSSION

At the time of diagnosis, most of FL patients do not exhibit noticeable symptoms related to the disease. For approximately 10-15% of FL patients diagnosed in early stages (I-II), there is a possibility of achieving a cure through radiotherapy treatment. For certain patients with early-stage disease, adopting a watch and wait strategy is considered an appropriate management approach[1,2,11,12]. For patients with advanced (stage III-IV) FL, different approaches are recommended based on their symptoms and tumor burden. Asymptomatic patients are advised to follow a watch and wait strategy. In cases where patients experience mild symptoms, rituximab monotherapy is the preferred treatment. However, for those with high tumor burden, combination therapy including rituximab is suggested[1,12,13]. The initiation of treatment for FL patients

Table 2. Comparison of patients with serum albumin ≤4.4 g/dL and serum albumin level >4.4 g/dL

Characteristic	Albumin ≤ 4.4 g/dL (n=13)	Albumin > 4.4 g/dL (n=12)	p value
Gender, n, (%)			
Female	6 (46%)	4 (33%)	0.688
Male	7 (54%)	8 (67%)	
Age, years, median (range)	56 (42-76)	46 (33-60)	0.238
Hemoglobin level, g/dL, n (%)			
<12	2 (17%)	2 (16%)	0.67
>12	10 (83%)	11 (84%)	
WBC, $10^3/mm^3$, median (range)	8370 (3930-15110)	8840 (4860-16000)	1
Platelet, $10^3/mm^3$, median (range)	235000 (32000-461000)	267000 (141000-476000)	0.434
LDH level, U/dL, median (range)	202 (150-289)	189 (152-709)	0.695
FLIPI score, n (%)			
<=4	12 (92%)	11 (92%)	1
>4	1 (8%)	1 (8%)	
Stage, n (%)			
Stage I-II	2 (15%)	3 (27%)	0.630
Stage III-IV	11 (85%)	8 (73%)	
B symptom, n (%)			
Present	3 (43%)	1 (12%)	0.282
Absent	4 (57%)	7 (88%)	
Bone marrow involvement, n (%)			
Present	6 (46%)	5 (50%)	1
Absent	7 (54%)	5 (50%)	
Liver involvement, n (%)			
Present	0	0	NA
Absent	11	11	
Splenomegaly, n (%)			
Present	6 (46%)	6 (50%)	1
Absent	7 (54%)	6 (50%)	
Unknown			
Bulky mass, n (%)			
Present	5 (42%)	0	0.029
Absent	7 (58%)	12 (100%)	
ECOG	0	0	NA
Tumor grade, n (%)			
Grade 1-2	8 (62%)	7 (58%)	1
Grade 3	5 (38%)	5 (42%)	
Time to treatment, months, median, (range)	2 (0-8)	5 (0-37)	0.101
Treatment demand, n, (%)			
Present	10 (77%)	7 (58%)	0.411
Absent	3 (23%)	5 (41%)	
Response to treatment, n (%)			
Present	8 (89%)	5 (83%)	1
Absent	1 (11%)	1 (17%)	

ECOG: Eastern Cooperative Oncology Group, FLIPI: Follicular Lymphoma International Prognostic Index, LDH: Lactate dehydrogenase, NA: Not applicable, WBC: White blood cell count

typically relies on the Groupe d'Etude des Lymphomes Folliculaires criteria. These guidelines consider several factors, including the presence of more than three nodal sites (each exceeding 3 cm in diameter), any nodal or extranodal tumor mass measuring 7 cm or larger, B symptoms, potential for local compressive symptoms that could compromise organ function, cytopenias (defined as leukocytes below 1.0 × 109/l and/or platelets under 100 × 109/l), leukemia (characterized by over 5.0 × 109/l malignant cells), enlarged spleen (exceeding 16 cm on CT scan), and the occurrence of pleural effusion or peritoneal ascites[1,13].

Despite those well-defined criteria, heterogeneous clinical course of the disease sometimes gives rise to uncertainty in terms of the initiation of treatment. Hence, any marker appraising about the treatment requirement might be beneficial in complex cases. In this instance albumin, being a readily available biochemical parameter, might be useful in treatment approach of FL patients. We aimed to evaluate the relationship of serum albumin levels with treatment demand, time to treatment and treatment response in FL patients. Although we found that treatment requirement was higher and time to treatment was shorter in patients with low serum albumin levels, they did not reach a statistical significance.

Previous studies have examined the significance of serum albumin levels in various blood cancers[6-9]. Research conducted by Bairey et al.[6] revealed that patients with DLBCL who had low albumin levels prior to treatment experienced poorer overall survival (OS) outcomes. In contrast to our research, the study mentioned used a threshold of 3.5 g/dL for albumin levels. In a related finding, Alici et al.[7] conducted research to identify prognostic factors specifically predicting survival in patients with localized aggressive NHL. Their results indicated that reduced serum albumin levels were associated with decreased survival rates. In addition to studying high-grade lymphomas, Bremnes et al.[8] examined the treatment outcomes and prognostic indicators in patients with low-grade NHL. Their research revealed that, unlike other types, FL patients with low pretreatment albumin levels were found to have reduced survival rates. Research on the predictive value of serum albumin levels extends beyond lymphoma patients to include myelodysplastic syndrome. A study by Sevindik et al.[9] demonstrated that serum albumin concentration serves as an autonomous indicator for both leukemia-free survival and OS. Unlike previous research, the slow-progressing nature of FL and the brief follow-up period prevented us from evaluating the connection between serum albumin levels and survival rates in FL patients. Nevertheless, this research is pioneering in its investigation of how serum albumin levels relate to treatment needs, the time before treatment initiation, and treatment efficacy in FL cases. The study's retrospective design and limited patient sample size may have hindered the ability to accurately determine the specific impact of serum albumin levels in FL.

Study Limitations

This study had some limitations that may have affected the results. Firstly, it included single center data and low number of patients. Additionally, since the data were collected retrospectively, not all data on FL may have been recorded.

CONCLUSION

We did not demonstrate an association between serum albumin level and treatment demand in FL patients. However, the precise contribution of serum albumin level to treatment decision has to be cleared with large number of FL patients before completely denial of its role.

Ethics

Ethics Committee Approval: The approval was obtained from the İstanbul Training and Research Hospital Ethics Committee of University of Health Sciences (decision no: 1085, date: 22.09.2017).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.K., C.A., E.S., Concept: A.K., B.G., E.S., Design: A.K., R.E., Data Collection or Processing: B.G., E.S., Analysis or Interpretation: R.E., C.A., Literature Search: R.E., C.A., Writing: C.A.

Conflict of Interest: One author of this article, (Abdulkadir KARIŞMAZ) is a member of the Editorial Board of the Namık Kemal Medical Journal. However, she did not take part in any stage of the editorial decision of the manuscript. The editors who evaluated this manuscript are from different institutions. The other authors declared no conflict of interest..

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REFERENCES

1. Dreyling M, Ghielmini M, Rule S, Salles G, Ladetto M, Tonino SH, et al. Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2021;32:298-308.
2. Gribben J.B., R.Hoffman, E.J.Benz Jr., et al. Clinical manifestations, staging and treatment of follicular lymphoma Hematology: Basic principles and practice. 6th Edition. Philadelphia, Elsevier, Saunders, 2012: 1215-1225.
3. Casulo C. Prognostic factors in follicular lymphoma: new tools to personalize risk. Hematology Am Soc Hematol Educ Program. 2016;2016:269-76.
4. Gupta D, Lis CG. Pretreatment serum albumin as a predictor of cancer survival: a systematic review of the epidemiological literature. Nutr J. 2010;9:69.

5. Greipp PR, San Miguel J, Durie BG, Crowley JJ, Barlogie B, Bladé J, et al. International staging system for multiple myeloma. J Clin Oncol. 2005;23:3412-20.

6. Bairey O, Shacham-Abulafia A, Shpilberg O, Gurion R. Serum albumin level at diagnosis of diffuse large B-cell lymphoma: an important simple prognostic factor. Hematol Oncol. 2016;34:184-92.

7. Alici S, Bavbek SE, Kaytan E, Eralp Y, Onat H. Prognostic factors in localized aggressive non-Hodgkin's lymphoma. Am J Clin Oncol. 2003;26:1-5.

8. Bremnes RM, Vik A, Helbekkmo N. Low-grade non-Hodgkin's lymphoma in northern Norway: treatment, outcome, and prognostic factors. Anticancer Res. 1998;18:1921-9.

9. Sevindik OG, Guc Z, Kahraman S, Medeni Solmaz S, Katgi A, Acar C, et al. Hypoalbuminemia is a surrogate biomarker of poor prognosis in myelodysplastic syndrome even when adjusting for comorbidities. Leuk Lymphoma. 2015;56:2552-5.

10. Lister TA, Crowther D, Sutcliffe SB, Glatstein E, Canellos GP, Young RC, et al. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. J Clin Oncol. 1989;7:1630-6.

11. Fowler N. Frontline strategy for follicular lymphoma: are we ready to abandon chemotherapy? Hematology Am Soc Hematol Educ Program. 2016;2016:277-83.

12. Kahl BS, Yang DT. Follicular lymphoma: evolving therapeutic strategies. Blood. 2016;127:2055-63.

13. Chen Q, Ayer T, Nastoupil LJ, Seward M, Zhang H, Sinha R, et al. Initial management strategies for follicular lymphoma. Int J Hematol Oncol. 2012;1:35-45.