Original Article

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Effect of Sarcopenia on Clinical Outcomes of Patients with Hairy Cell Leukemia

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Abstract

Aim: Sarcopenia may develop in patients with hairy cell leukemia (HCL). There is no study in the literature showing the prognostic importance of sarcopenia in patients with HCL. In this study, the effect of pretreatment sarcopenia on clinical outcomes in patients with HCL was investigated.

Methods: This study included 34 patients with pre-treatment abdominal computed tomography (CT) images who received cladribine (purine nucleoside analog) treatment between April 2006 and April 2022 at Ondokuz Mayıs University Hospital. To ensure measurement standardization, measurements were performed using abdominal CT sections showing the L3 vertebra. The optimal cut-off value for the skeletal mass index to be used for the prediction of sarcopenia was determined by receiver operating characteristic analysis. Patients were divided into two groups according to whether they were sarcopenic or not, and their clinical results were compared.

Results: Overall survival (OS) tended to be shorter in the sarcopenic group than in the non-sarcopenic group (p=0.046). Progression-free survival was significantly better in the non-sarcopenic group than in the sarcopenic group (p=0.009). In the multivariate analysis, sarcopenia (hazard ratio=0.154, p=0.043) was an effective variable for OS.

Conclusion: Sarcopenia is a prognostic factor for prognosis and treatment parameters in patients with HCL.

Keywords: Hairy cell leukemia, computed tomography, skeletal mass index, sarcopenia, prognostic factor

Introduction

Hairy cell (HC) leukemia (HCL) is a rare, mature B cell-derived chronic leukemia characterized by splenomegaly, pancytopenia, and peripheral HC (1-3). The annual incidence is 0.3 cases per 100,000 (4). The frequency is 4-5 times higher in men than in women. It is commonly observed between 55 and 60 years of age (5). Treatment for HCL initially uses purine analogs (cladribine or pentostatin). The full response rate during the first 5 years is 85-90% (6). At the 5-year follow-up, relapse was observed in 58% of patients who responded to treatment (7).

Sarcopenia is a progressive, generalized syndrome characterized by the loss of skeletal muscle mass and strength (8). The metabolic activity and systemic inflammation of cancer cells cause muscle loss, and sarcopenia develops (9). Computed tomography (CT) is a potential imaging biomarker for predicting survival outcomes in clinical practice because of its ability to provide objective quantitative and qualitative measurements of skeletal muscle and fat tissue. A meta-analysis showed the prognostic importance of sarcopenia in patients with hematological malignancies (10). Recent studies have demonstrated that early diagnosis of sarcopenia in patients with hematological malignancies can reverse the process of muscle loss and prevent the negative effects of sarcopenia syndrome on patient progression (11).

There is no study in the literature showing the prognostic importance of sarcopenia in patients with HCL. In this study, the effect of pretreatment sarcopenia on clinical outcomes in HCL patients receiving cladribine was investigated.

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Methods

Study Design and Compliance with Ethical Standards

This retrospective study included 50 patients aged >18 years attending Ondokuz Mayıs University Faculty of Medicine, Clinic of Hematology from April 2006 to April 2022 with HCL diagnosis. The study included 34 patients with pre-treatment abdominal CT images who received cladribine (purine nucleoside analog) treatment. Five patients receiving other treatments and 11 patients without pre-treatment abdominal CT imaging were excluded from the study (Figure 1). The retrospective study was approved by the Ondokuz Mayıs University Clinical Research Ethics Committee (approval no.: OMÜ KAEK 2022/576, date: December 28, 2022).

All demographic data were obtained from patient files and electronic medical records. Body mass index (BMI) was calculated using the formula kg/m^2 by measuring pre-treatment weight and height.

Patients received a 24-hour continuous cladribine infusion (0.1 mg/kg) for 7 days. Response to treatment was assessed using bone marrow biopsy and regression of splenomegaly based on physical examination in the third month. In peripheral blood (without transfusion), hemoglobin 11 g/dL, platelets 100,000/mL, and absolute neutrophil count 1500/mL, regression of splenomegaly according to physical examination, lack of HC with peripheral distribution, and in bone marrow were assessed as full response. Peripheral blood samples close to normalizing, close to 50% resolution of splenomegaly, and bone marrow HC were accepted as partial responses. Observation of HCs during follow-up of blood and bone marrow samples from patients with full or partial response was defined as morphologic relapse. Hematologic relapse was defined as the reappearance of cytopenia below the thresholds defined above for complete response (CR) and partial response (PR). Overall survival (OS) was defined as the duration from diagnosis until death. Progression-free survival (PFS) was defined as the duration from treatment until patient recurrence.

With the aim of pretreatment assessment by a radiology expert experienced in the field, patients in the study group were assessed for muscle and fat tissue quality using abdominal CT images. To ensure measurement standardization, measurements were performed using the ImageJ program (National Institutes of Health, Bethesda, Maryland, USA) on abdominal CT sections showing the L3 vertebra. Within this scope, the areas of total paravertebral muscle tissue, visceral adipose tissue (VAT), and subcutaneous adipose tissue (SAT) were separately calculated in mm^2. To normalize differences in body structure, values were divided by the square of the patient's height; thus, the skeletal mass index (SMI) was calculated as mm^2/m^2. Examples of CT assessments are shown in Figure 2. Patients were divided into two groups according to whether they were sarcopenic or not, and their clinical results were compared.

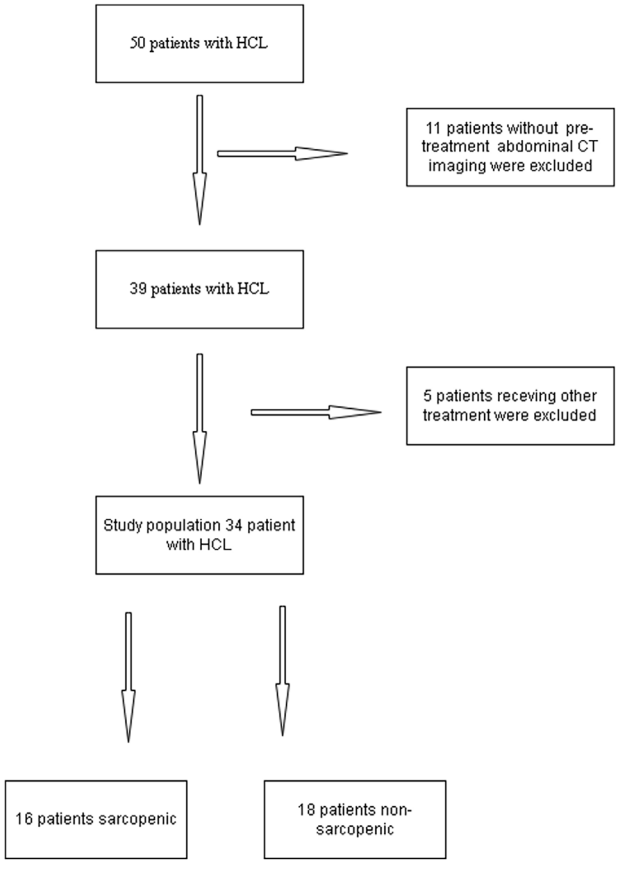

Figure 1. Study design and patient flowchart
HCL: Hairy cell leukemia, CT: Computed tomography

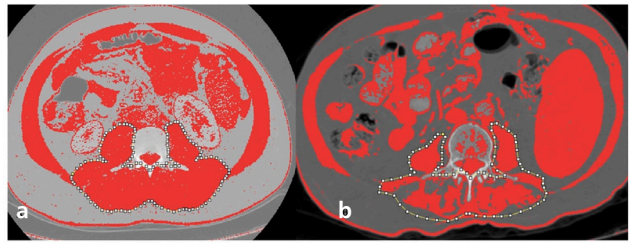

Figure 2. Sarcopenia assessment the areas of total paravertebral muscle at the mid-level of the third lumbar vertebrate by CT scan. (A) Example of a non-sarcopenic man with normal muscle mass, (B) Example of a sarcopenic man with reduced muscle mass
CT: Computed tomography

Statistical Analysis

Statistical analysis were performed using IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, NY). The assumption of normality was checked using the Shapiro-Wilk test. Descriptive analyses are presented as mean ± standard deviation [interquartile range (IQR)], median (IQR), or n (%), as appropriate. To determine the prognosis of HCL, categorical data were analyzed using the Pearson's chi-square test, and numerical data with non-normal and normal distribution were analyzed using the Mann-Whitney U test or Student's t-test, respectively. Receiver operating characteristic analysis was performed to determine the optimal cut-off point for SMI. The optimal cutoff value for SMI for predicting sarcopenia was determined by receiver operating characteristic analysis. Patients with SMI 3028.3 (mm^2/m^2) were assessed as being sarcopenic. Survival curves were created using the Kaplan-Meier method, and the Breslow, Tarone-Ware, and log-rank tests were used to assess differences between groups. Univariate logistic regression analysis was used to identify independent risk factors related to treatment response. Univariate and multivariate analyses for independent predictors of OS and PFS were performed using the Cox proportional risk regression model. Univariate analyses ($p<0.1$) included age, spleen size, response to treatment (RTT), SAT, total mass index (TMI), SMI, and sarcopenia, which were also tested in multivariate models. Hazard ratios equivalent to 95% confidence intervals or odds ratios are reported. Variables with p-values <0.05 were considered significant.

Results

Of the patients who participated in the study, 31 were men (91.2%) and 3 were women (8.8%). Among the patients, 16 (47%) were sarcopenic. Table 1 summarizes the characteristics of patients with and without sarcopenia. The sarcopenic group had significantly lower hemoglobin values than the non-sarcopenic group (9.15 vs. 11.26; p=0.030). The non-sarcopenic patients had lower TMI than the sarcopenic patients (4662.78 vs. 6180.67; p<0.01).

Table 1. The characteristics of patients according to the presence of sarcopenia

Variables	Overall (n=34)	S^+ (Sarcopenic) (nS^+=16)	S^- (Non-sarcopenic) (nS^-=18)	p-value
Age	53.38±12.59	56.75±14.48	50.38±10.13	0.144
Sex				
Female (%) Men (%)	3 (8.8) 31 (91.2)	3 (18.8) 13 (1.2)	0 (0) 18 (100)	0.094
Spleen size (mm)	183.61±44.21	181.5±51.17	185.5±38.43	0.797
Hemoglobin (gr/dL) WBC (mm^3) PLT (h/mL)	10.26±2.92 2940 (2137.5) 56.5 (43.25)	9.15±2.06 2695 (2182.5) 63 (78.75)	11.26±3.27 3285 (4392.5) 54.5 (25.25)	**0.030*** 0.164 0.932
BSA (m^2)	1.86±0.15	1.83±0.16	1,88±0,14	0.294
BMI (kg/m^2) TMI (mm^2/m^2) SMI (mm^2/m^2)	26.5 (3.77) 5466.37±1004.08 3002.73±541.84	24.47 (5.66) 4662.78±694.60 2540.66±328.40	27.24 (3.14) 6180.67±619.13 3413.46±308.53	**0.025*** **0.001*** **0.0001***
VAT	15153.52±7779.98	14171.68±8743.28	16026.27±6952.00	0.496
SAT	14903 (11026.5)	15250.5 (15073.7)	14704.5 (10162.7)	0.695
PFS	35.5 (50.75)	23.5 (32.25)	59 (44)	**0.009***
OS	46.5 (48.5)	26.5 (67)	63 (37)	**0.046***
RTT				
Yes (CR or PR) % No	31 (91.2) 3 (8.8)	13 (81.3) 3 (18.7)	18 (100) 0 (0)	0.094
Relapse				
Yes % No %	11 (2.4) 23 (67.6)	5 (31.3) 11 (68.7)	6 (33.3) 12 (66.7)	0.594
Survival				
Alive % Exitus %	29 (85.3) 5 (14.7)	12 (75) 4 (25)	17 (94.4) 1 (5.6)	0.133

Student's t test, Mann-Whitney U test, Pearson chi-square test. Data are presented with n (%), mean ± SD (IQR) or median (IQR)
*Bold values denote statistical significance at the p<0.05 level
S^+: Sarcopenic, S^-: Non-sarcopenic, WBC: White blood cell, PLT: Platelet, BMI: Body mass index, TMI: Total mass index, BSA: Body surface area, VAT: Visceral adipose tissue, SMI: Skeletal mass index, SAT: Subcutaneous adipose tissue, OS: Overall survival, PFS: Progression-free survival, RTT: Response to treatment, IQR: Interquartile range, SD: Standard deviation, CR: Complete response, PR: Partial response

Table 2 presents the results of a univariate logistic regression analysis to identify variables affecting treatment response in HCL patients and a Cox regression survival analysis to identify factors affecting PFS and OS. In the multivariate analysis, spleen size (HR=1.014, p=0.0041), RTT (HR=0.027, p=0.004), and sarcopenia (HR=0.154, p=0.043) were effective variables for OS. For PFS, spleen size (HR=1.012, p=0.037) and RTT (HR=0.033, p=0.003) were statistically significant variables (Table 3).

The sarcopenic group's OS was generally shorter than that of the non-sarcopenic group (Figure 3a). The 12-month mean OS rates for the sarcopenic and non-sarcopenic groups were 62.5% and 94.4%, respectively, whereas the median OS was 26 months in the sarcopenic group and 62 months in the non-sarcopenic group. There was a significant difference in PFS between the two groups. The PFS was significantly better in the non-sarcopenic group than in the sarcopenic group (Figure 3b). The 12-month mean PFS rates for the sarcopenic and non-sarcopenic groups were 62.5% and 94.4%, respectively, whereas the median PFS was 54 months in the non-sarcopenic group and 21 months in the sarcopenic group.

Table 2. Univariate logistic regression analysis for response to treatment and univariate Cox regression analysis for OS and PFS in patients with HCL

Variables	Response to treatment		OS		PFS	
	OR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Age	1.106 (0.99-1.23)	0.071	1.092 (1.013-1.18)	0.021*	1.04 (0.98-1.10)	0.226
Sex	0.998 (0.89-1.07)	0.990	1.17 (0.35-3.87)	0.802	23.45 (0-878518)	0.557
Spleen size	0.915 (0.83-1.01)	0.073	0.97 (0.95-1.01)	0.056	0.99 (0.98-1.01)	0.366
Hemoglobin	1.018 (0.676-1.53)	0.934	0.93 (0.69-1.25)	0.622	1.07 (0.86-1.32)	0.559
RTT	-	-	0.035 (0.01-0.22)	**0.001***	21.38 (2.93-155.7)	**0.003***
Relapse	0.952 (0.08-11.79)	0.990	0.448 (0.5-4.05)	0.475	-	-
BMI	0.552 (0.32-0.96)	**0.033***	0.78 (0.59-1.02)	0.280	0.89 (0.73-1.09)	0.280
BSA	0.001 (0-25)	0.182	0.01 (0-1.55)	0.073	0.01 (0.00005-1.5)	0.073
VAT	-	0.171	-	0.667	1.00 (0.99-1.00)	0.929
SAT	00.9996 (0.9993-0.9999)	**0.038***	-	0.061	1.00 (0.99-1.00)	0.509
TMI	0.99 (0.987-1.001)	0.080	0.998 (0.997-0.999)	**0.017***	1.00 (0.99-1.00)	0.964
SMI	0.998 (0.995-1.005)	0.093	0.998 (0.996-0.999)	**0.027***	0.998 (0.996-0.999)	**0.025***
Sarcopenia	-	0.998	0.161 (0.018-1.463)	0.105	0.379 (0.099-1.429)	0.150

*Bold values denote statistical significance at the p<0.05 level
OS: Overall survival, PFS: Progression-free survival, HCL: Hairy cell leukemia, HR: Hazard ratio, RTT: Response to treatment, BMI: Body mass index, BSA: Body surface area, VAT: Visceral adipose tissue, SAT: Subcutaneous adipose tissue, TMI: Total mass index, SMI: Skeletal mass index

Table 3. Multivariate Cox regression analysis for OS and PFS in patients with HCL

Variables	OS		PFS	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age	1.00 (0.96-1.06)	0.738	1.01 (0.96-1.1)	0.585
Spleen size	1.014 (1.001-1.027)	**0.041***	1.012 (0.97-1.33)	**0.037***
Hemoglobin	1.07 (0.92-1.25)	0.343	1.14 (1.02-1.42)	0.115
BMI	1.07 (0.91-1.26)	0.412	1.09 (0.94-1.25)	**0.021***
RTT	0.027 (0.02-0.31)	**0.004***	0.033 (0.003-0.32)	**0.003***
Relapse	0.311 (0.083-1.166)	0.083	-	-
VAT	1.000 (0.99-1.00)	0.263	1 (1-1)	0.418
SAT	1.000 (0.99-1.00)	0.210	1 (1-1)	0.274
TMI	0.999 (0.99-1.00)	0.549	0.999 (0.997-1.01)	0.358
SMI	1.002 (0.99-1.01)	0.383	1.002 (0.998-0.005)	0.325
Sarcopenia	0.154 (0.025-0.983)	**0.043***	0.17 (0.034-0.842)	0.137

*Bold values denote statistical significance at the p<0.05 level
OS: Overall survival, PFS: Progression-free survival, HCL: Hairy cell leukemia, RTT: Response to treatment, BMI: Body mass index, BSA: Body surface area, VAT: Visceral adipose tissue, SAT: Subcutaneous adipose tissue, TMI: Total mass index, SMI: Skeletal mass index

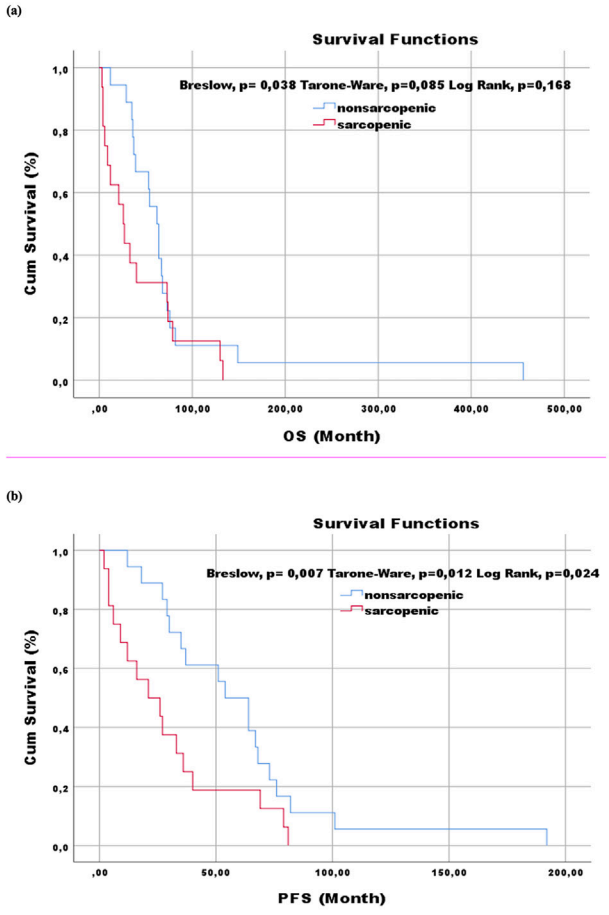

Figure 3. OS (a) and progression-free survival (b) according to SMI

OS: Overall survival, SMI: Skeletal mass index, PFS: Progression-free survival

Discussion

This study is significant because it is the first to demonstrate that sarcopenia is an independent factor affecting OS in HCL patients. Patients with diffuse large B cells, older patients, and those with early sarcopenia were reported to have shorter OS durations (12). Additionally, patients with Hodgkin lymphoma identified to have sarcopenia using SMI were reported to have shorter OS (13). Albano et al. (14) reported that sarcopenia did not affect the OS of patients with mantle cell lymphoma. In a study of leukemia patients, Nakamura et al. (15) showed that sarcopenic AML patients, especially aged over 60 years, had 0% 3-year OS. Patients with sarcopenic HCL had a significantly shorter OS duration in our study compared to those without sarcopenic HCL (26.5 vs. 63 months, p=0.046).

In our study, patients with sarcopenia had significantly lower BMI, TMI, and SMI. The prognostic importance of TMI and SMI for OS was shown. SMI was a statistically significant factor for PFS (p=0.025, HR=0.998). Inflammatory cytokines, tumor-derived factors, and growth factors released from tumors in patients with malignancy cause sarcopenia through both degradation and reduced protein synthesis (16). Linked to this, injury occurs in the muscles of the skeletal system. This leads to reductions in muscle strength, quality, amount, and yield. TMI and SMI values may be affected after treatment. Therefore, sarcopenia may be a factor affecting both treatment response and PFS, which is linked to the lack of full effect of the treatment protocol.

The most important feature distinguishing our study from other studies is the calculation of the sarcopenia cut-off value using a different method. Studies on sarcopenia trends do not have a standardized cutoff value because different patient populations and differences in muscle regions are used for calculations [SMI, psoas mass index (PMI)] (17). Several studies published in this field to reveal the sarcopenic status of patients used threshold values according to sex as a significant determinant of sarcopenia (18). Due to differences in PMI values between male and female patients, using sex-specific cut-off points obtained for PMI by receiver operating characteristic curve analysis, patients were divided into two groups: sarcopenic and non-sarcopenic. In our study, an index for all skeletal muscles was calculated, not just PMI, and no statistically significant difference was observed for SMI values between male and female patients. Accordingly, our study did not use sex-based threshold values. In our study, the presence of sarcopenia was determined using an effect size-based method using threshold values obtained from the ROC curve analysis for mean and median SMI.

Study Limitations

One of our study's most important limitations is the small number of patients. We believe that studies with more homogeneous and adequate patient numbers will allow for a better interpretation of the effects of sarcopenia on OS. Another limitation was that most patients did not undergo abdominal CT after treatment, making it impossible to assess sarcopenia after treatment. Finally, the Revised European Working Group on Sarcopenia in Older People-EWGSOP reported that muscle function is important for the assessment of sarcopenia (19). Muscle function could not be assessed in this retrospective study. Studies on HCL in previous years reported that splenomegaly (>3 cm), leukocytosis (>10^9/L), and high beta-2 microglobulin levels were poor prognostic factors in HCL patients (20). The major strength of this study is that our study differed from other studies in that the calculation of the sarcopenia cut-off value was performed using a different method.

Conclusion

Our study is significant because it is the first to show that sarcopenia is a prognostic factor for prognosis and treatment parameters. We believe that our study will guide future scoring studies related to sarcopenia during HCL patient diagnosis.

Footnote

Ethics Committee Approval: The study was approved by the Ondokuz Mayıs University Clinical Research Ethics Committee (approval no.: OMÜ KAEK 2022/576, date: December 28, 2022).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: M.H.A., T.T., O.A., F.U., Concept: M.H.A., T.T., Design: M.H.A., T.T., Data Collection or Processing: M.H.A., T.T., O.A., Analysis or Interpretation: M.H.A., T.T., Literature Search: M.H.A., T.T., Writing: M.H.A., T.T., O.A.

Conflict of Interest: No conflicts of interest were declared by the authors.

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