Original Article

The Prognostic Impact of Comorbidity, Nutritional and Performance Status on Patients with Diffuse Large B Cell Lymphoma

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Abstract

Background: The aim of the study was to investigate the impact of nutritional status, comorbidity, and performance status on patients with diffuse large B-cell lymphoma (DLBCL). **Methods:** A retrospective study was conducted on 112 DLBCL patients who were diagnosed at our center between 2009 and 2018. Demographic and disease characteristics and laboratory test results were recorded. Assessments were made using the age-adjusted Charlson comorbidity index (CCI-A) for comorbidity, albumin level for nutritional status, and Eastern Cooperative Oncology Group (ECOG) score for performance status. **Results:** The mean age of the patients was found to be 62.63 ± 15.16 years. The ECOG score of 65 patients (69.1%) was in the range of 0–1. The mean follow-up time of the patients was determined to be 25.24 ± 25.11 months, and at the end of the follow-up period, 64 patients (57.1%) were survivors. The progression-free survival (PFS), overall survival (OS), and 5-year OS rates of those with CCI-A > 4 were found to be significantly lower than those with CCI-A score ≤4 ($P < 0.05$). As a result of the Cox-Regression (Backward: LR method) analysis, ECOG and albumin levels were found to be independent risk factors for both OS and PFS ($P < 0.05$). **Conclusion:** This study demonstrated that CCI-A, ECOG, and nutritional status are independent prognostic markers for DLBCL patients. Initial evaluation of these patients should include all these parameters, which are easily available at the time of diagnosis.

Keywords: *Albumin, Charlson comorbidity, lymphoma, performance, prognosis*

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Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common histological type of all non-Hodgkin lymphomas (NHL).[1] Increasing incidence with age also refers to a highly heterogeneous disease group clinically, pathologically, and molecularly.[2-4] Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) are the standard initial treatments.[5] While the incidence of DLBCL increases with age, it is also associated with a poor prognosis.[6,7] It is generally associated with advanced age, the presence

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of an additional diagnosis, malnutrition, decreased organ function, and a weakened immune system. This causes an increase in toxicity due to changes in the metabolism of chemotherapeutic drugs.[8] Therefore, data on elderly patients is limited in studies.[9-11]

Today, the international prognostic index (IPI) and its various revisions are used to predict the clinical outcomes of DLBCL patients. IPI is a scoring system consisting of age, stage, performance status (Eastern Cooperative Oncology Group (ECOG)), serum lactate dehydrogenase level, and number of extranodal involvements.[12] However, it is insufficient to evaluate the frequent comorbidities and nutritional levels of elderly patients, who are now seen in increasing numbers and are at risk of inadequate treatment. In some elderly patients, increased chemotherapy side effects can be observed,[13] so the Charlson Comorbidity Index (CCI), developed by Charlson *et al*.[14] in 1987, is widely used.[15] However, data on the role of CCI in the follow-up and treatment of DLBCL patients are limited.[6,15-18] In particular, there are no data on age-adjusted CCI (CCI-A), despite its increasing importance considering the aging of societies in general and the increased frequency of disease with age.

In addition to the comorbidity and performance status of patients, nutritional status is also an important marker in the progression of malignant diseases.[19] Many studies have previously reported that low albumin levels at the time of diagnosis may reflect the current nutritional status of patients.[20,21] However, it has been shown that low serum albumin concentrations are associated with increased side effects in patients with DLBCL, and this may negatively affect the prognosis.[22-24]

The aim of this study was to determine the effect of comorbidities, nutritional status, and performance status at diagnosis on the prognosis of DLBCL patients.

Patients and Methods

Approval for this study was granted by Ankara Diskapi Training and researh Hospital Ethics Committee (Number: 97/07 Date: 05.10.2020). This retrospective study included patients who presented at our center between 2009 and 2018 and were diagnosed with DLBCL. The demographic data, disease-related findings, and laboratory results of the patients were recorded. Overall survival (OS) and progression-free survival (PFS) were calculated. The CCI-A [Table 1],[25,26] albumin levels, and the ECOG score were used to evaluate comorbidities, nutritional status, and performance status, respectively. In the CCI-A evaluation, diseases at the time of diagnosis, the presence of lymphoma, and age status were also included in the scoring. The patients were compared in two groups with CCI-A scores of ≤4 and >4.

Ethical approval and informed consent

All procedures performed in studies involving human participants 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 Ankara Diskapi Training and researh Hospital Ethics Committee (Number: 97/07 Date: 05.10.2020) As a standard of care/action of Ankara Diskapi Yildirim Beyazit Research and Training Hospital, the patient records confirmed that all the study patients gave informed consent at the time of hospitalization and before the administration of chemotherapy and other relevant diagnostic/therapeutic standards of care.

Statistical analysis

Data obtained in the study were analyzed statistically using SPSS Statistics vn. 20 software (IBM, Armonk, NY, USA). The Independent Samples *t*-test was used to compare two independent groups with a normal distribution of the measured values (t-table value), and the Mann–Whitney U-test (Z-table value) was applied to data with a non-normal distribution. $\chi 2$-cross tables were used to examine the relationships between two qualitative variables. A value of $P < 0.05$ was considered statistically significant. The Kaplan–Meier method was used for survival analysis. OS was measured from the time of diagnosis UNTIL death or until the final visit. PFS was measured from diagnosis to death, disease progression, or relapse, whichever was earlier, or until

Table 1: Age-adjusted Charlson comorbidity index (CCI-A)[25]

Point*	Condition
0	None
1	Myocardial infarct, congestive heart failure, peripheral vascular disease, cerebrovascular disease (except hemiplegia), dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, mild liver disease, diabetes (without complications)
2	Diabetes with end organ damage, hemiplegia, moderate or severe renal disease, second solid tumor (non-metastatic), leukemia, lymphoma, multiple myeloma
3	Moderate or severe liver disease
6	Second metastatic solid tumor, AIDS (acquired immunodeficiency syndrome)

For every decade over 40 years of age, 1 point was added to the comorbidity score.

the final visit. The Log-Rank test was applied in the comparisons between groups.

Results

The evaluation was made of a total of 112 DLBCL patients, comprising 58 (51.8%) females and 54 (48.2%) males with a mean age of 62.63 ± 15.16 years. The demographic and disease characteristics of the patients are shown in Table 2. All patients had at least one comorbidity, and the CCI-A score was found to be median 6 (min-max: 2–9). When ECOG performance was divided into two groups of 0–1 and 2–4 at the time of diagnosis, 65 (69.1%) patients had a score of 0–1, and 29 (30.9%) were in the 2–4 range. The mean follow-up period of the patients was 17.2 months (range, 0.2–109.2 months). At the end of the follow-up period, 64 (42.9%) patients were alive, and 48 (42.9%) patients had died.

The biochemical parameters of the patients are presented in Table 3. The median hemoglobin level, lactate dehydrogenase level, and albumin level were determined to be 12.0 (6.6–17.0) g/dl, 265 (120–2314) U/L, and 3.7 (2.2–5.3) g/dl, respectively.

The first-step treatments of the patients and their responses are presented in Table 2. RCHOP or R-mini CHOP (created with a 20% dose reduction) chemotherapy protocol (n: 94, 83.9%) was the most preferred first-line treatment. A complete response to first-line treatment was seen in 72 (64.2%) patients, a partial response in 6 (5.4%), and a relapse-refractory response in 34 (30.4%). The PFS of the patients was found to be mean 61.1 months (range, 18.3–103.9 months), and OS was mean 61.1 months (range, 16.4–105.8 months). OS at the end of 5 years was determined in 67 (59.8%) patients.

The patients were separated into two groups of CCI-A scores: ≤4 (n: 31, 27.7%) and >4 (n: 81, 72.3%). An ECOG performance score of 0–1 was observed in 25 (92.6%) patients with a CCI-A score of ≤4, and in 40 (59.7%) with a CCI-A score of >4, and for an ECOG performance score of 2–4, these rates were 2 (7.4%) and 27 (40.3%), respectively. The difference was evaluated as statistically significant (P = 0.004). When the ECOG performance status between the two groups was compared, the difference in the median values of 0 (min-max: 0–3) and 1 (min-max: 0–4) was considered statistically significant (P = 0.001). When albumin levels were evaluated to compare the nutritional status of the two groups, the difference between the mean values of 4.0 ± 0.72 g/dl and 3.53 (±0.61) g/dl was determined to be statistically significant (P = 0.004). PFS was calculated as mean 21.3 months (range, 0.7–109.2 months) and 12.4 months (range, 0.2–98.4 months), respectively, and the difference was statistically significant (P = 0.049). OS was calculated as the mean of 22 months (range, 0.7–109.2 months)

Table 2: Patients' characteristics and treatment response

Variable *n*=112	Findings	
	n	%
Age [$\bar{x}$±SS (*yıl*)]	62.63±15.16	
Sex		
Female	58	51,8
Male	54	48,2
Comorbidity [Median (Min-Max)]	1.0 [0.0–5.0]	
CCI-A [Median (Min-Max)]	6.0 [2.0–9.0]	
ECOG score (*n*=94)		
0-1	65	69,1
2-4	29	30,9
Diagnosis stage		
0-1	20	17,9
2-4	92	82,1
Diagnosis IPI		
0-1	26	23,2
2-4	82	73,2
≥5	4	3,6
Ki67 [Median (Min-Max)]	80.0 [10.0–100.0]	
Bulky disease		
Present	20	19,6
Absent	82	80,4
Extranodal involvement		
Present	42	43,8
Absent	54	56,2
First-line treatment		
Rchop-mrchop	94	83,9
Repoch	7	6,3
Diğer	11	9,8
Response to first-line treatment		
Cr	72	64,2
Pr	6	5,4
Rr	34	30,4
Final response		
Cr	66	58,9
Pr	3	2,7
Rr	43	38,4
Follow-up time (month) [Median (Min-Max)]	17.2 [0.2–109.2]	
PFS (month) [Median (Min-Max)]	61.1 [18.3–103.9]	
OS (month) [Median (Min-Max)]	61.1 [16.4–105.8]	
5-year OS		
Exitus	45	40.2
Alive	67	59.8
Final status		
Exitus	48	42.9
Alive	64	57.1

and 15.4 months (range, 0.2–98.4 months), respectively, in the two groups, and the difference was statistically significant (P = 0.040). The 5-year OS was calculated as 24 patients (77.4%) and 43 patients (53.1%), respectively, and the difference was determined to be statistically significant (P = 0.033) [Table 4].

Table 3: Patients' biochemical parameters

Variable *n*=112	Findings	
	$\bar{x}\pm SS$	Medyan [Min-Max]
Hb (g/dl)	11.99±2.23	12.0 [6.6–17.0]
Wbc (/µL)	8344.91±3681.58	8000.0 [1740.0–21900.0]
Plt (/µL)	281588.39±137643.89	264000.0 [10000,0–1089000.0]
Beta-2 microglobulin (mg/L)	5.06±11.79	2.9 [1.3–109.0]
Albumin (g/dl)	3.65±0.67	3.7 [2.2–5.3]
LDH (U/L)	419.71±364.35	265.0 [120.0–2314.0]

Table 4: Comparison of parameters according to CCI-A score groups

Variable n=112	CCI-A		*P*
	≤4 (*n*=31 27.7%)	>4 (*n*=81 72,3%)	
Age	44.16±12.10	69.70±9.01	*t*=-10.674, *P*=0.000
Sex			
Female	13 (41.9%)	45 (55.6%)	χ^2=1.165
Male	18 (58.1%)	36 (44.4%)	*P*=0.280
ECOG score (*n*=94)			
0-1	25 (92.6%)	40 (59.7%)	χ2=8.278
2-4	2 (7.4%)	27 (40.3%)	*P*=0.004
ECOG median (min-max)	0.0 [0.0–3.0]	1.0 [0.0–4.0]	*Z*=-3.383, *P*=0.001
Diagnosis stage			
0-1	9 (29.0%)	11 (13.6%)	χ^2=3.649
2-4	22 (71.0%)	70 (86.4%)	*P*=0.056
Diagnosis IPI			
0-1	12 (38.7%)	14 (17.3%)	χ^2=6.797
2-4	19 (61.3%)	63 (77.8%)	*P*=0.033
≥5	-	4 (4.9%)	
Bulky disease			
Present	6 (22.2%)	14 (18.7%)	χ^2=0.159
Absent	21 (77.8%)	61 (81.3%)	*P*=0.690
Hb (g/dl)	12.77±2.01	11.69±2.26	*t*=2.328, *P*=0.022
WBC (/µL)	7900.0 [1900.0–10900.0]	8100.0 [1740.0–21900.0]	*Z*=-0.930, *P*=0.352
ALBUMİN (g/dl)	4.00±0.72	3.53±0.61	*t*=2.962, *P*=0.004
LDH (U/L)	320.0 [146.0–1688.0]	248.0 [120.0–2314.0%]	*Z*=-0.793, *P*=0.428
First line treatment			
Rchop-mrchop	28 (90.3%)	66 (81.5%)	χ2=5.224
Repoch	3 (9.7%)	4 (4.9%)	*P*=0.073
Other	-	11 (13.6%)	
Response to 1st line treatment			
Cr	21 (67.7%)	51 (63.0%)	χ^2=0.468
Pr	2 (6.5%)	4 (4.9%)	*P*=0.791
Rr	25 (25.8)	26 (32.1%)	
PFS (month)	21.3 [0.7–109.2]	12.4 [0.2–98.4]	*Z*=-1.961, *P*=0.049
OS (month)	22.0 [0.7–109.2]	15.4 [0.2–98.4]	*Z*=-2.058, *P*=0.040
5-Yıllık OS			
Exitus	7 (22.6%)	38 (46.9%)	χ^2=4.557
Sağ	24 (77.4%)	43 (53.1%)	*P*=0.033

In the Cox regression analysis of the effect of ECOG performance status and albumin level on OS, both were found to be statistically significant (P = 0.000 and P = 0.010, respectively) [Table 5]. ECOG performance status and albumin levels were determined to be independent risk factors for PFS (P = 0.000 and P = 0.012, respectively) [Table 6].

Discussion

Although the frequency of DLBCL increases with age, it is 50–60% curable with standard R-CHOP therapy. However, the standard approach becomes difficult due to the physiological changes that occur in patients with aging, together with the loss of organ functions and comorbidities.[13] Therefore, it is important to determine which patients are suitable for the standard approach.[16] The presence of comorbidities can also cause patients not to receive adequate treatment.[7] Previous studies have shown that treatment with dose reductions of up to 50–70% is given to elderly patients.[27] Community-based studies have also shown that the presence of comorbidities in lymphoma patients reduces 5-year survival by 10–20%.[28] The IPI score has been used successfully in the risk stratification of patients for many years. Aging is observed in societies with prolonged life expectancy as a result of developments in healthcare practices throughout the world, and this leads to more patients being seen with more comorbidities, deteriorated performance, and nutritional problems. With this change in societies, new scoring systems are needed to predict patients, treatment options, and associated success rates.

With the CCI-A scoring system used in this study, both age and existing comorbidities were seen to have an impact on the success of the treatment applied to the patient at the time of the new diagnosis. This effect was observed to be statistically significant when evaluated separately for PFS, OS, and 5-year OS (P = 0.049, P = 0.040, P = 0.033, respectively. It has been previously shown in various studies that the CCI score is effective in predicting the survival of DLBCL patients, but there is no study that has evaluated the CCI-A scoring system.[6,15,17,29-31] In general, in those studies, while a CCI score of ≥2 was associated with a poor prognosis, from the results of the current study, it was concluded that a CCI-A score of ≥4 was associated with a poor prognosis.[6,16,29]

It is very important in hematology practice to evaluate and support the nutritional status of patients during diagnosis and follow-up. Malnutrition will adversely affect the patient's ability to tolerate treatment and can also adversely affect responses. The easiest parameter that will allow observation of this situation is serum albumin levels. In the current study, a serum albumin level of ≤3.5g/dl was found to be significant. This result was found to be an independent risk factor associated with a poor prognosis, consistent with previous findings in the literature.[24,32-35] Albumin levels were determined to have an effect on both PFS and OS (P = 0,012, P = 0,010, respectively). The decrease in serum albumin levels can be attributed to the decrease in albumin secretion from hepatocytes due to elevated TNF-α and IL-6 as a result of the inflammatory response to existing tumor tissue and to the malnutrition of patients.[36] Consequently, in patients with active malignancy, low albumin levels contribute to a poor prognosis by weakening the expected response and, at the same time, making it more difficult to tolerate treatment.

Performance status is frequently used as the most important and easily determined parameter in determining the treatment regimen of patients at the time of diagnosis. Although various scoring systems have been developed for this purpose, the ECOG performance system is still the most commonly used. In the current study, the effect of ECOG was observed independently on both PFS and OS (P = 0,000, P = 0,000, respectively). The performance status of the patients is an important parameter that determines the effectiveness of their treatments as well as their compliance and tolerance to the treatment they receive, which is reflected in the results of this study.

Table 5: Examination of factors affecting ex status (overall survival)

Variable	*B*	Standard error	Wald	SD	*P*	OR	95% GA (OR)	
							Lower Limit	Upper Limit
ECOG	0.709	0.170	17.425	1	0.000	2.031	1.456	2.833
Albumin	-0.704	0.273	6.629	1	0.010	0.495	0.289	0.845

Table 6: Examination of factors affecting Ex status (Progression-free survival)

Variable	B	Standard error	Wald	SD	*P*	OR	95% GA (OR)	
							Lower Limit	Upper Limit
ECOG	0.703	0.167	17.640	1	0.000	2.019	1.455	2.803
Albumin	-0.674	0.270	6.253	1	0.012	0.510	0.300	0.864

This study was conducted to determine treatment and follow-up strategies by predicting the prognosis and factors affecting the prognosis of DLBCL. The results showed that a CCI-A score >4 had a negative effect on PFS and OS. Albumin level and ECOG performance score were also determined as independent risk factors affecting both PFS and OS. These results were seen to be consistent with the literature.[18]

Conclusion

In the increasing elderly population, DLBCL disease is increasingly seen in patients with more than one comorbidity, whose performance levels and nutritional levels are quite different from each other. At the same time, as these are a very heterogeneous group of diseases in terms of pathology and molecular status, the scoring systems in current use need to be updated to meet the needs of the patient population. Although there have been various revisions, comorbidity, nutritional level, and performance level are not sufficiently included in scoring systems. The results of this study have shown that evaluating patients with these parameters will ensure that patients receive the optimum treatment and that follow-up will be more successful.

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Conflicts of interest

There are no conflicts of interest.

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