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ORIGINAL ARTICLE

Charlson Comorbidity Index (CCI) in Diffuse Large B-cell Lymphoma: A New Approach in a Multicenter Study

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Abstract

Purpose Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of adult lymphomas. The incidence of DLBCL increases with age and has a fairly rapid fatal course without treatment. Patients often have difficulty tolerating standard chemotherapy regimens due to their comorbidities. Charlson Comorbidity Index (CCI), which is calculated by considering 19 different comorbidities, was developed in 1987 and is widely used for mortality prediction in cancer patients. Literature data on CCI and hematological malignancies are limited. Main aim in this study is to evaluate the effectiveness of CCI and compare to the International Prognostic Index (IPI) scoring system in the DLBCL patient group.

Methods A total of 170 patients diagnosed with DLBCL between 1.1.2002- 1.12.2020 were included in the study. Statistical analyzes were performed among patients whose IPI and CCI scores were recorded by considering baseline data.

Results The median age of patients was 58 (range: 17–84). Thirty-five (20.6%) patients had stage III and 76 (44.7%) had stage IV disease. When the CCI, IPI and ECOG scores were compared with the mortality status of the patients as a reference, AUCs were resulted as 0.628 (95% CI: 0.506–0.749), 0.563 (95% CI: 0.484–0.639) and 0.672 (95% CI: 0.596–0.743), respectively. There was no significant difference between the ROC curves of CCI, IPI and ECOG scores. Patients with a CCI score of ≥ 4 had shorter OS comperad to those with a score of < 4.

Conclusion Rather than claiming that CCI is superior to IPI, ECOG or another scoring system in a single-center patient population, it should be stated that CCI is also an effective scoring system in patients diagnosed with DLBCL.

Keywords Diffuse large B-cell lymphoma · Charlson Comorbidity Index · prognosis · efficacy

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Background

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of adult lymphomas [1, 2]. The incidence of DLBCL increases with age and has a fairly rapid fatal course without treatment [1–4]. Patients often have difficulty tolerating standard chemotherapy regimens due to their comorbidities [5, 6].

The International Prognostic Index (IPI) has long been used for non-Hodgkin lymphoma (NHL) risk stratification [7, 8]. The IPI score assigns 1 point to each prognostic factor (age > 60 years, serum lactate dehydrogenase (LDH) above the upper limit of normal (ULN), Ann Arbor stage III/IV disease, Eastern Cooperative Oncology Group (ECOG) performance status ≥ 2, and > 1 site with extranodal involvement) and divides patients into 4 risk groups

Table 1 a. Charlson Comorbidity Index (CCI)

Comorbidity	Score
Age	< 50 0; 50–59 1; 60–69 2; 70–79 3; ≥ 80 4 points
Coronary artery disease (History of definite or probable MI (EKG changes and/or enzyme changes)	1 point
Congestive heart failure (Exertional or paroxysmal nocturnal dyspnea and has responded to digitalis, diuretics, or afterload reducing agents)	1 point
Peripheral vascular disease (Intermittent claudication or past bypass for chronic arterial insufficiency, history of gangrene or acute arterial insufficiency, or untreated thoracic or abdominal aneurysm (≥ 6 cm))	1 point
Cerebrovascular disease (History of a cerebrovascular accident with minor or no residua and transient ischemic attacks)	1 point
Dementia (Chronic cognitive deficit)	1 point
Chronic pulmonary disease	1 point
Connective tissue disorder	1 point
Peptic ulcer disease (Any history of treatment for ulcer disease or history of ulcer bleeding)	1 point
Liver disease (Severe = cirrhosis and portal hypertension with variceal bleeding history, moderate = cirrhosis and portal hypertension but no variceal bleeding history, mild = chronic hepatitis (or cirrhosis without portal hypertension)	Mild 1; Moderate to severe 3 points
Diabetes mellitus	Uncomplicated 1; End organ damage 2 points
Hemiplegia	2 points
Moderate or severe renal disease (Severe = on dialysis, status post kidney transplant, uremia, moderate = creatinine > 3 mg/dL)	2 points
Leukemia or lymphoma	2 points
Solid tumor	Localized 2; Metastatic 6 points
AIDS	6 points

based on the total score: 0/1 = low risk, 2 = low-intermediate risk, 3 = high-intermediate risk, and 4/5 = high risk. With the development of rituximab-based regimens, new risk scores have been developed and one of them, "the revised IPI" (R-IPI), has emerged [9]. The R-IPI used the same risk factors and scoring system as the IPI, but it redistributed the scores to form 3 risk groups: 0 = very good risk, 1/2 = good risk, and 3/4/5 = poor risk. Another scoring system, the National Comprehensive Cancer Network-IPI (NCCN), also uses parameters, but includes different scoring logic

Table 1 b. Dose Modifications for R-CHOP

Neutrophils ≥ 1×10^9/L	100% dose
Neutrophils 0,5 - <1 × 10^9/L	If patient was fit and well, proceeded with chemo and G-CSF from Day 6. If patient was unwell, delayed for 1 week.
Neutrophils < 0,5 × 10^9/L	Delayed by one week
Platelets ≥ 75 × 10^9/L	100% dose
Platelets 50–74 × 10^9/L	75% of cyclophosphamide and doxorubicin dose
Platelets < 50 × 10^9/L	Delayed by one week
Doxorubicin Dose Reductions	Bilirubin micromol/L Dose 20–51 50% 51–85 25% > 85 omitted If AST 2–3 x normal, 75% dose If AST > 3 x ULN, 50% dose
Vincristine Dose Reductions	Bilirubin 26–51 micromol/L or ALT/AST 60–180 u/L 50% dose, Bilirubin > 51 micromol/L & normal ALT/AST 50% dose, Bilirubin > 51 micromol/L & ALT/ AST > 180 u/L omitted
Cyclophosphamide Dose Reductions	GFR (mL/min) Dose > 20 100% 10–20 75% < 10 50%

Table 2 Patient Characteristics

Characteristics, (n)	
Gender, (170) n, (%)	69 (40.6)
Female	101 (59.4)
Male	
Age, years, (170), median (range)	58 (17–84)
LDH level, (170) n (%)	94 (55,3)
Normal	76 (44.7)
Elevated	
Stage, (170) n (%)	17 (10)
Stage I	42 (24.7)
Stage II	35 (20.6)
Stage III	76 (44.7)
Stage IV	
B symptoms, (170) n (%)	64 (37.6)
Present	106 (62.4)
Absent	
Extranodal involvement, (170) n (%)	102 (60)
Present	68 (40)
Absent	
ECOG, (170) n (%)	136 (80)
0–1	34 (20)
2–4	
IPI score, (167) n (%)	18 (10.8)
0	43 (25.7)
1	43 (25.7)
2	38 (22.8)
3	20 (12)
4	5 (3)
5	
Response to treatment, (167) n (%)	142 (85)
CR	7 (4.2)
PR	18 (10.8)
NR	
BMI, (81) n (%)	3 (3.7)
Underweight	26 (32.1)
Normal or healthy weight	32 (39.5)
Overweight	20 (24.7)
Obese	26 (14–47)
BMI, median (range)	
Comorbidity, (170) n (%)	91 (53.5)
Present	79 (46.5)
Absent	

LDH: lactate dehydrogenase, ECOG: Eastern Cooperative Oncology Group, IPI: International Prognostic Index, CR: complete Response, PR: partial response, NR: non-response

[10]. The NCCN- IPI is based on the same five parameters that are included in the IPI, the difference being how extranodal sites are considered: the NCCN-IP does not include the number of extranodal sites, but selects a group of distinct extranodal involvement sites, such as the bone marrow, central nervous system (CNS), liver, gastrointestinal tract, and lungs. Furthermore, it additionally grades LDH level and age [10]. Regarding age, it emphasizes that older age is an adverse prognostic factor for poorer outcomes in DLBCL patients, especially for those older than 75.

The ECOG performance status scoring system, which is also a subparameter of IPI, has a important place in the clinical practice of cancer patients [11]. The ECOG scale consists of 5 scoring points that increase from 0 to 5 defined as “dead”. Performance status “0” defines fully active patients without any performance restriction, while “4” describes patients who are completely disabled, totally confined to bed or chair [11].

Another index used in clinical practice to assess the risk of treatment-related toxicity and to predict outcomes in patients with multiple comorbidities is the Charlson Comorbidity Index (CCI) [12]. CCI, which is calculated by considering 19 different comorbidities, was developed in 1987 and is widely used for mortality prediction in cancer patients. Literature data on CCI and hematological malignancies are limited.

Table 3 Comparison of patients

Characteristics	0–2 (44)	3–4 (62)	5–6 (47)	7–8 (17)	p-value
Gender, n, (%)	14 (31.8)	30 (48.4)	20 (42.6)	5 (29.4)	0.270[1]
Female	30 (68.2)	32 (51.6)	27 (57.4)	12 (70.6)	
Male					
Age, years, median (range)	40.5 (17–50)	57 (23–67)	70 (51–78)	73 (29–84)	**< 0.001**[2a]
LDH level, n (%)	21 (47.7)	34 (54.8)	30 (63.8)	9 (52.9)	0.485[1]
Normal	23 (52.3)	28 (45.2)	17 (36.2)	8 (47.1)	
Elevated					
Stage, n (%)	1 (2.3)	10 (16.1)	4 (8.5)	2 (11.8)	0.378[3]
Stage I	16 (36.4)	13 (21)	10 (21.3)	3 (17.6)	
Stage II	9 (20.5)	11 (17.7)	12 (25.5)	3 (17.6)	
Stage III	18 (40.9)	28 (45.2)	21 (44.7)	9 (52.9)	
Stage IV					
B symptoms, n (%)	17 (38.6)	19 (30.6)	22 (46.8)	6 (35.3)	0.386[1]
Present	27 (61.4)	43 (69.4)	25 (53.2)	11 (64.7)	
Absent					
Extranodal involvement, n (%)	23 (52.3)	36 (58.1)	31 (66)	12 (70.6)	0.444[1]
Present	21 (47.7)	26 (41.9)	16 (34)	5 (29.4)	
Absent					
ECOG, n (%)	39 (88.6)	55 (88.7)	33 (70.2)	9 (52.9)	**0.001**[1b]
0–1	5 (11.4)	7 (11.3)	14 (29.8)	8 (47.1)	
2–4					
IPI score, n (%)	5 (11.6)	5 (8.2)	5 (10.9)	3 (17.6)	
0	7 (16.3)	18 (29.5)	16 (34.8)	2 (11.8)	
1	14 (32.6)	14 (23)	12 (26.1)	3 (17.6)	
2	13 (30.2)	12 (19.7)	9 (19.6)	4 (23.5)	
3	3 (7)	9 (14.8)	4 (8.7)	4 (23.5)	
4	1 (2.3)	3 (4.9)	0 (0)	1 (5.9)	
5					
Comorbidity, n (%)	5 (11.4)	32 (51.6)	37 (78.7)	17 (100)	**< 0.001**[1a]
Present	39 (88.6)	30 (48.4)	10 (21.3)	0 (0)	
Absent					
Response to treatment, n (%)	34 (77.3)	55 (90.2)	39 (86.7)	14 (82.4)	0.316[1]
CR	10 (22.7)	6 (9.8)	6 (13.3)	3 (17.6)	
PR/NR					

[1]Chi-square test, [2]Kruskal Wallis test, [3]Fisher Exact test

[a]Group 0–2 and 3–4 different than other groups, [b]Group 5–6 and 7–8 different than other groups

LDH: lactate dehydrogenase, ECOG: Eastern Cooperative Oncology Group, IPI: International Prognostic Index, CR: complete Response, PR: partial response, NR: non-response

Table 4 The CCI scores as two subgroups: (2) and (3–8)

		CCI (n)		
	All patients (170)	2 (44)	3–8 (126)	p
Follow-up duration, months Median (Minimum-Maximum)	36.5 (2-227)	44.6 (8-227)	35.4 (2-184)	**0.036***
*Mann-Whitney U test				
CCI	Ex n(%)	Alive n(%)	p*	
2	5 (11.4)	39 (88.6)	0.289*	
3–8	23 (18.3)	103 (81.7)		
Total	28 (16.5)	142 (83.5)		
*Chi-square test				

Main aim in this study is to evaluate the effectiveness of CCI and compare to IPI scoring system in the DLBCL patient group. The hypothesis of this study was that CCI could also be used effectively in patients with DLBCL.

Material and Method

A total of 170 patients diagnosed with DLBCL in different centers from Turkey, between 1.1.2002- 1.12.2020 were included in the study. In addition to demographic data (age,

Table 5 The CCI scores as four subgroups: (0–2), (3–4), (5–6) and (7,8)

CCI (n)	Follow-up duration, months Median (Minimum-Maximum)	p	
0–2 (44)	44.8 (8-227)	**0.013***	
3–4 (62)	36.8 (7-184)		
5–6 (47)	27.4 (2-125)		
7–8 (17)	17.4 (6-146)		
*Kruskal Wallis test			
CCI	Ex n(%)	Alive n(%)	p*
0–2	5 (11.4)	39 (88.6)	0.064
3–4	7 (11.3)	55 (88.7)	
5–6	10 (21.3)	37 (78.7)	
7–8	6 (35.3)	11 (64.7)	
Total	28 (16.5)	142 (83.5)	
*Chi-square test			

Table 6 Pairwise comparison of ROC curves

	Difference between areas	95% Confidence Interval	p
CCI-IPI	0.064	0.097–0.227	0.43
CCI-ECOG	0.044	0.076–0.165	0.46
IPI-ECOG	0.109	0.039–0.259	0.15

Table 7 The CCI scores as four subgroups: (0–2), (3–8) and (0–2), (3–4), (5–6), (7–8)

Categories	Overall Survival (OS)			p[1]
	Case	Event	5 years-OS	
CCI				
0–2	44	5	87.5% (SE:0.053)	0.233
3–8	126	23	79% (SE:0.04)	
CCI				
0–2	44	5	87.5% (SE:0.053)	
3–4	62	7	86.5% (SE:0.049)	**0.017**
5–6	47	10	75.9% (SE:0.068)	
7–8	17	6	56.3% (SE:0.136)	

[1]Log rank test

gender) of the patients, body mass indexes (BMI) at initial diagnosis, LDH levels (normal/high), stages (I-IV), presence of B symptoms, extranodal involvement (> 1 present or absent), ECOG, IPI, CCI scores, presence of comorbid disease (present or absent), and responses to first line therapies were recorded. All parameters were analyzed and recorded using our hospital patient information system, there was no missing data/patient to exclude. Statistical analyzes were performed among patients whose IPI and CCI scores were

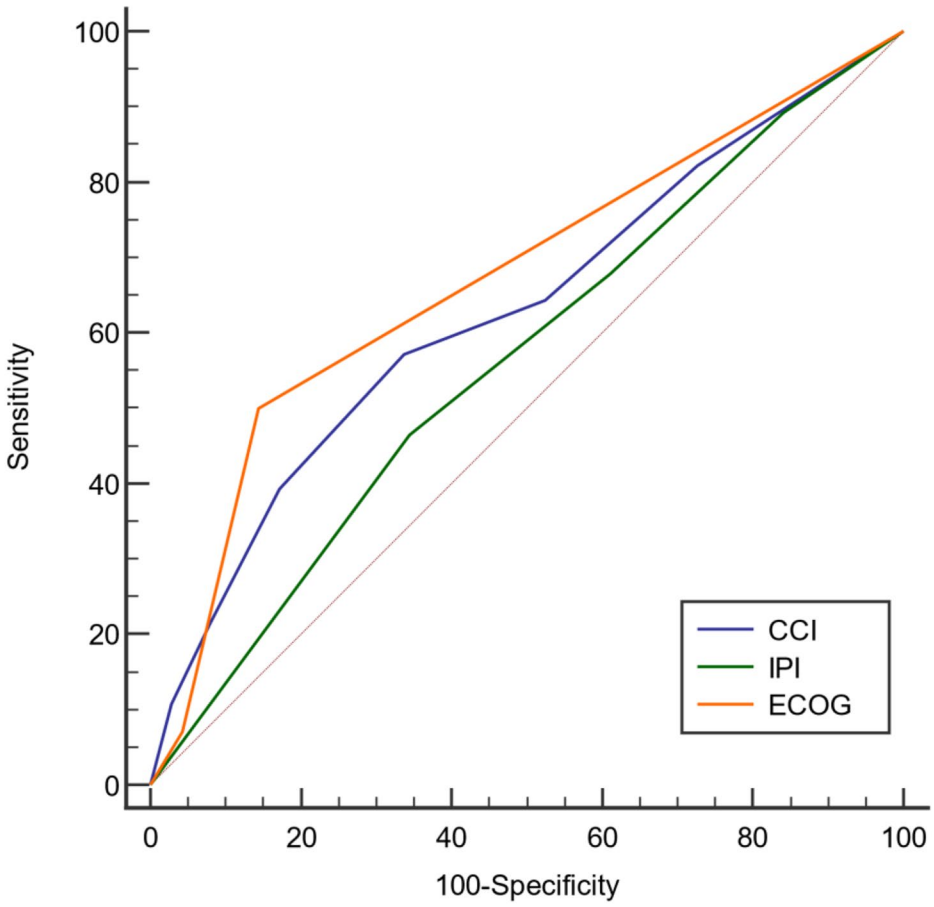

Fig. 1 ROC curves of CCI, IPI and ECOG

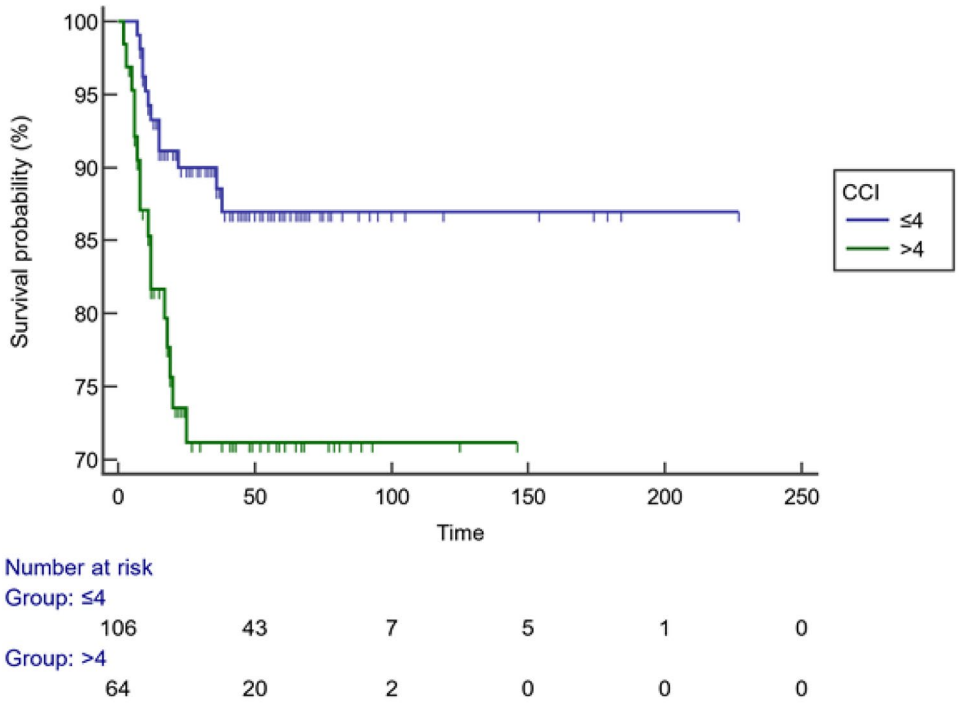

Fig. 2 Kaplan-Meier analysis for overall survival: the effect of CCI score

recorded by considering baseline data. Table 1a. was used to calculate the CCI score [12].

All of the patients included in the study received R-CHOP or CHOP treatment at the doses determined at the beginning of the treatment (Rituximab 375 mg/m^2 D1, cyclophosphamide 750 mg/m^2 D1, doxorubicin 50 mg/m^2 D1, vincristine 1.4 mg/m^2, maximum 2 mg/day D1, methylprednisolone 60 mg/m^2 D1-5). The doses were revised according to the fragility, renal and hepatic functions of the patients [13]. Dose modifications were shown in Table 1b. The treatment of the patients was evaluated according to the interim imaging after completing 4 cycles of treatment.

Statistical Analysis

SPSS v.21 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Kolmogrov-Smirnov test or Shapiro-Wilk tests, histograms and probability plots was used for assessing normality. Results were presented median (Minimum-maximum) for non-normally distributed variables and frequency (percentage) for categorical variables. Because of continuous variables are nonparametric, comparisons of the groups for continuous variables were made by Mann-Whitney U test for two groups, Kruskal Wallis for three and more groups. Chi-square test or Fisher's exact test was used to analyze categorical variables, where appropriate. ROC analysis was used for screening mortality of CCI, IPI and ECOG scores. Test quality for the area under the curve (AUC) values was defined as follows: 0.90-1 excellent, 0.80–0.90 very good, 0.70–0.80 good, 0.60–0.70 satisfactory and 0.50–0.60 unsatisfactory. CCI score on survival was inverstigated using the log rank test. The Kaplan-Meirer survival estimates were calculated. All tests are two-sided and significance level was accepted as $p < 0.05$.

Results

The median age of patients was 58 (range: 17–84). Thirty-five (20.6%) patients had stage III and 76 (44,7%) had stage IV disease (Table 2.). Table 3. shows the distribution of patients according to CCI subgroups and statistical evaluation. Presence of any comorbidity, high ECOG score and advanced age showed a statistically significant relationship with high CCI scores ($p < 0.001$) (Table 3.).

When the CCI scores were divided into two subgroups as 0–2 and 3–8 and the follow-up durations were compared, the follow-up duration of the subgroup with a CCI score of 0–2 was significantly higher than the subgroup with a score of 3–8 (44.6 months (8-227) vs. 35.4 months (2-184) ($p = 0.036$). No significant difference was found between the two groups in terms of mortality ($p = 0.289$) (Table 4).

When the CCI scores were divided into four subgroups as 0–2,3–4,5–6,7–8 and the follow-up durations were compared, there was a significant difference between the subgroups ($p = 0.013$). The significant difference in post-hoc tests resulted from the difference between the subgroups

with CCI scores of 0–2 and 7–8. No significant difference was found between the mortality rates of the subgroups (p = 0.064) (Table 5.).

When the CCI, IPI and ECOG scores were compared with the mortality status of the patients as a reference, AUCs were resulted as 0.628 (95% CI: 0.506–0.749), 0.563 (95% CI: 0.484–0.639) and 0.672 (95% CI: 0.596–0.743), respectively (Fig. 1.). In the statistical analysis examining the difference between the ROC curves of CCI, IPI and ECOG scores, there was no significant difference (Table 6.).

When the CCI scores were divided into two subgroups as 0–2 and 3–8, there was no significant difference in terms of overall survival (OS) (p > 0.05). It has been demonstrated that OS was decreased when the CCI scores went up (p = 0.017) (Table 7.). Patients with a CCI score of ≥ 4 had shorter OS comperad to those with a score of < 4 (Hazard ratio: 2.93, 95% CI: 1.33–6.44, p = 0.008) (Fig. 2.).

Discussion

This study has revealed important results in terms of demonstrating the effectiveness of CCI in our own patient population. In the study conducted by Kocher et al. in 2020 [14], the effectiveness of CCI and Hematopoietic Cell Transplantation Specific Comorbidity Index (HCT-CI) were examined in 181 patients with DLBCL. All patients received R-CHOP, and a higher CCI score was associated with a lower rate of complete response (p = 0.020). High CCI and HCT-CI were significantly associated with short OS (3-year OS: CCI ≥ 2 vs. 0–1, 38.9% vs. 81.3%, p < 0.001; HCT-CI ≥ 2 vs. 0–1, 56.9% vs. 84.9%, p < 0.001). In our study, the follow-up duration of the subgroup with a CCI score of 0–2 was significantly higher than the subgroup with a score of 3–8 (p = 0.036). In another study from 2018 [15], 3905 adults with DLBCL were examined; 997 of the patients (26%) had a CCI score of ≥ 2. Among patients selected for curative therapy, high CCI score was associated with an increased risk of mortality, but not disease-related mortality. In our study, the number of patients with a CCI score of > 2 was 126 (74.1%). The follow-up duration of the subgroup with a CCI score of 0–2 was significantly higher than the subgroup with a score of 3–8 (p = 0.036). However, there was no significant difference between the two subgroups in terms of mortality (p = 0.289). Another study [16] examined 11,780 DLBCL patients aged ≥ 65 years. All of the patients received R-CHOP regimen; being in advanced age or stage, having a CCI score of ≥ 1 were associated with DLBCL-related mortality.

Improving the power of standard prognostic indexes is a topic of recent literature. At this point, the use of CCI score to improve prognosis prediction is an important research topic. In a study from 2018 [17], the aim was to evaluate the prognostic significance of comorbidities in 962 DLBCL patients. A new comorbidity-NCCN-IPI (cNCCN-IPI) scoring system was developed by adding an additional 3 points if the patient had a CCI score of ≥ 2. The prognostic value of the new cNCCN-IPI was 2.1% better than IPI and 1.3% better than NCCN-IPI (p < 0.05). It was observed that cNCCN-IPI showed better discrimination power of 5.1% compared to IPI and 3.6% better than NCCN-IPI, especially in the elderly patients with increased comorbidities. In our study, when IPI and CCI scores were evaluated together and compared with mortality as a reference; the AUC for CCI was 0.628 (95% CI: 0.506–0.749), and the AUC for IPI was 0.563 (95% CI: 0.484–0.639). There was also no significant difference between ROC curves. Also, patients with a CCI score of ≥ 4 had shorter OS comperad to those with a score of < 4 (Hazard ratio: 2.93, 95% CI: 1.33–6.44, p = 0.008).

In another study from 2020 [18], CCI was used to examine the effect of comorbidities in patients with advanced age (60 years and older) with acute myeloid leukemia; 65% of the entire cohort had CCI 0, 24% CCI 1, and 11% had CCI 2. Patients with a CCI score of 0 were more likely to receive chemotherapy, especially multi-agent regimen, and underwent hematopoietic cell transplantation. In multivariate analyses, 1-month mortality and OS were significantly shorter in patients with a CCI score of 1 or 2 compared to CCI 0. In another study from 2020 [19], the relationship between the prevalence of comorbidity and OS in elderly patients with hematological malignancies was examined. CCI scores of patients were found to be significant prognostic factors for OS (p < 0.05). Similarly, the development of a scoring system for DLBCL that will take into account the impact of comorbidities and for a more effective prediction of prognosis in elderly patients and the use of CCI for this purpose might be seen as a significant step.

Although ECOG is generally used in combination with other scoring systems, significant results were obtained in terms of mortality in our study. The AUC for ECOG was resulted as 0.672 (95% CI: 0.596–0.743) in terms of mortality. There was also no significant difference in comparisons between the ROC curves of CCI, IPI and ECOG. These analyzes seem important to emphasize the importance of CCI as well as the proven power of IPI or ECOG for the lymphoma group.

Another important discussion point could be seen as the modified doses of regimen received by the patients in our study. Some modifications in R-CHOP regimen had to be made, especially in cases with renal and hepatic dysfunction. This may have caused the inability to obtain significant results in statistical comparisons based on high CCI scores. This result highlights the importance of considering the

initial comorbidity burden and especially in the treatment of advanced DLBCL in terms of OS.

The most important limitation point of this study is the presence of a limited patient population, especially when divided into subgroups have made the statistical analysis difficult. Also, PFS data of patients could not be obtained retrospectively because of lacking data.

In conclusion, in this study, the follow-up duration of the subgroup with a CCI score of 0–2 was significantly higher than the subgroup with a score of 3–8 ($p = 0.036$). When the CCI, IPI and ECOG scores were compared with the mortality status of the patients as a reference, AUCs were resulted as 0.628 (95% CI: 0.506–0.749), 0.563 (95% CI: 0.484–0.639) and 0.672 (95% CI: 0.596–0.743), respectively. There was no significant difference between the ROC curves of CCI, IPI and ECOG scores. Patients with a CCI score of ≥ 4 had shorter OS comperad to those with a score of < 4. Rather than claiming that CCI is superior to IPI, ECOG or another scoring system in a single-center patient population, it should be stated that CCI is also an effective scoring system in patients diagnosed with DLBCL. The efficacy of CCI could also be demonstrated and new prognocytic scoring systems could be developed with studies to be conducted in larger patient populations.

Abbreviations

DLBCL	Diffuse large B-cell lymphoma.
IPI	International Prognostic Index.
NHL	Non-Hodgkin lymphoma.
LDH	Lactate dehydrogenase.
ULN	The upper limit of normal.
ECOG	Eastern Cooperative Oncology Group.
R-IPI	The revised IPI.
NCCN	National Comprehensive Cancer Network.
CNS	Central nervous system.
CCI	Charlson Comorbidity Index.
AUC	Area under the curve.
HCT-CI	Hematopoietic Cell Transplantation Specific Comorbidity Index.
OS	Overall survival.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12288-022-01567-5.

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Authors' Contributions R.E. conceived the study; R.E., I.S., S.K., B.Z.P., N.E., A.I.G., D.A., N.D., E.E.D. and O.Y. acquired data; R.E. analyzed data; IS wrote the original draft; all authors revised and approved the final manuscript.

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Data Availability The authors declare that data supporting the findings of this study are available within the referenced articles.

Declarations

Ethics approval and Consent to Participate Ethical committee approval was received (Prof.Dr. Cemil Tascioglu Training and Research Hospital, Approval date and number: 19.4.2021-171) 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.

Patient Consent for Publication An informed consent obtained as written forms from all of our patients to publish.

Competing Interests None to declare.

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