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 $\geq 4$ had shorter OS compared 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

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 $\geq 4$ had shorter OS compared 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

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 $\geq 2$, and $>1$ site with extranodal involvement) and divides patients into 4 risk groups...
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 a. Charlson Comorbidity Index (CCI)

| Comorbidity | Score |
|-------------|-------|
| Age         | < 50; 50–59; 60–69; 70–79; ≥ 80 |
| Coronary artery disease | 1 point |
| Congestive heart failure | 1 point |
| Peripheral vascular disease | 1 point |
| Cerebrovascular disease | 1 point |
| Dementia     | 1 point |
| Chronic pulmonary disease | 1 point |
| Connective tissue disorder | 1 point |
| Peptic ulcer disease | 1 point |
| Liver disease | Mild; Moderate to severe 3 points |
| Diabetes mellitus | Uncomplicated; End organ damage 2 points |
| Hemiplegia   | 2 points |
| Moderate or severe renal disease | 2 points |
| Leukemia or lymphoma | 2 points |
| Solid tumor  | Localized; Metastatic 6 points |
| AIDS         | 6 points |

Table 1 b. Dose Modifications for R-CHOP

| Neutrophils ≥ 1 x 10^9/L | 100% dose |
|--------------------------|-----------|
| Neutrophils 0.5 - <1 x 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 x 10^9/L | Delayed by one week |
| Platelets ≥ 75 x 10^9/L | 100% dose |
| Platelets 50–74 x 10^9/L | 75% of cyclophosphamide and doxorubicin dose |
| Platelets < 50 x 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% |
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 an 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.
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,
gender) of the patients, body mass indexes (BMI) at initial
diagnosis, LDH levels (normal/high), stages (I-IV), pres-
ence of B symptoms, extranodal involvement (> 1 present or
absent), ECOG, IPI, CCI scores, presence of comorbid dis-
ease (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

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

| CCI (n) | Follow-up duration, months | 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* |
|------------|-----------------------|----|
| 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) |

*Log rank test

### Fig. 1
ROC curves of CCI, IPI and ECOG
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 investigated using the log rank test. The Kaplan-Meier 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

**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)

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**Fig. 2** Kaplan-Meier analysis for overall survival: the effect of CCI score
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 comparable 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 compared 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 analyses 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 compared 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 prognostic 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.

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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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