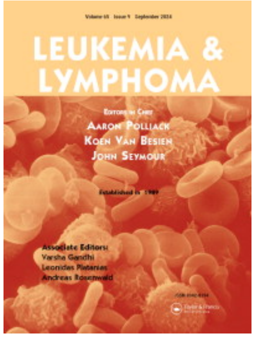

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ORIGINAL ARTICLE

A new scoring system to predict survival in elderly advanced stage Hodgkin lymphoma patients

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ABSTRACT
Predictive prognostic scoring (PS) systems are not primarily applicable to elderly patients with classical Hodgkin lymphoma (cHL). The objective of this study was to develop a PS system for these patients. The derivation cohort (DC) was utilized for model development, consisting of 97 variables. The resulting algorithm was named as Hodgkin's Lymphoma Early Death in the Elderly within 12 months (HEDEL12). Internal and external validation cohorts (IVC and EVC) were employed for validation. A total of 286 patients were evaluated retrospectively. In DC 38 of 178 patients died within the first 12 months and overall survival (OS) at 12-month was 78.6%. Independent predictors of HEDEL12 were female sex, low albumin levels (<3.5 g/dL), and ECOG scores 2-4. According to HEDEL12 scores 0–1, OS at 12- months were 89.8% and 91.0% for IVC and EVC, respectively. The HEDEL12 scoring is useful in predicting the survival of advanced-stage cHL patients.

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Elderly hodgkin lymphoma; prognostic scoring; advanced stage

KEY POINTS
1. Predictive prognostic scoring (PS) systems are not applicable to elderly patients with classical Hodgkin lymphoma
2. Female sex, low albumin levels (<3.5 g/dL), and ECOG scores 2-4 are independent predictors of survival in older advanced stage cHL patients.

1. Introduction

The majority of patients diagnosed with classical Hodgkin lymphoma (cHL) have a high chance of cure, and the standard treatment approach often involves positron emission tomography (PET) guided therapy to minimize the adverse effects of chemotherapy and radiation [1]. Older individuals, who are typically not included in clinical trials, have been largely excluded from new therapeutic options [2–5]. In the context of cHL, elderly patients are defined as those aged 60 years and older, comprising 15% to 30% of all newly diagnosed cases [6]. Unfortunately, the prognosis for elderly patients is significantly worse when compared to their younger counterparts [2,7]. Elderly individuals commonly exhibit risk factors associated with poorer outcomes, such as Epstein-Barr virus positivity, B

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symptoms, age over 70 years, comorbidities, advanced disease stage, and lower functional status [8].

In this population, the standard chemotherapy regimen for classical cHL is doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD). However, ABVD is highly toxic in elderly patients, often leading to dose reduction, treatment delay, increased toxicity, and treatment-related mortality [4,7]. Currently, there is a lack of consensus regarding the standard treatment approach for this specific age group. Concerningly, some experts estimate that approximately 5% of elderly individuals present with severe cases of undiagnosed HL and pass away before any treatment [9].

Currently, three scoring methods are utilized to predict the prognosis of patients with cHL: the International Prognostic Score (IPS), the German Hodgkin Study Group (GHSG) score, and the European Organization for the Research and Treatment of Cancer (EORTC) score. The EORTC and GHSG scores are employed in the early stages of the disease, while the IPS is used to evaluate advanced stages [10–12]. However, these predictive scoring methods are not primarily applicable to elderly patients. Given the distinctive clinical characteristics, treatment outcomes, and prognosis of elderly individuals, a new prognostic scoring method specifically designed for this age group is necessary. In this retrospective study, our objective was to develop a novel prognostic scoring system for elderly cHL patients in order to accurately predict their survival.

2. Methods

2.1. Study population

This study presents retrospective data of an inventory of elderly patients with cHL, which comprises a total of 97 variables regarding demographic and the disease- related variables including the disease histologic subtype, Ann-Arbor stage, the International Prognostic Score, extranodal involvement, splenic involvement, presence of B-symptoms, status of bulky disease, Eastern Cooperative Oncology Group (ECOG) performance status, and comorbidities; laboratory variables at diagnosis including serum lactate dehydrogenase level (LDH), C-reactive protein, erythrocyte sedimentation rate, creatinine, albumin levels, and complete blood count; imaging data such as response assessment tools, interim response, and end of treatment response; treatment data incorporating the first and subsequent lines of treatment, number of chemotherapy cycles, number of bleomycin cycles, accompanying radiotherapy, and granulocyte colony stimulating factor (G-CSF) need; adverse event data including any adverse event, which was attributed to the treatment received, bleomycin toxicity, and treatment-related deaths; and survival data.

Patients were classified into two groups based on the end-of-treatment evaluations: responders and non-responders according to PET-computed tomography (PET- CT) or CT. For patients evaluated with PET-CT, those with Deauville scores (DS) ranging from 1 to 3 were classified as responders, whereas those with a DS of 4 or 5 were considered non-responders. In the case of CT evaluations, all patients with complete responses were classified as responders, while all others were categorized as non-responders.

Patients in the inventory were diagnosed between 2004 and 2020. The inventory was first created in February 2020. Last patient data were recorded on March 2022. Data were collected from electronic databases and patient chart files in nine university-based hospitals (Supplemental Table A1). This cohort of patients was referred to as the derivation cohort, and it was also utilized as the internal validation cohort. An ethics committee approval was obtained for the study from the local institutional board (Decision No:2020/5 Date: 04.02.2020).

We enrolled patients aged 60 years and older who were diagnosed with cHL and received at least one cycle of chemotherapy. Additionally, patients were required to have available follow-up survival data. We excluded individuals with nodular lymphocyte-predominant Hodgkin lymphoma, those with incomplete laboratory or imaging data, patients who received alternative/complementary or herbal treatments, and individuals who did not undergo chemotherapy or radiotherapy.

The external validation cohort comprised data from patients recruited from nine additional university-based medical centers (supplemental Table A1). The geographic distribution of the centers in both the derivation and validation cohorts was similar. The same inclusion and exclusion criteria were applied to the external validation cohort as well.

2.2. Hypothesis

In our preliminary analyses, we observed that a total of 38 out of 178 patients (21.3%) died within the first year of treatment in derivation cohort. Based on this observation, we hypothesized that demographic, disease-related, treatment-related, or laboratory characteristics could potentially serve as predictors of early mortality in elderly patients with cHL.

2.3. Definitions

Early death in this study was defined as any death occurring within 12 months following the administration of the first dose of treatment. Overall survival (OS) was defined as the time interval between the first dose of treatment and either death from any cause or the last contact with the patient. Given our primary focus on early death, the survival data for patients who survived beyond 12 months were censored at the 12-month mark. The survival outcomes were reported as the median OS time with corresponding 95% confidence intervals (CIs) or as the proportion of patients who survived at least 12 months.

2.4. Model building

For model building, we utilized the derivation cohort. The dependent variable of interest was OS at 12 months. In the univariate analyses, we examined several independent variables, including age, sex, extranodal involvement, bulky disease, B-symptoms, splenic involvement, number of comorbidities, presence of hypertension, coronary heart disease, chronic obstructive pulmonary disease, stage, ECOG performance status, serum LDH and albumin levels, erythrocyte sedimentation rate, white blood cell count, lymphocyte count and percentage, and hemoglobin level. Continuous variables were dichotomized using receiver operating characteristic (ROC) curves, upper limits of reference ranges, clinically significant cutoff points, or values employed in existing prognostic scoring systems. Various iterations of the independent variables were tested in the univariate analyses, calculating hazard ratios and 95% CIs. Selection of the most appropriate variation of the independent variables took into account their predictive potential and clinical applicability (Supplemental Table A2). Models were constructed using a maximum number of candidate parameters that exhibited clinical relevance, significant effect size, and adequate discriminatory power. The Cox proportional hazards regression models were developed through a backward stepwise variable inclusion and exclusion procedure. Variables with a p-value less than 0.10 were included in the multivariate analyses, while the least significant variables were subsequently eliminated one by one. (Supplemental Table A3).

Cox-Snell residuals were employed to assess the overall goodness of fit of the model. Schoenfeld and scaled Schoenfeld residuals were utilized to examine and test the proportional hazards assumption. A global Schoenfeld p-value of 0.05 or higher indicated that the model satisfied the proportional hazards assumption. In cases where a predictor did not meet the proportional hazards assumption, a modification of the Cox proportional hazards model known as the "stratified Cox model" was employed to control for the predictor through stratification. To compare the log likelihood statistics between the interaction model and the no-interaction model, a likelihood ratio (LR) test was conducted. The calculation of the LR test statistic is as follows:

$$LR = \left[-2logLinteraction\right] - \left[-2logLno-interaction\right]$$

Under the null hypothesis, the no-interaction model is considered statistically valid. If the LR value is not statistically significant, it indicates that there is insufficient evidence to reject the null hypothesis.

The variables that were found to be predictors of 12-month mortality in the stratified Cox model were incorporated into the clinical scoring system. The β coefficients from the stratified Cox model were used to assign score weights. The resulting algorithm was named as Hodgkin's Lymphoma Early Death in Elderly within 12 months (HEDEL12).

2.5. Model validation

We excluded one patient from the derivation cohort due to missing HEDEL12 data. The remaining patients in the cohort were utilized as the internal validation cohort. Model validation was performed using both internal and external validation cohorts.

2.6. The model performance

The performance of the model was evaluated based on three aspects: discrimination, calibration, and clinical usefulness. The discriminatory ability of the novel scoring system was quantified using Harrell's concordance (C) statistic. Calibration refers to the accuracy of predicting survival or failure probabilities at different time points. Model calibration was assessed by plotting the predicted survival against the observed survival. A well-calibrated model demonstrates predictions that closely align with the 45° line on the calibration plot. To determine the clinical usefulness and net benefit of the scoring system, we conducted decision curve analysis. This analysis helps evaluate the tradeoff between potential benefits and harms of using the scoring system in clinical decision-making.

2.7. Statistical analyses

We assessed the normality of distribution for continuous variables using the Shapiro-Wilks test. Continuous variables were compared using Student's t-test if they had a normal distribution, while the Wilcoxon rank-sum test was used for variables with non-normal distribution. Categorical variables were compared using the chi-square test and Fisher's exact test when appropriate. Survival curves generated by Kaplan-Meier analysis were compared using the log- rank test. All statistical calculations were conducted using Stata version 14.0 (StataCorp, College Station, TX, USA).

3. Results

3.1. Patients

A total of 333 patients from 18 centers located in different geographic regions of the country were included in the analyses. Among them, 286 patients met the inclusion criteria. The derivation cohort consisted of 178 patients from nine different centers, while the external validation cohort included 108 patients from another nine different centers (Figure 1). Derivation and validation cohorts were obtained from various centers in the different parts of the country and had different characteristics in terms of several clinical and laboratory parameters (Table 1).

3.2. Overall survival in derivation cohort

Thirty-eight out of 178 patients died within the first 12 months of the treatment. Median time to death was 5.2 months (95% CI: 4.4 to 6 months) for the patients who passed away. OS proportion at 12-months was 78.6% (95% CI: 71.8% to 83.9%) (Supplemental Figure A1). In 37 out of 178 patients (20.8%), planned treatment could not be completed due to death or toxicity in the derivation cohort (Table 1).

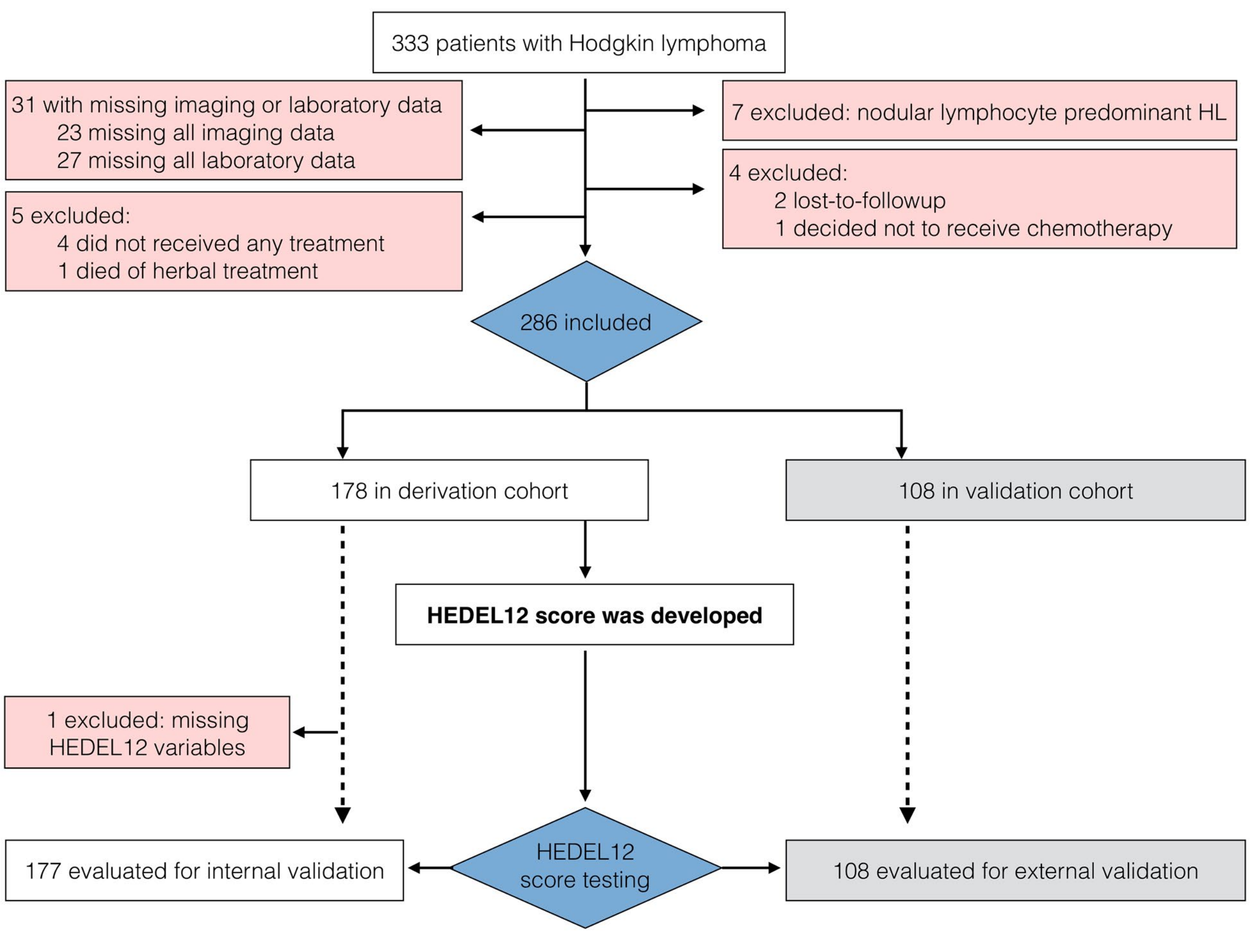

Figure 1. CONSORT diagram.

Table 1. Demographic, clinic, laboratory, and treatment-related factors in derivation and validation sets.

Variables	Nderiv	Derivation set (*N* = 178)	Nvalid	Validation set (*N* = 108)	*p*
Pre-treatment clinical variables					
Age, median (range) years	178	67.0 (60.0–85.0)	108	68 (60.0–86.0)	0.53
Male, *n* (%)	178	99 (55.2)	108	70 (64.8)	0.13
Extranodal involvement, *n* (%)	178	50 (28.1)	108	27 (25.0)	0.57
Bulky disease, *n* (%)	178	15 (8.4)	108	11 (11.1)	0.45
B symptoms, *n* (%)	178	110 (61.8)	108	59 (54.6)	0.23
Splenic involvement, n (%)	178	51 (28.7)	108	23 (21.3)	0.17
ECOG 2–4, *n* (%)	178	79 (44.4)	108	33 (30.6)	0.02
Any comorbidities, *n* (%)	178	112 (62.9)	108	79 (73.2)	0.08
≥2 comorbidities	178	46 (25.8)	108	21 (19.4)	0.22
Early stage, unfavorable, *n* (%)	178	33 (18.5)	108	17 (15.7)	0.47
Advanced stage, IPS ≥ 4, *n* (%)	178	49 (27.5)	108	42 (38.9)	0.05
Histologic subtype, *n* (%)	152		92		0.76
Mixed cellular		65 (42.8)		33 (35.9)	
Nodular sclerosis		60 (39.5)		41 (44.6)	
Lymphocyte-rich		19 (12.5)		13 (14.1)	
Lymphocyte-depleted		8 (5.3)		5 (5.4)	
Pre-treatment laboratory variables					
LDH, higher than ULN, *n* (%)	178	59 (33.2)	108	59 (54.6)	<0.001
Sedimentation, median (range), mm/h	178	45 (4–166)	108	51 (3–151)	0.57
WBC, median (range), x10^3/µL	178	7.5 (1.9–21.2)	108	7.5 (1.2–23.4)	0.84
Lymphocytes, median (range), x10^3/µL	178	1.3 (0.3–17.8)	106	1.4 (0.2–4.9)	0.17
Hemoglobin, median (range), g/dL	178	11.4 (6.7–16.9)	107	11.4 (7.5–16.4)	0.44
Albumin <3.5 g/dL, *n* (%)	177	60 (33.9)	108	30 (27.8)	0.28
Treatment-related variables					
First-line treatment	178		108		0.27
ABVD		158 (88.8)		98 (90.7)	
AVD		10 (5.6)		8 (7.4)	
Other		10 (5.6)		2 (1.9)	
Chemotherapy cycles, median (range)	178		108		<0.001
1–2		22 (12.4)		14 (13.0)	
3–4		57 (32.0)		13 (12.0)	
5–6		80 (44.9)		77 (71.3)	
7–8		19 (10.7)		4 (3.7)	
Treatment not completed, n (%)	178	37 (20.8)	108	14 (13.0)	0.09
Bleomycin toxicity, *n* (%)	159	44 (27.7)	100	25 (25.0)	0.64
G-CSF support, *n* (%)	178	93 (52.3)	108	84 (77.8)	<0.001
Radiotherapy, *n* (%)	178	37 (20.8)	108	23 (21.3)	0.92

Hemoglobin had normal distribution; hence mean comparison was performed by *t*-test. All other continuous variables were compared by the Wilcoxon rank-sum test. Chi-square test was used to compare categorical variables.
ABVD: Adriamycin bleomycin, vinblastine, dacarbazine; ECOG: eastern cooperative oncology group performance score; G-CSF: granulocyte colony-stimulating factor; LDH: lactate dehydrogenase; ULN :upper limit of norma; WBC: white blood cells.

3.3. Predictors of overall survival in the derivation cohort

The final model for predicting OS at 12 months included four independent predictor variables: female sex, advanced-stage, low albumin levels (<3.5 g/dL), and ECOG performance scores 2–4 (Supplemental Table A3). However, the Cox-Snell residual plot indicated that the model did not adequately fit the data (Supplemental Figure A2). Although the scaled Schoenfeld residuals showed a p-value of 0.15 in the global test, indicating that overall proportional hazards assumption was met, the variable "advanced-stage" did not satisfy the proportional hazard assumption (Supplemental Table A4). Therefore, we decided to stratify this variable. In the interaction model, different baseline hazard functions and coefficients were obtained for each stratum. The LR test showed that the LR chi-square value was not significant for 3 degrees of freedom (LR chi-square: 1.19, df: 3, $p = 0.76$), indicating that the interaction model was not significantly different from the no-interaction model (Supplemental Table A5). Consequently, the stratified Cox model with no interaction was deemed acceptable. Furthermore, the scaled Schoenfeld residual test demonstrated that all three parameters of the no-interaction model satisfied the proportional hazards assumption (global test *p*-value = 0.42) (Supplemental Table A6).

3.4. Hedel-12

The beta coefficients obtained from the stratified Cox model with no-interaction were utilized to assign score points for each variable in the final algorithm, known as HEDEL12 (Table 2). To validate the performance of HEDEL12, we tested it in two independent validation cohorts. The internal validation cohort was derived from the derivation cohort, which initially included 178 patients. However, one patient who lacked one of the HEDEL12 parameters was excluded from the analysis. As a result, the internal validation cohort consisted of 177 patients, and HEDEL12 was evaluated using this cohort.

In the internal validation cohort, the 12-month failure rates for HEDEL12 scores of 0- 1, 2, and 3 were found to be 10.2%, 30.0%, and 88.9%, respectively (Table 3). Due to the limited number of patients with a HEDEL12 score of 3 in both the internal and external validation cohorts (nine and seven patients, respectively), we made the decision to merge the scores of 2 and 3. The OS at 12 months was 89.8% (95% CI: 82.3% to 94.2%) for HEDEL12 scores of 0-1 and 62.2% (95% CI: 49.7% to 72.5%) for scores of 2-3, showing a statistically significant difference ($p < 0.001$, Figure 2). HEDEL12 demonstrated excellent calibration and yielded a Harrel's C-statistic of 0.67 (supplemental Figure A3). Furthermore, the decision curve analysis demonstrated that the use of the HEDEL12 score provided superior net benefit when the threshold probability was 10% or higher (supplemental Figure A4).

In the external validation cohort, OS rate at 12-months were 91.0% (95% CI: 82.1% to 95.6%), 65.2% (95% CI: 44.9% to 79.5%), for the HEDEL12 scores 0-1 and 2-3, respectively ($p < 0.001$, Figure 3). Harrel's C-statistics was 0.68 (supplemental Figure A5). Finally, the decision curve analysis confirmed superior net benefit of HEDEL12 from a threshold probability of 10% or higher (supplemental Figure A6).

4. Discussion

cHL manifests differently in elderly patients compared to younger patients, with one of the key distinctions being the significantly lower expected survival rate in the elderly population. It has been consistently observed that patients over the age of 60 years have relatively poor outcomes, with an expected 5-year event-free survival and OS rates ranging from 30% to 40% and 40% to 50%, respectively [13–15]. Numerous analyses have highlighted several factors that contribute to unfavorable prognosis in older patients, including pathogenetic pathways, tumor pathobiology, host-related factors, clinical presentation, and symptoms. These variables collectively shape the disease course and impact treatment responses and overall outcomes in the elderly. Understanding these factors is crucial for improve the management strategies and prognosis.

Mixed cellular type histology (31-50%) and higher frequency of B symptoms (50% vs 43%) are seen more commonly in elderly patients [2,16,17]. Our analyses were consistent with the previous observations regarding the prevalence of histological subtypes and B symptoms which may have a negative impact on the survival rates. According to the GHSG HD5 to HD9 trials, the

Table 2. HEDEL12 score for the prediction of early death in elderly patients with hodgkin's lymphoma within the first 12 months.

Parameter	Beta	SE	HR (95% CI	P	HEDEL12 score points
Female sex	0.90	0.34	2.47 (1.26 to 4.85)	0.009	1
ECOG score 2-4	0.94	0.36	2.56 (1.27 to 5.15)	0.008	1
Albumin <3.5 g/dL	1.18	0.34	3.26 (1.67 to 6.36)	0.001	1

ECOG; Eastern Cooperative Oncology Group performance score.

Table 3. Validation of HEDEL12.

	Internal validation			External validation		
Score	N	12-mo failure rate (%)	95% CI	N	12-mo failure rate	95%CI
0-1	108	10.2	5.8-17.7	79	9.0	4.4 to 17.9
2	60	30.0	20.1-43.3	22	32.1	16.7 to 55.9
3	9	88.9	61.2-99.4	7	42.9	16.3 to 82.8

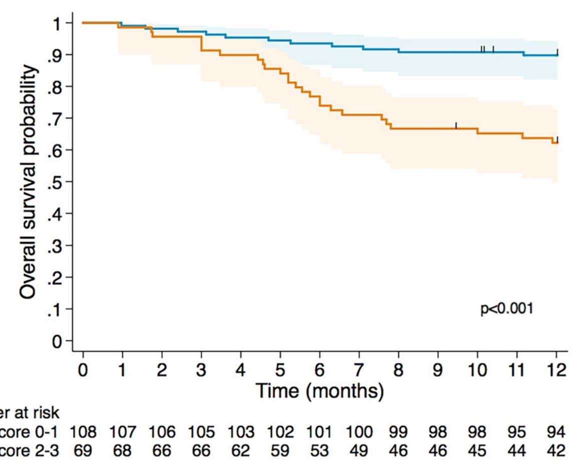

Figure 2. Overall survival in internal validation cohort.

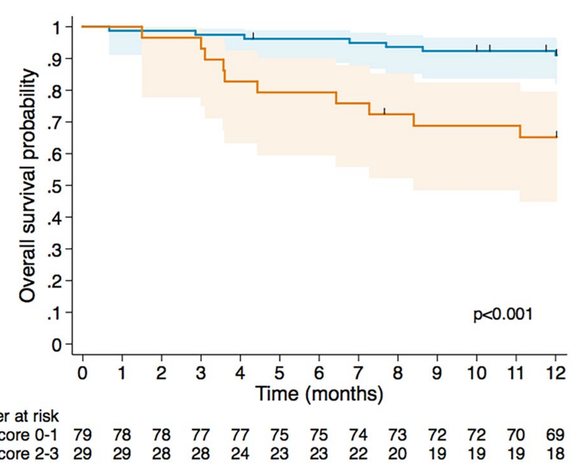

Figure 3. Overall survival in external validation cohort.

prevalence of grade III-IV infection was about 15% and 6% in older and younger patients, respectively. Six percent of elderly patients died due to adverse events caused by acute treatment toxicity [2]. We also observed that a total of 177 out of 286 patients (61.9%) required G-CSF support during their treatment courses.

Providing clinical care for senior cHL remains a highly challenging task due to the limitations in studies specifically focused on this population. While cHL is largely curable in younger patients, the outcomes for older patients especially with advanced-stage are unsatisfactory [16]. The prognosis of individuals with advanced HL is currently determined using IPS. However, the study from which the IPS was generated included only patients between the age of 15 and 65, with a relatively small proportion of 9% falling within the 55 to 65-year-old range [12]. Our analyses demonstrated that an IPS score of ≥4 had no noticeable impact on the survival of elderly patients. Therefore, prognostic assessment in older patients with HL would require additional information beyond what the IPS system can provide [18].

Finally, a new prognostic scoring system for advanced-stage disease, known as the Advanced-stage cHL International Prognostication Index (A-HIPI), has been published recently. Similar variables to those in the IPS were found to be associated with 5-year survival. Additionally, age and absolute lymphocyte count showed nonlinear relationships with outcomes. However, it is worth noting that, similar to the IPS, the A-HIPI scoring system was developed based on data from a population under the age of 65 [19]. Thus, it is clear that current prognostic assessment tools in advanced cHL are not applicable to elderly patient population.

As our primary focus in this study was early death, we censored the survival data at 12 months for patients who survived beyond this time frame. We determined that the majority of these deaths were attributed to toxicity or infections. Then we developed a novel and informative scoring system, named the HEDEL12, which exhibited a satisfactory discriminatory power in predicting early death among elderly cHL. OS rates ranged between 89.2% to 91.0% in patients with an HEDEL12 scores of 0-1 and 62.2% to 65.2% for those of 2-3. HEDEL12 is easy-to-use scoring system, which only utilizes three parameters: female sex, low albumin levels (<3.5 g/dL), and ECOG performance scores 2 to 4. Since most of the patients in our analyzes had an advanced disease, it should be noted that the HEDEL12 is applicable to the elderly patients with advanced cHL only.

Comorbidity and frailty, two significant factors influencing the prognosis of cHL patients, have been extensively studied in various research. It was observed that 54% of the patients had at least one severe comorbidity, as indicated by a Cumulative Illness Rating Scale (CIRS) score grade ≥ 3. Furthermore, patients with severe comorbidity were more likely to have advanced disease, an IPS score greater than 3, and were less likely to receive anthracycline-included therapy [20]. We observed that 62.9% to 73.2% of elderly patients had any comorbidity in our cohort. However, neither the presence of a specific comorbidity nor the number of comorbidities had an impact on early death.

Another trial that focused on frailty among older individuals with cHL, showed that a decline in the ability to perform activities of daily living was an independent predictor of poorer progression-free survival and OS. Additionally, a CIRS score of 10 or higher was associated with early discontinuation of treatment due to toxicity [21]. Due to the retrospective nature of this analysis, we were unable to evaluate the frailty of the patients. However, we observed that patients with an ECOG performance score of 2–4 had a substantial survival disadvantage. Sykorova et al. reported that 23% of patients had an ECOG performance score of 2 points or higher and it was associated with an inferior OS (HR: 1.691 *p*:0.049) [22]. Performance status is an important predictor of survival in various subtypes of lymphoma as well [12,23].

Male gender is one of the negative key parameters of IPS and A-HIPI scoring systems in youngsters with advanced cHL [12,19]. However, studies examining the predictors of survival in elderly cHL report conflicting results regarding gender [22,24–27]. Here we report that the female gender has a negative impact on early death. According to a systematic review, elderly females exhibited a higher frailty index compared to men and they often experience poorer health conditions due to having longer lifespans. Frailty is associated with a greater vulnerability to disease-related processes as well as treatment-related side effects [26].

Supporting our observations, Kumar et al. emphasized that elderly cHL patients exhibited a higher 12-month mortality rate, with approximately 20% of patients succumbing during this period. This study specifically examined patients aged over 65 and identified the Charlson comorbidity index, B-symptoms, advanced stage, and age (in 5-year increments) as the four primary factors influencing mortality within the first year. However, the researchers did not evaluate ECOG performance scores and albumin levels in this particular study [24]. Our analyses primarily focused on patients with advanced-stage disease. Prevalence of B symptoms and comorbidities is high among patients with advanced stage [28]. We performed several uni- and multivariate analyses to test the impacts of the different variations of age, the Ann-Arbor stage, B-symptoms, and comorbidities. However, multivariate analyses did not show a relationship between these parameters and early death, when the HEDEL12 parameters were included in the models.

First-line management of the cHL is still a matter of debate because the lower disease prevalence in older patients and the scarcity of research specifically designed for this group. Early mortality poses a significant concern in older individuals with cHL, underscoring the importance of carefully evaluating this risk before initiating treatment for these patients. The HEDEL12 score is a simple risk assessment tool, which can be used to determine patients in low and high risk groups. In high-risk patients, adopting an approach of initiating treatment at a lower intensity regimen such as single agent and/or combination of AVD chemotherapy with anti CD30 (brentuximab vedotin) and anti PD-1 therapies (nivolumab, pembrolizumab) and progressively increasing it based on tolerability would be a more suitable strategy. It is noteworthy that, HEDEL12 scoring system should be reevaluated in the era of new therapeutic options in elderly HL.

An important limitation of HEDEL12 is the fact that HEDEL12 cohort included only 19 patients (~10% of all cohort) with 80 years of age or older. Seven out of 19 patients died within seven months of first-line treatment. So, octogenarians were underrepresented in HEDEL12 population. If the cohort included more patients with an age ≥80 years, age could be a predictor of mortality. A validation in this population is needed.

In conclusion, the probability of death within the first 12 months of treatment in elderly patients with advanced HL is high. So, it is important to determine the patients who are at higher risk of early death. The HEDEL12 score, which utilizes female gender, ECOG performance score of 2-4, and low albumin levels as the parameters, can successfully stratify patients into low- and high-risk groups.

Ethical approval

The authors declare that the procedures were followed according to the Helsinki Declaration of the World Medical Association updated in 2013. The authors declare having followed the protocols in use at their working center regarding patients' data publication. The study was approved by Kocaeli University, Clinical Research Ethics Committee (Decision No:2020/5 Date: 04.02.2020). Informed consents from patients were obtained. The authors have declared that no competing interests exist.

Authors' contributions

O.M.: ** managing the patients, literature search, collecting data, writing and editing the manuscript.
T.T.: ** managing the patients, literature search, collecting and analyzed data, writing and editing the manuscript.
M.S.D.: managing the patients, literature search, collecting data and editing the manuscript.
F.K.K.: literature search, collecting data, writing and editing the manuscript.
U.A.: literature search, collecting data, writing and editing the manuscript.
All the other authors performed managing the patients and collecting data.

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