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A simplified, two-factor clinical prognostic scoring system for patients with newly diagnosed Hodgkins Lymphoma

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Dear Editor,

Outcomes in patients with Hodgkin Lymphoma (HL) have drastically improved in the last few decades as a result of better treatment protocols, the use of novel agents in the front-line setting, and utilizing a PET-based strategy to limit chemotherapy duration and toxicity [1–4]. While we have adopted newer regimens into the frontline treatment of HL, our methods of prognostication have remained the same. In addition, there are limitations in applying the prognostic models in different parts of the world. PET is the recommended modality for initial staging in HL, which is not available or accessible to many patients across the globe [5, 6]. Thus, there is a need to formulate a simplified scoring system for patients with HL, which can be easily utilized globally.

After institutional ethics committee approval, we retrospectively analyzed all patients with newly diagnosed classical HL treated at our center from 2011 to February 2023. Patient records were reviewed, and information regarding demographics, therapy, and survival were noted. An event was defined as refractory disease, relapse, or death due to any cause. Event-free survival (EFS) was defined as the time from diagnosis to time to event or last follow-up. Overall Survival (OS) was defined as the time from diagnosis to time of death due to any cause or last follow-up. Time to progression (TTP) was defined as the time from diagnosis to documentation of relapse or refractory disease or death due to progressive disease only. Data was censored on 28th February 2024.

To create a prognostic model, we divided our patient cohort into two groups—patients treated from 2018 to February 2023 were included in the Derivation Cohort, and patients treated from 2011 to 2017 were included in the Validation Cohort. Univariate Cox proportional hazard analysis (UVA) was done to look for baseline characteristics associated with OS. Factors found to be significantly associated with OS were included in a multivariate Cox proportional hazard analysis (MVA), and factors that emerged as independent predictors of OS in MVA were included in the prognostic model. A receiver operating characteristic (ROC) curve was made for continuous variables, and the Youden Index was calculated based on which the variable was dichotomized for the prognostic model. The discriminatory power of the different models and goodness of fit were assessed by calculating the Harrells concordance index. Kaplan–Meier was used for time-to-event analysis, and the log-rank test was used to compare survival. All statistical analysis was carried out in R (version 4.4.0).

Three hundred ten patients were treated between 2018 and 2023 and were a part of the derivation cohort, and 340 patients were treated between 2011 and 2017 and were included in the validation cohort. The baseline characteristics of the derivation cohort are shown in Supplementary Table 1. The median age of the patients in the derivation cohort was 32 years (IQR: 21–44.2 years), with the majority being male (63.5%). Most patients had advanced-stage disease ($N = 200$, 64.5%) and B symptoms at presentation ($N = 221$, 71.3%). Nine patients (2.9%) did not receive any therapy, either due to their choice or as the diagnosis was made after their death. Among the 301 patients who received therapy, 286 patients (95%) received ABVD as initial therapy. None of the patients received either checkpoint inhibitors or brentuximab as upfront therapy. Two-hundred sixty-nine patients (86.8%) were able to complete the pre-determined cycles of therapy (4 or 6 depending on stage).

SURVIVAL ANALYSIS

The median follow-up for patients in the derivation cohort was 28 months (IQR 16–54 months). Seventy-four patients (23.9%) had relapsed or refractory disease—56 patients (18.1%) with refractory disease and 18 patients (5.8%) with relapse after attaining initial response. Forty-eight patients (15.5%) died during follow-up. The most common cause of death was progressive disease in 27 patients (56.3%), followed by a combination of disease and infection ($n = 8$; 16.7%). Seven patients (14.6%) died due to infection alone, while 3 patients (6.3%) died due to chemotherapy toxicity. The median OS was not reached, and the estimated 5-year OS was 81% (95% confidence intervals 76–86.3%). On univariate analysis, age, baseline ECOG performance status, stage (early vs advanced), presence of extranodal disease, clinical jaundice at presentation, hemoglobin, lymphocyte percentage, and albumin were found to be significant predictors of OS. On multivariate analysis, only age, albumin, and clinical jaundice at presentation were identified as independent predictors of OS (Supplementary Table 2).

PROGNOSTIC SCORE CALCULATION

Based on the multivariate analysis, age, albumin and jaundice at presentation were considered as factors to create a prognostic score. Since jaundice was only seen in a minority of patients ($n = 17$, 5.5%), only age and albumin were used to develop a prognostic model, referred to from here on as the Simplified Prognostic Score (SPS). Both age and albumin were dichotomized for simplicity. The cutoff value for age was calculated as 40 years, and the cutoff value for albumin was calculated as 3.6 gm/dl based on the ROC curve and Youden index. Given the difference in hazard ratios for age and albumin, one score was allocated to patients 40 years and above, and 0 score was assigned to patients below 40 years. Similarly, a score of 2 was allocated to patients with an albumin of below 3.6 gm/dl, and a score of 0 was allocated to patients with an albumin of 3.6 gm/dl or above.

Survival outcomes were calculated according to the SPS. Given the similar survival in patients with a composite score of 1 and 2, it was decided to simplify the score further and divide patients into

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three groups—*Low risk*—Age > 40 years AND Albumin ≥ 3.6 gm/dl, *Intermediate risk*—Age ≤ 40 years OR Albumin < 3.6 g/dl and *High risk*—Age ≤ 40 years AND Albumin < 3.6 g/dl (Table 1). One hundred twenty patients (43.7%) were classified as low risk, 109 (39.6%) as intermediate risk, and 46 (16.7%) as high risk. The estimated 5-year OS was 92.9% (95% CI 85.2–1), 76.8% (95% CI 66.1–89.1), and 52.6% (95% CI 38.3–72.3) in low, intermediate, and high-risk groups, respectively ($p < 0.0001$). The EFS and OS curves for the derivation cohort are shown in Fig. 1A, B (Supplementary Table 3). The model was also able to divide the cohort into 3 distinct groups in terms of TTP, with the estimated 5-year TTP being 77.7% (95% CI 69.5–86.9), 66.3% (95% CI 55.7–78.9) and 62.7% (95% CI 49–80.3) in the three groups respectively ($p = 0.015$).

Table 1. Simplified Prognostic Score calculation.

Factors	Prognostic Score	
Age ≤ 40 years Albumin < 3.6 gm/dl	Low Risk	No factor present
	Intermediate Risk	Any 1-factor present
	High Risk	Both factors present

VALIDATION OF THE SPS

We next looked to see the performance of the SPS in our validation cohort. One hundred forty-two patients were classified as low risk, 117 patients as intermediate risk, and 59 patients as high risk as per the SPS, while 22 patients did not have albumin levels available. The estimated 5-year OS for patients with low, intermediate, and high-risk SPS was 93.6% (95% CI 89.4–98), 77.6% (95% CI 69.6–86.5), and 66.4% (95% CI 54.3–81.1) ($p < 0.0001$) (Fig. 1C, D). The difference in outcomes of the high-risk group in the derivation and validation cohort may be explained by the small number of patients in the high-risk group in each cohort (16.7% and 18.5%, respectively), which led to wide confidence intervals of the OS estimates. In addition, COVID-19 infections were a cause of death in a few patients in the derivation cohort, which could have possibly skewed outcomes.

PERFORMANCE COMPARISON WITH ESTABLISHED PROGNOSTIC SCORES

We sought to compare the performance of the SPS with existing prognostic models. The estimated 5-year OS of patients with Early Favorable, Early Unfavorable, and Advanced HL was 86.8% (95% CI

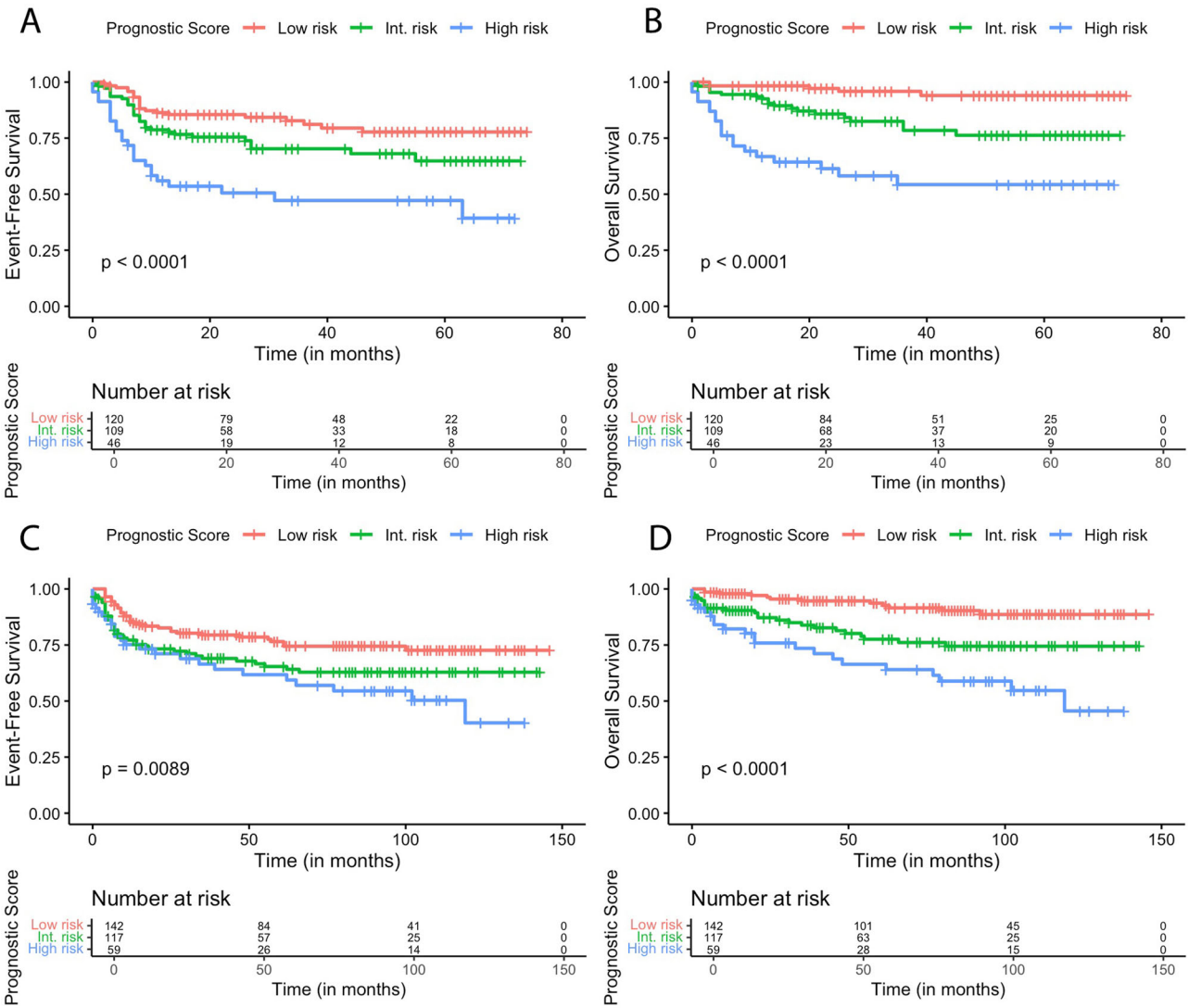

Fig. 1 Kaplan–Meier curves showcasing the difference in outcomes on the basis of the SPS. The different panels highlight **A** event free survival in the derivation cohort, **B** overall survival in the derivation cohort, **C** event-free survival in the validation cohort, **D** overall survival in the validation cohort.

75.1–1), 58.4% (46.1–74.1), and 59.3% (51.8–67.8), respectively, with a concordance index of 0.59. In comparison, the concordance index of the SPS was 0.75, suggesting a much higher goodness of fit. Among the patients in the derivation cohort, the SPS led to the down-staging of many patients with advanced-stage disease into the low-risk and intermediate-risk groups (Supplementary Fig. 1).

Taking into account only patients with advanced HL, the 5-year OS of patients with an IPS of 0–3 was 90.5% (95% CI 84.6–96.9), and for patients with an IPS of 4–7 was 60.9% (95% CI 49.7–74.8) with a concordance index of 0.70. In comparison, the SPS was able to delineate three clear groups, with the estimated 5-year OS being 92.9% (95% CI 85.2–1), 76.8% (95% CI 66.2–89.1), and 52.6% (95% CI 38.3–72.3) in the three groups with a higher concordance index of 0.74.

The SPS is a simple, 2 factor, clinical prognostic model for application in all patients with newly diagnosed HL. The model's strength lies in its simplicity and ease of application across different resource settings.

Age can impact the outcomes of patients with HL in different ways. Older patients with HL are thought to have a different disease biology with a higher incidence of advanced-stage disease in comparison to younger patients [7]. Additionally, the presence of comorbidities and increased risk of bleomycin toxicity may also lead to alteration of therapy, compromising response and outcomes [8]. Similarly, low serum albumin has consistently been shown to adversely affect the prognosis of patients with various hemato-lymphoid malignancies [9–11]. Low serum albumin levels may occur secondary to the poor nutritional status of the patient, sub-clinical or clinical hepatic involvement which affects albumin synthesis, or the overall cytokine-mediated catabolic state characterized by an increase in Th2 response, including Interleukin 6 [12].

In current practice, therapy for HL is tailored to the patient, with the choice of therapy, number of cycles of therapy, and omission of radiotherapy being dependent on stage. This has significant issues in terms of applicability in many regions across the world, where PET Scans are not easily accessible and available [6]. Lack of PET imaging at baseline may lead to down-staging of the disease stage by missing focal bone marrow involvement and extra-nodal disease involvement [13]. The SPS circumvents this issue and categorizes patients into three risk categories based on just two clinical factors that are almost universally available.

Our study has some limitations. It is a retrospective, single-center analysis, so differences in outcomes based on ethnicity and geography could not be captured. Most patients in our cohort received ABVD as initial therapy, so the applicability of the SPS in populations utilizing other protocols still needs to be established. Further validation of this model in other geographical settings is needed before treatment strategies adapted to the model are formulated. If the score is validated on a larger scale, patients with a score of 0 could be allocated to a simple ABVD based treatment strategy, while patients with a score 2 could potentially benefit from a BEACOPP based strategy or inclusion of novel agents upfront. This could help in triaging of resources in resource-constrained settings while avoiding chemotherapy-related toxicity in patients who could be cured with simple ABVD. However, any therapeutic strategy would need to be explored through a prospective trial, for which our study is the first step.

Charanpreet Singh[1], Lekshmon KS[1], Arihant Jain[1], Deepesh Lad[1], Alka Khadwal[1], Rajender Basher[2], Amanjit Bal[3], Radhika Srinivasan[4], Subhash Varma[1], Pankaj Malhotra[1] and Gaurav Prakash[1]✉

[1]*Department of Clinical Hematology and Medical Oncology, Postgraduate Institute of Medical Education and Research, Chandigarh, India.* [2]*Department of Nuclear Medicine, Postgraduate Institute of Medical Education and Research, Chandigarh, India.* [3]*Department of Histopathology, Postgraduate Institute of Medical Education and Research, Chandigarh, India.* [4]*Department of Cytology and Gynaecological Pathology, Postgraduate Institute of Medical Education and Research, Chandigarh, India.*
✉*email: drgp04@gmail.com*

DATA AVAILABILITY

The data will be made available on reasonable request to the corresponding authors.

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AUTHOR CONTRIBUTIONS

CS—Involved in patient care, collected the data, performed the analysis, and wrote the paper. LKS—Involved in patient care, collected the data and performed the analysis. AJ—Involved in patient care and edited the paper. DL—Involved in patient care and edited the paper. AK—Involved in patient care and edited the paper. RB—Involved in the diagnostic workup for the patients and edited the paper. AB—Involved in the diagnostic workup for the patients and edited the paper. RS—Involved in the diagnostic workup for the patients and edited the paper. SV—Involved in patient care and edited the paper. PM—Involved in patient care, formulated the hypothesis and protocol, and edited the paper. GP—Involved in patient care, formulated the hypothesis and protocol, performed the analysis, and edited the paper. All authors—read and approved the paper.

COMPETING INTERESTS
The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT
The study was carried out after approval by the Institute Ethics Committee (Reference Number—IEC-INT/2024/Study-2006) and was conducted in accordance to the declaration of Helsinki. Informed consent was obtained from patients for use of their data for the study.

ADDITIONAL INFORMATION
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Correspondence and requests for materials should be addressed to Gaurav Prakash.

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