haematologica
Journal of the Ferrata Storti Foundation

Navigating murky waters: risk scores for nodular lymphocyte-predominant Hodgkin lymphoma

by Emily J. Smith and Michael Sargent Binkley

Received: August 3, 2026.
Accepted: August 7, 2026.

Citation: Emily J. Smith and Michael Sargent Binkley.
Navigating murky waters: risk scores for nodular lymphocyte-predominant Hodgkin lymphoma.
Haematologica. 2026 Aug 20. doi: 10.3324/haematol.2026.301632 [Epub ahead of print]

Navigating murky waters: risk scores for nodular lymphocyte-predominant Hodgkin lymphoma

[1,*]Emily J. Smith, [1,*,#]Michael Sargent Binkley
[1]Department of Radiation Oncology, Stanford University, Stanford, CA, United States

*Equal contribution

#Corresponding Author:
Michael Sargent Binkley
875 Blake Wilbur Drive, Stanford, CA 94305
Tel: 650-725-9361 Fax: 650-723-3919 Email: msb996@stanford.edu

The authors declare no conflicts of interest to disclose.

Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) is a rare subtype of B-cell lymphoma characterized by a persistent risk of relapse but an excellent overall survival.[1] However, there is a subset that follow a more aggressive course and carry a higher risk of transformation to a large B-cell lymphoma. Historically, this disease was included in Hodgkin lymphoma (HL) trials and therefore was risk-stratified and treated similarly, which likely resulted in non-optimal treatment for patients.[2] Further highlighting the ambiguity in managing NLPHL, the National Comprehensive Cancer Network guidelines and the European Hematology Association guidelines recommend a wide range of treatment pathways depending on clinical stage, anywhere from observation to escalated chemotherapy regimens.[3,4] There have been efforts to refine clinical risk for patients with NLPHL beyond clinical staging (Figure 1).[1,5–7] In this issue of *Haematologica*, Eichenauer *et al.* compare two risk stratification scoring systems for NLPHL, the German Hodgkin Study Group (GHSG) score and the Lymphocyte-Predominant International Prognostic Score (LP-IPS), as well as test the utility of combining these two scores.[7]

The history of risk stratification scores started with the International Prognostic Score (IPS), which was derived from a large cohort of patients with HL that included a small percentage with NLPHL (Figure 1).[5] As it became clearer that NLPHL follows a distinct clinical course compared to classic HL, in 2013, Hartmann *et al.* proposed the GHSG risk stratification score specifically for NLPHL based on 5-year progression-free survival (PFS) and overall survival (OS) rates of 413 patients treated within prospective GHSG trials.[6] This score counts 1 point for a variant pattern of C, D, E, or F; 1 point for an albumin <4 g/dL; and 2 points for male. High-risk per the GHSG score is ≥3 points.

While males account for a slight majority of NLPHL diagnoses, the structure of this scoring system does not allow females to be categorized as high-risk.

The significance of variant patterns emerged with this GHSG score, identifying that patterns C, D, E, and F were prognostic for increased risk of progression or relapse when lumped as a binary risk category.[6] In the current study by Eichenauer and colleagues, a modified GHSG score was proposed, which included only variant patterns D or E, likely as some studies have shown patterns C and F have a more favorable prognosis after therapy, more similar to typical patterns. However, interpreting variant pattern remains complicated as highlighted by a Children's Oncology Group report from 2018 that found >25% involvement of pattern C within a sample had worse event-free specific survival than those with <25%.[8]

To address the need for a unique and readily implementable prognostic scoring system, the LP-IPS was proposed in 2024, based on 2,243 patients from a multi-institutional database. The LP-IPS assigns 1 risk point for the following: ≥45 years of age, stage III-IV, splenic involvement, and hemoglobin <10.5 g/dL.[1] This score was developed using multiple clinically relevant outcomes: 10-year rates of PFS, OS, lymphoma-specific death, and transformation. Of note, variant patterns were not included in this scoring system as they were not found to be associated with PFS or OS after adjusting for other risk factors using multivariable analysis.

In the current study, using 583 patients with NLPHL treated within GHSG studies, the authors compared the associations between the LP-IPS score, the GHSG score, a modified GHSG score, and the combination LP-IPS+modified GHSG score (Figure 1) with the clinical endpoints PFS and OS. The authors validated the predictive utility of the LP-IPS for the endpoints of PFS (c-statistic=0.64) and OS (c-statistic=0.81) as compared to the modified GHSG score (c-statistic=0.6 for PFS and 0.66 for OS) or the combination score (c-statistic=0.64 for PFS and 0.83 for OS). Additionally, when looking at the combination scores, only Group 3 and 4 (where LP-IPS was high-risk) had hazard ratio confidence intervals >1 (Figure 1). Thus, as the authors state, the LP-IPS remains the most valuable individual score. Interestingly, the authors did show that accounting for variant pattern in the combination model resulted in a very low-risk group that had no NLPHL-related deaths whereas a very high-risk group had 66.7% of deaths related to NLPHL. Thus, there certainly may be additional value added when considering the immunoarchitectural patterns present or other biologic markers.

Ongoing biological studies are extremely important in further refining risk strategies. The identification of variant patterns was an important step in including histologic markers for prognostication; however, the previously mentioned studies highlight the need for

ongoing investigation given challenges of scoring patterns and clinically interpreting them depending on the percentage of variant pattern present. There have been further studies defining distinct immune microenvironment states through multimodal next-generation sequencing.[9] Others have focused on identifying additional biomarkers, including association with pathogens such as *Moraxella catarrhalis* and *Rothia mucilaginosa*.[10] Overall, establishing reliable biomarkers to further guide management for patients with NLPHL remains critical.

Refocusing back towards immediate clinical impact, now that the LP-IPS has been validated in this present study, there remains a need to conduct prospective clinical trials using the LP-IPS. The Global nLPHL One Working Group (GLOW) was established in 2020 as a global collaboration among physicians, researchers, and patient advocates dedicated to further study of this disease. GLOW has published numerous retrospective studies and will soon be opening a multi-institutional prospective trial studying the de-intensification of therapy in low-risk patients, using the LP-IPS as the risk stratification score. In summary, standardizing the use of risk grouping for future NLPHL studies is integral to the goal of refining treatment selection and optimizing outcomes for these patients.

References:

1. Binkley MS, Flerlage JE, Savage KJ, et al. International prognostic score for nodular lymphocyte-predominant Hodgkin lymphoma. J Clin Oncol. 2024;42(19):2271-2280.

2. Binkley MS, Advani RH. SOHO state of the art updates and next questions |Treatment approaches for nodular lymphocyte-predominant Hodgkin lymphoma. Clin Lymphoma Myeloma Leuk. 2023;23(7):471-476.

3. Advani RH, Kelsey CR, Hoppe RT, Yang J. NCCN Clinical practice guidelines in oncology (NCCN Guidelines®): Hodgkin Lymphoma. *NCCN*. https://www.nccn.org/professionals/physician_gls/pdf/hodgkins.pdf (accessed June 28, 2026).

4. Eichenauer DA, André M, Borchmann P, et al. Hodgkin lymphoma: EHA clinical practice guidelines for diagnosis, treatment, and follow-up. Hemasphere. 2026;10(6):e70422.

5. Hasenclever D, Diehl V, Armitage JO, et al. A Prognostic score for advanced Hodgkin's disease. N Engl J Med. 1998;339(21):1506-1514.

6. Hartmann S, Eichenauer DA, Plütschow A, et al. The prognostic impact of variant histology in nodular lymphocyte-predominant Hodgkin lymphoma: a report from the German Hodgkin Study Group (GHSG). Blood. 2013;122(26):4246-4252; quiz 4292.

7. Eichenauer DA, Bühnen I, Basaran A, et al. Comparison and combination of prognostic scores for nodular lymphocyte-predominant Hodgkin lymphoma: an analysis from the German Hodgkin Study Group. Haematologica. xxx

8. Untanu RV, Back J, Appel B, et al. Variant histology, IgD and CD30 expression in low-risk pediatric nodular lymphocyte predominant Hodgkin lymphoma: a report from the Children's Oncology Group. Pediatr Blood Cancer. 2018;65(1):e26753.

9. Subramanian A, Su S, Flerlage J, et al. Distinct cell state ecosystems for nodular lymphocyte-predominant Hodgkin lymphoma. Nat Commun. 2025;16(1):8473.

10. Lossos IS, Jiang X, Patel K, et al. Association Between Moraxella catarrhalis and Nodular Lymphocyte-Predominant Hodgkin Lymphoma. Am J Hematol. 2025;100(9):1543-1556.

Figure Legend:

Figure 1. Five risk stratification scores for Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL): International Prognostic Score (IPS), German Hodgkin Study Group (GHSG) score, Lymphocyte-Predominant International Prognostic Score (LP-IPS), modified GHSG (mGHSG) score, and the combination LP-IPS + mGHSG score. For each score, its respective panel outlines the components of the scoring system, risk groups, method of derivation, and performance in the present study by Eichenauer et al. In the combined LP-IPS + mGHSG panel, rather than the derivation section, there is a validation section which represents the methods in the present study. HL: Hodgkin lymphoma; PFS: progression-free survival; OS: overall survival; HR: hazard ratio; CI: confidence interval.

IPS score

Hasenclever et al. (NEJM 1998)[5]

Components (1 point each)

- Age ≥45 years
- Stage IV disease
- Male sex
- Albumin <4 g/dL
- Hemoglobin <10.5 g/dL
- WBC ≥15,000/mm³
- Lymphocytes <600/mm³ or <8%

Score range

0 1 2 3 4 ≥5

5-year PFS decreases by ~8% with each additional risk factor for entire HL cohort

Derivation

Cohort
5,141 patients with HL & NLPHL (3%)

Statistical model
Multivariable Cox regression

Outcomes
5-year PFS and OS

Performance in Eichenauer et al. (2026)[7]

Not tested

GHSG score

Hartmann et al. (Blood 2013)[6]

Components

Variant pattern (C, D, E, F)	1 point
Albumin <4 g/dL	1 point
Male sex	2 points

Risk groups

0 1 2 3 4

Low: 0-2 High: 3-4

Derivation

Cohort
423 patients with NLPHL

Statistical model
Multivariate logistic regression

Outcomes
5-year PFS and OS

Performance in Eichenauer et al. (2026)[7]

Low-risk vs. high-risk

PFS
HR 1.59 (95% CI: 1.04-2.45)

OS
HR 2.45 (95% CI: 1.1-5.45)

LP-IPS

Binkley et al. (JCO 2024)[1]

Components (1 point each)

- Age ≥45 years
- Stage III-IV
- Hemoglobin <10.5 g/dL
- Splenic involvement

Risk groups

0 1 2 3 4

Low: 0-1 High: 2-4

Derivation

Cohort
2,243 patients with NLPHL

Statistical model
Multivariable Cox regression

Outcomes
10-year PFS, OS, lymphoma-specific death, transformation

Performance in Eichenauer et al. (2026)[7]

Low-risk vs. high-risk

PFS
HR 2.71 (95% CI: 1.76-4.18)

OS
HR 8.24 (95% CI: 3.7-18.34)

C-statistics

PFS, c=0.64 OS, c=0.81

mGHSG score

Eichenauer et al. (Haematologica 2026)[7]

Components

Variant pattern (D, E)	1 point
Albumin <4 g/dL	1 point
Male sex	2 points

Risk groups

0 1 2 3 4

Low: 0-2 High: 3-4

Derivation

Modification of the GHSG score based on prior studies of variant patterns

Performance in Eichenauer et al. (2026)[7]

Low-risk vs. high-risk

PFS
HR 1.97 (95% CI: 1.25-3.09)

OS
HR 4.15 (95% CI: 1.86-9.23)

C-statistics

PFS, c=0.60 OS, c=0.66

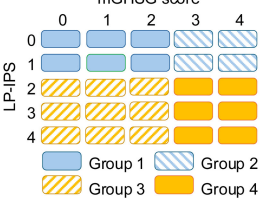
LP-IPS + mGHSG score

Eichenauer et al. (Haematologica 2026)[7]

Components

Scored per respective system

Risk groups



Validation

Cohort
583 patients with NLPHL

Statistical model
Cox regression

Outcomes
5- and 10-year PFS and OS

Performance in Eichenauer et al. (2026)[7]

Group comparison (Group 1=ref.)

PFS
Group 2, HR 1.42 (95% CI: 0.74-2.74)
Group 3, HR 2.10 (95% CI: 1.11-3.96)
Group 4, HR 3.74 (95% CI: 2.09-6.70)

OS
Group 2, HR 1.60 (95% CI: 0.33-7.72)
Group 3, HR 5.80 (95% CI: 1.84-18.30)
Group 4, HR 13.52 (95% CI: 5.03-36.35)

C-statistics

PFS, c=0.64 OS, c=0.83