haematologica
Journal of the Ferrata Storti Foundation

Comparison and combination of prognostic scores for nodular lymphocyte-predominant Hodgkin lymphoma: an analysis from the German Hodgkin Study Group

Dennis A. Eichenauer, Ina Bühnen, Aylin Basaran, Michael Fuchs, Hishan Tharmaseelan, Paul J. Bröckelmann, Bastian von Tresckow, Peter Borchmann, Wolfram Klapper and Sylvia Hartmann

Received: January 29, 2026.
Accepted: July 3, 2026.

Citation: Dennis A. Eichenauer, Ina Bühnen, Aylin Basaran, Michael Fuchs, Hishan Tharmaseelan, Paul J. Bröckelmann, Bastian von Tresckow, Peter Borchmann, Wolfram Klapper and Sylvia Hartmann. Comparison and combination of prognostic scores for nodular lymphocyte-predominant Hodgkin lymphoma: an analysis from the German Hodgkin Study Group.
Haematologica. 2026 July 16. doi: 10.3324/haematol.2026.300633 [Epub ahead of print]

Comparison and combination of prognostic scores for nodular lymphocyte-predominant Hodgkin lymphoma: an analysis from the German Hodgkin Study Group

Dennis A. Eichenauer[1,2], Ina Bühnen[1,2], Aylin Basaran[1,2], Michael Fuchs[1,2], Hishan Tharmaseelan[1,2], Paul J. Bröckelmann[1,2], Bastian von Tresckow[2,3], Peter Borchmann[1,2], Wolfram Klapper[4] and Sylvia Hartmann[5]

[1]University of Cologne, First Department of Internal Medicine, Center for Integrated Oncology Aachen Bonn Cologne Dusseldorf, Cologne, Germany; [2]German Hodgkin Study Group (GHSG), University Hospital Cologne, Cologne, Germany; [3]Department of Hematology and Stem Cell Transplantation, West German Cancer Center and German Cancer Consortium (DKTK partner site Essen), University Hospital Essen, University of Duisburg-Essen, Essen, Germany; [4]Institute of Pathology, Hematopathology Section and Lymph Node Registry, University Hospital Schleswig-Holstein Campus Kiel, Kiel, Germany; [5]Institute of Pathology, University Hospital Essen, University Duisburg-Essen, Essen, Germany

Correspondence to

Dennis A. Eichenauer, MD

First Department of Internal Medicine

University Hospital Cologne

Kerpener Str. 62

D-50937 Cologne, Germany

Phone: 0049-(0)221-478-42770

Fax: 0049-(0)221-478-1423037

Mail: dennis.eichenauer@uk-koeln.de

ORCID-ID: 0000-0002-1927-3514

Running Title: Prognostic scores in NLPHL

Data availability statement

Data can be made available upon reasonable request. Decisions regarding data sharing will be made on a case-by-case basis by the corresponding author considering data protection and other applicable regulations.

Funding statement

No funding.

Conflict of interest disclosure

DAE received honoraria from Takeda; PJB is an advisor or consultant for Hexal, Merck Sharp & Dohme, Need Inc., Stemline and Takeda; holds stock options in Need Inc., has received honoraria from AstraZeneca, BeOne, Bristol-Myers Squibb/Celgene, Eli Lilly, Merck Sharp & Dohme, Need Inc., Stemline and Takeda and reports research funding from BeOne (Inst), Bristol-Myers Squibb/Celgene (Inst), Merck Sharp & Dohme (Inst) and Takeda (Inst); BvT is an advisor or consultant for AbbVie, Allogene, Amgen, Bristol-Myers Squibb/Celgene, Cerus, Gilead Kite, Incyte, IQVIA, Janssen-Cilag, Lilly, Merck Sharp & Dohme, Miltenyi, Novartis, Noscendo, Pentixapharm, Pfizer, Pierre Fabre, Qualworld, Regeneron, Roche, Serb, Sobi and Takeda; has received honoraria from AbbVie, AstraZeneca, Bristol-Myers Squibb/Celgene, Gilead Kite, Incyte, Janssen-Cilag, Lilly, Merck Sharp & Dohme, Novartis, Roche, Serb and Takeda; reports research funding from Esteve (Inst), Merck Sharp & Dohme (Inst), Novartis (Inst), and Takeda (Inst); reports travel support from AbbVie, AstraZeneca, Gilead Kite, Janssen-Cilag, Lilly, Merck Sharp & Dohme, Pierre Fabre, Roche, Takeda, and Novartis; is member of steering committees for Regeneron (Inst) and Takeda; the other authors declare no potential conflicts of interest.

Author contributions

DAE, IB and SH analyzed data.

All authors provided study material or patients.

DAE and SH wrote the manuscript.

All authors provided final approval of the manuscript.

Abstract

The LP-IPS including four (age, stage, splenic involvement, hemoglobin; 1 point for each factor) and the GHSG score comprising three (sex, albumin, variant histopathological growth pattern (GP); 2 points for sex, 1 point for albumin and variant GP) risk factors represent prognostic tools for nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL). A comparison of the scores has not been conducted until now. We thus performed an analysis comprising 583 NLPHL patients treated within GHSG studies. In addition to the LP-IPS and the original GHSG score, a modified GHSG score (GP DE replacing GP CDEF as risk factor variant GP) was also investigated. Low-risk *vs* high-risk groups were defined as 0-1 *vs* 2-4 points for the LP-IPS and 0-2 *vs* 3-4 points for the GHSG scores. Regarding progression-free survival (PFS) and overall survival (OS), Cox regression analyses revealed hazard ratios (HR) for the high-risk *vs* low-risk groups of 2.71 (95%-CI: 1.76-4.18) and 8.24 (95%-CI: 3.7-18.34) for the LP-IPS, 1.59 (95%-CI: 1.04-2.45) and 2.45 (95%-CI: 1.1-5.45) for the original and 1.97 (95%-CI: 1.25-3.09) and 4.15 (95%-CI: 1.86-9.23) for the modified GHSG score. The combination of the LP-IPS and the modified GHSG score (low-risk/low-risk *vs* high-risk/high-risk) resulted in high HR for the high-risk/high-risk group in terms of both PFS (HR: 3.74; 95%-CI: 2.09-6.7) and OS (HR: 13.52; 95%-CI: 5.03-36.35). Thus, the LP-IPS represents the most reliable standalone risk score for NLPHL. The combination of the LP-IPS and the modified GHSG score may help to further characterize specific risk groups.

Introduction

Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) is a rare lymphoma entity with an incidence of 0.1 to 0.2/100.000/year [1]. As some characteristics of NLPHL including a consistent CD20 positivity on the malignant lymphocyte predominant cells, negativity for CD30, a mostly indolent clinical course and an increased rate of late disease recurrence resemble low-grade B-cell non-Hodgkin lymphoma (B-NHL), nodular lymphocyte-predominant B-cell lymphoma has been proposed as alternative name in the International Consensus Classification [1,2]. However, the name NLPHL has been retained in the WHO classification [3].

The overall outcome of patients with NLPHL is favorable. The 10-year progression-free survival (PFS) and overall survival (OS) rates of 471 adult patients treated within randomized studies for newly diagnosed HL were 75.5% and 92.1%, respectively [4]. A large analysis comprising patients of all ages and stages treated at institutions worldwide indicated 10-year PFS and OS estimates of 70.8% and 91.6% [5]. A low excess mortality for NLPHL patients in comparison with the general population has been demonstrated by a population-based analysis from the Netherlands [6]. Thus, improved tools allowing for the discrimination between low-risk patients that are probably treated sufficiently with reduced-intensity approaches and individuals who require more intensive treatment are needed.

Two prognostic scores based on larger patient numbers have been developed in the last years. One score is based on data from 413 patients who had treatment within prospective studies conducted by the German Hodgkin Study Group (GHSG). It includes the factors sex (males: 2 points), albumin (< 4 g/dl: 1 point) and variant histopathological growth pattern (GP) according to Fan et al. (GP CDEF: 1 point) and enables the definition of risk groups in terms of PFS and OS [7,8]. The question of whether an improved risk group discrimination can be achieved by integrating a refined definition of variant GP (GP DE instead of GP CDEF) into the score has not been answered until now [9]. Data from 2243 patients included in the database of the international GLOW consortium were used for the development of the lymphocyte-predominant international prognostic score (LP-IPS). The

LP-IPS is composed of four risk factors: age (≥ 45 years: 1 point), stage (stage III/IV: 1 point), splenic involvement (splenic involvement: 1 point) and hemoglobin (< 10.5 g/dl: 1 point). A higher LP-IPS is associated with reduced PFS and OS rates, an increased risk for lymphoma-specific and NLPHL-specific death and a higher likelihood of histological transformation into aggressive B-NHL [5].

To elucidate differences in terms of risk group discrimination between the LP-IPS, the original GHSG score and a modified GHSG score using a refined definition of variant GP (GP DE instead of GP CDEF), we performed an analysis comprising NLPHL patients who had their first-line treatment within GHSG studies. In addition, it was investigated whether the combination of scores further improves risk group discrimination.

Methods

Patients and treatment

The patients included in the present analysis have been described previously [9]. In short, patients with NLPHL (as confirmed by expert review) and available information on the GP at initial diagnosis (as determined by expert review) who had their first-line treatment within 12 GHSG trials (LP, LPHD and RIPL studies for stage IA disease without risk factors; HD10, HD13 and HD16 studies for early favorable stages; HD11, HD14 and HD17 studies for early unfavorable stages; HD12, HD15 and HD18 studies for advanced stages) conducted between 1998 and 2017 were eligible. Patients had radiotherapy (RT) alone, single-agent anti-CD20 antibody treatment with rituximab, chemotherapy alone, chemotherapy plus consolidation RT and chemotherapy plus rituximab optionally followed by consolidation RT, respectively. Chemotherapy consisted of ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine), ABVD-like regimens or different BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) variants. Details regarding the treatment within the studies have been published elsewhere [4,10–13]. The studies were approved by the review boards of the participating sites and were conducted in accordance with the Declaration of Helsinki. All

patients gave written informed consent for study participation. This is a retrospective analysis using data from individuals that had been treated within the respective prospective studies.

Statistical methods

Comparisons of outcomes between low-risk (0-1 points for the LP-IPS, 0-2 points for the original and the modified GHSG score) and high-risk (2-4 points for the LP-IPS, 3-4 points for the original and the modified GHSG score) groups according to the different scores were performed descriptively. PFS was defined as time from completion of initial staging until disease progression or death from any cause. If none of these events had occurred, PFS was censored at the date of last information on the disease status. OS was defined as time from completion of initial staging until death from any cause and was censored at the date of last information for surviving patients. Time-to-event endpoints were analyzed using the Kaplan-Meier method and Cox regression analyses including hazard ratios (HR) and 95% confidence intervals (95%-CI). The proportional hazards (PH) assumption was verified by visual inspection of scaled Schoenfeld residual plots and formal testing using the Supremum test. Performance of the LP-IPS and the modified GHSG score was evaluated using Harrell´s C-statistics. Statistical interaction between the scoring models was assessed within the multivariable Cox framework. SAS version 9.4 for Microsoft Windows (SAS Institute, Cary, NC) was used for all analyses.

Results

Patient characteristics

A total of 583 NLPHL patients were included in the present analysis. In summary, patients had a median age of 39 years (range: 16 - 75 years) and were mostly male (433/583 patients; 74.3%). They had been diagnosed with stage IA disease without risk factors in 168/583 (28.8%), other early stages in 275/583 (47.2%) and advanced stages in 140/583 cases (24%). Baseline characteristics are displayed in Table 1 and have in part been published previously [9]. The LP-IPS could be calculated for 556/583 patients (95.4%). Of

these, 467 (84%) and 89 (16%) were allocated to the low-risk (0-1 points) and the high-risk (2-4 points) group, respectively. Sufficient information to allocate patients to risk groups according to the original and the modified GHSG score was available for 513/583 patients (88%). Low-risk groups (0-2 points) consisted of 361/513 patients (70.4%) for the original and 410/513 patients (79.9%) for the modified GHSG score; high-risk groups (3-4 points) included 152/513 (29.6%) and 103/513 patients (20.1%), respectively (Table 2).

Association between clinical stage and risk group allocation according to different scores

Among patients with stage IA disease without risk factors (n=147 for the LP-IPS; n=122 for the GHSG scores), other early stages (n=270 for the LP-IPS; n=260 for the GHSG scores) and advanced stages (n=139 for the LP-IPS; n=131 for the GHSG scores), all 147 (100%) with stage IA disease without risk factors were allocated to the low-risk and none to the high-risk group, 268/270 (99.3%) and 2/270 (0.7%) with other early stages to the low-risk and the high-risk group and 52/139 (37.4%) and 87/139 (62.6%) with advanced stages to the low-risk and the high-risk group, respectively, when the LP-IPS was applied. According to the original GHSG score, 95/122 (77.9%), 193/260 (74.2%) and 73/131 patients (55.7%) with stage IA disease without risk factors, other early stages and advanced stages, respectively, were allocated to the low-risk group and 27/122 (22.1%), 67/260 (25.8%) and 58/131 patients (44.3%), respectively, to the high-risk group; 108/122 (88.5%), 217/260 (83.5%) and 85/131 patients (64.9%) with stage IA disease without risk factors, other early stages and advanced stages, respectively, were allocated to the low-risk group and 14/122 (11.5%), 43/260 (16.5%) and 46/131 patients (35.1%), respectively, to the high-risk group when the modified GHSG score was applied (Table 3).

Congruence of risk groups in different scores

All parameters to calculate the LP-IPS, the original and the modified GHSG score were documented for 504/583 patients (86.4%) of which 422 (83.7%) had a low-risk and 82 (16.3%) a high-risk LP-IPS. Of the 422 patients with a low-risk LP-IPS, 314 (74.4%) and 357 (84.6%) were also allocated to the low-risk groups according to the original and the modified GHSG score, respectively; 108 (25.6%) and 65 patients (15.4%) had a low-risk

LP-IPS but met the criteria for allocation to the high-risk groups according to the original and the modified GHSG score, respectively. Patients with a high-risk LP-IPS were also allocated to the high-risk groups according to the original and the modified GHSG score in 43/82 (52.4%) and 37/82 cases (45.1%), respectively, whereas 39/82 (47.6%) and 45/82 patients (54.9%), respectively, were not (Table 4).

Progression-free survival according to the different scores

After a median observation time of 78 months in terms of PFS, the 5-year and 10-year rates for all 583 patients were 85.9% and 76.6%, respectively [9]. Patients with a low-risk LP-IPS had 5-year and 10-year PFS rates of 89.6% (95%-CI: 86.7-92.6%) and 81.1% (95%-CI: 75.8-86.4%) whereas individuals with a high-risk LP-IPS had 5-year and 10-year PFS rates of 69.9% (95%-CI: 59.9-79.9%) and 57.2% (95%-CI: 43.9-70.5%) (HR: 2.71, 95%-CI: 1.76-4.18). Patients from the low-risk and high-risk groups according to the original GHSG score had 5-year PFS rates of 89.8% (95%-CI: 86.4-93.1%) and 76.6% (95%-CI: 69.3-84%) and 10-year PFS rates of 78.9% (95%-CI: 72.7%-85.2%) and 70.3% (95%-CI: 60.6-79.9%) (HR: 1.59, 95%-CI: 1.04-2.45), respectively. The 5-year and 10-year PFS rates for the low-risk group according to the modified GHSG score were 89.3% (95%-CI: 86.2-92.5%) and 79% (95%-CI: 73.2-84.8%), the corresponding rates for the high-risk group were 72.1% (95%-CI: 62.7-81.6%) and 65.5% (95%-CI: 53.4-84.8%) (HR: 1.97, 95%-CI: 1.25-3.09) (Figure 1).

Overall survival according to the different scores

After a median follow-up of 86 months regarding OS, the 5-year and 10-year OS rates for all 583 patients were 95.8% and 94.5%, respectively [9]. The 5-year and 10-year OS rates for patients with a low-risk LP-IPS were 98.1% (95%-CI: 96.9-99.4%) and 96.8% (95%-CI: 94.4-99.2%) whereas the rates for patients with a high-risk LP-IPS were 84% (95%-CI: 76.3-91.7%) each (HR: 8.24, 95%-CI: 3.7-18.34). The 5-year and 10-year OS rates were 96.8% (95%-CI: 94.8-98.7%) and 96.3% (95%-CI: 94.3-98.4%) for the low-risk group and 92.9% (95%-CI: 88.7-97.2%) and 90.3% (95%-CI 83.7-96.9%) for the high-risk group according to the original GHSG score (HR: 2.45, 95%-CI: 1.1-5.45). The low-risk group

according to the modified GHSG score had 5-year and 10-year OS rates of 97.2% (95%-CI: 95.5-98.8%) and 96.8% (95%-CI: 95-98.6%), the rates for the high-risk group were 89.6% (95%-CI: 83.5-95.8%) and 86.1% (95%-CI: 77-95.1%) (HR: 4.15, 95%-CI: 1.86-9.23), respectively (Figure 2).

Combination of scores

It was also investigated whether the combination of the two most reliable scores, namely the LP-IPS and the modified GHSG score, resulted in a further improvement of the risk group discrimination. Different groups were defined. Group one consisted of low-risk patients according to both the LP-IPS and the modified GHSG score (n=357), group two of patients with a low-risk LP-IPS and a high-risk modified GHSG score (n=65), group three of patients with a high-risk LP-IPS and a low-risk modified GHSG score (n=45) and group four of high-risk patients according to both the LP-IPS and the modified GHSG score (n=37). Patients from group one had 5-year and 10-year PFS rates of 91.2% (95%-CI: 88.1-94.3%) and 82% (95%-CI: 75.9-88%), the corresponding OS rates were 98.2% (95%-CI: 96.8-99.6%) and 97.7% (95%-CI: 96.1-99.4%). In contrast, the 5-year and 10-year PFS rates were 81.2% (95%-CI: 70.5-91.8%) and 74.9% (95%-CI: 59.9-88%) (HR: 1.42, 95%-CI: 0.74-2.74) for group two, 81% (95%-CI: 69.1-93%) and 62.5% (95%-CI: 43.6-81.4%) (HR: 2.1, 95%-CI: 1.11-3.96) for group three and 58.5% (95%-CI: 41.6-75.5%) and 52% (95%-CI: 32.8-71.3%) (HR: 3.74, 2.09-6.7) for group four; the 5-year and 10-year OS rates were 98.1% (95%-CI: 94.3-100%) and 91.5% (95%-CI: 78.7-100%) (HR: 1.6, 95%-CI:0.33-7.72) for group two, 88.8% (95%-CI: 79.6-98.1%) (HR: 5.8, 95%-CI: 1.84-18.3) each for group three and 77.8% (95%-CI: 64.1-91.4%) (HR: 13.52, 95%-CI: 5.03-36.35) each for group four (Figure 3). When restricting this analysis to patients with advanced stages, the 5-year and 10-year PFS rates were 92.6% (95%-CI: 84.5-100%) and 81% (95%-CI: 58.6-100%) for group one (n=41). The corresponding rates were 77.8% (95%-CI: 50.6-100%) (HR: 2.31, 95%-CI: 0.42-12.64) each for group two (n=9), 82.9% (95%-CI: 71.3-94.5%) and 63.9% (95%-CI: 44.8-83.1%) (HR: 2.74, 95%-CI: 0.87-8.58) for group three (n=44) and 58.5% (95%-CI: 41.6-75.5%) and 52% (95%-CI: 32.8-71.3%) (HR: 5.32, 95%-CI: 1.77-16.05) for group four (n=37). In terms of OS, the 5-year and 10-year

rates were 97.6% (95%-CI: 92.8-100%) each for group one, 100% (95%-CI: 100%) each for group two, 88.6% (95%-CI: 79.2-98%) (HR: 4.98, 95%-CI: 0.58-42.69) each for group three and 77.8% (95%-CI: 64.1-91.4%) (HR: 11.14, 95%-CI: 1.41-88) each for group four (Supplemental Figure 1).

To further explore the interaction between the two scores, a multivariable Cox regression analysis including an interaction term was performed. For PFS, the LP-IPS remained an independent predictor (p=0.0003; HR: 1.56, 95%-CI: 1.23-1.98) whereas the modified GHSG score did not (p=0.1858; HR: 1.17, 95%-CI: 0.93-1.46). A significant interaction between LP-IPS and the modified GHSG score was observed (p=0.0309), indicating that the prognostic impact of one score depends on the value of the other. However, this interaction did not lead to an increase in model discrimination. When using Harrell´s C-statistics, the C-indices regarding PFS were 0.64 for the LP-IPS and 0.6 for the modified GHSG score. When combining the scores, the C-index was 0.64. In terms of OS, the LP-IPS had independent prognostic power (p<0.0001; HR: 2.77, 95%-CI: 1.75-4.36). This was not true for the modified GHSG score (p=0.3499; HR: 1.24, 95%-CI: 0.79-1.93). No significant interaction between the scores was observed (p=0.4264). The C-indices for OS were 0.81 for the LP-IPS, 0.66 for the modified GHSG score and 0.83 for the combination of the scores (Supplemental Table 1). Despite the very small difference between the LP-IPS and the combination of the scores, the major causes of death differed between the groups and appeared to depend at least in part on whether or not patients were allocated to the high-risk group according to the modified GHSG score. Second malignancies represented the major cause of death (7/9 cases; 77.8%) in group one (low-risk LP-IPS and low-risk modified GHSG score). Deaths due to NLPHL were not documented for this group. The same was true for group two (low-risk LP-IPS and high-risk modified GHSG score) and group three (high-risk LP-IPS and low-risk modified GHSG score). Conversely, NLPHL was the most frequent cause of death (6/9 cases; 66.7%) in group four (high-risk LP-IPS and high-risk modified GHSG score) (Table 5).

Visual inspection of scaled Schoenfeld residuals confirmed that the PH assumption was generally met. Although a formal test suggested a deviation for the modified GHSG score

in the PFS model (p=0.0130), the residuals showed no systematic patterns over time, justifying the use of the Cox framework (Supplemental Table 1).

Discussion

To our knowledge, this is the largest analysis investigating and comparing different prognostic scores for NLPHL with regard to their congruence in terms of patient allocation to low-risk and high-risk groups and their performance. A possibly improved discrimination of low-risk and high-risk patients by a combination of scores was also evaluated. The major findings were as follows: (1) According to the LP-IPS as well as the original and the modified GHSG score, the majority of patients (ranging between 70.4% and 84%) were allocated to the low-risk group; (2) 74% and 85% of the patients with a low-risk LP-IPS were also allocated to the low-risk group according to the original and the modified GHSG score but only 48% and 55% of the patients with a high-risk LP-IPS also met the criteria for allocation to the high-risk group according to the original and the modified GHSG score, respectively; (3) The LP-IPS allowed for a better discrimination between low-risk and high-risk groups as compared to the modified GHSG score which in turn discriminated better than the original GHSG score; (4) combining the LP-IPS and the modified GHSG score resulted in a refined discrimination, especially with regard to the causes of death.

Patients included in the present analysis were allocated to the low-risk groups according to the LP-IPS, the original and the modified GHSG score in 84%, 70.4% and 79.9% of cases, respectively. Despite the differences in terms of the patient proportions allocated to the low-risk group, the PFS rates were similar for all three scores with 5-year rates of 89.6%, 89.8% and 89.3% and 10-year rates of 81.1%, 78.9% and 79% for the LP-IPS, the original and the modified GHSG score, respectively. In contrast, the PFS rates for the high-risk groups differed between the scores with 5-year rates of 69.9%, 76.6% and 72.1% and 10-year rates of 57.2%, 70.3% and 65.5% for the LP-IPS, the original and the modified GHSG score, respectively. This finding suggests that fewer patients at a low risk for disease recurrence were allocated to the high-risk group with the LP-IPS than with the original and the modified GHSG score, respectively, resulting in a better discrimination

between high-risk and low-risk groups regarding PFS when using the LP-IPS (HR: 2.71 *vs* 1.59 *vs* 1.97). The LP-IPS also allowed for a better risk group discrimination than the modified GHSG score concerning OS which in turn discriminated better than the original GHSG score (HR: 8.24 *vs* 4.15 *vs* 2.45). Given these results and its easy applicability, the LP-IPS represents a robust prognostic score for NLPHL that is suitable for the use in daily clinical practice [5].

A significant proportion of patients allocated to the low-risk and high-risk groups differed between the LP-IPS and the original and the modified GHSG score, respectively. Of the patients with a low-risk LP-IPS, 74.4% and 84.6% of patients were also allocated to the low-risk groups according to the original and the modified GHSG score, respectively. The congruence in terms of allocation to the high-risk group between the LP-IPS and the original and the modified GHSG score was only 52.4% and 45.8%, respectively. A major cause for this finding probably consists of the different composition of the LP-IPS on one hand and the original and the modified GHSG score on the other hand with no overlapping risk factors [5,7,9].

Using Cox regression analyses, the combination of the LP-IPS and the modified GHSG score resulted in a sharp distinction between a very low-risk (low-risk LP-IPS and low-risk modified GHSG score) and a very high-risk (high-risk LP-IPS and high-risk modified GHSG score) group whereas no relevant performance improvement in comparison with the LP-IPS alone was observed when Harrell´s C-statistics were applied. The precise distinction between a very low-risk (low-risk LP-IPS and low-risk modified GHSG score) and a very high-risk (high-risk LP-IPS and high-risk modified GHSG score) group revealed in the Cox regression analysis is also mirrored by different major causes of death in both groups. None of the deaths in the very low-risk group was due to NLPHL. In contrast, 66.7% of deaths in the very high-risk group were NLPHL-related. Patients allocated to the very low-risk group may thus be candidates for reduced-intensity treatment whereas patients from the very high-risk group may require intensive approaches. Especially in advanced NLPHL with a wide range of possible approaches ranging from active surveillance over protocols such as R-CHOP (rituximab, cyclophosphamide, doxorubicin,

vincristine, prednisone) to intensive therapy with escalated BEACOPP depending on baseline characteristics and clinical presentation, the combination of the two scores may help choosing the appropriate treatment for the individual patient [13–18].

The present analysis has limitations such as the fact that the patients taken into account were in part also included in the development of the LP-IPS and the GHSG scores. Independent validation of the results is thus required. Nonetheless, it provides additional evidence that the LP-IPS represents a robust prognostic score for NLPHL allowing for a reliable risk group discrimination. In addition, the further improvement in terms of risk group differentiation especially regarding causes of death by combining the LP-IPS and the modified GHSG score suggests that the determination of both scores may be useful.

References

1. Eichenauer DA, Engert A. Nodular lymphocyte-predominant Hodgkin lymphoma: a unique disease deserving unique management. Hematology Am Soc Hematol Educ Program. 2017;2017(1):324-328.

2. Campo E, Jaffe ES, Cook JR, et al. The international consensus classification of mature lymphoid neoplasms: a report from the Clinical Advisory Committee. Blood. 2022;140(11):1229-1253.

3. Alaggio R, Amador C, Anagnostopoulos I, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. Leukemia. 2022;36(7):1720-1748.

4. Eichenauer DA, Plütschow A, Fuchs M, et al. Long-term follow-up of patients with nodular lymphocyte-predominant hodgkin lymphoma treated in the HD7 to HD15 trials: a report from the German Hodgkin Study Group. J Clin Oncol. 2020;38(7):698-705.

5. 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.

6. Posthuma HLA, Zijlstra JM, Visser O, Lugtenburg PJ, Kersten MJ, Dinmohamed AG. Primary therapy and survival among patients with nodular lymphocyte-predominant Hodgkin lymphoma: a population-based analysis in the Netherlands, 1993-2016. Br J Haematol. 2020;189(1):117-121.

7. Hartmann S, Eichenauer DA, Plutschow 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.

8. Fan Z, Natkunam Y, Bair E, Tibshirani R, Warnke RA. Characterization of variant patterns of nodular lymphocyte predominant hodgkin lymphoma with immunohistologic and clinical correlation. Am J Surg Pathol. 2003;27(10):1346-1356.

9. Eichenauer DA, Basaran A, Bühnen I, et al. Refining histopathological growth pattern-based risk group discrimination in nodular lymphocyte-predominant Hodgkin lymphoma: an analysis from the German Hodgkin Study Group. Leukemia. 2025;39(7):1735-1743.

10. Eichenauer DA, Plutschow A, Fuchs M, et al. Long-term course of patients with stage IA nodular lymphocyte-predominant hodgkin lymphoma: a report from the German Hodgkin Study Group. J Clin Oncol. 2015;33(26):2857-2862.

11. Eichenauer DA, Plutschow A, Fuchs M, et al. Rituximab in newly diagnosed stage IA nodular lymphocyte-predominant Hodgkin lymphoma: long-term follow-up of a phase 2 study from the German Hodgkin Study Group. Leukemia. 2020;34(3):953-956.

12. Eichenauer DA, Bühnen I, Baues C, et al. Interim PET-guided treatment for early-stage NLPHL: a subgroup analysis of the randomized GHSG HD16 and HD17 studies. Blood. 2023;142(6):553-560.

13. Eichenauer DA, Kreissl S, Bühnen I, et al. PET-2-guided escalated BEACOPP for advanced nodular lymphocyte-predominant Hodgkin lymphoma: a subgroup analysis of the randomized German Hodgkin Study Group HD18 study. Ann Oncol. 2021;32(6):807-810.

14. Borchmann S, Joffe E, Moskowitz CH, et al. Active surveillance for nodular lymphocyte-predominant Hodgkin lymphoma. Blood. 2019;133(20):2121-2129.

15. Fanale MA, Cheah CY, Rich A, et al. Encouraging activity for R-CHOP in advanced stage nodular lymphocyte-predominant Hodgkin lymphoma. Blood. 2017;130(4):472-477.

16. Eichenauer DA, Engert A. How I treat nodular lymphocyte-predominant hodgkin lymphoma. Blood. 2020;136(26):2987-2993.

17. Salvaris RT, Allanson BM, Collins G, Cheah C. Nodular lymphocyte-predominant Hodgkin lymphoma: advances in disease biology, risk stratification, and treatment. Haematologica. 2024;109(11):3476-3487.

18. Shankar A, Hall GW, McKay P, Gallop-Evans E, Fielding P, Collins GP. Management of children and adults with all stages of nodular lymphocyte predominant Hodgkin lymphoma – All StAGEs: a consensus-based position paper from the Hodgkin lymphoma subgroup of the UK National Cancer Research Institute. Br J Haematol. 2022;197(6):679-690.

Table 1: Patient characteristics

Parameter	
Age in yrs	
Median (min – max)	39 (16-75)
Sex	
Female	150/583 (25.7%)
Male	433/583 (74.3%)
Risk group according to GHSG criteria	
Stage IA without risk factors	168/583 (28.8%)
Other early-stage favorable	206/583 (35.3%)
Early-stage unfavorable	69/583 (11.8%)
Advanced stages	140/583 (24%)
Localizations of interest	
Spleen*	56/567 (9.9%)
Liver*	12/571 (2.1%)
Bone marrow*	16/571 (2.8%)
Treatment	
Stage IA without risk factors	RIPL, LP, LPHD, HD10, HD13 and HD16 studies
Other early-stage favorable	HD10, HD13 and HD16 studies
Early-stage unfavorable	HD11, HD14 and HD17 studies
Advanced stages	HD12, HD15 and HD18 studies

* information not available for all patients

Table 2: Patient distribution in the LP-IPS and the oGHSG and the mGHSG risk scores

	Points	n (%)
LP-IPS (N=556)	0	263/556 (47.3)
	1	204/556 (36.7)
	2	68/556 (12.2)
	3	20/556 (3.6)
	4	1/556 (0.2)
	0-1	467/556 (84)
	2-4	89/556 (16)
oGHSG score (N=513)	0	79/513 (15.4)
	1	47/513 (9.2)
	2	235/513 (45.8)
	3	133/513 (25.9)
	4	19/513 (3.7)
	0-2	361/513 (70.4)
	3-4	152/513 (29.6)
mGHSG score (N=513)	0	92/513 (17.9)
	1	35/513 (6.8)
	2	283/513 (55.2)
	3	89/513 (17.3)
	4	14/513 (2.7)
	0-2	410/513 (79.9)
	3-4	103/513 (20.1)

Abbreviations: LP-IPS: lymphocyte-predominant international prognostic score; oGHSG score: original GHSG score; mGHSG: modified GHSG score

Table 3: Patient distribution according to stages at diagnosis and points according to the LP-IPS and the oGHSG and mGHSG risk scores

		Stage IA without risk factors	Other early stages	Advanced stages	n (%)
LP-IPS (N=556)	0	93/147 (63.3%)	170/270 (63%)	0	263/556 (47.3)
	1	54/147 (36.7%)	98/270 (36.3%)	52/139 (37.4%)	204/556 (36.7)
	2	0	2/270 (0.7%)	66/139 (47.5%)	68/556 (12.2)
	3	0	0	20/139 (14.4%)	20/556 (3.6)
	4	0	0	1/139 (0.7%)	1/556 (0.2)
	0-1	147 (100%)	268/270 (99.3%)	52/139 (37.4%)	467/556 (84)
	2-4	0	2/270 (0.7%)	87/139 (62.6%)	89/556 (16)
oGHSG score (N=513)	0	25/122 (20.5%)	44/260 (16.9%)	10/131 (7.6%)	79/513 (15.4)
	1	9/122 (7.4%)	27/260 (10.4%)	11/131 (8.4%)	47/513 (9.2)
	2	61/122 (50%)	122/260 (46.9%)	52/131 (39.7%)	235/513 (45.8)
	3	22/122 (18%)	64/260 (24.6%)	47/131 (35.9%)	133/513 (25.9)
	4	5/122 (4.1%)	3/260 (1.2%)	11/131 (8.4%)	19/513 (3.7)
	0-2	95/122 (77.9%)	193/260 (74.2%)	73/131 (55.7%)	361/513 (70.4)
	3-4	27/122 (22.1%)	67/260 (25.8%)	58/131 (44.3%)	152/513 (29.6)
mGHSG score (N=513)	0	27/122 (22.1%)	53/260 (20.1%)	12/131 (9.2%)	92/513 (17.9)
	1	7/122 (5.7%)	19/260 (7.3%)	9/131 (6.9%)	35/513 (6.8)
	2	74/122 (60.7%)	145/260 (55.6%)	64/131 (48.9%)	283/513 (55.2)
	3	11/122 (9%)	41/260 (15.8%)	37/131 (28.2%)	89/513 (17.3)
	4	3/122 (2.5%)	2/260 (0.8%)	9/131 (6.9%)	14/513 (2.7)
	0-2	83/122 (68%)	217/260 (83.5%)	85/131 (64.9%)	410/513 (79.9)
	3-4	14/122 (11.5%)	43/260 (16.5%)	46/131 (35.1%)	103/513 (20.1)

Abbreviations: LP-IPS: lymphocyte-predominant international prognostic score; oGHSG score: original GHSG score; mGHSG: modified GHSG score

Table 4: Congruence between LP-IPS risk groups and risk groups according to the oGHSG and mGSHG scores

		LP-IPS 0-1	LP-IPS 2-4	Total
oGHSG score	0	71/422 (16.8%)	4/82 (4.9%)	75/504 (14.9%)
	1	40/422 (9.5%)	7/82 (8.5%)	47/504 (9.3%)
	2	203/422 (48.1%)	28/82 (34.1%)	231/504 (45.8%)
	3	100/422 (23.7%)	33/82 (40.2%)	133/504 (26.4%)
	4	8/422 (1.9%)	10/82 (12.2%)	18/504 (3.6%)
	0-2	314/422 (74.4%)	39/82 (47.6%)	353/504 (70%)
	3-4	108/422 (25.6%)	43/82 (52.4%)	151/504 (30%)
mGHSG score	0	82/422 (19.4%)	6/82 (7.3%)	88/504 (17.5%)
	1	30/422 (7.1%)	5/82 (6.1%)	35/504 (6.9%)
	2	245/422 (58.1%)	34/82 (41.5%)	279/504 (55.4%)
	3	60/422 (14.2%)	28/82 (34.1%)	88/504 (17.5%)
	4	5/422 (1.2%)	9/82 (11%)	14/504 (2.8%)
	0-2	357/422 (84.6%)	45/82 (54.9%)	402/504 (79.8%)
	3-4	65/422 (15.4%)	37/82 (45.1%)	102/504 (20.2%)

Abbreviations: LP-IPS: lymphocyte-predominant international prognostic score; oGHSG score: original GHSG score; mGHSG: modified GHSG score

Cause of death	LP-IPS, mGHSG score								Total	
	LP-IPS 0-1, mGHSG score 0-2		LP-IPS 0-1, mGHSG score 3-4		LP-IPS 2-4, mGHSG score 0-2		LP-IPS 2-4, mGHSG score 3-4			
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
NLPHL-related	-	-	-	-	-	-	6	66.7	6	24
Treatment-related	-	-	-	-	2	40	1	11.1	3	12
Second malignancy	7	77.8	-	-	2	40	1	11.1	10	40
Other	1	11.1	2	100	-	-	1	11.1	4	16
Unknown	1	11.1	-	-	1	20	-	-	2	8
Total	9	100	2	100	5	100	9	100	25	100

Table 5: Causes of death for different combinations of LP-IPS and mGHSG score

Abbreviations: LP-IPS: lymphocyte-predominant international prognostic score; mGHSG: modified GHSG score

Figure legends

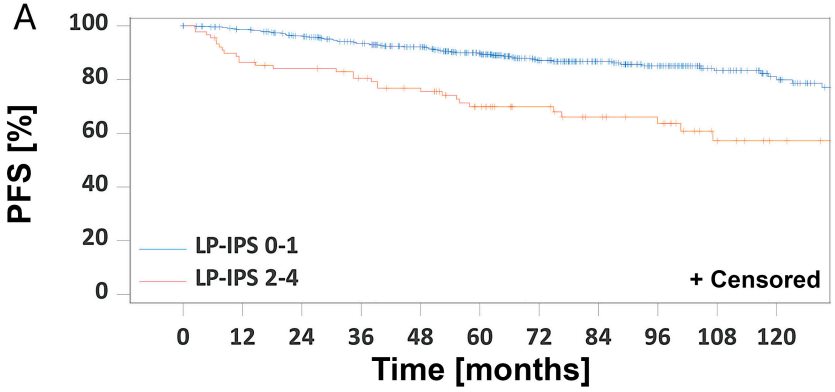
Figure 1: Progression-free survival of low-risk and high-risk groups according to different scores. (A) According to the LP-IPS. (B) According to the original GHSG score. (C) According to the modified GHSG score.

Figure 2: Overall survival of low-risk and high-risk groups according to different scores. (A) According to the LP-IPS. (B) According to the original GHSG score. (C) According to the modified GHSG score.

Figure 3: Survival outcomes for different risk group combinations of the LP-IPS and the modified GHSG score. (A) Progression-free survival for the different combinations. (B) Overall survival for the different combinations.

Abbreviations: LP-IPS: lymphocyte-predominant international prognostic score; oGHSG score: original GHSG score; mGHSG score: modified GHSG score

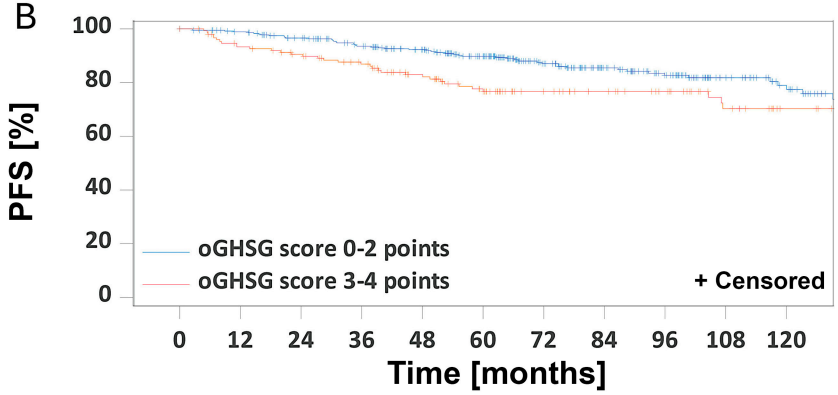
A



Number at risk (number censored)		
467 (0)	294 (130)	68 (341)
89 (0)	47 (17)	11 (48)

LP-IPS 0-1:
5-year PFS 89.6% (95% CI 86.7%-92.6%)
10-year PFS 81.1% (95% CI 75.8%-86.4%)
LP-IPS 2-4:
5-year PFS 69.9% (95% CI 59.9%-79.9%)
10-year PFS 57.2% (95% CI 43.9-70.5%)
HR: 2.71 (95% CI 1.76-4.18)

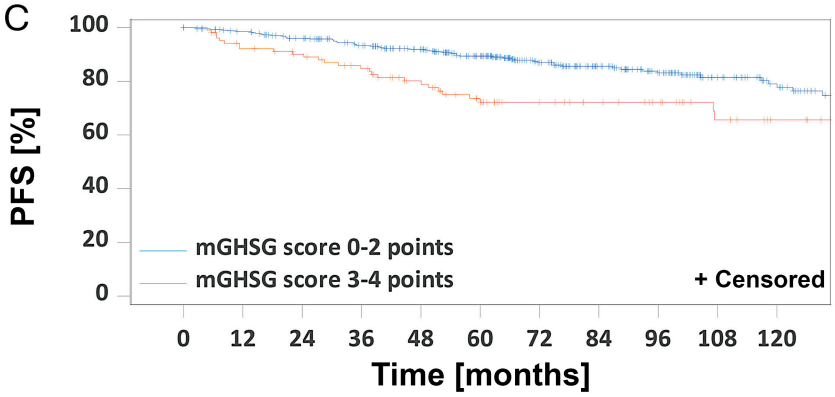
B



Number at risk (number censored)		
361 (0)	234 (94)	53 (259)
152 (0)	81 (40)	23 (95)

oGHSG score 0-2 points:
5-year PFS 89.8% (95% CI 86.4%-93.1%)
10-year PFS 78.9% (95% CI 72.7%-85.2%)
oGHSG score 3-4 points:
5-year PFS 76.6% (95% CI 69.3%-84%)
10-year PFS 70.3% (95% CI 60.6%-79.9%)
HR: 1.59 (95% CI 1.04-2.45)

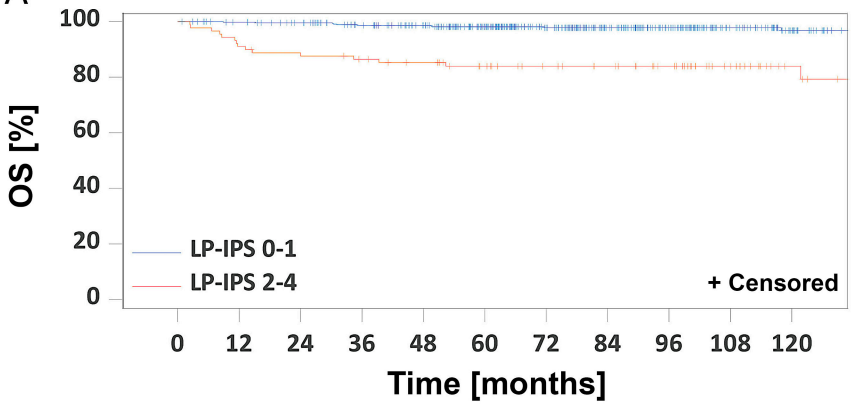
C



Number at risk (number censored)		
410 (0)	264 (107)	62 (292)
103 (0)	51 (27)	14 (62)

mGHSG score 0-2 points:
5-year PFS 89.3% (95% CI 86.2%-92.5%)
10-year PFS 79% (95% CI 73.2%-84.8%)
mGHSG score 3-4 points:
5-year PFS 72.1% (95% CI 62.7%-81.6%)
10-year PFS 65.6% (95% CI 53.4%-84.8%)
HR: 1.97 (95% CI 1.25-3.09)

A

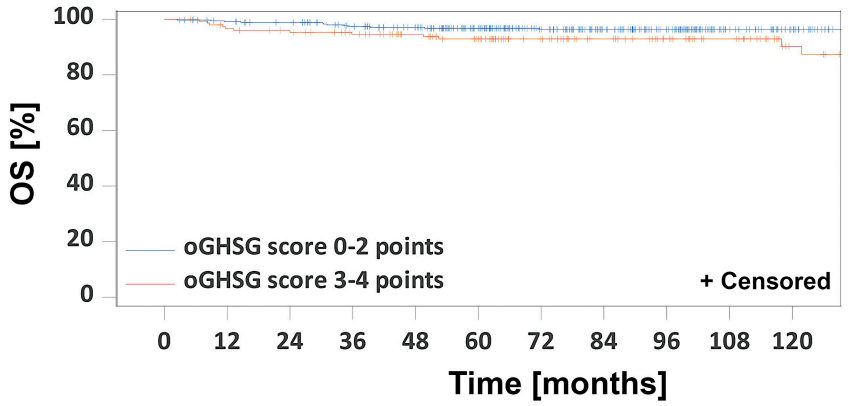


Number at risk (number censored)

467 (0)	347 (112)	93 (364)
89 (0)	62 (13)	18 (57)

LP-IPS 0-1:
5-year OS 98.1% (95% CI 96.9%-99.4%)
10-year OS 96.8% (95% CI 94.4%-99.2%)
LP-IPS 2-4:
5-year OS 84% (95% CI 76.3%-91.7%)
10-year OS 84% (95% CI 76.3%-91.7%)
HR: 8.24 (95% CI 3.7-18.34)

B

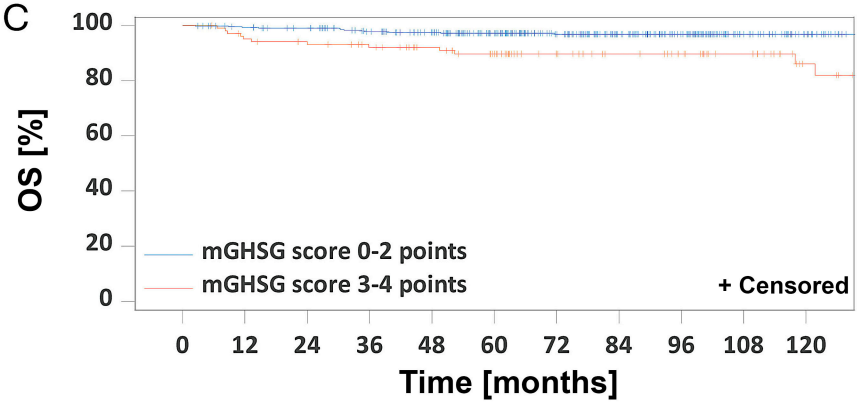


Number at risk (number censored)

361 (0)	271 (79)	75 (274)
152 (0)	107 (35)	31 (110)

oGHSG score 0-2 points:
5-year OS 96.8% (95% CI 94.9%-98.7%)
10-year OS 96.3% (95% CI 94.3%-98.4%)
oGHSG score 3-4 points:
5-year OS 92.9% (95% CI 88.7%-97.2%)
10-year OS 90.3% (95% CI 83.7%-96.9%)
HR: 2.45 (95% CI 1.1-5.45)

C



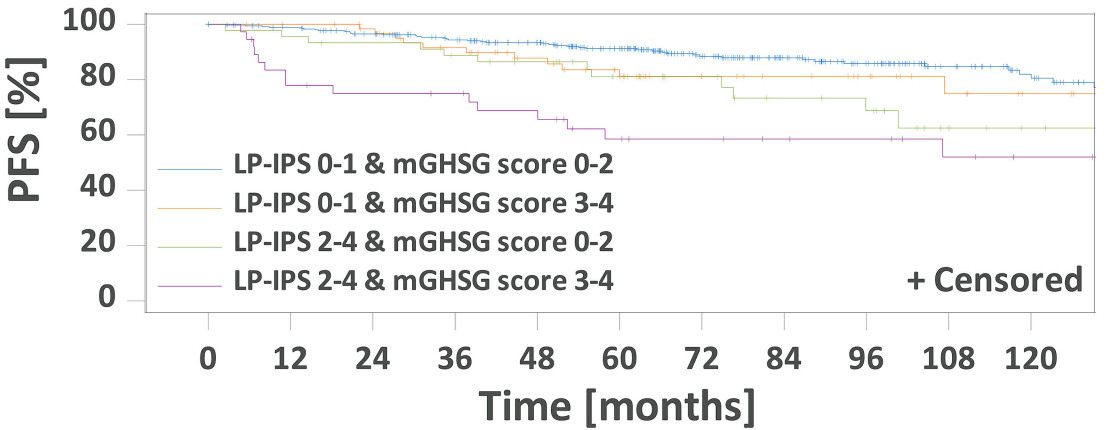
Number at risk (number censored)

410 (0)	308 (91)	85 (313)
103 (0)	70 (23)	21 (71)

mGHSG score 0-2 points:
5-year OS 97.2% (95% CI 95.5%-98.8%)
10-year OS 96.8% (95% CI 95%-98.6%)
mGHSG score 3-4 points:
5-year OS 89.6% (95% CI 83.5%-95.8%)
10-year OS 86.1% (95% CI 77%-95.1%)
HR: 4.15 (95% CI 1.86-9.23)

Figure 3

A



Number at risk (number censored)

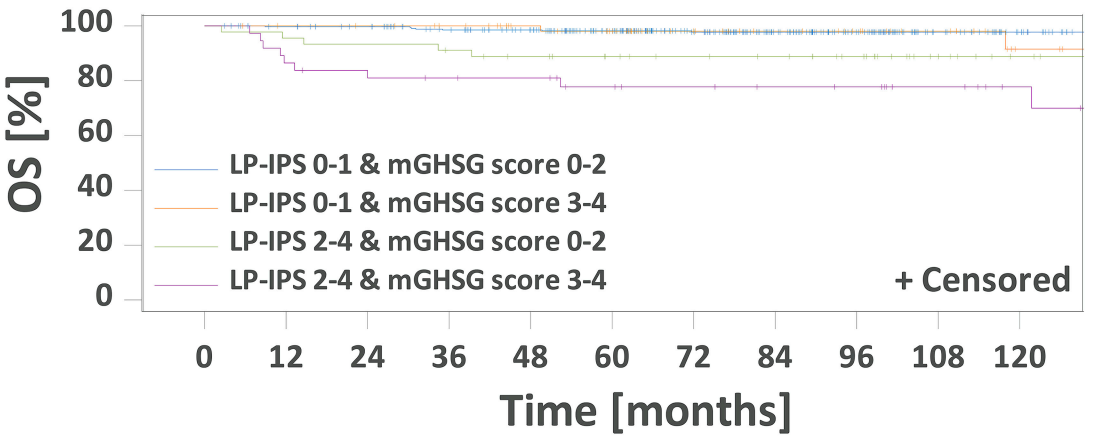
357 (0)	234 (95)	57 (259)
65 (0)	35 (20)	8 (46)
45 (0)	28 (9)	4 (29)
37 (0)	16 (7)	6 (16)

5-year PFS:
91.2% (95% CI 88.1-94.3)
81.2% (95% CI 70.5-91.8)
81% (95% CI 69.1-93)
58.5% (95% CI 41.6-75.5)

10-year PFS:
82% (95% CI 75.9-88)
74.9% (95% CI 59.9-88)
62.5% (95% CI 43.6-81.4)
52% (95% CI 32.8-71.3)

HRs (95% CI):
LP-IPS 0-1 & mGHSG score 0-2: Ref.
LP-IPS 0-1 & mGHSG score 3-4: 1.42 (0.74-2.74)
LP-IPS 2-4 & mGHSG score 0-2: 2.1 (1.11-3.96)
LP-IPS 2-4 & mGHSG score 3-4: 3.74 (2.09-6.7)

B



Number at risk (number censored)

357 (0)	270 (81)	77 (273)
65 (0)	47 (17)	11 (52)
45 (0)	33 (7)	7 (33)
37 (0)	23 (6)	10 (19)

5-year OS:
98.2% (95% CI 96.8-99.6)
98.1% (95% CI 94.3-100)
88.8% (95% CI 79.6-98.1)
77.8% (95% CI 64.1-91.4)

10-year OS:
97.7% (95% CI 96.1-99.4)
91.5% (95% CI 78.7-100)
88.8% (95% CI 79.6-98.1)
77.8% (95% CI 64.1-91.4)

HRs (95% CI):
LP-IPS 0-1 & mGHSG score 0-2: Ref.
LP-IPS 0-1 & mGHSG score 3-4: 1.60 (0.33-7.72)
LP-IPS 2-4 & mGHSG score 0-2: 5.80 (1.84-18.3)
LP-IPS 2-4 & mGHSG score 3-4: 13.52 (5.03-36.35)

Supplemental Table 1: Multivariable Cox regression analysis for PFS and OS

Endpoint	Variable	Hazard Ratio[1]	95% CI	p-value	PH-test (p-value)[2]
PFS	**Univariate model**				
	LP-IPS	1.56	1.23-1.98	0.0003	0.0940
	mGHSG score	1.17	0.93-1.46	0.1858	0.0130
	Interaction (LP-IPS x mGHSG)			**0.0309**	
	mGHSG x LP-IPS = 0	0.91	0.67-1.24		
	mGHSG x LP-IPS = 1	1.15	0.92-1.44		
	mGHSG x LP-IPS = 2	1.45	1.07-1.97		
	mGHSG x LP-IPS = 3	1.83	1.14-2.95		
	mGHSG x LP-IPS = 4	2.31	1.18-4.52		
OS	**Univariate model**				
	LP-IPS	2.77	1.75-4.36	<0.0001	0.1250
	mGHSG score	1.24	0.79–1.93	0.3499	0.5530
	Interaction (LP-IPS x mGHSG)			**0.4264**	
	mGHSG x LP-IPS = 0	1.72	0.67-4.37		
	mGHSG x LP-IPS = 1	1.43	0.8-2.57		
	mGHSG x LP-IPS = 2	1.2	0.76-1.89		
	mGHSG x LP-IPS = 3	1	0.5-1.98		
	mGHSG x LP-IPS = 4	0.83	0.29-2.41		

[1] Hazard ratios per 1-point increase in score (continuous variables).
[2] Based on the formal Supremum test for the proportional hazards (PH) assumption.

[3] C-indices for PFS when using Harrell´s C-statistics: LP-IPS: 0.64; mGHSG: 0.60; combined model: 0.64. C-indices for OS when using Harrell´s C-statistics: LP-IPS: 0.81; mGHSG: 0.66; combined model: 0.83.

Abbreviations: LP-IPS: lymphocyte-predominant international prognostic score; mGHSG: modified GHSG score; PFS: progression-free survival; OS: overall survival

Supplemental Figure 1: Progression-free survival (A) and overall survival (B) for different combinations of the LP-IPS and the modified GHSG score in NLPHL patients with advanced stages