International Prognostic Score for Nodular Lymphocyte–Predominant Hodgkin Lymphoma

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DOI https://doi.org/10.1200/JCO.23.01655

ABSTRACT

PURPOSE Nodular lymphocyte–predominant Hodgkin lymphoma (NLPHL) is a rare cancer, and large international cooperative efforts are needed to evaluate the significance of clinical risk factors and immunoarchitectural patterns (IAPs) for all stages of pediatric and adult patients with NLPHL.

METHODS Thirty-eight institutions participated in the Global nLPHL One Working Group retrospective study of NLPHL cases from 1992 to 2021. We measured progression-free survival (PFS), overall survival (OS), transformation rate, and lymphoma-specific death rate. We performed uni- and multivariable (MVA) Cox regression stratified by management to select factors for the lymphocyte-predominant international prognostic score (LP-IPS) validated by five-fold cross-validation.

RESULTS We identified 2,243 patients with a median age of 37 years (IQR, 23-51). The median follow-up was 6.3 years (IQR, 3.4-10.8). Most had stage I to II (72.9%) and few B symptoms (9.9%) or splenic involvement (5.4%). IAP was scored for 916 (40.8%). Frontline management included chemotherapy alone (32.4%), combined modality therapy (30.5%), radiotherapy alone (24.0%), observation after excision (4.6%), rituximab alone (4.0%), active surveillance (3.4%), and rituximab and radiotherapy (1.1%). The PFS, OS, transformation, and lymphoma-specific death rates at 10 years were 70.8%, 91.6%, 4.8%, and 3.3%, respectively. On MVA, IAPs were not associated with PFS or OS, but IAP E had higher risk of transformation (hazard ratio [HR], 1.81; $P < .05$). We developed the LP-IPS with 1 point each for age ≥45 years, stage III-IV, hemoglobin <10.5 g/dL, and splenic involvement. Increasing LP-IPS was significantly associated with worse PFS (HR, 1.52) and OS (HR, 2.31) and increased risk of lymphoma-specific death (HR, 2.63) and transformation (HR, 1.41).

CONCLUSION In this comprehensive study of all ages of patients with NLPHL, we develop the LP-IPS to identify high-risk patients and inform upcoming prospective clinical trials evaluating de-escalation of therapy for patients with low LP-IPS scores (<2).

ACCOMPANYING CONTENT

Appendix

Accepted January 11, 2024
Published March 26, 2024

J Clin Oncol 00:1-10

View Online Article

INTRODUCTION

Nodular lymphocyte–predominant Hodgkin lymphoma (NLPHL) is an indolent, rare subtype of HL representing approximately 5%-10% of cases.[1-3] The majority of patients are male, present with early-stage disease, and are diagnosed in the fourth decade of life.[4,5] Historically, patients with NLPHL have been treated on frontline protocols for classic HL (cHL) with chemotherapy, radiotherapy, or combined modality therapy (CMT = chemotherapy and

CONTEXT

Key Objective

What clinical and pathologic factors predict outcomes for nodular lymphocyte–predominant Hodgkin lymphoma (NLPHL) across all ages and clinical stages?

Knowledge Generated

On the basis of the results of this comprehensive retrospective study of patients of all ages and stages with NLPHL, a lymphocyte-predominant international prognostic score was developed, which identifies most patients as having a low risk of progression, lymphoma-specific death, and transformation. This analysis also demonstrated that individual immunoarchitectural patterns are not associated with progression-free survival or overall survival (OS).

Relevance *(S. Bhatia)*

This novel prognostic score can identify patients with NLPHL at low risk of disease progression that can be evaluated for therapy de-escalation.*

*Relevance section written by *JCO* Associate Editor Smita Bhatia, MD, MPH, FASCO.

radiotherapy) which often overtreat this indolent disease.[4] Overall survival (OS) remains very high even in patients who are initially observed after excision or who relapse. Therapy-related late effects and nonlymphoma deaths outweigh lymphoma-specific deaths.[4,6-9] Given the rarity of this diagnosis, there are consensus guidelines but no prospective standard of care for treatment of patients with NLPHL, with varied treatment approaches globally.[10-12]

Current efforts focus on deintensification of treatment to preserve outcomes and minimize therapy-related acute and long-term toxicities and include active surveillance or observation alone.[8,10,13] This is challenging as there are no well-validated biomarkers to aid in risk stratification, and clinical factors alone do not sufficiently identify high-risk cases. After the characterization of six immunoarchitectural patterns (IAPs) of NLPHL in 2003, an association between advanced-stage NLPHL and IAP C/D/E has been identified in some studies.[14,15] In addition, when grouping IAP C/D/E/F together (variant patterns), patients appear to have worse progression-free survival (PFS) compared with those with IAP A/B (typical patterns).[7,16] However, the prognostic validity of IAP has not been fully validated because of the rarity, small sample sizes, and frequent co-occurrence of IAP within individual nodes, limiting the ability to analyze the association of specific IAPs with differences in outcomes.[17]

With this context, we established the Global nLPHL One Working Group (GLOW), an international consortium dedicated to studying NLPHL. We assembled the largest retrospective database of patients with NLPHL to date. This has allowed rigorous analysis, to our knowledge, for the first time in the history of the disease, across the age continuum, investigating the relationship between clinical factors and individual IAPs with clinical outcomes.

METHODS

Patients

We performed an international retrospective analysis of patients diagnosed with NLPHL from 1992 to 2021. Individual institutions obtained institutional review board approval, queried databases within select date ranges available, obtained data use agreements, and centrally reviewed pathology for scoring of IAP when available. Data were transferred using a prospective survey tool to ensure uniformity. Inclusion criteria were (1) initial diagnosis of NLPHL and (2) management and follow-up at the participating center. Patients with a concurrent diagnosis of large cell lymphoma or composite lymphoma at diagnosis were excluded.

Diagnosis, Management, and Follow-Up

Data collected included pathology immunostaining, IAPs present, complete blood count values, serum lactate dehydrogenase levels, Ann Arbor staging and extranodal sites of involvement, the presence of B symptoms, imaging modalities used, and the maximum size of the largest involved site. Management details captured included the completeness of excision or resection of involved tissue, systemic therapy regimen and number of cycles, radiotherapy dose and technique, and any first response to treatment by imaging. Cohorts included individual site cohorts and patients treated on prospective clinical trials (ie, German Hodgkin Study Group [GHSG] protocols HD7-HD15).[4]

End Points

The primary end points were PFS defined as the time interval in years from NLPHL diagnosis date to relapse, progressive

TABLE 1. Characteristics of Patients With NLPHL

Parameter	Total (N = 2,243), No. (%)	CT (n = 727), No. (%)	CMT (n = 684), No. (%)	RT (n = 538), No. (%)	Observation (n = 104), No. (%)	Rituximab Alone (n = 90), No. (%)	Active Surveillance (n = 76), No. (%)	Rituximab and RT (n = 24), No. (%)
Age at diagnosis, years								
Median	37	34	36	40	20	44	57	35
IQR	23-51	19-47	24-48	28-53	14-52	31-60	42-71	24-43
Range	2-89	2-88	3-82	11-89	4-80	16-85	12-84	18-65
Sex								
Male	1,681 (74.9)	575 (79.1)	508 (74.3)	398 (74.0)	71 (68.3)	64 (71.1)	47 (61.8)	18 (75.0)
Female	562 (25.1)	152 (20.9)	176 (25.7)	140 (26.0)	33 (31.7)	26 (28.9)	29 (38.2)	6 (25.0)
ECOG PS								
0-1	2,198 (98.0)	704 (96.8)	676 (98.8)	531 (98.7)	103 (99.0)	89 (98.9)	72 (94.7)	23 (95.8)
>1	45 (2.0)	23 (3.2)	8 (1.2)	7 (1.3)	1 (1.0)	1 (1.1)	4 (5.3)	1 (4.2)
Stage								
I	852 (38.0)	98 (13.5)	190 (27.8)	395 (73.4)	104 (100.0)	54 (60.0)	0 (0.0)	11 (45.8)
Extranodal	23 (1.0)	3 (0.4)	6 (0.9)	10 (1.9)	3 (2.9)	1 (1.1)		0 (0.0)
B symptoms	35 (1.6)	7 (1.0)	10 (1.5)	13 (2.4)	4 (3.9)	1 (1.1)		0 (0.0)
Spleen	2 (0.1)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)		1 (4.2)
II	784 (34.9)	164 (22.6)	427 (62.4)	136 (25.3)	0 (0.0)	15 (16.7)	31 (40.8)	11 (45.8)
Extranodal	40 (1.8)	5 (0.7)	21 (3.1)	9 (1.7)		2 (2.2)	3 (3.9)	0 (0.0)
B symptoms	53 (2.4)	11 (1.5)	32 (4.7)	7 (1.3)		1 (1.1)	1 (1.3)	1 (4.2)
Spleen	7 (0.3)	2 (0.3)	3 (0.4)	0 (0.0)		1 (1.1)	1 (1.3)	0 (0.0)
III	460 (20.5)	345 (47.5)	47 (6.9)	7 (1.3)	0 (0.0)	19 (21.1)	40 (52.6)	2 (8.3)
Extranodal	31 (1.4)	22 (3.0)	6 (0.9)	0 (0.0)		3 (3.3)	0 (0.0)	0 (0.0)
B symptoms	80 (3.6)	63 (8.7)	9 (1.3)			3 (3.3)	4 (5.3)	1 (4.2)
Spleen	60 (2.7)	40 (5.5)	10 (1.5)			7 (7.8)	3 (3.9)	0 (0.0)
IV	147 (6.6)	120 (16.5)	20 (2.9)	0 (0.0)	0 (0.0)	2 (2.2)	5 (6.6)	0 (0.0)
Extranodal	110 (4.9)	90 (12.4)	13 (1.9)			2 (2.2)	5 (6.6)	
B symptoms	52 (2.3)	43 (5.9)	9 (1.3)			0 (0.0)	0 (0.0)	
Spleen	51 (2.3)	44 (6.1)	5 (0.7)			0 (0.0)	2 (2.6)	
Immunoarchitecture								
A/B typical	676 (30.1)	152 (20.9)	262 (38.3)	187 (34.8)	31 (29.8)	31 (35.6)	9 (12.2)	4 (16.7)
C	78 (3.5)	26 (3.6)	25 (3.7)	19 (3.5)	4 (3.8)	3 (3.4)	1 (1.4)	0 (0.0)
D	82 (3.6)	42 (5.8)	25 (3.7)	8 (1.5)	3 (2.9)	4 (4.6)	0 (0.0)	0 (0.0)
E	67 (3.0)	33 (4.5)	26 (3.8)	2 (0.4)	2 (1.9)	2 (2.3)	2 (2.7)	0 (0.0)
F	13 (0.6)	2 (0.3)	5 (0.7)	5 (0.9)	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)
Unknown	1,327 (59.2)	472 (64.9)	341 (49.9)	317 (58.9)	64 (61.5)	56 (64.4)	62 (87.8)	20 (83.3)
Follow-up, years								
Median	6.3	5.8	7.6	6.4	3.9	6.5	4.4	3.5
IQR	3.4-10.8	3.3-9.8	4.5-12.3	3.2-11.6	1.6-6.1	3.2-8.2	2.5-6.6	1.9-12.4

Abbreviations: CMT, combined modality therapy; CT, chemotherapy alone; ECOG PS, Eastern Cooperative Oncology Group performance score; NLPHL, nodular lymphocyte–predominant Hodgkin lymphoma; RT, radiotherapy.

lymphoma, and/or death from any cause. OS was defined as the time interval in years from NLPHL diagnosis date to death from any cause. Lymphoma-specific survival was defined as the time interval in years from diagnosis date to death because of progressive lymphoma (transformed or NLPHL). NLPHL-specific death was similarly defined but did not include deaths because of transformed lymphoma. Time to transformation was defined as the time interval in years from the date of NLPHL diagnosis to biopsy-confirmed diagnosis of diffuse large B-cell lymphoma or T-cell/histiocyte-rich B-cell lymphoma or in the absence of biopsy clinical suspicion as previously described.[18]

Statistical Analysis

Follow-up was measured using the reverse Kaplan-Meier method. PFS and OS were measured using the Kaplan-Meier method. Incidence of transformation was measured using the cumulative incidence function adjusted for the competing risk of death. Lymphoma-specific death and NLPHL-specific death were measured with adjustment for nonlymphoma deaths. PFS for patients with variant IAP with only a single growth pattern was individually assessed before grouping those with multiple composite patterns according to the highest risk pattern present in concordance with previous studies.[15,16] We performed threshold analyses to identify prognostic cut points for continuous variables including age, hemoglobin (HgB), size, and the number of sites involved using the log-rank statistic with bootstrap resampling (100 iterations).

On the basis of our results and in conjunction with previously published cutoff points, we selected age ≥45 years, stage III-IV, and HgB <10.5 g/dL as risk thresholds.[19,20] Stratified Cox regression, accounting for management type, was performed with variables significant by univariable analysis selected for inclusion in multivariable (MVA) analyses. This forward selection method was chosen because of smaller numbers of patients having some clinical and poor prognostic risk factors such as B-symptoms, splenic involvement, variant IAP, and the small number of transformation events. Missing data were imputed using nearest neighbor modeling on the basis of age, stage, and sex. Logistic regression splines were used to assess the functional form of continuous variables. We performed five-fold cross-validation using our Cox regression model adjusted for management type with 200 iterations to test prognostic model performance and for validation. This method was chosen as opposed to a split-sample technique of validation to avoid unbalance in potential prognostic factors and given fewer death and transformation events.[21] All analyses were performed with significance defined as a two-tailed *P* value <.05 and were conducted using R (version 4.2.2).

RESULTS

Patients

A total of 2,243 patients from 38 international institutions were diagnosed from 1992 to 2021 with a median follow-up of 6.3 years (IQR, 3.4-10.8, range, 0.1-25.9). At 10 years after diagnosis, almost half of patients (40.6%) either experienced a PFS event or maintained clinical follow-up.[22] The median age was 37 years (quartiles: 2-23 years, >23-37 years, >37-51 years, >51 years). As summarized in Table 1, the majority of patients were male (74.9%), had excellent performance status (98.0% with Eastern Cooperative Oncology Group 0-1), and had stage I-II disease (72.9%). Few patients had splenic involvement (5.4%) or B symptoms (9.9%).

Almost half (40.8%, Table 1) had pathology reviewed at the local managing institution with scoring of IAP available. There was no significant difference in age ($P = .87$), percent male ($P = .99$), or clinical stages ($P = .49$) for those with IAP versus all others. Of those with IAP available, typical pattern A/B was most common (73.8%) followed by D (9.0%), C (8.5%), E (7.3%), and F (1.4%). There was a higher percentage of patients diagnosed with advanced-stage NLPHL within the IAP D and E groups ($P < .0001$, Appendix Table A1, online only).

The majority of patients were treated per physician preference. However, nearly a third (31.0%) were enrolled on clinical trials of the GHSG.[4] As shown in Table 1 and in order of frequency, managements were chemotherapy alone (32.4%), CMT (30.5%), radiotherapy alone (24.0%), observation after excision (4.6%), rituximab alone (4.0%), active surveillance (3.4%), and radiotherapy and rituximab (1.1%). Nearly all patients receiving radiotherapy had stage I-II NLPHL (98.7%).

Outcomes and Age-Specific Risks

In total, 522 PFS events, 137 deaths, 54 lymphoma-specific deaths, and 81 transformation events occurred. The 5- and 10-year PFS rates were 82.5% (95% CI, 80.7 to 84.2) and 70.8% (95% CI, 68.2 to 73.3), respectively (Fig 1A), with progression events continuing well beyond 10 years post-diagnosis. The 5- and 10-year OS rates were 96.1% (95% CI, 95.1 to 96.9) and 91.6% (95% CI, 89.8 to 93.1), respectively (Fig 1B). The 5- and 10-year incidence rates of transformation were 2.8% (95% CI, 1.2 to 4.4) and 4.8% (95% CI, 2.2 to 7.5), respectively (Fig 1C). The lymphoma-specific death rate was low at 1.8% (95% CI, 0.5 to 3.1) and 3.3% (95% CI, 1.2 to 5.4) at 5 and 10 years, respectively.

A logistic regression spline analysis to determine age-specific risks of clinical outcomes demonstrated that PFS and transformation had a linear increase in risk with an increase in age (Appendix Figs A1A and A1B). The risk of death and lymphoma-specific death had an inflection point with increased risk beginning shortly after age 40 years with an approximately >10% risk of death and nearly 5% risk of lymphoma-specific death at age 60 years (Appendix Figs A1C and A1D).

Prognostic Impact of Immunoarchitectural Patterns

In 40.8% of patients who had pathology available for review and scoring of IAP, we observed a nonsignificant difference

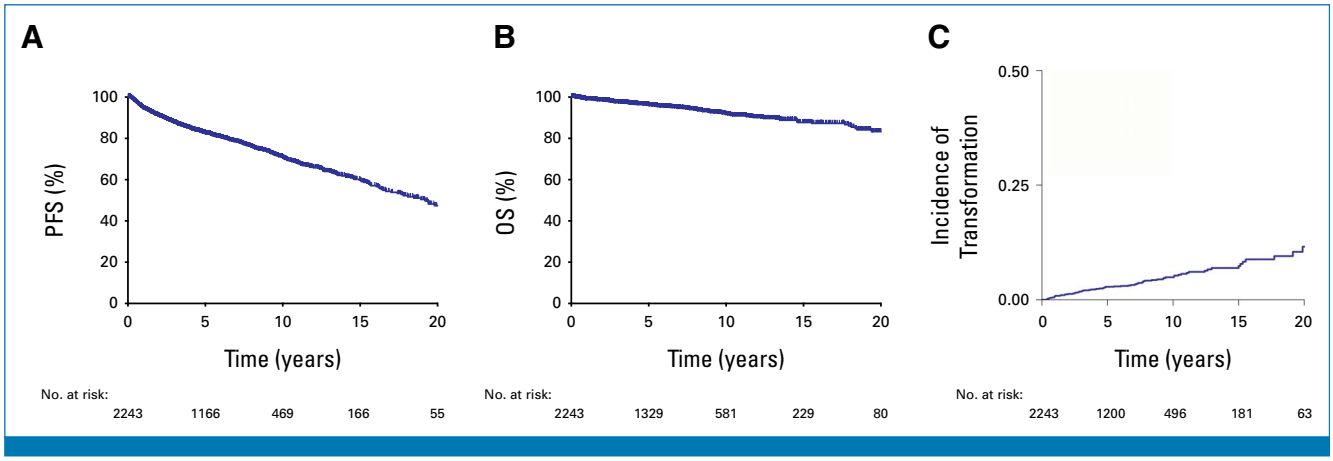

FIG 1. Outcomes for the entire cohort. (A) PFS, (B) OS, and (C) incidence of transformation for the entire cohort of patients with NLPHL. NLPHL, nodular lymphocyte–predominant Hodgkin lymphoma; PFS, progression-free survival; OS, overall survival.

in PFS when stratifying by individual variant patterns (P = .06, Fig 2A) but no significant difference in OS (P = .27, Fig 2B). Patients with pattern E had significantly worse PFS compared with all other patterns (P = .01). Similarly, although there was no significant difference comparing rates of transformation across all IAP (P = .16), the 5-year incidence of transformation was 8.5% (95% CI, 6.3 to 11) for pattern E versus 1.7% (95% CI, 1.6 to 1.8) for all others (P = .06, Fig 2C). There was no significant difference in age for pattern E versus all others (P = .17).

We next looked at PFS stratified by IAP for those receiving chemotherapy, CMT, or radiotherapy. Although there was no significant difference in PFS for patients receiving chemotherapy alone across IAPs (Fig 2D), IAP E had a nonsignificant worse PFS versus all others (P = .07). There was no significant difference in PFS for patients receiving CMT stratifying by IAP (Fig 2E). There was a significant difference (P = .0008) in PFS for patients receiving radiotherapy alone, which was primarily driven by the poor outcomes of patients with IAP C (Fig 2F). The 5-year PFS was 77.6% (95% CI, 56.6 to 89.3) for IAP C/D/E versus 92.9% (95% CI, 87.5 to 96.0) for IAP A/B/F (P = .002). Only 40 patients who were observed after excision of stage I NLPHL had IAP scored, and although there was a significant difference in PFS when stratifying by IAP (Appendix Fig A2, P = .007), two of the five relapses occurred in patients who had incomplete excisions, suggesting that the number of relapses may be smaller with a complete excision.

Outcomes and Prognostic Factors

We sought to identify clinical and pathologic factors associated with clinical outcomes using a stratified Cox regression analysis accounting for the treatment modality. While there were many PFS events, total deaths and transformations were fewer. This, in combination with rare factors such as pattern E, led us to analyze the cohort as a whole with additional means of performing internal validation when assessing prognostic model performance (see below) as opposed to using a split-sample technique. In addition, we performed two multivariable analyses for each outcome of interest as only approximately half of the cohort had IAP scored (one with [MVA2] and the other without IAP E [MVA1]). IAP pattern F was very rare with few adverse outcomes observed and was included with the reference group.

Several continuous variables were significantly associated with PFS, OS, and transformation on univariable analysis. Given previous risk thresholds and our goal of obtaining a prognostic score, we used the log-rank statistic to optimize potential cutoff values with bootstrap resampling (100 iterations). As explained in the Methods section, we identified age ≥45 years, stage III-IV, number of nodal sites >2, and serum HgB <10.5 g/dL as risk factors associated with worse outcomes (Appendix Table A2). In addition, both IAP E and splenic involvement (a previously identified risk factor for transformation[18]) were significantly associated with worse PFS and OS and higher risk of transformation.

On MVA1, which included the full cohort, only age ≥45 years was significantly associated with all three outcomes of interest. However, B symptoms, stage III-IV, elevated lactate dehydrogenase, and HgB <10.5 g/dL were significantly associated with worse PFS and OS (Appendix Table A2). Results for MVA2, which included only patients with available IAP scores, were similar, but IAP E only remained significant for higher risk of transformation and was not associated with worse PFS or OS.

Lymphocyte-Predominant International Prognostic Score

In developing a lymphocyte-predominant international prognostic score (LP-IPS), we tested potential models that included variables significantly associated with at least two of the three primary end points, that is, PFS, OS, and

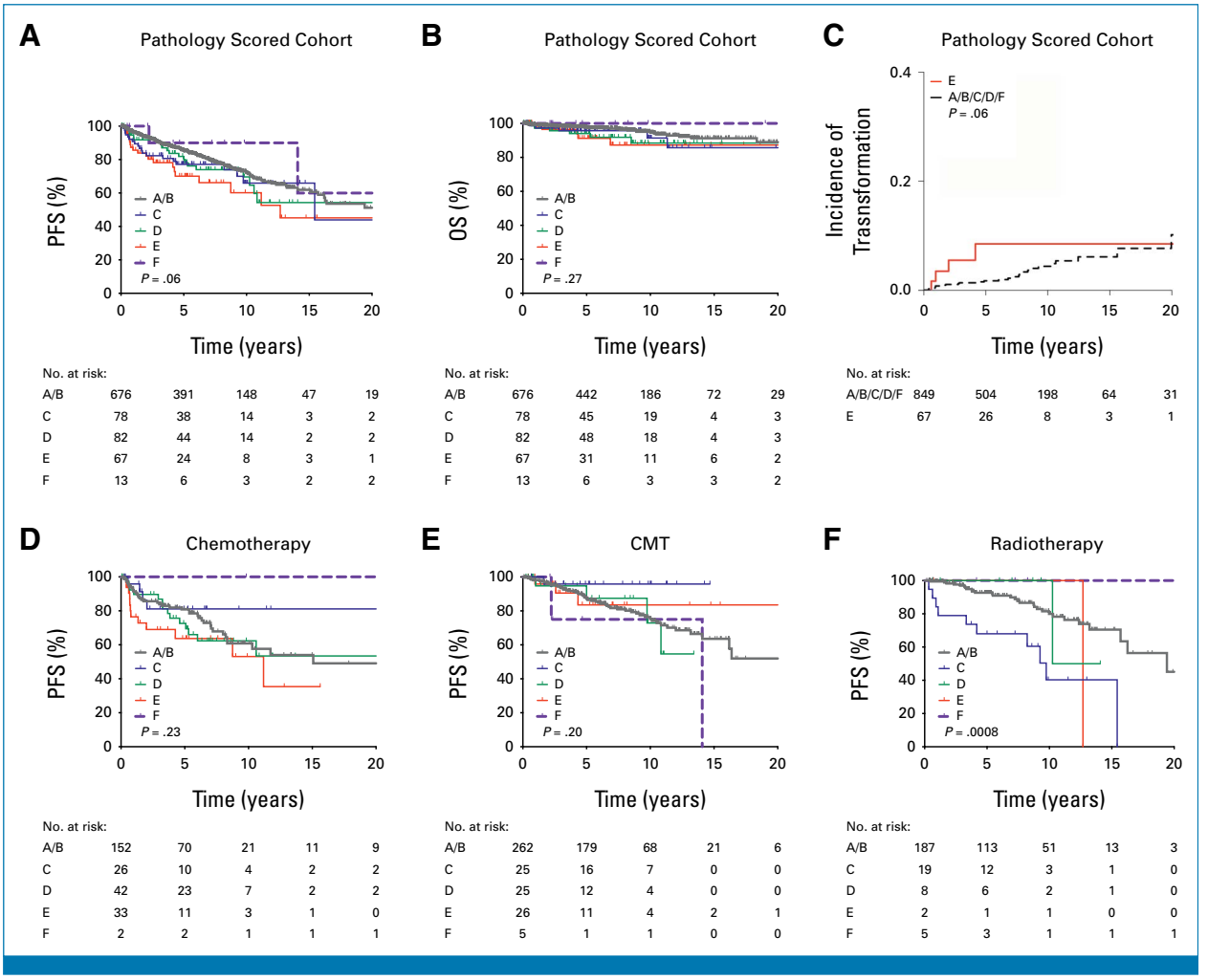

FIG 2. Outcomes for individual immunoarchitectural patterns. (A) PFS and (B) OS for all patients with IAP performed. (C) demonstrates the cumulative incidence of transformation for those with IAP E versus all other IAPs. (D-F) demonstrate PFS for patients receiving chemotherapy, CMT, or radiotherapy, respectively. CMT, combined modality therapy; IAP, immunoarchitectural pattern; OS, overall survival; PFS, progression-free survival.

transformation (Figs 3A-3C and Appendix Table A2). We compared models visually using Kaplan-Meier curves, assessed hazard ratios via stratified Cox regression, and assessed performance of models in our Cox regression using 5-fold cross-validation with 200 iterations to measure confidence intervals (Appendix Table A3). Most potential NLPHL models performed similarly with comparable C-statistics and nearly all outperformed the follicular lymphoma international prognostic index. Furthermore, only 12.1% of patients were older than 60 years, whereas 35.1% were 45 years or older. Thus, on the basis of improved separation of Kaplan-Meier survival curves, Cox model HR, and C-statistic values, we chose a final LP-IPS which assigns one risk point each for age ≥45 years, HgB <10.5 g/dL, stage III to IV, and splenic involvement. The C-statistics for PFS, OS, transformation, lymphoma-specific death, and NLPHL-specific death were 0.657, 0.734, 0.633, 0.770, and 0.801, respectively. Increasing LP-IPS was significantly associated with worse PFS (Fig 4A), OS (Fig 4B), and increased risk of transformation (Fig 4C). The 5-year PFS rates were 88.1%, 82.3%, 69.2%, and 59.0% for those with 0, 1, 2, and 3-4 risk points. The 5-year OS rates were 99.3%, 95.2%, 89.0%, and 83.3% for those with 0, 1, 2, and 3-4 risk points. The 5-year transformation incidence rates were 1.4%, 3.8%, 4.8%, and 7.1% for those with 0, 1, 2, and 3-4 risk points. Finally, increasing LP-IPS was significantly associated with higher risk of lymphoma-specific death (HR, 2.63 [95% CI, 2.16 to 3.20]; $P < .00001$) and NLPHL-specific death (HR, 3.18 [95% CI, 2.37 to 4.27]; $P < .00001$). The 5-year incidence of lymphoma-specific death was 0.1%, 1.9%, 5.9%, and 11.3% for those with 0, 1, 2, and 3-4 risk points ($P = 3.0e-11$). The 5-year incidence of NLPHL-specific death was 0.1%, 0.9%, 5.0%, and 11.3% for those with 0, 1, 2, and 3-4 risk points ($P = 4.5e-13$).

We were also interested to assess the outcomes for patients who were selected to receive more intensive treatment with chemotherapy or CMT stratified by the LP-IPS. For this

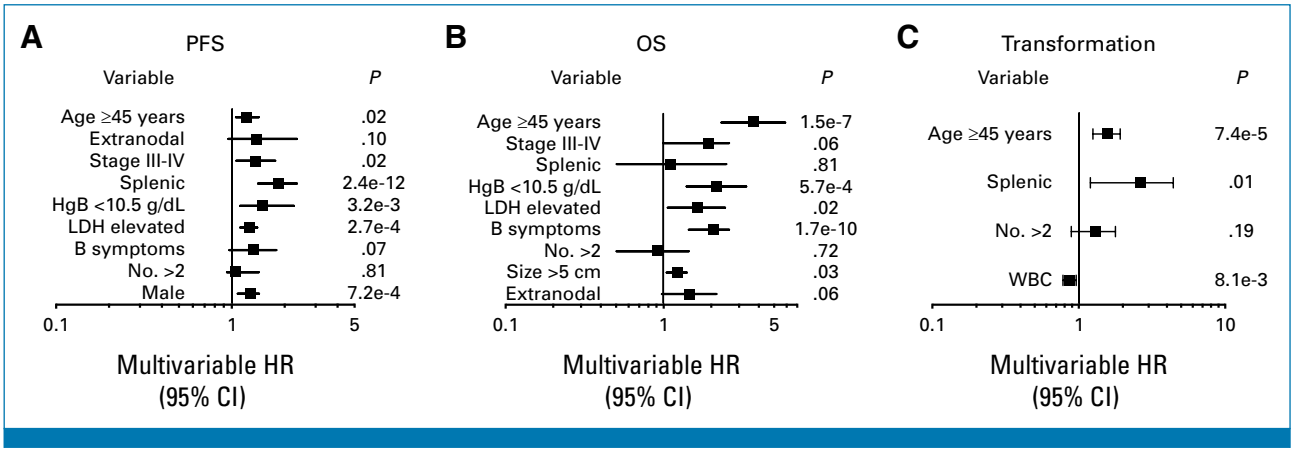

FIG 3. Multivariable models for the entire cohort. Forest plots demonstrate results of the MVA1 for (A) PFS, (B) OS, and (C) transformation. HR, hazard ratio; MVA, multivariable; OS, overall survival; PFS, progression-free survival.

subgroup, the 5-year PFS rates were 89.6%, 80.6%, 70.9%, and 57.0% for those with 0, 1, 2, and 3-4 risk points (Appendix Fig A3A, $P < .0001$). Interestingly, these 5-year PFS rates compared similarly with those for all other patients who did not receive chemotherapy as part of primary management with 5-year PFS rates of 85.3%, 83.5%, 59.6%, and 54.5% for those with 0, 1, 2, and 3-4 risk points (Appendix Fig A3C, $P < .0001$).

DISCUSSION

In this retrospective study, to our knowledge, we report survival outcomes for the largest cohort of patients with NLPHL of *all* ages and stages, allowing for analysis of IAPs and prognostic factors. Median follow-up was robust at 6.3 years, with one quarter having follow-up beyond 10 years. Our approach identified a linear increase in risk of PFS or transformation events with increasing age, and relapses continued to occur beyond 10 years after diagnosis. Overall transformation rates were low at <1% per year and <5% at 5 years. Nearly half of our patients had pathology available for review with scoring of IAP representing the largest study with available pathology paired with long-term clinical outcomes. Notably, age, sex, and stage were not different for those with IAP versus those without IAP available, suggesting that this subset was representative of the larger cohort. We report several observations including a novel LP-IPS that has high predictive performance for lymphoma-specific (C-statistic = 0.770) and NLPHL-specific death (C-statistic = 0.801). This model was derived using data from 38 institutions with robust validation using 5-fold cross-validation, a technique favored over split-sample

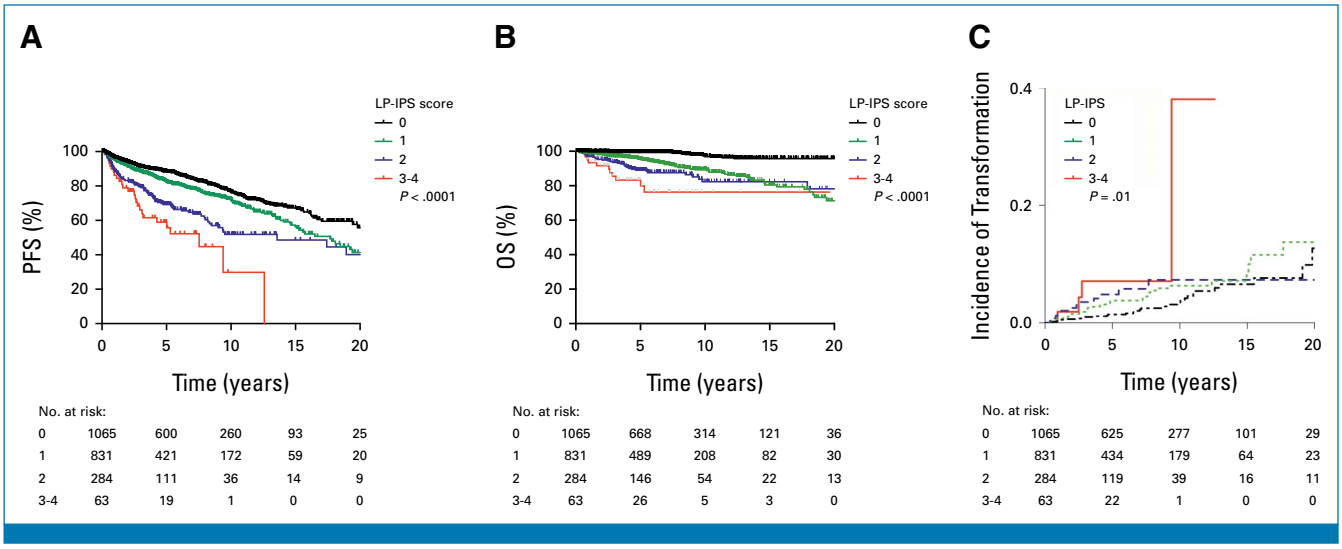

FIG 4. Outcomes stratified by the LP-IPS. The LP-IPS assigns one risk point for each clinical factor: age ≥45 years, stage III-IV involvement, hemoglobin <10.5 g/dL, and splenic involvement. Increasing LP-IPS is significantly associated with (A) worse PFS, (B) worse OS, and (C) higher incidence of transformation. LP-IPS, lymphocyte-predominant international prognostic score; OS, overall survival; PFS, progression-free survival.

approaches.[21] The LP-IPS will aid in the study of treatment de-escalation and form the basis for prospective clinical trials executed by our GLOW consortium.

In this study, we were able to validate previous findings from smaller cohorts across all ages regarding histologic pattern–specific outcomes in NLPHL. Previous studies have shown a higher prevalence of IAP C/D/E in patients with advanced-stage NLPHL,[15] and we confirm and extend these findings, with our small group of IAP F being predominantly early stage. Regarding outcomes, a smaller study showed that pediatric patients with IAP C and E were at higher risk of relapse.[17] Subsequently, two studies reported worse prognosis for variant IAP when grouping IAP C/D/E/F together, and these patients were included in the current analysis.[7,16] As these earlier studies were underpowered to assess individual variant pattern outcomes, we believe that IAP C/D/E/F should not be combined for clinical analyses. Only IAP E was associated with a worse outcome for all end points (PFS, OS, and transformation), and after adjustment for other prognostic factors on MVA, it was also associated with an increased rate of large cell transformation. Nevertheless, we did observe that the 5-year PFS for patients with IAP C/D/E was 15% worse than those with IAP A/B after being treated with radiotherapy alone. This is similar to our earlier publication suggesting that IAP C/D/E has worse prognosis for patients with early-stage NLPHL receiving radiotherapy.[7] Only 40.8% of our cohort had IAP designated at diagnosis, and with a small proportion of the cohort having IAP E, further clinical study of the prognostic impact of individual variant IAPs will be important to evaluate on prospective clinical trials. Therefore, we recommend hematopathologists continue to qualitatively report the presence of any variant IAP.

We developed the LP-IPS to include clinically relevant variables associated with PFS, OS, and risk of transformation, which aid in the decision of treatment regimens for patients with NLPHL. Our LP-IPS successfully stratifies 2.7% of patients as a high-risk subset (score 3-4) where transformation incidence exceeds 5% and lymphoma-specific death is higher than 10% at 5 years. Three of the clinical factors selected for our final model (advanced stage, HgB <10.5 g/dL, and age ≥45 years) are identical to the risk factors on NLPHL reported by the GHSG as being associated with worse freedom from treatment failure or OS.[20] It is important to note that some patients included in the earlier report are present in the current study. The LP-IPS is novel in that we were able to assess for the prognostic significance of IAP, which was not part of the GHSG analysis. In addition, the LP-IPS applies to all ages and all stages of patients. Interestingly, several variables selected for the LP-IPS are similar to prognostic scoring for cHL and follicular lymphoma.[19,23,24] As IAP E was only associated with transformation on MVA, we did not include it as an adverse factor in the LP-IPS model. This is in contrast to a previous prognostic model which used a logistic regression model at 5 years and did include variant patterns (C/D/E/F).[16]

Our study has several limitations primarily related to its retrospective nature which is subject to an inferior level of evidence compared with a prospective study. First, diagnosis and staging were conducted over a 30-year period across institutions where practices likely vary widely. Some serologic markers such as erythrocyte sedimentation rate and albumin were not reliably collected. Although the follow-up was >5 years for the majority of patients, as relapses and transformations continue to occur beyond 10 years, our rates of PFS and transformation may be underestimated. Finally, recent subgroup analyses of the patients enrolled on the HD16 clinical trial by the GHSG showed omission of radiotherapy after two cycles of doxorubicin, bleomycin, vinblastine, dacarbazine chemotherapy resulted in worse outcomes for patients with early-stage favorable NLPHL even in the case of a negative interim positron emission tomography.[25] Thus, an alternative interpretation of our data may be that the definitive therapies administered were necessary to achieve the overall good outcomes seen in our cohort.

In conclusion, this collaborative large retrospective study of a rare lymphoma has identified a new LP-IPS, a novel prognostic score in NLPHL, which allows for identification of low-risk patients (score <2) in whom deintensification should be further studied. In this study, variant IAPs are not associated with an inferior PFS or OS after adjusting for other prognostic risk factors and call for further research into new diagnostic categories for this heterogeneous disease. Our database will serve as a resource for additional follow-up studies and in the design of prospective clinical trials in NLPHL across the age spectrum.

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PRIOR PRESENTATION

Presented in part at the 17th International Conference on Malignant Lymphoma in Lugano, Switzerland, June 16, 2023.

SUPPORT

Supported in part by the Lymphoma Research Foundation, National Institutes of Health Cancer Center Support Core Grant (CA-21765), and the American Lebanese Syrian Associated Charities (J.E.F).

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.23.01655.

DATA SHARING STATEMENT

All patient-level data are protected health information and will not be available for public download because of protection laws for these data.

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ACKNOWLEDGMENT

We would like to thank Suzi Birz for her assistance with the GLOW efforts. The investigators from the Australia and New Zealand Lymphoma and Related Diseases Registry (LaRDR) acknowledge the additional contribution from the patients, participating sites, principal investigators, and registry management team of the LaRDR.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

International Prognostic Score for Nodular Lymphocyte–Predominant Hodgkin Lymphoma

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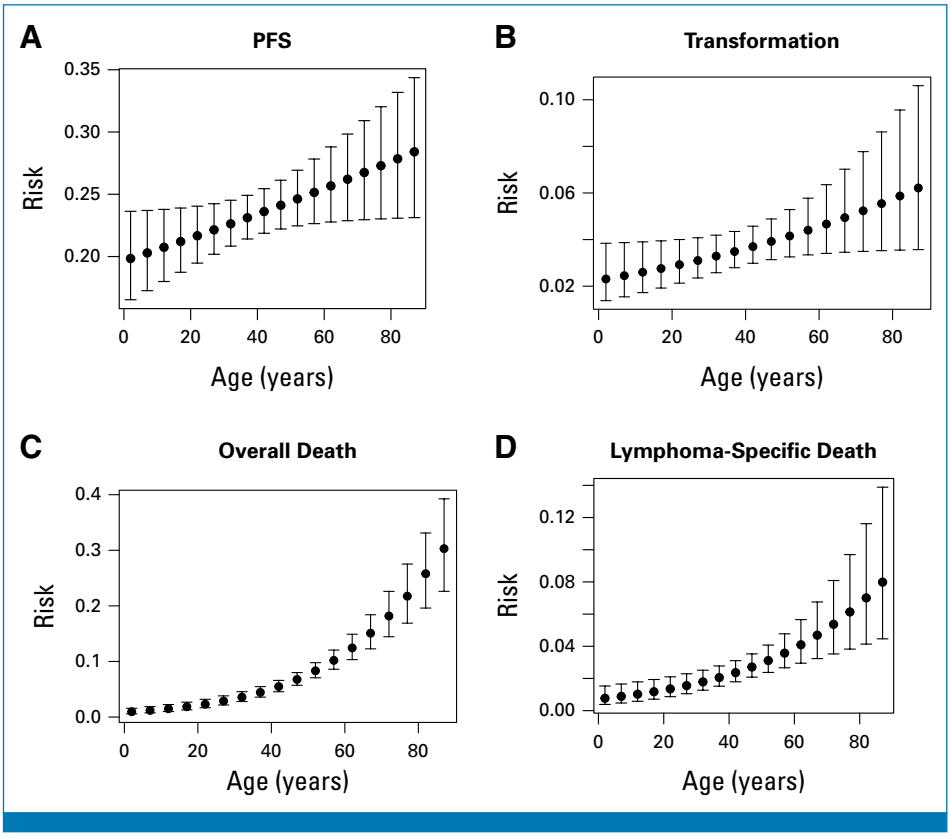

FIG A1. Logistic regression spline analyses to determine age-specific risks of clinical outcomes. PFS, progression-free survival.

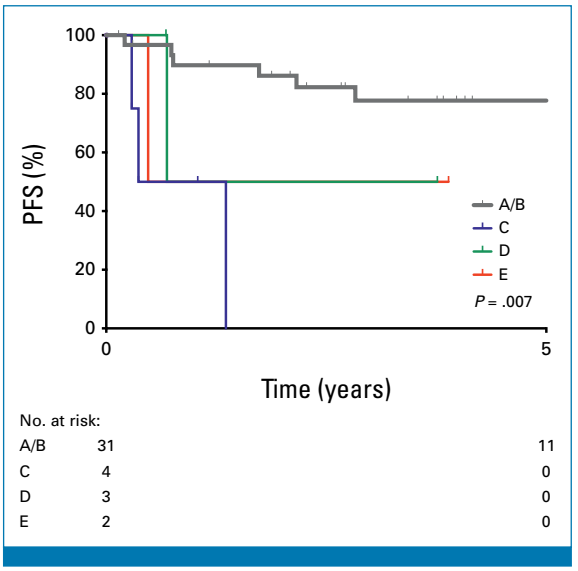

FIG A2. PFS analysis by individual immunoarchitectural patterns for patients undergoing observation after excision. PFS, progression-free survival.

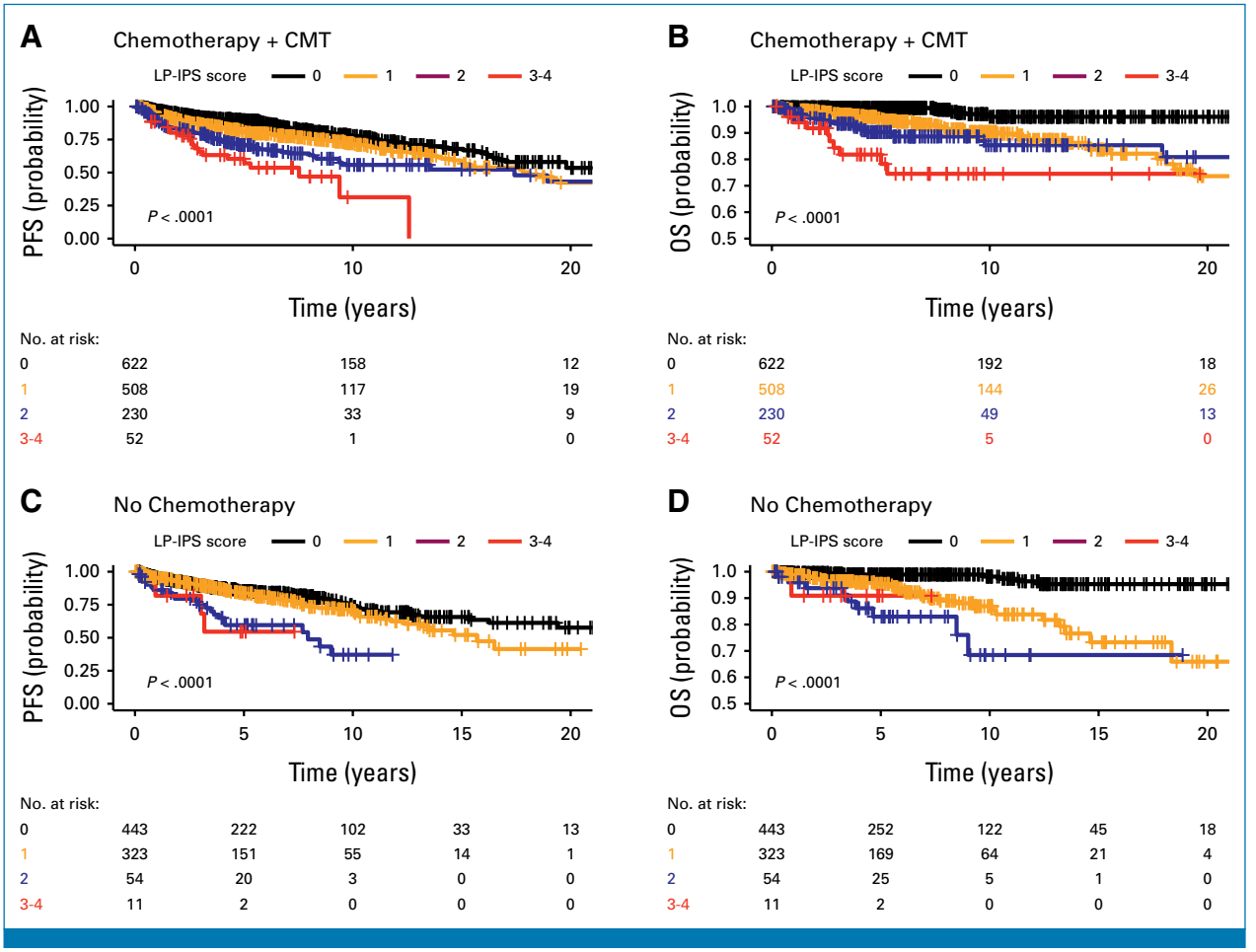

FIG A3. PFS stratified by the LP-IPS for patients receiving either chemotherapy/CMT or all other treatments without chemotherapy. CMT, combined modality therapy; LP-IPS, lymphocyte-predominant international prognostic score; OS, overall survival; PFS, progression-free survival.

TABLE A1. Number of Cases by Stage and IAP

IAP	Stage I	Stage II	Stage III	Stage IV	Total
A/B	272	262	116	26	676
C	27	31	14	6	78
D	15	23	29	15	82
E	16	16	19	16	67
F	7	4	2	0	13
				Total	916

Abbreviation: IAP, immunoarchitectural patterns.

TABLE A2. Univariable and Multivariable Analyses (Cox regression) for PFS, OS, and Transformation

	PFS (522 events)			OS (137 events)			Transformation (81 events)		
Variable	Univariable	MVA1	MVA2[a]	Univariable	MVA1	MVA2[a]	Univariable	MVA1	MVA2[a]
Age ≥45 years	**1.22**	**1.21**	**1.22**	**3.68**	**3.69**	**3.66**	**1.57**	**1.55**	**1.61**
HR									
95% CI	**1.02 to 1.45**	**1.04 to 1.42**	**1.06 to 1.40**	**2.22 to 6.11**	**2.27 to 5.99**	**2.30 to 5.85**	**1.25 to 1.98**	**1.25 to 1.92**	**1.30 to 1.99**
P	**.03**	**.02**	**4.6e-3**	**4.2e-7**	**1.5e-7**	**5.3e-8**	**1.4e-4**	**7.4e-5**	**1.4e-5**
B symptoms									
HR	**1.77**	1.33	1.35	**2.86**	**2.08**	**2.16**	1.09		
95% CI	**1.37 to 2.31**	0.98 to 1.80	0.99 to 1.82	**2.00 to 4.08**	**1.66 to 2.61**	**1.64 to 2.84**	0.60 to 1.97		
P	**1.8e-5**	.07	.06	**8e-9**	**1.7e-10**	**5.3e-8**	.78		
IAP									
A/B or F (ref)									
HR	—	—	—	—	—	—	—	—	—
95% CI									
P									
C or D									
HR	1.23			1.28			0.52		
95% CI	0.74 to 2.03			0.91 to 1.79			0.11 to 2.35		
P	.42			.15			.39		
E									
HR	**1.77**		1.33	**1.56**		1.05	**2.10**		**1.81**
95% CI	**1.02 to 3.07**		0.94 to 1.88	**1.06 to 2.31**		0.53 to 2.08	**1.40 to 3.15**		**1.16 to 2.82**
P	**.04**		.11	**.03**		.90	**.0003**		**9.2e-3**
Extranodal disease									
HR	**2.11**	1.38	1.32	**2.32**	1.45	1.24	1.35		
95% CI	**1.36 to 3.28**	0.94 to 2.04	0.88 to 1.99	**1.89 to 2.85**	0.98 to 2.15	0.87 to 1.76	0.72 to 2.52		
P	**8.9e-4**	.10	.18	**1.1e-15**	.06	.24	.35		
Stage III-IV									
HR	**1.88**	**1.37**	**1.39**	**2.36**	1.91	**1.72**	1.30		
95% CI	**1.40 to 2.52**	**1.06 to 1.77**	**1.03 to 1.88**	**1.82 to 3.07**	0.99 to 2.58	**1.22 to 2.41**	0.93 to 1.83		
P	**3.1e-5**	**.02**	**.03**	**1.2e-10**	.06	**1.8e-3**	.13		
LDH elevated									
HR	**1.45**	**1.26**	**1.24**	**1.95**	**1.63**	**1.55**	1.59		
95% CI	**1.25 to 1.68**	**1.11 to 1.43**	**1.02 to 1.49**	**1.38 to 2.77**	**1.10 to 2.41**	**1.01 to 2.37**	0.96 to 2.64		

(continued on following page)

TABLE A2. Univariable and Multivariable Analyses (Cox regression) for PFS, OS, and Transformation (continued)

	PFS (522 events)			OS (137 events)			Transformation (81 events)		
Variable	Univariable	MVA1	MVA2[a]	Univariable	MVA1	MVA2[a]	Univariable	MVA1	MVA2[a]
P	**8.5e-7**	**2.7e-4**	**.03**	**1.8e-4**	**.02**	**4.4e-2**	.07		
Male sex									
HR	**1.29**	**1.28**	**1.25**	1.24			1.21		
95% CI	**1.11 to 1.50**	**1.11 to 1.48**	**1.08 to 1.46**	0.71 to 2.17			0.62 to 2.33		
P	**.001**	**7.2e-4**	**2.8e-3**	.46			.58		
No. >2									
HR	**1.57**	1.05	1.05	**1.75**	0.91	0.88	**1.50**	1.26	1.27
95% CI	**1.17 to 2.12**	0.72 to 1.53	0.75 to 1.47	**1.35 to 2.28**	0.56 to 1.50	0.59 to 1.32	**1.14 to 1.97**	0.89 to 1.78	0.90 to 1.78
P	**.003**	.81	.78	**2.4e-5**	.72	.54	**.004**	.19	.17
Splenic involvement									
HR	**3.15**	**1.84**	**1.88**	**2.33**	1.11	1.15	**2.93**	**2.31**	**2.49**
95% CI	**2.34 to 4.25**	**1.55 to 2.18**	**1.55 to 2.28**	**1.54 to 3.54**	0.50 to 2.45	0.47 to 2.78	**1.59 to 5.38**	**1.20 to 4.42**	**1.22 to 5.06**
P	**5.1e-14**	**2.4e-12**	**2.2e-10**	**7.1e-5**	.81	.76	**5.5e-4**	**.01**	**1.2e-2**
Size >5 cm									
HR	1.32			**1.66**	**1.23**	**1.29**	1.30		
95% CI	0.93 to 1.88			**1.38 to 1.99**	**1.02 to 1.48**	**1.09 to 1.54**	0.62 to 2.73		
P	.12			**5.8e-8**	**.03**	**4.1e-3**	.49		
HgB <10.5									
HR	**1.97**	**1.50**	**1.36**	**3.46**	**2.17**	**2.03**	0.90		
95% CI	**1.51 to 2.57**	**1.15 to 2.18**	**1.04 to 1.79**	**2.58 to 4.65**	**1.40 to 3.36**	**1.14 to 3.59**	0.30 to 2.69		
P	**7.5e-7**	**3.2e-3**	**2.5e-2**	**2.2e-16**	**5.7e-4**	**1.6e-2**	.84		
WBC									
HR	0.99			0.98			**0.86**	**0.87**	**0.87**
95% CI	0.96 to 1.03			0.90 to 1.06			**0.76 to 0.96**	**0.78 to 0.96**	**0.79 to 0.96**
P	.69			.57			**.008**	**8.1e-3**	**7.5e-3**

NOTE. Bold demarcates factors with a *P* value <.05.

Abbreviations: LDH, lactate dehydrogenase; HgB, hemoglobin; HR, hazard ratio; MVA, multivariable analysis; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival; ref, reference.

[a]MVA2 including immunoarchitectural pattern scoring (n = 916).

TABLE A3. Evaluation of Prognostic Models and Performance Assessment (mean C statistic or HR with 95% CI in parentheses)

Model	Variable	C—PFS (95% CI)	C—OS (95% CI)	C—Transformation (95% CI)	C—LS Death (95% CI)	C—NLPHL Death (95% CI)	HR—PFS (95% CI)	HR—OS (95% CI)	HR—Transformation (95% CI)	HR—LS Death (95% CI)	HR—NLPHL Death (95% CI)
1	Stage III-IV, HgB <10.5, age ≥45 years	0.652 (0.651 to 0.654)	0.729 (0.726 to 0.731)	0.627 (0.623 to 0.632)	0.758 (0.755 to 0.761)	0.787 (0.783 to 0.790)	1.48 (1.26 to 1.73)	2.68 (2.07 to 3.45)	1.35 (1.12 to 1.64)	3.00 (2.16 to 4.18)	3.73 (2.24 to 6.19)
2	Stage III-IV, HgB <10.5, age ≥45 years, splenic	0.657 (0.655 to 0.658)	0.734 (0.732 to 0.737)	0.633 (0.629 to 0.638)	0.770 (0.767 to 773)	0.801 (0.797 to 0.805)	1.52 (1.34 to 1.73)	2.31 (1.95 to 2.74)	1.41 (1.16 to 1.70)	2.63 (2.16 to 3.20)	3.18 (2.37 to 4.27)
3	Stage III-IV, LDH elevated, age ≥45 years	0.658 (0.657 to 0.660)	0.739 (0.736 to 0.741)	0.644 (0.640 to 0.649)	0.774 (0.771 to 0.778)	0.793 (0.789 to 0.796)	1.45 (1.34 to 1.58)	2.09 (1.80 to 2.44)	1.45 (1.17 to 1.79)	2.28 (1.99 to 2.62)	2.46 (2.05 to 2.94)
4	Stage III-IV, HgB <10.5, age ≥45 years, LDH elevated, splenic	0.660 (0.658 to 0.662)	0.744 (0.742 to 0.747)	0.641 (0.637 to 0.646)	0.784 (0.781 to 0.788)	0.813 (0.804 to 0.812)	1.45 (1.34 to 1.58)	2.07 (1.80 to 2.38)	1.39 (1.17 to 1.66)	2.30 (1.96 to 2.69)	2.55 (2.07 to 3.15)
5	Stage III-IV, HgB <10.5, age ≥45 years, LDH elevated	0.656 (0.654 to 0.658)	0.740 (0.738 to 0.743)	0.635 (0.631 to 0.640)	0.776 (0.773 to 0.780)	0.798 (0.794 to 0.801)	1.43 (1.29 to 1.58)	2.31 (1.88 to 2.85)	1.37 (1.13 to 1.66)	2.57 (1.98 to 3.34)	2.87 (2.04 to 4.02)
6	Stage III-IV, HgB <10.5, age ≥45 years, B symptoms	0.654 (0.652 to 0.656)	0.742 (0.739 to 0.744)	0.625 (0.621 to 0.629)	0.779 (0.776 to 0.783)	0.815 (0.812 to 0.819)	1.45 (1.30 to 1.61)	2.35 (2.05 to 2.71)	1.27 (1.03 to 1.56)	2.66 (2.22 to 3.19)	3.26 (2.37 to 4.47)
7	Stage III-IV, HgB <12, LDH elevated, >4 sites, age >60 years	0.656 (0.654 to 0.658)	0.742 (0.739 to 0.745)	0.627 (0.622 to 0.632)	0.782 (0.777 to 0.786)	0.805 (0.801 to 0.809)	1.47 (1.32 to 1.63)	2.07 (1.77 to 2.43)	1.40 (1.19 to 1.64)	2.39 (1.97 to 2.89)	2.49 (1.79 to 3.47)

Abbreviations; HgB, hemoglobin; HR, hazard ratio; LDH, lactate dehydrogenase; LS, lymphoma-specific; NLPHL, nodular lymphocyte–predominant Hodgkin lymphoma; OS, overall survival; PFS, progression-free survival.