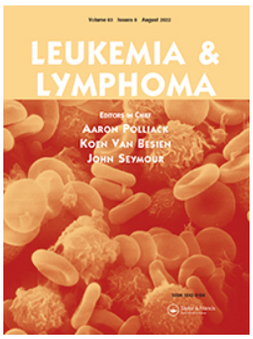

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LETTER TO THE EDITOR

Practice patterns for the management of nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL): an international survey by the Global NLPHL One Working Group (GLOW)

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To the Editor

Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) is a rare subtype of Hodgkin lymphoma (HL) in both children and adults. In contrast to classic HL, NLPHL nearly always expresses CD20, has a mostly indolent clinical course with high overall survival despite frequent relapses, and may undergo aggressive transformation [1–4].

No standard management for NLPHL is established. Early-stage NLPHL is frequently managed with surgical excision, active surveillance, localized radiation therapy (RT), rituximab monotherapy, chemotherapy alone, or combined modality treatment (CMT); and advanced-stage disease is frequently treated with both HL- and aggressive B-cell lymphoma-type chemotherapy regimens [1,2,5–9]. Further, practice patterns vary widely between adult and pediatric oncologists [1,2,5,10–13], as well as internationally given different availability of both diagnostic and therapeutic resources, particularly in low- and middle-income countries (LMICs) [14–16].

Given recent reports suggesting active surveillance or resection alone may be reasonable strategies for the treatment of NLPHL [5,6], there is a pressing need for prospective data for patients of all ages to guide decision-making and a more personalized approach for NLPHL. Given the rarity of the disease, a multicenter international trial presents an opportunity to enroll an adequately sized cohort of patients to robustly study management and outcomes. To build a framework for future prospective studies, we performed an international survey of adult and pediatric providers who treat NLPHL about patient volume, practice patterns, available treatment resources, and collaborative research interests.

The Global NLPHL One Working Group (GLOW) developed an electronic survey instrument which was distributed to the email distribution lists for nine international hematology/oncology groups or consortia and lymphoma-focused professional societies. The survey was open from 16 October 2020 to 11 July 2021 and was distributed to approximately 630 physicians via e-mail to listservs of 13 lymphoma-related cooperative groups, eight of which are focused on pediatric practice, two focused

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Supplemental data for this article can be accessed here.

on adult practice, and three focused on both pediatric and adult practice. The survey instrument is available in the Data Supplement. Statistical comparisons between practice patterns of adult and pediatric providers were performed by Pearson's chi-squared test.

There were 237 respondents to the survey (38%), the majority of which were medical hematologists/oncologists (84%) followed by radiation oncologists (8%), pathologists (6%), and other health professionals (2%). Most respondents treated primarily pediatric patients up to age 18 (56%), followed by those treating primarily adult patients (33%) and 11% who treated both adults and children. Physicians were mostly located in the United States and Canada (26%), followed by South America (23%), Asia (21%), Europe (19%), Oceania (9%), and Africa (2%).

With respect to practice patterns, most physicians reported treating less than five NLPHL cases at their center in the past 5 years (30%), with 30% reporting 5–10 cases, 18% reporting 10–20 cases, and 17% reporting more than 20 cases. Physicians treating adults were significantly more likely to incorporate RT into the treatment of NLPHL (94% versus 59% of physicians treating children and 60% of physicians treating both; $p<.001$), particularly for early-stage disease (Table 1). A greater proportion of physicians treating children would consider surgery in the treatment of NLPHL, compared to physicians treating adults or physicians treating both age groups (62% versus 45% versus 44%, respectively; $p<.001$). Physicians treating adults were significantly more likely to consider age, sex, comorbidities, surgical resectability, and disease location and size ($p<0.001$) in decisions regarding incorporation of RT into the upfront treatment of early-stage NLPHL (Table 1). However, a greater proportion of physicians treating children would consider response to initial chemotherapy in deciding whether to incorporate RT ($p=.013$), and physicians treating both age groups did not consider patient preference in the use of RT.

With respect to chemotherapy utilization, physicians treating adults are significantly more likely to utilize ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) and R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) regimens for early-stage NLPHL as compared to physicians treating pediatric patients ($p<.001$), and are particularly more likely to incorporate rituximab into treatment at 68% compared to 27% of physicians treating pediatric patients and 44% of physicians treating both age groups ($p<.001$, Table 1). For early-stage NLPHL, AV-PC is most frequently utilized by physicians treating children ($p<.001$), whereas for advanced-stage NLPHL, AV-PC is most frequently utilized by physicians treating both adults and children ($p<.001$).

Table 1. Surgery, radiation therapy, and chemotherapy practice patterns among physicians who treat pediatric patients, adult patients, and both pediatric and adult patients with NLPHL.

	Pediatric $n=132$	Adult $n=78$	Adult and pediatric $n=25$	p value
Surgery is incorporated into the treatment of NLPHL	82 (62%)	35 (45%)	11 (44%)	**<.001**
RT is incorporated into the treatment of NLPHL	78 (59%)	73 (94%)	15 (60%)	**<.001**
RT is incorporated into the upfront treatment of early-stage NLPHL				**<.001**
Never or rarely	95 (72%)	7 (9%)	6 (24%)	
Sometimes, usually, or always	25 (19%)	70 (90%)	12 (48%)	
Factors that are considered in the incorporation of RT into the upfront treatment of early-stage NLPHL				
Age	16 (12%)	47 (60%)	11 (44%)	**<.001**
Sex	5 (4%)	28 (36%)	3 (12%)	**<.001**
Comorbidities	11 (8%)	35 (45%)	4 (16%)	**<.001**
Surgical resectability	15 (11%)	28 (36%)	9 (36%)	**.001**
Disease location	20 (15%)	62 (79%)	11 (44%)	**<.001**
Disease size	18 (14%)	47 (60%)	7 (28%)	**<.001**
Patient preference	1 (1%)	0	0	.878
Response to initial chemotherapy	60 (45%)	17 (22%)	7 (28%)	**.013**
Chemotherapy regimen utilized for early-stage NLPHL				
ABVD	45 (34%)	35 (45%)	10 (40%)	**<.001**
AV-PC (i.e. CHOP)	21 (16%)	5 (6%)	3 (12%)	**<.001**
R-CHOP	33 (25%)	29 (37%)	7 (28%)	**<.001**
R-CVP	21 (16%)	17 (22%)	2 (8%)	**<.001**
Any rituximab	36 (27%)	53 (68%)	11 (44%)	**<.001**
Chemotherapy regimen utilized for advanced-stage or bulky NLPHL				
ABVD	33 (25%)	38 (49%)	7 (28%)	**<.001**
AV-PC (i.e. CHOP)	2 (2%)	4 (6%)	4 (16%)	**<.001**
R-CHOP	23 (17%)	53 (68%)	7 (28%)	**<.001**
R-CVP	8 (6%)	18 (23%)	3 (12%)	**<.001**
ABVE-PC	16 (12%)	1 (1%)	5 (20%)	**<.001**
R-OEPA/COPDac	38 (29%)	1 (1%)	1 (4%)	**<.001**
Any rituximab	66 (50%)	63 (81%)	11 (44%)	**<.001**

NLPHL: nodular lymphocyte-predominant Hodgkin lymphoma; RT: radiation therapy; ABVD: doxorubicin, bleomycin, vinblastine, dacarbazine; AV-PC: doxorubicin, vincristine, prednisone, cyclophosphamide; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; ABVE-PC: doxorubicin, bleomycin, vincristine, etoposide, prednisone, cyclophosphamide; R-OEPA/COPDac: rituximab, vincristine, etoposide, prednisone, doxorubicin, followed by cyclophosphamide, vincristine, prednisone, dacarbazine.
Bold values represent the p-values that are statistically significant (i.e., $<=0.05$).

Table 2. Practice patterns and resource availability between LMIC and non-LMICs.

	Non-LMIC $n = 137$	LMIC $n = 100$	p value
Therapies incorporated into the treatment of NLPHL			
RT	102 (74%)	64 (64%)	.22
Surgery	81 (59%)	47 (47%)	.17
Chemotherapy	125 (91%)	92 (92%)	.23
Immunotherapy (rituximab or other CD20-antibody)	108 (79%)	53 (53%)	**<.001**
Availability of resources for NLPHL management			
Computed tomography (CT)	131 (96%)	96 (96%)	.94
Positron emission tomography (PET)	133 (97%)	55 (55%)	**<.001**
Ultrasound	124 (91%)	91 (91%)	.96
Rituximab	125 (91%)	69 (69%)	**<.001**
Hematopathology	129 (94%)	70 (70%)	**<.001**
RT	130 (95%)	86 (86%)	**.05**
Magnetic resonance imaging (MRI)	128 (93%)	76 (76%)	**<.001**

Low- and middle-income countries (LMICs) represented: Argentina, Armenia, Bolivia, Brazil, China, Colombia, Costa Rica, Dominican Republic, Ecuador, Egypt, El Salvador, Georgia, Haiti, Honduras, India, Iraq, Jordan, Kazakhstan, Kyrgyz Republic, Lebanon, Malaysia, Mexico, Myanmar, Nicaragua, Nepal, Pakistan, Panama, Peru, Philippines, Russia, Syria, Tajikistan, Tanzania, Uganda, Venezuela, Yemen; non-LMICs represented: Australia, Belgium, Canada, Chile, France, Germany, Italy, Kuwait, Netherlands, New Zealand, Norway, Oman, Palestine, Saudi Arabia, Singapore, Spain, Sweden, United Kingdom, United States, Uruguay.
Bold values represent the p-values that are statistically significant (i.e., <=0.05).
RT: radiation therapy; LMIC: low- and middle-income countries. Other abbreviations like CT, PET and MRI are defined directly in the text of the table.

For advanced-stage or bulky disease, a greater proportion of physicians treating children would utilize the ABVE-PC (doxorubicin, bleomycin, vincristine, etoposide, prednisone, cyclophosphamide) and R-OEPA/COPDac (R-OEPA: rituximab, vincristine, etoposide, prednisone, doxorubicin; COPDac: cyclophosphamide, vincristine, prednisone, dacarbazine) regimens as compared to physicians treating adults ($p<.001$), whereas physicians treating adults would more commonly utilize ABVD and R-CHOP ($p<.001$). Of note, physicians treating adults are significantly more likely to incorporate rituximab into advanced-stage treatment at 81% compared to 50% of physicians treating children ($p<.001$).

In comparing LMICs versus non-LMICs, there were no differences between the incorporation of RT, surgery, or chemotherapy, although physicians from LMICs are significantly less likely to incorporate rituximab into NLPHL treatment at 53% versus 79% in non-LMIC countries ($p<.001$, Table 2). There was also significantly less availability of PET, rituximab, hematopathologists, MRI ($p<.001$) and RT ($p=.05$) available in LMICs as compared to non-LMICs.

Survey respondents were very willing to participate in an international NLPHL retrospective study (72%), with slightly lower rates of interest for a prospective registry (68%) and a prospective clinical trial (62%).

In summary, our international survey of NLPHL practice patterns revealed considerable variability in the use of RT and various chemoimmunotherapy regimens between physicians treating adults versus children versus both age groups, as well as among LMICs and non-LMICs. Physicians treating children are more likely to incorporate surgery in the treatment of NLPHL, whereas physicians treating adults reported significantly greater incorporation of RT in early-stage NLPHL and significantly greater incorporation of rituximab into the management of early- and advanced-stage NLPHL. These findings are important in designing a prospective study, as the roles of RT and rituximab are not universally established in NLPHL. For example, stage IA NLPHL in adults is commonly treated with involved-site RT as outcomes are comparable between RT and CMT [17], whereas RT is avoided in children and young adults with NLPHL due to concerns about late toxicities in a disease with very long survival [5]. The role of rituximab in NLPHL is controversial, with some evidence for prolonged progression-free survival when it is incorporated into frontline management but other studies demonstrating its limited efficacy as a single agent [13,18,19].

Although there was strong interest from respondents in participation in an international prospective clinical trial, this survey elucidates several significant barriers to trial design and execution. First, availability of rituximab and RT in LMICs may make prospective study of both modalities challenging. Second, there are diagnostic challenges to accurate diagnoses of this rare subtype, especially in LMICs with less availability of hematopathologists and fewer PET resources which may make adapted treatment protocols difficult to execute. Prospective trial execution will require a nuanced appraisal of local resources, with a potential need for the development of adapted treatment regimens in LMICs [16]. However, availability and utilization of chemotherapy appears to be amenable to study in an international cohort. In conclusion, these findings set the foundation for future international prospective registry and clinical trial work in NLPHL by GLOW.

Author contributions

A.C.L. designed the research, performed the research, analyzed data, and wrote the paper; A.M. designed the

research, performed the research, analyzed and wrote the paper; B.A. designed the research, performed the research, and wrote the paper; A.S. designed the research, performed the research, and wrote the paper; L.S.C. designed the research, performed the research, and wrote the paper; L.J.M designed the research, performed the research, and wrote the paper; K.M.K. designed the research, performed the research, and wrote the paper; M.L.M. designed the research, performed the research, and wrote the paper; I.B. designed the research, performed the research, and wrote the paper; C.M.K. designed the research, performed the research, and wrote the paper; A.R.B. designed the research, performed the research, and wrote the paper; M.S.B. designed the research, performed the research, analyzed data, and wrote the paper; J.F. designed the research, performed the research, analyzed data, and wrote the paper.

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