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Low Risk of Central Nervous System Relapse Among Patients With T-Cell/Histiocyte-Rich Large B-Cell Lymphoma Despite High-Risk Disease Presentation

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ABSTRACT

T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL) is a rare subtype of large B-cell lymphoma (LBCL) for which central nervous system (CNS) relapse remains a devastating complication. The CNS International Prognostic Index (IPI) is usually used to predict the risk of CNS relapse. However, the overall risk of CNS relapse among patients with THRLBCL remains poorly known. To clarify the risk of CNS relapse in THRLBCL, data for 106 patients with THRLBCL diagnosed between 2000 and 2020 were collected from seven hospitals throughout Finland. The control data consisted of 660 patients with diffuse LBCL (DLBCL) diagnosed and treated in Oulu University Hospital. Most of the patients with THRLBCL and DLBCL presented with advanced stage disease and were classified as high-intermediate or high-risk groups based on their IPI score. 368 patients received R-CHOP as first line therapy. Our data included patients who had received CNS prophylaxis. For the entire patient population, we found a 5-year CNS relapse risk of 1.04% and 5.29% among patients with THRLBCL and DLBCL, respectively ($p < 0.001$). In conclusion, THRLBCL has lowered CNS relapse risk compared to DLBCL.

1 | Introduction

The World Health Organization classification of hematolymphoid tumors (WHO-HAEM5), defines T-cell/histiocyte-rich B-cell lymphoma (THRLBCL) as a rare subtype of large B-cell lymphoma (LBCL) [1], which has been thought to originate from nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) [2, 3]. THRLBCL is characterized by large malignant B-cells and reactive non-neoplastic T-cells (predominantly CD8+ T-cells). B-cells typically constitute less than 10% of the total cell count, whereas T-cells and histiocytes dominate [4].

THRLBCL has previously been classified as a subtype of diffuse LBCL (DLBCL) and is treated using regimens like that for DLBCL. For DLBCL, the most common treatment regimen utilized is rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP), with or without etoposide, which is also the main treatment for THRLBCL in Finland [5]. Approximately 5%

of DLBCL cases experience central nervous system (CNS) relapse with fatal consequences [6]. A study by Puckrin et al. reported that the median overall survival after CNS relapse was less than 7 months [7].

To decrease the risk of CNS relapse, several oncology centers provide CNS prophylaxis with systemic high-dose methotrexate (HD-MTX) for patients with high-risk DLBCL. However, methotrexate treatment has been associated with toxic adverse effects, and evidence regarding its efficacy for CNS prophylaxis remains conflicting [8, 9]. Given the lack of available data regarding the risk of CNS relapse with THRLBCL or whether patients with THRLBCL require CNS prophylaxis, the current retrospective study aimed to evaluate the CNS relapse risk among patients with THRLBCL.

2 | Materials and Methods

2.1 | Data Collection

Information regarding demographic, pathological, and prognostic factors; the type of treatment; and treatment outcomes were collected. The baseline information included age, sex, underlying diseases, serum lactate dehydrogenase (LDH) levels, Ann Arbor stage, B-symptoms (unexplained weight loss, fever, and night sweats), and IPI score. Treatment information included the type of therapy, response to therapy, patient survival status (assessed in months), disease progression, re-treatment, and deaths (classified as deaths due to lymphoma, treatment for lymphoma, or other causes). After an experienced hematopathologist (OJ, JB, SV, and JPV) reviewed the samples, only patients confirmed to have been diagnosed with THRLBCL between 2000 and 2020 were ultimately included for analysis. Comparisons between patients with THRLBCL and DLBCL were then conducted.

All patients in this LBCL cohort were diagnosed and/or treated at Oulu University Hospital, including high-risk patients referred from the regional cities of Rovaniemi and Kajaani.

LBCL data was collected from Oulu University Hospital with local research permit number 267/2023 and TCHRLBCL data by approval from the ethics committee of Northern Ostrobothnia hospital district. The following seven Finnish hospitals participated in the study: Kuopio, Oulu, Tampere, and Turku University Hospitals and Central Hospitals in Jyväskylä, Joensuu (North Karelia), and Mikkeli.

2.2 | Statistical Analysis

The collected data and demographic variables were reported using descriptive and exploratory statistics. Time to CNS relapse was calculated from the date of diagnosis to the date of diagnosis of CNS relapse, or the date of the last follow-up and death has been regarded as competing risk. Cumulative incidence estimates were computed using the competing risks analysis. Based on these estimates, five-year risk estimates of CNS relapse were determined.

Survival analyses with the corresponding p values were calculated using the Kaplan Meier method. When estimating THRLBCL- or DLBCL-specific mortality, deaths from THRLBCL or DLBCL were considered as an event of interest, whereas those from any other cause were considered a competing event. Progression-free survival (PFS) was calculated from the day of diagnosis to the date of disease progression, death, or last follow-up. Overall survival (OS) was calculated from the date of diagnosis to the date of death from any cause or last follow-up.

The log-rank test was performed to compare the statistical significance of the survival distributions for patients with DLBCL and THRLBCL. Pearson's chi-squared test was used to assess the statistical significance of the prognostic factors between patients with THRLBCL and DLBCL. All statistical analyses were performed using IBM SPSS Statistics version 27.0 (IBM Corp, Armonk, NY, USA) and R software version 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria), with a p value of 0.05 indicating statistical significance.

Cox multivariable regression analysis was performed to compare DLBCL and THRLBCL, adjusted for baseline differences between the groups.

For the purposes of this study, first-line therapy was defined and analyzed as follows. In cases where patients received multiple treatment options in the first line, the therapy most frequently administered was considered the first-line treatment.

3 | Results

3.1 | Patient Demographics

Patient demographics during the primary diagnosis are presented in Table 1. Specifically, patients with DLBCL were older than those with THRLBCL (67 vs. 57 years; $p < 0.001$). The male/female ratio was 2.3 and 1,2 in the THRLBCL and DLBCL groups. Advanced-stage disease and elevated LDH were more common among patients with THRLBCL than among those with DLBCL. Moreover, 23 (21.7%) patients with THRLBCL and 169 (25.6%) patients with DLBCL had received HD-MTX as CNS prophylaxis. Complete clinical information regarding IPI scores, performance status, LDH levels, and stage was not available from some patients, primarily from the early study years when electronic medical records were not in use.

Most of the patients received R-CHOP as first line therapy (Table 2) with or without etoposide.

Median follow up time was 52.5 months with DLBCL patients and 50 months with THRLBCL patients.

3.2 | CNS Relapses

In the current patient population, only one patient with THRLBCL was diagnosed with CNS relapse 10 months after diagnosis.

Forty-five CNS relapses were diagnosed among the patients with DLBCL. The 2-year CNS relapse risk in patients with DLBCL and THRLBCL was 2.49% and 1.04%. The 5-year cumulative CNS relapse risk in patients with DLBCL and THRLBCL was 5.29% and 1.04%, respectively ($p = 0.02$; Figure 1A).

TABLE 1 | Patient demographics.

Variable	THRLBCL ($n=106$) n (%)	DLBCL ($n=660$) n (%)	p (Pearson's chi-squared test)
Age at diagnosis, years, mean (range)	57 (22–90)	67 (19–97)	<0.001*
Male/female ratio	2.3	1.2	0.006*
IPI			0.088
0	3 (2.8%)	5 (0.8%)	
1	6 (5.7%)	70 (10.6%)	
2	20 (18.9%)	94 (14.2%)	
3	33 (31.1%)	112 (17.0%)	
4	21 (19.8%)	92 (13.9%)	
5	9 (8.5%)	44 (6.7%)	
Missing	14 (13.2%)	243 (36.8%)	
Stage			<0.001*
I	3 (2.8%)	86 (13.0%)	
II	10 (9.4%)	73 (11.1%)	
III	18 (17%)	89 (13.5%)	
IV	61 (57.5%)	225 (34.1%)	
Missing	14 (13.2%)	187 (28.3%)	
ECOG			0.022*
0	30 (28.3%)	61 (9.2%)	
1	39 (36.8%)	115 (17.4%)	
2	16 (15.1%)	77 (11.7%)	
3	10 (9.4%)	33 (5.0%)	
4	3 (2.8%)	33 (5.0%)	
Missing	8 (7.5%)	341 (51.7%)	
LDH			<0.001*
Normal	19 (17.9%)	147 (22.3%)	
Elevated	72 (67.9%)	380 (57.6%)	
Missing	15 (14.2%)	133 (20.2%)	
Number of extranodal lesions			0.001*
None	22 (20.8%)	200 (30.3%)	
One	38 (35.8%)	291 (44.1%)	
Two or more	40 (37.7%)	167 (25.3%)	
Missing	6 (5.6%)	2 (0.3%)	
Suprarenal			
Yes	0 (0%)		
No	98 (92.5%)		
Missing	8 (7.5%)		

(Continues)

TABLE 1 | (Continued)

Variable	THRLBCL ($n=106$) n (%)	DLBCL ($n=660$) n (%)	p (Pearson's chi-squared test)
Renal			
Yes	2 (1.9%)		
No	96 (90.6%)		
Missing	8 (7.5%)		
Received HD-MTX-prophylaxis			0.536
Yes	23 (21.7%)	169 (25.6%)	
No	78 (73.6%)	490 (74.2%)	
Missing	5 (4.7%)	1 (0.2%)	
Translocations			< 0.001
None	7 (6.6%)	106 (16.1%)	
MYC	—	8 (1.2%)	
BCL-2	3 (2.8%)	41 (6.2%)	
BCL-6	19 (17.9%)	39 (5.9%)	
BCL-2 + MYC	—	20 (3.0%)	
BCL-6 + MYC	1 (0.9%)	5 (0.8%)	
BCL-2 + BCL-6 + MYC	3 (2.8%)	8 (1.2%)	
BCL-2 + BCL-6	16 (15.1%)	10 (1.5%)	
Unknown	33 (31.1%)	422 (63.9%)	
Missing	24 (22.6%)	1 (0.2%)	
GC-phenotype			< 0.001
GC	3 (2.8%)	227 (34.4%)	
Non-GC	2 (1.9%)	228 (34.5%)	
Unknown	65 (61.3%)	204 (30.9%)	
Missing	36 (34%)	1 (0.2%)	

Abbreviations: ECOG, Eastern Cooperative Oncology Group performance status; HD-MTX, high-dose methotrexate; IPI, international prognostic index; LDH, lactate dehydrogenase.
*Statistically significant.

Among DLBCL patients, most of the CNS relapses were isolated events occurring in the parenchymal tissue (Table 3).

The THRLBCL patient who experienced CNS relapse had an unknown GC phenotype and translocation status. At diagnosis, the patient had 4 IPI and CNS-IPI points. Two or more extranodal sites were involved during diagnosis, without renal or suprarenal involvement. The patient did not receive prophylactic high-dose methotrexate.

3.3 | Treatment Outcomes

The 5-year PFS for patients with THRLBCL and DLBCL were 59.1% and 64.7%, respectively ($p=0.4019$; Figure 2A). The 5-year DSS for patients with THRLBCL and DLBCL were 78.3% and 77.5%, respectively ($p=0,3266$; Figure 2B). The 5-year OS for patients

TABLE 2 | First-line therapy and number of treated patients.

First line therapy	Number of treated n (%)
R-CHOP	368 (48.7%)
biotCHIC	< 5 (0.1%)
DAEPOCH	14 (1.9%)
R-CEOP	132 (17.5%)
R-CHOEP	99 (13.1%)
R-CVOP	46 (6.1%)
MACOPB	5 (0.7%)
Other	90 (11.9%)
All	755 (100%)

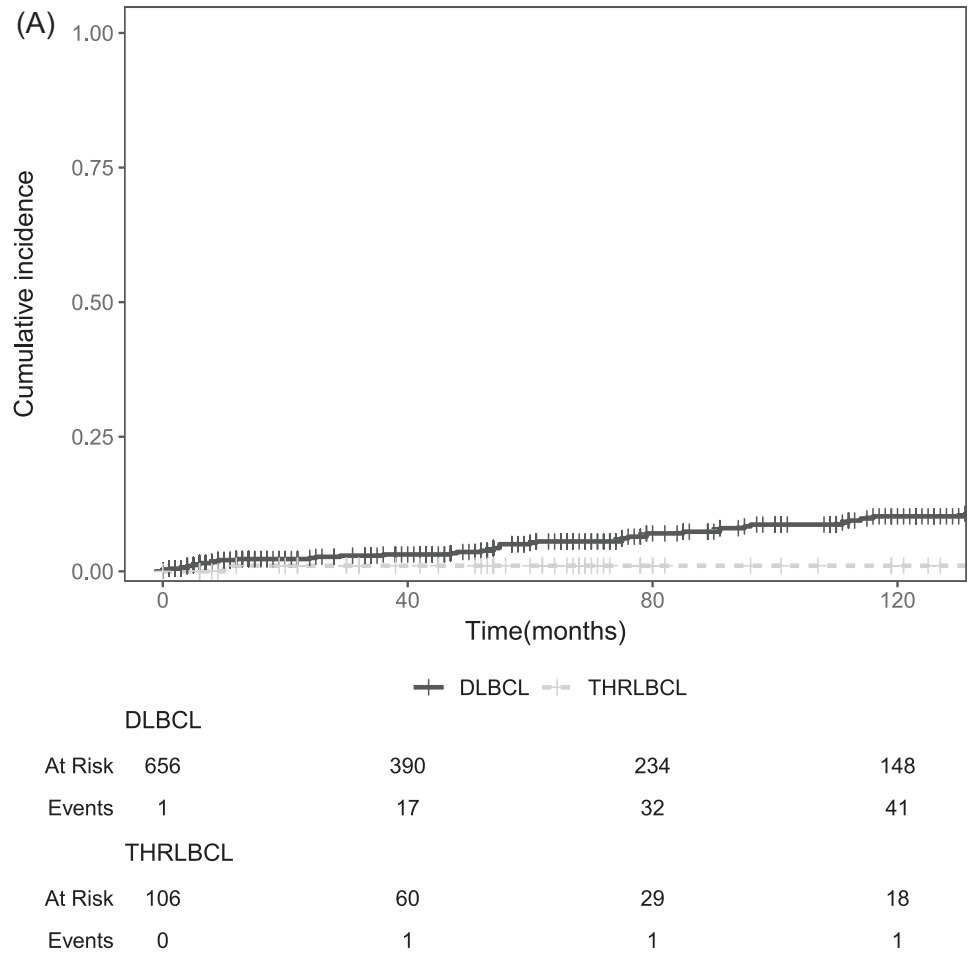

FIGURE 1 | (A) Competative risk analysis estimate of central nervous system (CNS) relapse risk based on given diagnosis.

TABLE 3 | Location of CNS relapse.

DLBCL	
Location of CNS relapse	***n***
Isolated+parenchymal	24 (53.3%)
Isolated+parenchymal+cerebrospinal fluid	9 (20%)
Isolated+leptomeningeal	6 (13.3%)
Systemic+leptomeningeal	3 (6.7%)
Systemic+parenchymal	2 (4.4%)
Systemic+no info	1 (2.2%)
THRLBCL	
Location of CNS relapse	***n***
Isolated+parenchymal	1 (100%)

with THRLBCL and DLBCL were 63.7% and 67.6% ($p=0{,}6983$, Figure 2C).

In the adjusted multivariate analysis of THRLBCL and DLBCL cases, age (HR; 1.02, $p=0.039$) was identified as statistically significant baseline risk factor in PFS. In DSS, age (HR; 1.02, $p=0.030$), cell of origin (HR; 1.55, $p=0.010$) and number of extranodal lesions (HR; 1.57, $p=0.019$) were identified as statistically significant baseline risk factor. In OS, age (HR; 1.04, $p<0.001$) was statistically significant. For CNS relapse, the number of extranodal lesions was statistically significant (HR; 2.53, $p=0.035$).

4 | Discussion

This is the first study to describe the risk of CNS dissemination in THRLBCL. Accordingly, the present study found that patients with THRLBCL were at low risk for CNS dissemination despite presenting with an advanced stage disease, a high number of extranodal lesions, and elevated LDH, indicating that these patients probably do not need CNS-directed therapies.

The patients included in this study had consistent clinical presentation like those included in existing literature. In particular, patients with THRLBCL were 10 years younger than those with DLBCL. Many of our patients exhibited B-symptoms, had involvement of several extranodal sites, such as the spleen and bone marrow, and were diagnosed at an advanced (III–IV) stage [10–12]. Patients with THRLBCL were treated with similar chemotherapy regimens to those with DLBCL. R-CHOP or CHOP chemotherapy regimens with or without etoposide were the most commonly used first-line treatment [5].

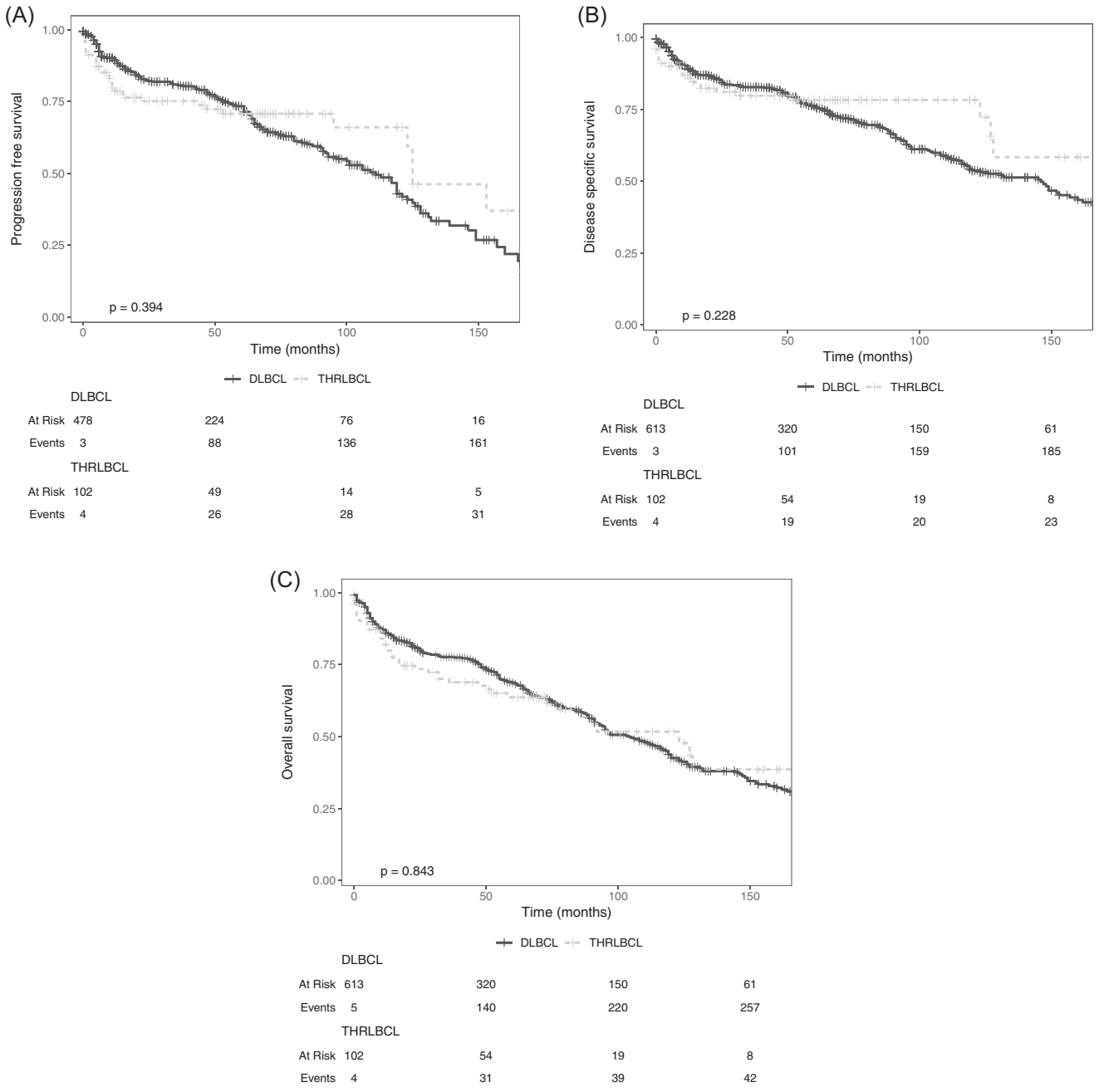

FIGURE 2 | Kaplan–Meier survival analyses. (A) Progression-free survival (PFS) according to diagnosis given. (B) Disease-specific survival (DSS) according to diagnosis given. (C) Overall survival (OS) according to diagnosis given.

LBCLs have been associated with a risk for CNS relapse with devastating complications. For DLBCL, this risk is thought to be around 5%. Several studies have attempted to identify predictive markers for an increased risk of CNS relapse [13]. In line with this, the CNS International Prognostic Index (CNS-IPI) has been the most commonly used predictive index. Risk factors identified by the CNS-IPI include an age over 60 years, elevated LDH, stage III–IV disease, one or more extranodal sites, involvement of the kidneys or adrenals, and WHO/ECOG performance status >1 [14, 15]. In several oncologic centers, patients at high risk for CNS relapse typically receive systemic HD-MTX to decrease the risk of CNS relapse, although evidence regarding efficacy remains inconsistent [9]. CNS prophylaxis for patients with THRLBCL has usually been administered based on the same indications as for DLBCL.

After conducting matched pair comparisons, Kuitunen et al. (2020) reported that the 5-year risk for isolated CNS relapse in DLBCL was 5% and 26% among patients who received HD-MTX prophylaxis and those who did not, respectively [16]. In contrast, Lewis et al. (2023) reported that HD-MTX did not achieve a clinically significant reduction in the risk of CNS progression among patients with B-cell lymphoma [17]. The 5-year risk difference between patients who did and did not receive HD-MTX prophylaxis was only 1.6% [17]. No existing studies have investigated the risk of CNS relapse and the possible benefit of prophylaxis in THRLBCL.

In our study, the 5-year cumulative risk for CNS lymphoma was 1.04% and 5.29% in patients with THRLBCL and DLBCL This finding remained true despite THRLBCL patients presenting with more high-risk features, such as advanced stage, extranodal lesions, and elevated LDH levels. These findings highlight the fundamental biological differences between these two lymphoma entities, which also interferes with their predilection of dissemination sites. Previous studies have shown that the gene expression profile of THRLBCL resembles that of Hodgkin's lymphoma and nodular lymphocyte predominant Hodgkin's disease, both of which rarely affect the CNS.

23 (21.7%) and 169 (25.6%) patients with THRLBCL and DLBCL had received HD-MTX as CNS prophylaxis. In later years of the study, patients were selected to receive CNS prophylaxis based on high IPI classification, the presence of 2 or more extranodal lesions, or elevated LDH. Earlier in this study period, CNS prophylaxis was rarely given or administered. Our study contains a long time period, and multiple treatment centers are involved, with treatment methods having evolved over time, both between centers and within individual centers.

The diagnosis of THRLBCL remains challenging for pathologists given that it shares similar features with other lymphomas, particularly with NLPHL [10]. The strength of our study was that experienced hematopathologists reviewed all patients included. Although THRLBCL is a rare lymphoma type, we were able to identify a moderate number of patients for evaluation.

Some limitations of our study need to be acknowledged. Given that this study investigated a rare endpoint event of a rare disease, the confidence interval was quite wide. Therefore, the contribution of chance to the outcome of the study cannot be excluded. A confounding factor in this study was that some of the patients had received CNS prophylaxis, which may have affected the cumulative CNS relapse risk rate. However, there was no difference in the number of patients with received prophylaxis between these two patient groups. Patient data were insufficient to perform a matched pair analysis for CNS-IPI risk factors to assess the risk of CNS relapse between these patient groups.

5 | Conclusions

This is the first study to evaluate the CNS relapse risk of THRLBCL. Based on the findings reported in this study, patients with THRLBCL exhibited a low risk for CNS relapse, indicating that CNS prophylaxis may not be necessary. However, more investigations are necessary to better determine whether or not patients with THRLBCL need CNS prophylaxis considering that the outcomes of this study could have also been affected by chance.

Author Contributions

Mr. Atte Karhu was responsible for data analysis, data collection, and writing the manuscript. Ms. Sara Aronen was responsible for data analysis, data collection, and writing the manuscript. Ms. Sonja Nousiainen, Mr. Hanne Kuitunen, Mr. Juho Kangas, Mr. Eetu Pellonperä, Mr. Henri Kurttila, Mr. Miko Pietilä, and Mr. Jaakko Tirkkonen were responsible for data collection. Ms. Ulla-Mari Arkko, Ms. Annikki Aromaa-Häyhä, Dr. Aino Rönkä, Dr. Tuula Klaavuniemi, Dr. Milla Kuusisto, Dr. Otto Jokelainen, Dr. Jan Böhm, Dr. Kristiina Vuolukka, Dr. Samuli Vaittinen, Dr. Minna Harmanen, Dr. Juha P. Väyrynen, and Associate Professors Kaisa Sunela and Hanne Kuitunen were responsible for reviewing and editing. Professor Outi Kuittinen was responsible for supervision.

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Ethics Statement

Ethics committee of Northern Ostrobothnia hospital district has approved this study.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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