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ORIGINAL RESEARCH ARTICLE

Non-Hodgkin lymphoma in South East Asia: An analysis of the histopathology, clinical features, and survival from Thailand

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Abstract

Systemic reports on the descriptive epidemiology of non-Hodgkin lymphoma (NHL) from Southeast Asia are scarce. A nationwide multi-institutional registry was conducted to compare the histopathology, clinical features, and survival of Thai adult patients with NHL using large registries, especially those from Far East Asia (FEA). Using a web-based registry system, 13 major medical centers from the 4 geographic regions of Thailand prospectively collected, from 2007 to 2014, the diagnostic pathology, according to the World Health Organization classification, 2008, clinical features and survival of 4056 patients who were newly diagnosed with NHL. The median age of the patients was 56 years (range, 16-99 years). The male-to-female ratio was 1.3:1. From the total of 4056 patients, T/NK-cell lymphoma (TNKCL) accounted for 12.6% of cases, and 5.1% had human immunodeficiency virus–associated lymphoma. The four leading histological subtypes were diffuse large B-cell lymphoma, not otherwise specified (58.1%); follicular lymphoma (5.6%); extranodal mucosa-associated lymphoid tissue lymphoma (5.2%); and peripheral T-cell lymphoma, not otherwise specified (4.0%). With a median follow-up duration of 46.1 months, the median overall survival of B-cell NHL was significantly longer than that of patients with TNKCL (76.5 vs 28.8 months, P = .0001). Compared to FEA, the Thai registry had an approximately one-half lower relative frequency of TNKCL; the prevalence of extranodal mucosa-associated lymphoid tissue lymphoma was much lower than in Korea, and the frequency of extranodal TNKCL, nasal type, was strikingly low compared to China. It is concluded that while the median age of Thai patients with NHL was approximately a decade younger than for Caucasians, the long-term survival rates for most histological subtypes were comparable. While the histological distribution generally complied with the characteristic Asian features, some differences from FEA were observed.

KEYWORDS

descriptive epidemiology, non-Hodgkin lymphoma, pathology, survival, Thailand

1 | INTRODUCTION

Geographic variations in the relative frequency of histological subtypes of non-Hodgkin lymphoma (NHL) are well recognized. Compared to western countries, the incidences of follicular lymphoma (FL) and chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) are lower in Asia, whereas the incidences of T/NK-cell lymphomas (TNKCL) are significantly higher.[1–3] A possible explanation for this disparity could be a different complex interplay between genetic susceptibility and various environmental risk factors.

In Thailand, NHL is the sixth most common malignancy; it has an age-standardized incidence rate per 100 000, compared to the world population of 10.2. At present, there is only one previous nationwide analysis of the clinicopathological features of NHL in Thai patients.[4] The study showed the characteristic histologic distribution among Asians, ie, a very low incidence of FL (4%) and a preponderance of the diffuse aggressive entities (40%). However, the classification used in the report was based on the Working Formulation. In 2004, Sukpanichnant et al reported 1983 cases of malignant lymphoma based on the World Health Organization (WHO) classification. The 4 most common pathological subtypes[5] included diffuse large B-cell lymphoma (DLBCL), 46%; peripheral T-cell lymphoma (PTCL), 12%; FL, 8%; and mucosa-associated lymphoid tissue (MALT)–associated lymphoma, 4%. However, the study was based on data from a single center, and extranodal NK/T-cell lymphoma (ENKTL) was not noted as a separate entity.

Epidemiological data of NHL in Asia are mostly derived from studies reported from Far East Asia (FEA).[6–11] Large systemic studies on the descriptive epidemiology of the disease in South East Asia (SEA) are quite scarce. Herein, we reported the pathological distribution[12] based on the WHO classification 2008, clinical features, and survival outcomes of patients with NHL from the Thai Lymphoma Study Group registry. The histological pattern was then compared with data from other national registries, especially the FEA. One-thousand thirty cases from the cohort were randomly selected for an expert consensus pathological review.

2 | METHODS

The Thai Lymphoma Study Group is a nationwide, multi-institutional cooperative body that consists of 27 hematologists and 11 hematopathologists who work at the 13 major medical centers with most of the lymphoma cases at the 4 geographic regions of Thailand (Figure 1). From January 2007 to December 2014, all newly diagnosed NHL patients aged ≥15 years were included in the registry. Detailed baseline characteristics, diagnostic pathology[12] according to the WHO classification 2008, treatment data, disease response, and survival outcomes were retrieved from patients' medical records and entered into the web-based registry by data managers at each participating site. Patients with B- and T-cell prolymphocytic leukemia, hairy cell leukemia, heavy chain diseases, plasma cell neoplasms, and T-cell large granular lymphocytic leukemia were not enrolled because the primary intention of the investigators was to thoroughly evaluate patients with NHL alone. The primary hematologists at each center followed patients based on the institution's protocols. The patients' statuses were prospectively updated every 6 months by medical record review, follow-up phone calls, or national vital statistics database review. The protocol was approved by the Board of Ethics Committee at each participating center and was conducted in accordance with the Declaration of Helsinki.

2.1 | Pathological consensus and data comparison

To verify the primary diagnoses of histologic subtypes according to the WHO classification 2008, a panel of 9 expert hematopathologists (PW,

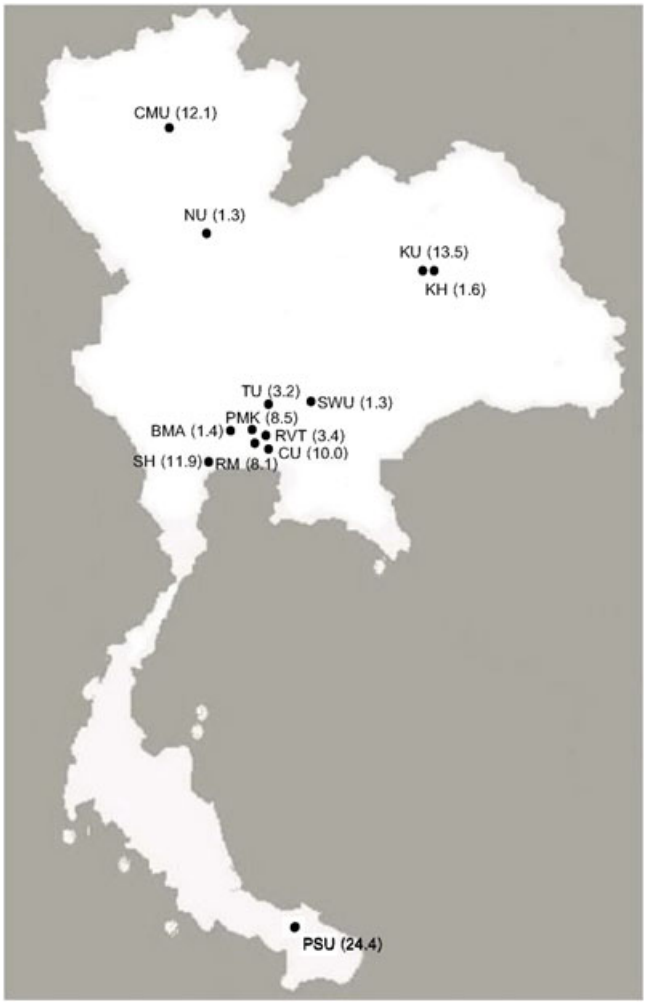

FIGURE 1 Geographic locations of participating sites with percentages of contributing cases (N = 4056). BMA, Bangkok metropolitan administration medical college; CMU, Chiang Mai University; CU, Chulalongkorn University; KH, Kon Kaen Hospital; KU, Kon Kaen university; NU, Naresuan University; PMK, Pramongkutkloa College of Medicine; PSU, prince of Songkhla University; RM, Ramathibodi Hospital; RVT, Rajvithi Hospital; SH, Siriraj hospital; SWU, Srinakharinwirot University; TU, Thammasat University

TA, SS, PB, WK, CY, KK, WM, and NW) acted as a pathological reviewer committee. The original diagnostic stained slides and the immunostains obtained before therapy were randomly selected for independent review by 2 committees. If the primary diagnosis was in question, the case was then reviewed by the entire panel. Additional histochemical, immunohistochemical, and/or molecular genetic studies were performed accordingly. The final diagnosis was made by a consensus meeting. While major discordance was defined as the reclassification of a primary diagnosis that had an impact on the treatment decision, minor discordance was a change in the histological subtype that had no significant clinical effect, such as from FL grade 1 to grade 2.

For comparison of the histopathological distribution of NHL between countries, data from other national registries, based on the WHO classification and consisting of ≥2000 patients, were reviewed and tabulated.[6–11,13–16]

2.2 | Staging and outcome assessment

All patients underwent standard staging procedures. The diagnosis of human immunodeficiency virus (HIV) infection was made using standard methods for detecting the antigen and/or antibody to HIV. The international prognostic index (IPI) score was calculated using the 5 IPI risk factors.[17] Tumor response was assessed by computed tomography scan at 4 weeks after the last course of chemotherapy and was defined as complete remission (CR), complete remission/unconfirmed (CRu), partial remission, stable disease, and progressive disease.[18] Objective response was defined as the rates of CR/CRu and partial remission. The overall survival (OS) duration was calculated from the date of diagnosis to the date of death or final follow-up evaluation.

2.3 | Statistical analysis

All analyses were based on the intention to treat. The results were analyzed as of December, 31, 2014. Comparison of the categorical variables was performed using the Fisher exact or chi-square test. Survival curves were estimated by the actuarial method of Kaplan-Meier and were compared using the log-rank test. All tests of significance were 2-sided with a P value ≤.05. The STATA11 software program was used for statistical analysis.

3 | RESULTS

3.1 | Relative frequency of the histological subtypes

The percentages of cases enrolled by each participating site are shown in Figure 1. Of the total 4056 patients, 12.6% had TNKCL. The 4 leading histological subtypes were DLBCL, not otherwise specified (NOS) (58.1%); FL (5.6%); extranodal MALT lymphoma (5.2%); and PTCL, NOS (4.0%) (Figure 2). The 4 most common subtypes of TNKCL were PTCL, NOS (4%); ENKTL (2.7%); anaplastic large cell lymphoma (ALCL) (1.7%); and angioimmunoblastic T-cell lymphoma (AITL) (1.4%). The frequency of ALCL, anaplastic lymphoma kinase positive, was not known because the anaplastic lymphoma kinase immunostaining was not widely available in most participating centers. Of the 361 unclassifiable cases (8.9%), 65.7% were diffuse large cell, 4.1% were low grade, and 4.1% were high-grade NHL.

Comparison of the relative frequencies of histological subtypes between registries from Europe, the United States, Australia, the FEA, and the current study is shown in Table 1. Compared to Caucasians, the rates of CLL/SLL and FL among Asians were much lower, whereas the frequency of TNKCL was much more common. Compared to FE, the Thai registry had a lower relative frequency of TNKCL and higher frequency of DLBCL. Although the prevalence of extranodal MALT lymphoma was much lower than Korea, the frequency of ENKTL among Thai patients was strikingly low compared to China. The rate of adult T-cell leukemia/lymphoma was much lower than in Japan, but it was comparable to the rates from Korea and China.

On the review of randomly selected diagnostic slides from 1030 cases, the diagnosis could be independently agreed upon by the 2 committees in 97.8% of the cases. The rates of major and minor discordances were 1.9% and 4.6%, respectively. Histological subtypes with

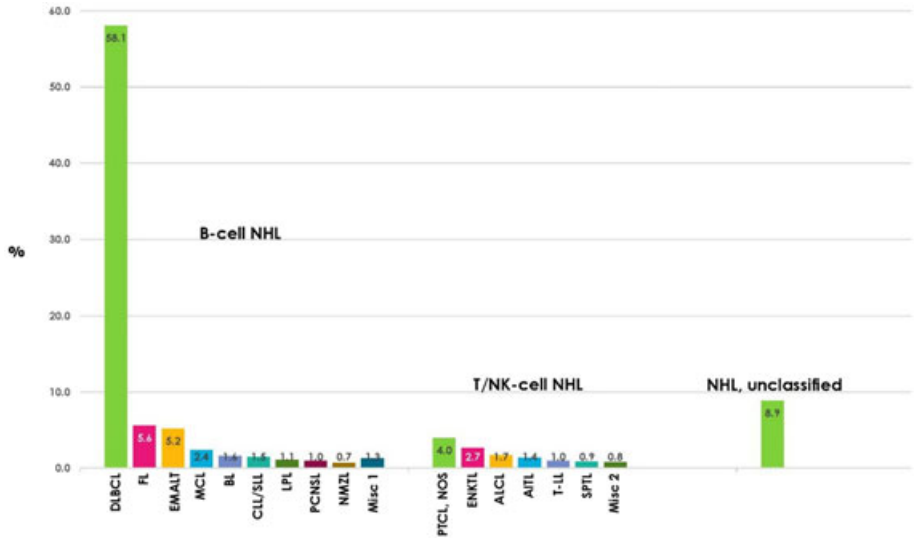

FIGURE 2 Distribution of histological subtypes of NHL according to WHO classification 2008 (N = 4056). Misc 1, splenic marginal zone lymphoma, primary mediastinal large B-cell lymphoma, intravascular B-cell lymphoma, B lymphoblastic leukemia/lymphoma, primary effusion lymphoma, lymphomatoid granulomatosis, plasmablastic lymphoma, Epstein-Barr virus positive DLBCL of the elderly, primary cutaneous follicle center lymphoma, T-cell/histiocyte-rich large B-cell lymphoma, B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and BL. Misc 2, mycosis fungoides/Sezary syndrome, hepatosplenic lymphoma, enteropathy-associated T-cell lymphoma, primary cutaneous anaplastic large cell lymphoma, aggressive NK cell leukemia. AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large cell lymphoma; BL, Burkitt lymphoma; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; EMALT, extranodal mucosa-associated lymphoid tissue associated lymphoma; ENKTL, extranodal NK/T-cell lymphoma; FL, follicular lymphoma; LPL, lymphoplasmacytic lymphoma; PCNSL, primary central nervous system lymphoma; MCL, mantle cell lymphoma; NHL, non-Hodgkin lymphoma; NMZL, nodal marginal zone lymphoma; PTCL, NOS, peripheral T-cell lymphoma, not otherwise specified; SPTL, subcutaneous panniculitis-like T-cell lymphoma; T-LL, T lymphoblastic leukemia/lymphoma; WHO, World Health Organization

the highest rates of major discordance were mantle cell lymphoma (MCL) (0.7%), Burkitt lymphoma (BL) (0.3%), and FL grade 1/3 (0.2%).

3.2 | Baseline demographics and clinical features

The median age of the patients was 56 years (range, 15-99) (Figure 3). The youngest age-groups were seen for subcutaneous panniculitis-like T-cell lymphoma (SPTL) (median age, 27 years) and precursor T-lymphoblastic lymphoma (median age, 31 years) (Table 2). The male-to-female ratio was 1.3:1 with a male preponderance seen in all age groups (Figure 3).as well as in most histological subtypes, especially the MCL (78.8%), BL (69.7%), and ENKTL (68.5%) (Table 2). SPTL was the only entity for which females constituted the majority (65.8%).

B-symptoms was present in most histological subtypes, except for the extranodal MALT lymphoma, where they were detected in less than 1/5 of the patients (Table 2). The frequencies of patients with low-, low-intermediate, high-intermediate and high-risk IPI were 22.7%, 31.6%, 30.6%, and 15.1%, respectively. The proportions of patients with high and high-intermediate risk IPI were highest for BL (62.1%), PTCL, NOS (57.3%), and SPTL (52.6%) (Table 2).

Of the 2014 patients for whom diagnostic biopsied sites were recorded (excluding lymph nodes and bone marrow), the 4 leading organs were sinonasal tissue (9.2%), stomach (8.3%), Waldeyer ring (8.2%), and the central nervous system (7.9%). Among the 211 cases with extranodal MALT lymphoma, the 4 most common primary sites of involvement were ocular/adnexa tissue (39.8%), stomach (9.5%), thyroid glands (4.7%), and salivary glands (4.7%).

The rate of HIV positivity was 5.1%. Of the 207 patients with HIV-associated lymphomas (HAL), 10.6% had TNKCL. The 4 leading histological subtypes were DLBCL, 65.2%; BL, 9.2%; ENKTL, 3.9%; and PTCL, NOS, 2.4%. The histological subtypes with the highest frequency of HIV positivity were BL (28.8%) and ENKTL (7.2%) (Table II). Approximately 5.7% of patients with DLBCL were HAL. The HIV status was negative in most of the indolent B-cell lymphomas. The distribution of histological subtypes among the 22 patients with HIV-associated TNKCL was ENKTL (36.4%), PTCL, NOS (22.7%), AITL (9.1%); and precursor T-lymphoblastic lymphoma (9.1%).

3.3 | Tumor response and survival

Eighty-three percent of the patients were treated with chemotherapy, mostly with the cyclophosphamide, doxorubicin, vincristine, and prednisolone regimen. Of the 3402 patients with B-cell lymphoma, 24.8% received a rituximab-containing regimen. Of all cohorts, the rate of an objective response was 54.4% with 44.6% CR/CRu.

With a median follow-up duration for the surviving patients of 46.1 months (95% confidence interval [CI] 43.9-48.5), the 5-year OS rate was 52.2% (95% CI 50.4-54.0). The median OS of B-cell NHLs was significantly longer than for patients with TNKCL (76.6 vs 28.8 months, P = .0001). Among patients with mature B-cell lymphomas, patients with marginal zone lymphoma had the highest 5-year OS rate (79.9%, 95% CI 73.3-85.1), whereas patients with MCL had the lowest survival rate (5-year OS rate, 36.8%, 95% CI 25.2-48.4) (Figure 4A). For patients with mature TNKCL, patients with SPTL had the highest 5-year OS (72.8%, 95% CI 53.9-84.9), whereas patients

TABLE 1 The relative frequencies of histological subtypes of NHL according to the WHO classification among registries that enrolled ≥2000 patients

Histological subtypes	U.S. [13] (N = 75 250)	U.S. [14a] (N = 596 476)	Poland [15] (N = 8254)	Australia [16] (N = 39 806)	Japan [6] (N = 3025)	Japan [7] (N = 2050)	Korea [8] (N = 4314)	Korea [9] (N = 3778)	China [10] (N = 5549)	China [11] (N = 4001)	Current study[b] (N = 4056)
B:T/NK-cell lymphoma	11.1:1	23.1:1	12.2:1	13.9:1	2.7:1	2.8:1	3.9:1	3.5:1	2.1:1	2.3:1	6.7:1
B-cell NHL											
DLBCL (%)	32.2	32.5	31.3[c]	29.5	33.8[c]	36.5	37.6[c]	43.0	41.2	42.0	58.1[c]
FL (%)	14.2	17.1	6.9	19.0	7.1	20.1	2.1	2.9	5.9	3.4	5.6
Extranodal MALT lymphoma (%)	-	8.3[d]	4.7	1.8	8.9	4.6	15.3	19.1	6.3	8.9	5.2
MCL (%)	2.2	4.1	8.6	2.9	3.6	3.0	2.3	2.4	3.1	2.8	2.4
BL (%)	1.5	1.6	1.3	1.4	1.1	0.7	2.6	2.0	1.9	1.2	1.6
CLL/SLL	22.6	18.6	30.3	26.3	1.4	1.6	2.2	1.3	4.6	4.3	1.5
LPL (%)	2.7	1.1	2.1	3.3	0.7	0.2	0.3	0.3	1.1	0.4	1.1
PCNSL (%)	-	-	-	-	-	-	3.6	-	-	-	1.0
NMZL (%)	-	-	1.5	0.9	1.0	1.5	1.2	1.2	1.1	0.2	0.7
SMZL (%)	-	-	1.4	0.3	0.1	0.4	0.1	0.2	0.4	0.5	0.3
PMBCL (%)	-	-	1.0	-	0.3	0.4	0.4	0.5	-	1.5	0.3
IVBL (%)	-	-	0.05	-	0.1	0.4	0.1	-	-	-	0.2
Precursor B-LL	3.9	-	-	8.1[e]	2.5	0.2	13.9	1.6	5.4[e]	0.7	0.2
PEL (%)	-	-	0.02	-	0.1	0.05	0.1	0.1	-	-	0.1
T-cell/histiocyte rich large B-cell (%)	-	-	0.1	-	0.1	-	0.2	-	-	-	0.1
Unclassifiable, with features between DLBCL and BL (%)	-	-	0.1	-	0.5	-	-	-	-	-	0.1
EBV positive DLBCL, elderly (%)	-	-	0.01	-	-	-	0.2	-	-	-	0.02
LG (%)	-	-	0.1	-	0.03	-	-	-	-	-	0.02
T/NK-cell NHL											
PTCL, NOS (%)	1.4	1.7	2.8	1.7	7.0	5.0	4.9	6.3	4.0	4.5	4.0
ENKTL (%)	-	-	0.2	0.2	2.7	1.7	4.8	6.3	17.1	12.7	2.7
ALCL (%)	1.1	1.0	1.7	-	1.6	2.2	2.4	3.1	3.5	2.8	1.7
AITL (%)	0.2	-	0.6	-	2.5	5.7	1.0	1.7	3.3	1.7	1.4
Precursor T-LL (%)	1.1	-	-	-	1.8	0.7	4.8	2.4	5.4[e]	3.6	1.0
SPTL (%)	-	-	0.1	-	0.1	-	0.4	0.7	1.0	0.7	0.9
MF/SS (%)	-	-	1.3	1.7	1.2	0.5	0.5	0.7	0.4	0.1	0.4
EATL (%)	-	-	0.2	-	0.3	0.05	0.4	0.4	0.1	0.2	0.1
HSTL (%)	-	-	0.01	-	0.1	0.05	0.07	0.2	0.4	0.4	0.1
Aggressive NK (%)	-	-	-	-	0.1	0.2	0.7	0.2	-	0.2	0.05

(*Continues*)

TABLE 1 (Continued)

Histological subtypes	U.S.[13] (N = 75 250)	U.S.[14a] (N = 596 476)	Poland[15] (N = 8254)	Australia[16] (N = 39 806)	Japan[6] (N = 3025)	Japan[7] (N = 2050)	Korea[8] (N = 4314)	Korea[9] (N = 3778)	China[10] (N = 5549)	China[11] (N = 4001)	Current study[b] (N = 4056)
PCALCL (%)	-	-	0.2	-	0.3	-	0.2	0.2	0.7	0.4	0.02
ATLL (%)	-	-	0.04	0.1	7.9	11.0	0.02	0.1	-	-	-
NHL, unclassified (%)	11.6	10.8	1.8	16.4	2.1	2.3	1.5	-	-	6.6	8.9

Abbreviations: ALCL, anaplastic large cell lymphoma; AITL, angioimmunoblastic lymphoma; ATLL, adult T-cell leukemia/lymphoma; B-LL, B lymphoblastic leukemia/lymphoma; BL, Burkitt lymphoma; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; EATL, enteropathy-associated T-cell lymphoma; EBV, Epstein-Barr virus; ENKTL, extranodal NK/T-cell lymphoma; FL, follicular lymphoma; HSTL, hepatosplenic T-cell lymphoma; IVBL, intravascular B-cell lymphoma; LG, lymphomatoid granulomatosis; LPL, lymphoplasmacytic lymphoma; MALT, mucosa associated lymphoid tissue; MCL, mantle cell lymphoma; MF/SS, mycosis fungoides/Sezary syndrome; NMZL, nodal marginal zone lymphoma; NHL, non-Hodgkin lymphoma; PCALCL, primary cutaneous anaplastic large cell lymphoma; PCNSL, primary central nervous system lymphoma; PEL, primary effusion lymphoma; PMBCL, primary mediastinal large B-cell lymphoma; PTCL, NOS, peripheral T-cell lymphoma, not otherwise specified; SMZL, splenic marginal zone lymphoma; SPTL, subcutaneous panniculitis-like T-cell lymphoma; T-LL, T lymphoblastic leukemia/lymphoma; WHO, World Health Organization.

[a]Enrolled patients aged ≥18 years.

[b]Enrolled patients aged ≥15 years.

[c]Diffuse large B-cell lymphoma, not otherwise specified.

[d]Marginal zone lymphoma.

[e]Included precursor B- and T-cell neoplasms.

with AITL had the worst outcomes (5-year OS rate, 30.5%, 95% CI 17.5-44.5) (Figure 4B). Based on the extranodal biopsy sites, the 2 most superior 5-year OS rates were observed in patients with ocular (81.4%, 95 CI 71.5-88.2) and skeletal involvement (78.5%, 95 CI 63.4-87.9); patients with central nervous system diseases had the worst outcome (5-year OS rate, 35.1% (95% CI 26.0-44.3).

The 5-year OS rate of patients with HIV positivity was inferior to patients with negative serology (45.5%, 95% CI 37.7-52.9 vs 52.0%, 95% CI 50.1-53.9, P = .0008). The 5-year OS rates of patients with low-, low-intermediate, high-intermediate, and high-risk IPI were 70.2% (95% CI 66.6-73.4), 58.1% (95% CI 54.9-61.3), 45.4% (95% CI 42.2-48.6), and 24.1% (95% CI 20.1-28.3), respectively (P < .0001). The 5-year OS rate of patients with mature B-cell lymphomas treated with rituximab-containing regimens was significantly longer than for patients who were not (61.3%, 95% CI 57.3-65.1 vs 46.8%, 95% CI 44.5-49.2, P < .0001).

4 | DISCUSSION

Given the age-standardized incidence rate of 10.2 and recruitment of 4056 patients from the 4 geographic regions in the country, the reported histopathological distribution could be generalized as a feature of NHL in Thailand although our study did not report the age-adjusted incidence rates because not all major provincial and private hospitals participated. Compared to the western population, the Thai registry demonstrated the characteristic Asian pattern of histological distribution, ie, low rates of CLL/SLL and FL with a higher proportion of TNKCL.[13–16] However, when compared with the FEA, the Thai registry had an approximately one-half lower relative frequency of TNKCL and higher rate of DLBCL.[6–11] The incorporation of expert consensus review, which revealed a very low major-discordant rate between primary and expert consensus diagnoses of 1.9% would argue against any significant misclassifications of histologic subtypes reported in the study.

The international NHL classification project recently compared the histopathological distributions of NHL in Hong Kong, Shanghai, Indonesia, and Thailand.[3] Notwithstanding a much smaller number of cases, the average relative frequencies, for FEA vs SEA, of TNKCL (28.0% vs 12.6%); DLBCL (44.0% vs 58.1%); and ENKTL, nasal type (13.5% vs 2.7%) showed similar trends as in our report. Our study also revealed that the prevalence of extranodal MALT lymphoma in Thai patients was much lower than in Korea,[8,9] whereas the proportion of ENKTL, nasal type, was strikingly low compared to in China.[10,11] A previous study by Sukpanichnant et al also reported data supporting the histologic distribution of NHL reported in the current study.[5]

The median age of Thai patients with NHL was similar to what had been noted among Asians, although the patients were approximately 1 to 2 decades younger than the western population.[3,9,11,14] It is notable that the median age of 229 patients with FL in our series was 58 years (range, 20-98) and 57.2% were younger than 60. This rather young age of patients was also seen in Thai patients with myelodysplastic syndromes and chronic myelogenous leukemia.[19,20] We do not have a clear explanation for this observation, but racial disparity in the polymorphisms of some critical genes or differences in the exposure

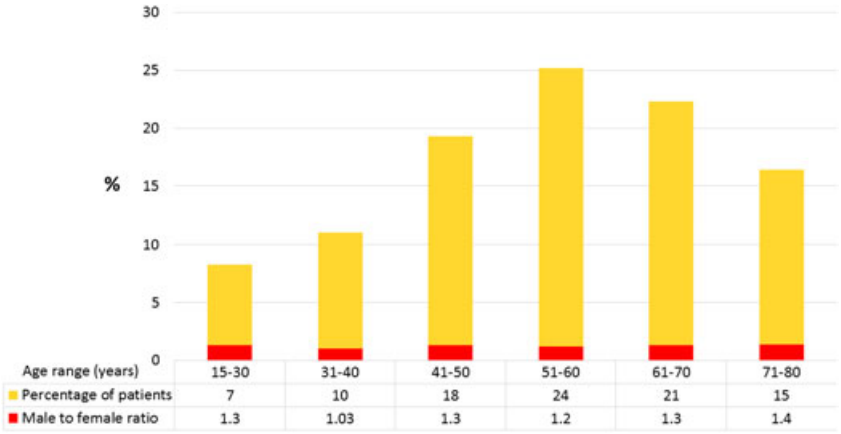

FIGURE 3 Sex ratios according to the age distribution

TABLE 2 Baseline characteristics and outcomes according to histological subtypes

Histological subtypes	N	Median age (years)	% age > 60 years	% male	% B-symptoms	% stage III/IV	% elevated serum LDH	% ECOG PS > 1	% high/HI IPI	% HIV positivity	% OR (CR/CRu)	% 5-yr OS (95% CI)
CLL/SLL	61	62 (29-83)	54.1	60.7	41.0	67.2	37.7	8.2	31.1	0	41.0 (21.3)	52.3 (36.5-66.0)
LPL	43	62 (20-91)	58.1	60.5	41.9	76.7	44.2	27.9	44.2	2.3	48.8 (27.9)	48.9 (31.4-64.4)
Extranodal MALT	211	60 (17-88)	49.3	56.4	18.5	34.6	22.7	9.0	15.6	0.5	65.4(54.0)	79.9 (72.9-85.4)
Nodal MZL	27	56 (19-86)	33.3	63.0	40.7	55.6	66.7	14.8	48.1	0	51.8 (48.1)	87.7 (8.8-96.8)
SMZL	13	70 (48-87)	69.2	61.5	38.5	92.3	53.8	15.4	7.7	0	69.2 (46.1)	62.2 (21.3-86.4)
FL, grade I	91	57 (24-86)	39.6	48.3	37.4	63.7	34.1	17.6	36.3	1.1	63.7 (50.5)	79.2 (68.1-86.8)
FL, grade II	62	59 (20-98)	40.3	48.4	30.6	69.3	35.5	6.4	37.1	0	75.8 (58.1)	80.7 (62.1-90.8)
FL, grade IIIA	76	58 (28-88)	48.7	59.2	36.8	65.8	44.7	19.7	38.1	3.9	65.7 (50.0)	72.6 (59.0-82.4)
MCL	99	60 (34-87)	52.5	78.8	46.2	83.8	47.5	16.2	46.5	1.0	48.4 (35.3)	36.8 (25.2-48.4)
DLBCL, NOS	2358	57 (16-99)	42.8	53.9	49.7	58.9	61.1	26.2	49.2	5.7	56.7 (47.3)	48.8 (46.5-51.1)
BL	66	42 (16-85)	18.2	69.7	54.5	66.7	81.8	43.9	62.1	28.8	39.4 (30.3)	46.4 (32.8-58.8)
PTCL, NOS	164	54 (15-89)	34.8	60.4	54.3	71.9	62.2	29.9	57.3	3.0	46.9 (37.8)	38.5 (29.8-47.2)
ENKTL	111	46 (16-92)	23.4	68.5	48.6	38.7	50.4	20.7	32.4	7.2	40.5 (34.2)	43.8 (33.4-53.7)
SPTL	38	27 (16-81)	7.9	34.2	52.6	52.6	81.6	18.4	52.6	0	73.6 (55.3)	72.8 (53.9-84.9)
AITL	55	59 (36-81)	43.6	60.0	69.1	76.4	61.8	27.3	50.9	3.6	38.1 (32.7)	30.5 (17.5-44.5)
ALCL	64	43 (16-68)	14.1	51.6	60.9	57.8	48.4	17.2	42.1	4.7	56.2 (44.4)	59.3 (44.5-71.3)

Abbreviations: AITL, angioimmunoblastic lymphoma; ALCL, anaplastic large cell lymphoma; BL, Burkitt lymphoma; CI, confidence interval; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; CR, complete remission; CRu, complete remission undetermined; DLBCL, NOS, diffuse large B-cell lymphoma, not otherwise specified; ECOG PS, Eastern Cooperative Oncology Group performance status; ENKTL, extranodal NK/T-cell lymphoma; FL, follicular lymphoma; HI, high-intermediate; HIV, human immunodeficiency virus; IPI, international prognostic index; LDH, lactate dehydrogenase; LPL, lymphoplasmacytic lymphoma; MALT, mucosa associated lymphoid tissue; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; OR, objective response; OS, overall survival; PTCL, peripheral T-cell lymphoma; SMZL, splenic marginal zone lymphoma; SPTL, subcutaneous panniculitis-like T-cell lymphoma.

intensity to causative agents in countries of various economic potentials might play a role.[21–23] In accordance with most reports, our study revealed a male preponderance in almost all histological subtypes, except for the SPTL subtype for which female was the predominant gender.[13,14,24,25] In agreement with our data, a recent analysis of 118 patients with SPTL showed a young age of the patients (median, 47 years) and reported a series with 67% women.[25]

It is noteworthy that, for the 211 patients with extranodal MALT lymphoma in our series, the 9% frequency of gastric MALT lymphoma was strikingly low compared with other reports that consistently revealed the stomach as the most common primary organ of involvement.[26–28] Among patients with gastric lymphoma in the present study, gastric MALT lymphoma represented only 12%, although 72% were subtyped as DLBC without pathological evidence of transformation. The overall prevalence of *Helicobacter pylori* among the 1546 Thai patients who presented with dyspepsia[29] was recently noted to be as high as 46%. Interestingly, most of these patients were infected with the non-East-Asian type CagA, which is the strain associated with a low incidence of gastric cancer and gastric MALT lymphoma. Further studies are needed to determine whether this finding has pathogenic significance.

The 5.1% overall prevalence of HAL in the current study was comparable to previous reports.[30,31] It is notable that the prevalence of HIV in the Thai population decreased from 1.3% in 2009 to 1.1% in 2014.[32] The distribution of the histological subtypes of HAL shown in our report was correlated with most previous studies in that DLBCL

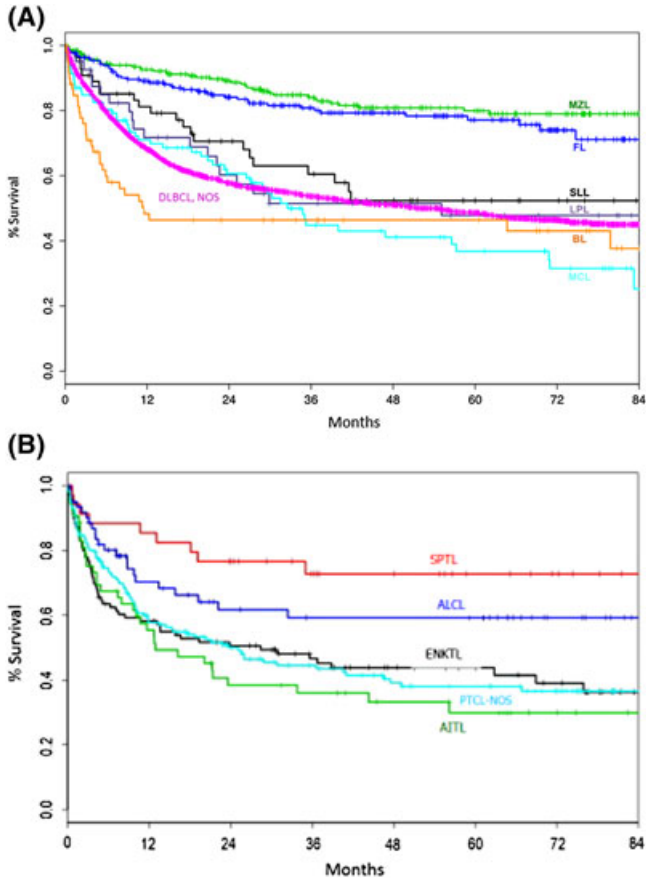

FIGURE 4 Kaplan-Meier overall survival curves according to, A, histological subtypes of mature B-cell lymphomas and, B, histological subtypes of mature T/NK-cell lymphomas. AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large cell lymphoma; BL, Burkitt lymphoma; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; DLBCL, NOS, diffuse large B-cell lymphoma, not otherwise specified; ENKTL, extranodal NK/T-cell lymphoma; FL, follicular lymphoma; LPL, lymphoplasmacytic lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; PTCL, NOS, peripheral T-cell lymphoma, not otherwise specified; SPTL, subcutaneous panniculitis-like T-cell lymphoma

was the most common subtype and the entity with the highest proportion of positive cases was BL.[30,31] The histological pattern of HIV-associated TNKCL, however, was different from previous reports. Instead of PTCL, NOS, the most common subtype was ENKTL (36% of HIV-associated TNKCL). In a multicountry study of 51 HIV-associated PTCLs, Castillo et al[33] reported the distribution of histological subtypes as PTCL, unspecified, 61%; ALCL, 22%; and NK/T-cell lymphoma, 14%. The 10% prevalence of HAL among patients with TNKCL in our study was lower than those reported in Africa (15%), whereas it was higher than those reported in the U.S. (4%).[34,35]

The 5-year OS rates of most subtypes of TNKCL in the Thai registry were generally comparable to data reported from the International peripheral T-cell and natural killer/T-cell lymphoma study, although those of B-cell lymphomas were approximated with data from the Non-Hodgkin's Lymphoma Classification Project, a large multicountry study of 1403 patients that was published before the worldwide use of rituximab.[2,36] It is notable that our analysis revealed the superior outcomes of patients with SPTL and patients with skeletal involvement. In accordance with our study, Bhatt et al[25] recently reported a better 5-year OS of patients with SPTL compared to PTCL, NOS (57% vs 40%, $P < .01$). In a recent review of lymphomas with skeletal involvement, patients with limited stage primary bone lymphoma and patients with multifocal disease exclusively involving the skeleton exhibited superior prognoses.[37] Of the 59 patients with skeletal involvement in our series, 29.8% had limited disease and 75.4% had exclusive bone involvement.

5 | CONCLUSION

The histological pattern of NHL in Thai patients was generally characterized by low FL and CLL/SLL. Compared with FEA, Thai patients, however, had a lower relative frequency of TNKCL. While the relative frequency of extranodal MALT lymphoma was much lower than from Korea, the ENKTL, nasal type, was much lower than in China. Although the median age of the patients was younger than for Caucasians, the long-term survivals for most subtypes were comparable. Other remarkable features in the Thai registry were the low relative frequency of gastric MALT lymphoma, high prevalence of HAL among patients with ENKTL, and superior outcomes of SPTL and patients with skeletal lymphoma. The incorporation of expert hematopathologist consensus review strengthened the reliability of the reported histological distribution. To consolidate the described SEA feature of NHL, further studies of this kind from the neighboring countries are warranted.

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CONFLICT OF INTEREST

The authors have no competing interest.

AUTHOR CONTRIBUTIONS

TI designed the study, enrolled the patients, analyzed the data, and wrote the manuscript. UB designed the study, enrolled the patients, analyzed the data, and critically revised the manuscript. NW designed the study, analyzed the data, wrote the manuscript, and was part of the expert hematopathologist panel. PW and SS designed the study and were part of the expert hematopathologist panel. TA, PB, WK, CY, KK, and WM were part of the expert hematopathologist panel. KW analyzed the data and critically revised the manuscript. AL, KC, CS, LN, SC, WN, AK, TN, TS, NK, and SW designed the study and enrolled the patients. NS, JJ, KP, PN, RP, PW, and NM enrolled the patients. All authors reviewed and approved the final version of the manuscript.

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