Original Article

Overall survival of Non-Hodgkin lymphoma in HIV-positive patients at Siriraj Hospital

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Abstract:

Background: *Although the prognosis of non-Hodgkin lymphoma (NHL) in HIV-positive patients could be predicted by clinical factors including International Prognosis Index (IPI) but few data were available among these Thai patients. The study aimed to determine the clinical characteristics, 2-year survival rate and prognostic factors among Thai HIV-positive patients with NHL.* ***Methods:*** *A retrospective study among HIV-positive patients with NHL diagnosed during 2006 and 2016 and aged over 15 years old at Siriraj Hospital was conducted. Clinical and laboratory data were collected from first diagnosis of NHL to death or until the last available clinical follow-up. The 2-year survival rate, clinical outcomes, and prognostic factors associated with survival were analyzed. Multivariate analyses were performed calculating Kaplan-Meier estimates.* ***Results:*** *A total of 120 patients (82 men) had a median age of 42 years (range 19-76). Lymphoma and HIV infection were diagnosed at the same time (within 1 month) in 63 (52.5%) patients, whereas, among the other 57 patients, lymphoma was diagnosed after HIV infection at a median time of 3.7 years (interquartile range [IQR], 1.1-5.6). The three most common subtypes of NHL included diffuse large B-cell lymphoma (66.1%), Burkitt lymphoma (11.0%) and plasmablastic lymphoma (11.0%). The median absolute CD4 count was 135 cells/μL (IQR 60-245). The most common first-line chemotherapy was CHOP-like regimen (81.2%). Response to first-line treatment included complete response among 41 patients (34.7%), partial response among 17 patients (14.4%), stable disease among 22 patients (18.6%), progressive disease among 16 patients (13.6%) and unknown among 22 patients (18.6%). Factors significantly associated with overall response to first-line treatment were B-cell subtype (p = 0.02; Fisher's Exact test) and NCCN-IPI (p = 0.004; likelihood ratio). Median overall survival was not reached. Survival rates at 1 and 2 years were 75.8% and 73.2%, respectively. Using multivariate analysis, higher NCCN-IPI score was significantly associated with higher risk of death. Adjusted hazard ratio of NCCN-IPI score was 10.44 (95%CI: 1.27-86.06) for high intermediate risk groups and 28.74 (95%CI: 2.42-341.05) for high risk group.* ***Conclusion:*** *Median overall survival among HIV-positive patients with NHL at Siriraj Hospital was not reached. Greater than 3 points of NCCN-IPI score was associated with poor prognosis.*

Keywords : ● *Non-Hodgkin lymphoma* ● *HIV* ● *Overall survival* ● *Prognosis*

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นิพนธ์ต้นฉบับ

ระยะเวลาการรอดชีวิตของผู้ป่วยติดเชื้อเอชไอวีที่เป็นโรคมะเร็งต่อมน้ำเหลืองชนิดนอนฮอดจ์กินในโรงพยาบาลศิริราช

คณิน เหรียญทองเลิศ พลอยเพลิน พิกุลสด วีรภัทร โอวัฒนาพานิช เอกพล อัจฉริยะประสิทธิ์ ฉัตรี หาญทวีพันธุ์ เอกพันธ์ ครุพงศ์ อาจรบ คูหาภินันทน์ บุณฑริกา สุวรรณวิบูลย์ ธีระ ฤชุตระกูล สนั่น วิสุทธิศักดิ์ชัย นพดล ศิริธนารัตนกุล และ ยิ่งยง ชินธรรมมิตร์

สาขาวิชาโลหิตวิทยา ภาควิชาอายุรศาสตร์ คณะแพทยศาสตร์ศิริราชพยาบาล มหาวิทยาลัยมหิดล

บทคัดย่อ

หลักการและเหตุผล *ในปัจจุบันการพยากรณ์อัตราการรอดชีวิตผู้ป่วยมะเร็งต่อมน้ำเหลืองชนิดนอนฮอดจ์กินที่ติดเชื้อเอชไอวีสามารถใช้ปัจจัยหลาย ๆ อย่างมาคำนวนเป็นคะแนนที่เรียกว่าอินเตอร์เนชั่นแนลพรอกโนสติกอินเด็ก (IPI) แต่ข้อมูลดังกล่าวไม่ได้ทำการศึกษาในคนไทย การศึกษานี้จึงทำการศึกษาว่าปัจจัยใดที่มีผลต่อการอัตราการรอดชีวิตที่สองปีในผู้ป่วยมะเร็งต่อมน้ำเหลืองชนิดนอนฮอดจ์กินที่ติดเชื้อเอชไอวีในโรงพยาบาลศิริราช และปัจจัยที่มีผลต่อการรอดชีวิต* ***วิธีการ*** *การศึกษาติดตามข้อมูลย้อนหลังในผู้ป่วยที่ได้รับการวินิจฉัยโรคมะเร็งต่อมน้ำเหลืองชนิดนอนฮอดจ์กินที่ติดเชื้อเอชไอวี อายุตั้งแต่ 15 ปีขึ้นไปที่โรงพยาบาลศิริราชตั้งแต่ปี พ.ศ. 2549-2559 โดยเก็บข้อมูลทางคลินิกและผลตรวจเลือดทางห้องปฏิบัติการตั้งแต่ที่รับการวินิจฉัยมะเร็งต่อมน้ำเหลืองชนิดนอนฮอดจ์กินจนเสียชีวิตหรือจนมาตรวจติดตามครั้งสุดท้าย โดยนำข้อมูลทั้งหมดมาวิเคราะห์หาอัตราการอดชีวิตที่ 2 ปี ผลลัพธ์ของการรักษา และปัจจัยที่มีผลต่อการรอดชีวิต* ***ผลการศึกษา*** *ผู้ป่วยทั้งหมด 120 คน (ผู้ชาย 82 คน) อายุเฉลี่ยมัธยฐานเท่ากับ 42 ปี (พิสัย 19 ถึง 76 ปี) มะเร็งต่อมน้ำเหลืองชนิดนอนฮอดจ์กินได้รับการวินิจฉัยภายใน 1 เดือนหรือพร้อมกับโรคเอชไอวี 62 คน (52.5%) และอีก 57 คน ได้รับการวินิจฉัยมะเร็งต่อมน้ำเหลืองชนิดนอนฮอดจ์กินหลังการวินิจฉัยเอชไอวีที่ระยะเวลาเฉลี่ยมัธยฐาน 3.7 ปี (ระหว่าง 1.1 ถึง 5.6 ปี) ชนิดของมะเร็งต่อมน้ำเหลืองชนิดนอนฮอดจ์กินที่พบบ่อย 3 อันดับแรกคือ มะเร็งต่อมน้ำเหลืองชนิด Large B-cell (66.1%) มะเร็งต่อมน้ำเหลืองชนิด Burkitt (11%) และมะเร็งต่อมน้ำเหลืองชนิด plasmablastic (11%) ค่ามัธยฐานของระดับซีดี 4 เท่ากับ 135 เซลล์ต่อไมโครลิตร (ระหว่าง 60 ถึง 245) การรักษาด้วยสูตรเคมีบำบัดชนิดแรกคือ CHOP-like (81.2%) การตอบสนองต่อยาเคมีบำบัดชนิดแรกคือ โรคตอบสนองโดยสมบูรณ์ 41 คน (34.7%) โรคตอบสนองบางส่วน 17 คน (14.4%) โรคคงที่ 22 คน (18.6%) โรคลุกลามมากขึ้น 16 คน (13.6%) และไม่ทราบการตอบสนอง 22 คน (18.6%) ปัจจัยที่มีผลต่อการตอบสนองต่อการรักษาด้วยยาเคมีบำบัดชนิดแรก คือ มะเร็งต่อมน้ำเหลืองชนิด B-cell (p = 0.02; Fisher's Exact test) และ NCCN-IPI (p = 0.004; likelihood ratio) ค่ามัธยฐานของอัตราการรอดชีวิตยังไม่ถึง อัตราการรอดชีวิติที่ 1 และ 2 ปี คือร้อยละ 75.8 และ 73.2 ตามลำดับ ในการวิเคราะห์พหุตัวแปรพบว่า NCCN-IPI ที่คะแนนสูงจะสัมพันธ์กับอัตราการเสียชีวิตที่สูงกว่า ค่าอัตราส่วนที่มีการปรับแล้วของกลุ่มความเสี่ยง high intermediate เท่ากับ 10.44 (ค่าความเชื่อมั่นที่ 95% อยู่ที่ 1.27 ถึง 86.06) และ กลุ่มความเสี่ยงสูง อยู่ที่ 28.74 (ค่าความเชื่อมั่นที่ 95% อยู่ที่ 2.42 ถึง 341.05)* ***สรุป*** *ค่ามัธยฐานของอัตราการเสียชีวิตในผู้ป่วยมะเร็งต่อมน้ำเหลืองชนิดนอนฮอดจ์กินที่ติดเชื้อเอชไอวียังไม่ถึง คะแนนของ NCCN-IPI ที่มากกว่า 3 คะแนนจะสัมพันธ์กับอัตราการพยากรณ์โรคที่ไม่ดี*

คำสำคัญ : ● *มะเร็งต่อมน้ำเหลืองชนิดนอนฮอดจ์กิน* ● *เอชไอวี* ● *ระยะเวลาการรอดชีวิต* ● *การพยากรณ์โรค*

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Introduction

Although the global commitment to control the HIV/AIDS pandemic has increased significantly in recent years, the virus continues to spread.[1] Advanced HIV infection can be the cause of acquired immune deficiency syndrome (AIDS) which is not only defined by opportunistic infections but also by cancers such as Kaposi sarcoma, primary CNS lymphoma, diffuse large B-cell lymphoma (DLBCL) and Burkitt lymphoma. Non-Hodgkin lymphoma (NHL) is the second most common malignancy among HIV-positive patients (the most common cancer is Kaposi sarcoma).[2,3] NHL has been classified as an AIDS-defining disease since 1985.[4] In prospective (cohort) studies, the risk of developing NHL is increased 70 to 300 fold among patients with HIV/AIDS.[5-7]

Lymphoma, a hematologic malignancy developed at the lymph nodes, is generally classified as NHL and Hodgkin lymphoma. In the American Cancer Society, NHL was found at a ratio of 19.6:100,000 people per year in 2009. It is the most frequently found cancer over other cancers and ranks fifth of overall cancers.[8]

In 1993 the International NHL Prognostic Factor Project developed the international prognostic index (IPI), consisting of five factors: age, tumor stage, serum lactate dehydrogenase (LDH) level, performance status and number of extranodal disease sites, to predict the prognosis of patients with aggressive B-cell lymphoma.[9] Likewise, to predict the prognosis of Systemic AIDS-related NHL, IPI factors have been successfully applied in recent studies.[10-12] However, in the current era of rituximab-based therapy, NHL (NCCN)-IPI is a robust and useful tool to stratify prognostically relevant subgroups of patients with DLBCL. Compared with the IPI and other modifications of the IPI, it would be better to incorporate two known continuous prognostic variables, age and LDH. Compared with the IPI, the NCCN-IPI better discriminated low and high risk subgroups. The NCCN-IPI is easy to apply and more powerful than the IPI for predicting survival in the rituximab era.[13-16] Nonetheless, systemic AIDS-related NHL is an AIDS-defining disease or HIV related NHL, while none of the IPI or NCCN-IPI factors are related to HIV status. Recently published data indicated that after rituximab and active retroviral therapy introduction, patients with AIDS-related DLBCL and patients with immunocompetent DLBCL treated with curative intent showed similar long term survival.[17]

Thus, the study of HIV-related factors together with NCCN-IPI factors is necessary to archive the precise prognosis of this cancer. To manage and improve prognosis of HIV-related NHL, this study focused on the impact factors including NCCN-IPI factors and HIV-related factors of NHL among Thai HIV-positive patients and to determine the overall 2-year survival rate.

Objective

The primary objective was to evaluate the 2-year overall survival rate of NHL among HIV-positive patients at Siriraj Hospital. The secondary objective was to determine prognostic factors related to survival outcome.

Materials and Methods

Patients aged over 15 years old diagnosed with NHL among HIV-positive patients at Siriraj Hospital from 2006 to 2016 were included in this study. All were Thai. This study was approved by the institutional ethics review board of Siriraj Hospital. The inclusion criteria included biopsy confirmed NHL for which Anti-HIV is positive before or within one month after the diagnosis of NHL and more than three time or six months of follow-up time. The clinical and laboratory data collected included: age, sex, recent CD4 count assessed before or after NHL diagnosis, viral load before NHL diagnosis or 1st viral load after NHL diagnosis, NCCN-International Prognostic Index (NCCN-IPI), type and number of antiretroviral therapy (ARV), Ann Arbor staging, B-symptom, number of extranodal involvement, type of lymphoma, ECOG performance status, chemotherapy regimen, bone marrow involvement and survival outcome. The NCCN-IPI

consisted of five factors including age (> 40 to 60, 1 point (pt); > 60 to 75, 2 pts; > 75, 3 pts), LDH ratio (> 1 to 3, 1 pt; > 3, 2 pts) upper limit of normal, stage III-IV (1 pt), extranodal site (bone marrow, central nervous system, liver/gastrointestinal tract, or lung; 1 pt), and performance status ≥ 2 (1 pt). Then four risk groups were formed: low (0 to 1), low intermediate (2 to 3), high intermediate (4 to 5), and high (6 to 8).

Definition of related indicators

The follow-up time was defined as the duration from the time of NHL diagnosis to death or last clinical follow-up. The cutoff point for follow-up was 31 December 2018. The follow-up endpoint was the patient's death. The starting point of survival time was defined as the date of an established diagnosis of NHL. Complete remission was defined as the disappearance of all clinical evidence of the disease and the normalization of all laboratory values and radiographs that had been considered abnormal before starting treatment, including a normalization of BM, when initially involved. Moreover, patients who achieved a CR during therapy, but relapsed within 30 days after therapy had been completed, were classified as nonresponders. Partial remission (PR) was defined as a greater than 50% reduction in the largest dimension of each anatomic site of measurable disease for at least one month. No response (NR) was defined as a less than 50% regression or stable or progressive disease. Patients lost to follow-up before response evaluation or had no evaluations of response were considered as unknown response. Progression-free survival (PFS) was measured from the date of diagnosis until either the date of disease progression, relapse or death from any cause.

Statistical analysis

The t-test for independent samples or the Mann-Whitney U-test was used to compare the continuous data between groups. The differences between the categorical variables were assessed using Fisher's exact test. Cox proportional hazards were used to calculate the hazard ratios (HRs) for each variable. The p-value reported was two-sided, and $p < 0.05$ was considered to be statistically significant. All analyses were performed using SPSS Software, Version 20.0, SPSS, Inc., Chicago, IL, USA).

Results

Epidemiological and Clinical Features

From 2006 to 2016, a total of 120 patients with a diagnosis of NHL) among HIV-positive cases were enrolled. The main characteristics of NHL among HIV-positive patients are shown in Table 1. The median age at presentation of HIV infection was 42 years old (range, 19 to 76 years). The male to female ratio was 2.16:1 (82 males and 38 females).

Fifty-five point eight percent of 120 cases presented B symptom, 56.8% of 118 cases presented bone marrow involvement and 15% of 73 cases presented central nervous system involvement. Lymphoma and HIV infection were diagnosed simultaneously (within one month) among 63 (52.5%) patients, whereas, among the other 57 patients, lymphoma was diagnosed after HIV infection at a median time of 3.7 years [interquartile range (IQR), 1.1-5.6]. The three most common subtypes of NHL included diffuse large B-cell lymphoma (DLBCL; 66.1%), Burkitt lymphoma (11.0%) and plasmablastic lymphoma (11.0%). The median absolute CD4 count was 135 cells/μL (IQR, 60 to 245). Nine patients received a diagnosis of primary central nervous system lymphoma (five DLBCL, one B-lymphoblastic lymphoma, two B-cell lymphoma and one unknown subtype).

Treatment Response (Table 2)

The most common first-line chemotherapy was CHOP-like regimen (81.2%). Of the 96 evaluable patients, the overall response rate to chemotherapy was 60.4% (complete response, 42.7%; partial response, 17.7%). Forty-eight percent of 120 patients received rituximab (Table 1). CD4 counts between patients receiving and those not receiving rituximab did not differ [median CD4 count = 164 (IQR, 75-297) and 113 (IQR, 52-207), respectively; $p = 0.069$]. Factors significantly associated with response

Table 1 Selected characteristics of 120 patients with NHL and HIV infection

Characteristic	n	%
Age (years)	120	
Median (IQR), 42 (35-52)		
40-59	53	44.2
60-75	15	12.5
> 75	1	0.8
Sex	120	
Male	82	68.3
Female	38	31.7
NCCN-IPI	120	
Median (IQR), 4 (2.3-5.0)		
Low (0-1)	11	9.2
Low intermediate (2-3)	47	39.2
High intermediate (4-5)	57	47.5
High (6-8)	5	4.1
Time from HIV diagnosis to NHL diagnosis (years)	120	
Median (IQR), 3.7 (1.1-5.6)		
Diagnosis of lymphoma at the same time with HIV (within one month)	63	52.5
Diagnosis of HIV before lymphoma	57	47.5
ARV use in known case of HIV infection	49	
NHL while not on ARV	12	24.5
NHL while on ARV (within one month)	37	75.5
CD4 count (cells/μL)	115	
Median (IQR), 135 (60-245)		
1-50	26	22.6
51-100	19	16.5
101-150	20	17.4
151-200	13	11.3
201-500	30	26.1
501-1,000	7	6.1
Type of NHL	118	
B-cell	113	95.8
T-cell	4	3.4
NK-cell	1	0.8
Subtype of lymphoma	118	
Diffuse large B-cell lymphoma	78	66.1
Marginal zone lymphoma	1	0.8

Table 1 Selected characteristics of 120 patients with NHL and HIV infection (continue)

Characteristic	n	%
Mantle cell lymphoma	2	1.7
Burkitt lymphoma	13	11
Plasmablastic lymphoma	13	11
Peripheral T cell lymphoma	3	2.5
Others*	8	6.8
Ann Arbor stage	120	
I-II	21	17.5
III-IV	99	82.5
Bulky	119	
Nonbulky	98	81.7
Bulky mass ≥7 cm	21	18.3
1st CMT regimen	101	
CHOP-like	82	81.2
CVP-like	2	2.0
mini-CHOP	2	2.0
ICE	1	1.0
HyperCVAD	3	3.0
CODOX-M	7	6.9
HD-MTX	4	4.0
Rituximab	120	
Received	58	48.3
Not received	62	51.7
Response to first-line treatment	118	
Complete response	41	34.7
Partial response	17	14.4
Stable disease	22	18.6
Progressive disease	16	13.6
Unknown	22	18.6

Abbreviations: IQR, Interquartile range; NHL, Non-Hodgkin lymphoma; ARV, antiretroviral therapy; NCCN-IPI, National Comprehensive Cancer Network International Prognostic Index; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CVP, cyclophosphamide, vincristine, prednisone; ICE, Ifosfamide, carboplatin, and etoposide; Hyper-CVAD, fractionated cyclophosphamide, vincristine, adriamycin, and dexamethasone; CODOX-M, cyclophosphamide, cytarabine, vincristine, methotrexate, leucovorin, doxorubicin

*B-cell lymphoma (n = 3), T-cell lymphoma (n = 2), NK-cell lymphoma (n = 1), precursor B-cell lymphoblastic lymphoma (n = 1), unknown subtype (n = 1)

Table 2 Tumor response data according to types and subtypes of NHL with HIV infection*

Type/Subtype NHL	1st line treatment response			
	Complete response n (%)	Partial response n (%)	Stable n (%)	Progression n (%)
Type of NHL (n = 96)				
B-cell (n = 92)	41 (44.6)	17 (18.5)	19 (20.7)	15 (16.3)
T-cell (n = 3)	0	0	3 (100)	0
NK-cell (n = 1)	0	0	0	1 (100)
Type of NHL subset				
Diffuse large B cell lymphoma (n = 61)	30 (49.2)	11 (18.0)	6 (9.8)	14 (23.0)
Marginal zone lymphoma (n = 1)	0	1 (100)	0	0
Peripheral T-cell lymphoma (n = 2)	0	0	2 (100)	0
Burkitt lymphoma (n = 13)	5 (38.5)	1 (7.7)	6 (46.2)	1 (7.7)
Plasmablastic lymphoma (n = 13)	6 (46.2)	2 (15.4)	5 (38.5)	0
Others (n = 6)	0	2 (33.3)	3 (50.0)	1 (16.7)

*Patients with unknown response (n = 22) were not included in this table. Abbreviations: NHL, Non-Hodgkin lymphoma

Table 3 Analysis of prognostic factors for survival among patients with NHL and HIV-infection

Variable	Crude hazard ratio (95%CI)	Adjusted hazard ratio* (95%CI)	*p*-value
NCCN-IPI (n = 116)			
Low risk (0-1)	1	1	
Low intermediate risk (2-3)	0.92 (0.10-8.29)	0.98 (0.11-8.95)	0.982
High intermediate risk (4-5)	8.75 (1.15-66.35)	10.44 (1.27-86.06)	0.029
High risk (≥ 6)	25.96 (2.75-245.44)	28.74 (2.42-341.05)	0.008
ARV (n = 118)			
NHL while not on ARV	1	1	
NHL while on ARV	0.21 (0.10-0.44)	0.23 (0.11-0.49)	< .001
CD4 count (n = 114)			
≤ 100	2.33 (1.13-4.80)	2.35 (1.13-4.85)	0.021
> 100	1	1	
1st-line chemotherapy regimen (n=98)			
CHOP-like	1	1	
Others	1.98 (0.72-5.40)	1.85 (0.65-5.29)	0.251
Rituximab (n = 118)			
Received	1	1	
Not received	1.53 (0.77-3.06)	1.56 (0.78-3.11)	0.209
Response to first line chemotherapy (n = 92)			0.001
CR	1	1	
PR	9.41 (1.74-51.05)	8.33 (1.44-48.30)	0.018
No response	15.44 (3.28-72.80)	19.06 (3.89-93.26)	< .001

*Adjusted hazard ratio for age and sex.

Abbreviations: NHL, Non-Hodgkin lymphoma; NCCN-IPI, National Comprehensive Cancer Network International prognostic index; ARV, antiretroviral therapy; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CR, complete response; PR, partial response

to first-line treatment included B-cell type (p = 0.02; Fisher's Exact test), ARV use (p = 0.013; Fisher's Exact test) and NCCN-IPI (p = 0.004; likelihood ratio). CD4 count ≤ 100 cells/μL was not associated with response to first-line treatment (p = 0.624).

Survival Analysis

The median follow-up time was 63 weeks (IQR, 19 to 213). The median overall survival time for 118 patients was not reached, with 1-year, 2-year and 5-year overall survival rates of 75.8%, 73.2% and 67.0%, respectively (Figure 1, Table 4). Using univariate analysis (Table 3), factors significantly associated with overall survival included NCCN-IPI (p < 0.001), ARV use (p < 0.001), CD4 count ≤ 100 (p = 0.022) and response (either complete or partial response) to first-line chemotherapy (p = 0.002), while CHOP or other regimens and adding on rituximab were unassociated factors. When evaluating survival among patients with low and high risk disease using the NCCN-IPI, a statistically significant survival advantage was found for the former group (median overall survival time, not reached versus one month). Sex was unassociated with overall survival (crude HR 0.86; 95%CI: 0.42 to 1.77; p = 0.689). Age was significantly associated with OS (crude HR 1.036; 95%CI: 1.009 to 1.064; p = 0.008). However, age was one factor in the NCCN-IPI scoring system. When CD4 count was categorized into two groups (≤ 100 and > 100), CD4 count ≤ 100 was significantly associated with shorter overall survival (crude HR 2.33; 95%CI: 1.13 to 4.80; p = 0.022) (Table 3). Using multivariate analysis, factors significantly associated with overall survival included NCCN-IPI (p = 0.017) and response to first-line chemotherapy (p = 0.033).

The median progression-free survival was 18.0 months (95%CI: 6.2 to 29.8). The estimated 1-year, 2-year and 5-year progression-free survival rates were 53.4%, 44.8% and 37.6%, respectively (Table 6, Figure 2). In univariate analysis (Table 5), NCCN-IPI, ARV use and complete response to first-line chemotherapy were significantly associated with progression-free survival (p < 0.001). Patients having low or low intermediate risk of NCCN-IPI had longer progression-free survival than those in the high intermediate and high risk group. Sex (crude HR, 1.28; 95%CI: 0.81 to 2.36; p = 0.237), age (crude HR, 1.02; 95%CI: 0.997 to 1.04; p = 0.089), CD4 count, CHOP-like therapy and rituximab use were unassociated with progression-free survival. Using multivariate analysis, factors significantly associated with PFS included NCCN-IPI (p = 0.003), ARV use (p = 0.001) and response to chemotherapy (p < 0.001).

Discussion

The characteristics of the patients in our series were similar to others, i.e., median age, male predominance, high grade of malignancy, B phenotype and complete response.[12,18-21]

The overall survival of our study was higher than others. This was probably because many patients were in the era of highly active antiretroviral therapy. In Thailand, every HIV-positive patient should receive ARV since 2017.[22] From prior studies, the survival among patients with HIV-associated NHL has gradually increased. Chow *et al*. reported 1-year survival probability of all screened patients with AIDS-related NHL from 1983 to 1999 was 54% and 5-year survival was only 5%.[23] Later, Bohlius *et al*. reported the survival after 1 year of was estimated at 66% (95%CI: 63 to 70%) and after 5 years at 55% (95%CI: 51 to 60%).[21]

Different chemotherapy regimens have been used, i.e., MBACOD, MACOP-B, CHOP, infusional chemotherapy, with a percentage of complete response ranging from 30 to 65%.[22-30] In our study, complete response of 34.8% was achieved.

No evidence was found of longer survival with more intensive regimens. It should be realized that higher intensity therapies were possibly given to patients with higher disease risk, who may have a worse prognosis, introducing a potential bias in our results.[31] The addition of rituximab to standard chemotherapy has improved the response of diffuse large B-cell lymphoma (DLBCL).[32,33]

Table 4 One-year, 2-year and 5-year survival rates among patients with NHL and HIV infection

	Survival rate (%)		
	1-year	**2-year**	**5-year**
Overall survival	75.8	73.2	67.0
NCCN-IPI (n = 116)			
Low risk (0-1)	100	100	83.3
Low intermediate risk (2-3)	97.7	97.7	90.8
High intermediate risk (4-5)	58.2	49.8	49.8
High risk (≥ 6)	0	0	0
ARV (n = 118)			
No ARV use	38.7	38.7	19.3
ARV use	82.2	79.2	75.3
CD4 count (n = 114)			
≤ 100	64.6	61.2	57.4
> 100	84.8	82.5	79.2
Response to first line chemotherapy (n = 93)			
CR	100	96.9	96.9
PR	76.5	65.5	65.5
No response	64.9	64.9	46.4

Abbreviations: NHL, Non-Hodgkin lymphoma; NCCN-IPI, National Comprehensive Cancer Network International prognostic index; ARV, antiretroviral therapy; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CR, complete response; PR, partial response

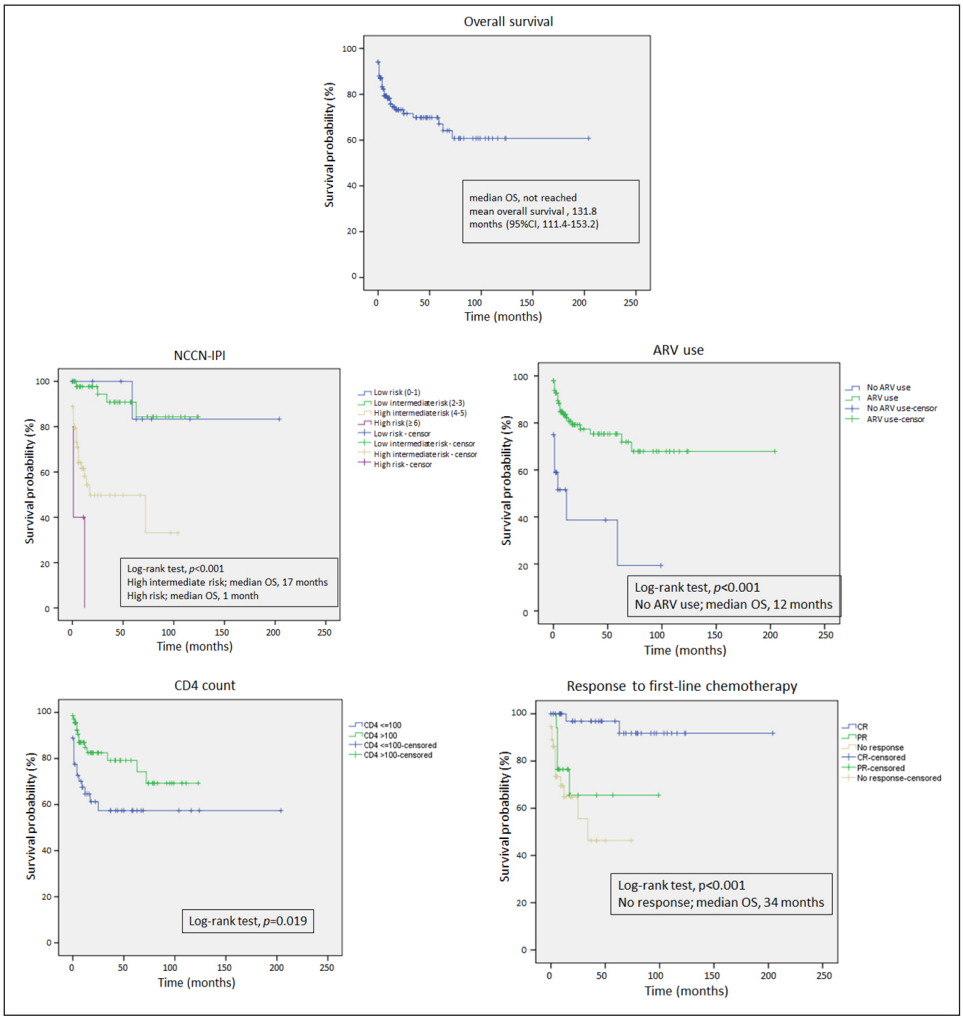

Figure 1 Kaplan-Meier curve of overall survival estimate among patients with NHL and HIV infection

Table 5 Analysis of prognostic factors for progression-free survival among patients with NHL and HIV infection

Variable	Crude hazard ratio (95%CI)	Adjusted hazard ratio* (95%CI)	*p*-value
NCCN-IPI (n = 110)			
Low risk (0-1)	1	1	
Low intermediate risk (2-3)	0.98 (0..37-2.63)	1.63 (0.45-5.85)	0.456
High intermediate risk (4-5)	3.06 (1.19-7.92)	6.00 (1.57-22.95)	0.009
High risk (≥ 6)	6.26 (1.62-24.17)	4.65 (0.31-70.15)	0.267
ARV (n = 112)			
NHL while not on ARV	1	1	
NHL while on ARV	0.30 (0.17-0.52)	0.23 (0.09-0.61)	0.003
CD4 count (n = 108)			
≤ 100	1.23 (0.75-2.02)	0.78 (0.42-1.46)	0.439
> 100	1	1	
1st-line chemotherapy regimen (n = 99)			
CHOP-like	1	1	
Others	1.16 (0.55-2.45)	0.60 (0.24-1.53)	0.286
Rituximab (n = 112)			
Received	1	1	
Not received	1.11 (0.69-1.79)	0.60 (0.31-1.14)	0.118
Response to first line chemotherapy (n = 93)			< 0.001
CR	1	1	
PR	3.97 (1.68-9.41)	3.29 (1.09-9.94)	0.035
No response	9.57 (4.44-20.63)	9.55 (3.67-24.84)	< 0.001

*Adjusted hazard ratio used sex, NCCN-IPI, ARV use, CD4 count, CHOP-like regimen, and rituximab use for adjustment

Abbreviations: NHL, NonHodgkin lymphoma; NCCN-IPI, National Comprehensive Cancer Network International prognostic index; ARV, antiretroviral therapy; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CR, complete response; PR, partial response

Among HIV-positive patients with DLBCL, the addition of rituximab probably improves the therapeutic response, although some caveats exist regarding its safety because of the increase in infectious complications, particularly among patients with profound immunosuppression.[34,35] The role of rituximab is unclear in the treatment of HIV-associated NHL, but might be of benefit among the small proportion of patients whose lymphoma cells express CD20.[35,36] Rituximab used in our study showed insignificant good prognostic outcomes because rituximab may be associated with an increased risk of infectious deaths among patients with ARV use and low base-line CD4 counts.[35]

The IPI and age-adjusted IPI (aaIPI) are prognostic factor for NHL among HIV-positive patients.[11,12,18,37]

Compared with the IPI, the National Comprehensive Cancer Network International Prognostic Index (NCCN-IPI) and the aaIPI had better discrimination in different scores among all patients treated with or without rituximab. Both the NCCN-IPI and aaIPI had power in discriminating low, low intermediate and high intermediate risk groups. In comparison, the NCCN-IPI discriminated low intermediate and high intermediate risk groups better than the aaIPI among all patients and in the R-CHOP group.[38]

A CD4+ count ,100 cells/μL predicted shorter survival only in the precombination Antiretroviral Therapy (cART) era[37] whereas in the cART era, low nadir CD4 cell counts (< 25 cells/μL) were the dominant risk factor for death in another paper.[21] However, in our study, low

Table 6 One-year, 2-year and 5-year progression free survival rates among patients with NHL and HIV infection

	Progression free rate (%)		
	1-year	**2-year**	**5-year**
Overall progression free survival	53.4	44.8	37.6
NCCN-IPI (n = 110)			
Low risk (0-1)	88.9	77.8	55.6
Low intermediate risk (2-3)	75.0	64.4	55.3
High intermediate risk (4-5)	29.8	25.0	25.0
High risk (≥ 6)	0	0	0
ARV (n = 112)			
No ARV use	16.7	16.7	5.6
ARV use	60.6	50.2	45.5
CD4 count (n = 108)			
≤ 100	50.2	39.1	32.2
> 100	55.6	48.0	43.7
Response to first line chemotherapy (n = 93)			
CR	89.1	79.9	79.9
PR	57.5	39.4	19.7
No response	25.3	16.4	10.9

Abbreviations: NHL, Non-Hodgkin lymphoma; NCCN-IPI, National Comprehensive Cancer Network International prognostic index; ARV, antiretroviral therapy; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CR, complete response; PR, partial response

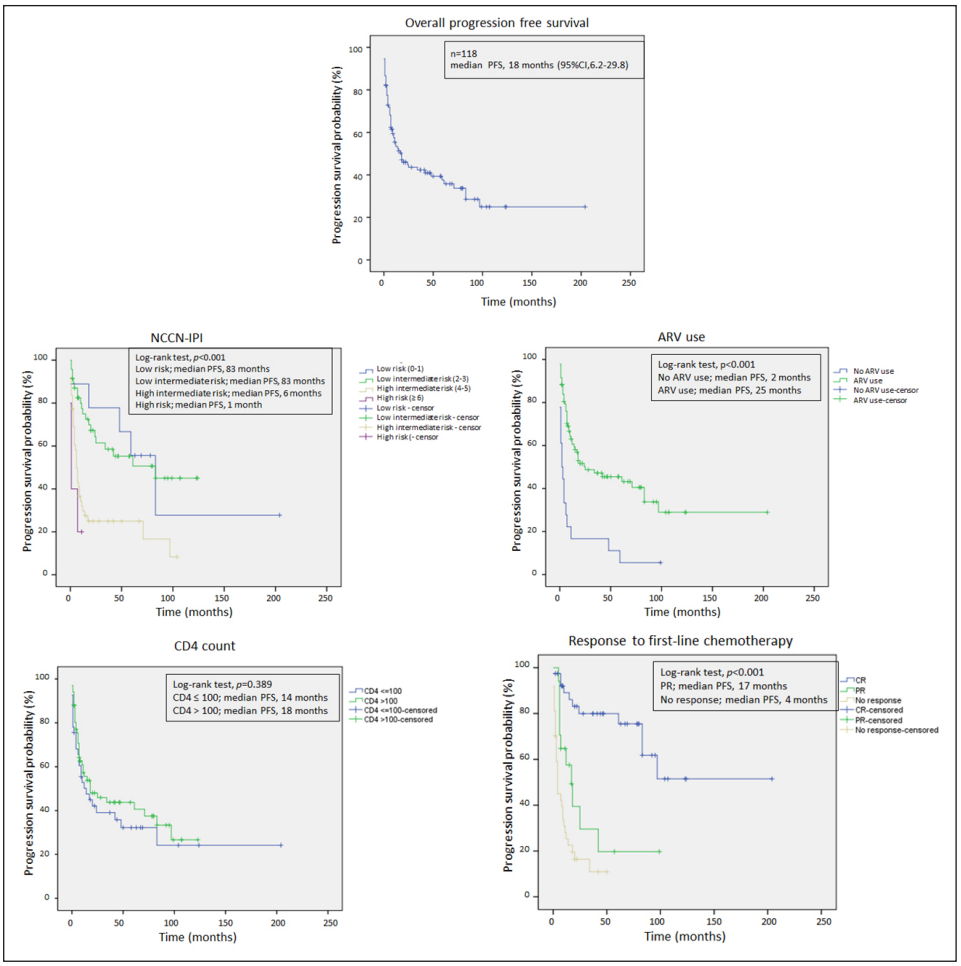

Figure 2 Kaplan–Meier curve of progression-free survival estimate among patients with NHL and HIV infection

CD4 lymphocyte count (< 100 cells/μL) could predict poorer outcomes.

Presently, almost all patients with HIV receive ARV, and survival probably tends to be no longer influenced by HIV-related factors; rather, they rely exclusively on tumor-related factors.[12] Conconi A reported that acquired immunodeficiency syndrome-related DLBCL and patients with immunocompetent-DLBCL treated with curative intent have similar long term survival (5-year overall survival 63% and 68%, respectively).[17] Among 76 patients with DLBCL in our study, the 5-year overall survival was 70.6%. For further research, it would be important to define the prognostic factors of this population.

Limitations of this study included the retrospective design leading to incomplete data especially the HIV viral load. Moreover, our study was conducted in a small group of sample sizes; hence, we could not exclude the possibility that the captured association was observed by chance. Finally, this study was restricted to only Thai patients. Therefore, these results may not be applicable to people in other ethnic groups. Overall survival in our study seemed discordant with progression-free survival. This may be because the last follow-up date among many patients with disease progression was at the same date of progression evaluation. Therefore, these patients were counted as censored cases in survival analysis leading to a maintained survival rate despite occurrence of patients with disease progression. Another explanation was the treatment for patients with progression of lymphoma mostly combined rituximab with salvage regimens leading to responses in many patients.

Conclusion

Median overall survival among HIV-positive patients with NHL at Siriraj Hospital was not reached. The NCCN-IPI score of 0 to 3 and response to first-line chemotherapy were the most important favorable prognostic factors for survival. Survival of HIV-positive patients with NHL seemed to gradually increase because of the era of highly active antiretroviral therapy. However, to identify exact predictive factors, further research conducted in populations during the era after highly active antiretroviral therapies are needed.

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