Original Article

# Survival outcomes among Thai, elderly, Non-Hodgkin lymphoma patients: a 5-year cohort study

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**Abstract:**

**Objectives:** *The number of elderly patients with nonHodgkin lymphoma (NHL) has increased in recent years because most countries are facing an aging society.  This study aimed to compare the baseline clinical characteristics, treatments, and clinical outcomes of younger and older patients with NHL.  **Methods:** This 5-year, single-center study was conducted among newly diagnosed patients with NHL between January 1, 2013 and December 31, 2017 at Vachira Phuket Hospital, Phuket, Thailand.  The clinical features, initial laboratory findings, histopathological findings, stagings, treatments, and clinical outcomes were recorded.  **Results:** A total of 105 NHL cases were diagnosed during the study period.  Their mean age was 57 ± 14.4 years, with a male predominance.  Two thirds of the patients were aged under 65.  The most common NHL subtype was diffuse large B-cell lymphoma (61.5%), followed by follicular lymphoma (12.5%) and marginal zone B-cell lymphoma (12.5%).  Higher proportions of low international prognostic index scores and better Eastern Cooperative Oncology Group performance statuses were shown more by younger patients than the elderly group.  The results revealed 3-year overall survival rates of 57% and 35% for the younger and older groups, respectively, with no significant difference in their CR rates (59.2% vs. 49.2%, p = 0.199; OR 2.07, CI 0.68-6.36).* **Conclusions:** *Although the distribution of the lymphoma subtypes among the younger and older patients was quite similar, the survival outcome of the elderly group was poor.*

**Keywords :**  ● *Clinicopathological features*  ● *Elderly*  ● *Non-Hodgkin lymphoma*  ● *Survival*

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# นิพนธ์ต้นฉบับ

# อัตราการอยู่รอดของผู้ป่วยสูงอายุที่เป็นมะเร็งต่อมน้ำเหลืองชนิดนอนฮอดกินจ์

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**บทคัดย่อ**

***ความเป็นมา*** ปัจจุบันพบผู้ป่วยโรคมะเร็งต่อมน้ำเหลืองชนิดนอนฮอดกินจ์ในกลุ่มผู้สูงอายุจำนวนมากขึ้น การศึกษานี้มีวัตถุประสงค์เพื่อเปรียบเทียบข้อมูลทางคลินิก การรักษารวมถึงผลการรักษาระหว่างผู้ป่วยในกลุ่มที่สูงอายุและกลุ่มผู้ป่วยที่มีอายุน้อยกว่า 65 ปี ***วิธีการศึกษา*** การศึกษาแบบย้อนหลังเก็บข้อมูลผู้ป่วยมะเร็งต่อมน้ำเหลืองชนิดนอนฮอดกินที่ได้รับการวินิจฉัยใหม่ที่โรงพยาบาลวชิระภูเก็ต จังหวัดภูเก็ต ตั้งแต่เดือนมกราคม พ.ศ. 2556 ถึงเดือนธันวาคม พ.ศ. 2560 โดยเก็บรวบรวมข้อมูล ได้แก่ ลักษณะทางคลินิก ผลการตรวจทางห้องปฏิบัติการเบื้องต้น ลักษณะทางพยาธิวิทยา ระยะของโรค วิธีการการรักษาและผลของการรักษา ***ผลการศึกษา*** ผู้ป่วยมะเร็งต่อมน้ำเหลืองชนิดนอนฮอดกินจ์ จำนวนทั้งสิ้น 105 ราย อายุเฉลี่ย 57 ± 14.4 ปีสัดส่วนของเพศชายมากกว่าเพศหญิง กลุ่มผู้ป่วยที่มีอายุน้อยกว่า 65 ปี มีจำนวนร้อยละ 66.6 ชนิดของมะเร็งต่อมน้ำเหลืองนอนฮอดกินจ์ที่พบบ่อยที่สุดในทุกกลุ่มอายุ คือ มะเร็งต่อมน้ำเหลืองชนิดDiffuse large B cell lymphoma พบร้อยละ 61.5 รองลงมาคือ Follicular lymphoma และ Marginal zone B cell lymphoma คิดเป็นร้อยละ 12.5 และร้อยละ 12.5 ตามลำดับ ในกลุ่มผู้ป่วยอายุน้อยมีสัดส่วนของการพยากรณ์โรคตาม international prognostic index (IPI) ต่ำกว่าและคะแนนการประเมินสมรรถภาพการทำกิจวัตรประจำวันต่ำกว่ากลุ่มผู้ป่วยสูงอายุ สำหรับอัตราการอยู่รอดที่ 3 ปีในผู้กลุ่มผู้ป่วยอายุน้อยและกลุ่มผู้ป่วยสูงอายุคิดเป็นร้อยละ 57 และ 35 ตามลำดับ Complete remission rate (CR rate) ในผู้ป่วยทั้งสองกลุ่ม ไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ (ร้อยละ 59 *vs.* ร้อยละ 49, p = 0.199; OR 2.07, CI 0.68-6.36) ***สรุป*** ถึงแม้ว่าชนิดย่อยของมะเร็งต่อมน้ำเหลืองในผู้ป่วยอายุน้อยและผู้สูงอายุจะค่อนข้างคล้ายคลึงกันแต่ผลลัพธ์ของการอยู่รอดของกลุ่มผู้สูงอายุนั้นไม่ดี

***คำสำคัญ :*** ● ลักษณะทางพยาธิวิทยา ● ผู้ป่วยสูงอายุ ● มะเร็งต่อมน้ำเหลืองชนิดนอนฮอดกินจ์ ● การรอดชีวิต

***วารสารโลหิตวิทยาและเวชศาสตร์บริการโลหิต. 2562;29:347-54.***

## Introduction

Non-Hodgkin lymphomas (NHLs) are heterogeneous subtypes of lymphoproliferative disorders of B lymphocytes, T lymphocytes, and natural killer (NK) lymphocytes[1]. B-cell NHLs account for 80 to 90% of the total NHL cases; by comparison, 15 to 20% of lymphoma cases are T-cell lymphomas, while NK lymphomas are very rare[1]. NHLs represent approximately 5 to 6% of all malignancies and are the fifth most frequently occurring type of cancer in the US[1].

The definitions of "elderly" patients are vary. One generally accepted definition was proposed by Coiffier, who defined an elderly patient as an individual aged more than 65 to 70 years[2]. Diffuse large B-cell lymphomas (DLBCLs) represent more than 60% of all lymphomas seen among elderly patients[3]. Their clinical presentations and prognostic parameters are fairly similar to those found with younger patients; however, the overall response rate of elderly patients with DLBCL appears to be lower than that for younger patients with DLBCL[3]. Moreover, a study found that inferior overall survival (OS) rates are displayed by elderly patients[4]. In fact, several unfavorable prognostic factors, such as a poor performance status (PS) and multiple comorbidities, render elderly patients intolerant to intensive treatment and result in dismal disease outcomes[4]. Therefore, this study aimed to compare the baseline clinical characteristics, treatments, and clinical outcomes of younger and older patients with NHL.

## Materials and Methods

This 5-year, retrospective, single-center study was conducted on newly diagnosed patients with NHL between January 1, 2013 and December 31, 2017, at Vachira Phuket Hospital, Medical Education Center, School of Medicine, Walailak University, Phuket, Thailand. The clinical features, initial laboratory findings, histopathological findings, stagings, treatments and clinical outcomes were recorded. The study complied with the Declaration of Helsinki and its amendments, and it was conducted in accordance with the Good Clinical Practice Guidelines and approved by the Institutional Ethics Committee.

## Terminology

The lymphoma classification used in the study complied with the 2008 WHO classification[5], and the lymphoma staging was based on Ann Arbor classification[6]. Comorbidity was defined as the presence of any of the following: significant cardiovascular disease (cardiac arrhythmia, myocardial infarction, coronary disease, congestive heart failure or an ejection fraction $\leq 50\%$); respiratory disease (dyspnea at rest or the need for oxygen therapy); urogenital system disease (serum creatinine > 2 mg/dL, dialysis, or transplantation); and liver failure (cirrhosis, fibrosis, blood urea nitrogen > $1.5 \times$ upper limit of normal, or aspartate transaminase/alanine aminotransferase > $2.5 \times$ upper limit of normal at the time of lymphoma diagnosis)[7]. The five treatment regimens are described below. First, was the CHOP regimen (750 mg/m$^2$ of cyclophosphamide on day 1, 50 mg/m$^2$ of doxorubicin on day 1, 1.4 mg/m$^2$ of vincristine on day 1, plus 100 mg/day of prednisolone on days 1-5). Second consisted of the mini-CHOP regimen (400 mg/m$^2$ of cyclophosphamide on day 1, 25 mg/m$^2$ doxorubicin on day 1, 1 mg of vincristine on day 1, plus 60 mg of prednisolone on days 1-5). The third comprised R-CHOP regimen (375 mg/m$^2$ of rituximab plus CHOP). The fourth constituted R-CVP regimen (rituximab, cyclophosphamide, vincristine, and prednisone) and the last was CVP regimen (cyclophosphamide, vincristine, and prednisone). For unfit patients or patients with multiple comorbidities, less intensive regimens including mini-CHOP, R-CVP or CVP regimens were preferable to the intensive regimens. Primary G-CSF prophylaxis was given for one patient receiving CHOP or R-CHOP or R mini-CHOP regimen. The response criteria after treatment included complete remission (CR); partial remission; complete remission unconfirmed; stable disease; relapsed disease; progressive disease based on a physical examination, chest X-ray, and computed tomography scan[8]. Observations ended at the time of

the last contact with the patients still alive, and OS was defined as the time from the date of the lymphoma diagnosis until death from any cause.

**Statistical analysis**

Median and interquartile ranges, or means ± standard deviations, as appropriate, were used for continuous variables. To compare continuous variables, either the Mann-Whitney U test or student's t-test was employed. Categorical variables were presented as frequency and percentage, and were compared using Fisher's exact test or the chi-square test. Factors associated with the OS of younger and older patients with NHL were assessed using a log-rank test and presented as a Kaplan-Meier survival curve. Univariate and multivariate analyses of the predictors of survival outcome were evaluated using Cox proportional hazards analysis (backward stepwise method) and presented as hazard ratio (HR) and 95%CI. A p-value less than .05 was regarded as statistically significant. PASW Statistics for Windows, Version18.0 (SPSS Inc., Chicago, IL, USA) was used for all data analyses.

### Results

**Patient baseline characteristics**

A total of 105 NHL cases were diagnosed during the period. Their mean age was 57 ± 14.4 years, with a male predominance. Two thirds of the patients were aged under 65 years. The patients' Eastern Cooperative Oncology Group (ECOG) performance statuses were ECOG-PS 0, 52.9%; ECOG-PS 1, 40.4% and ECOG-PS 2, 6.7%. Over 90% of the patients presented superficial lymphadenopathy as the initial manifestation, followed by palpable mass (27.1%), B symptoms (26%), splenomegaly (6.5%), hepatomegaly (2.8%), cutaneous involvement (3.7%) and pancytopenia (1.9%). The most common NHL subtype was DLBCL (61.5%), while the remainder were follicular lymphoma (12.5%), marginal zone B-cell lymphoma (12.5%), mantle cell lymphoma (4.8%) and other subtypes (8.6%; Table 1). Forty-two percent of the patients had limited stage (stages I-II) while those

with advanced stage (stages III-IV) accounted for 57.3%

Complete blood count showed a mean hemoglobin level of 11.6 ± 2.4 g/dL, a median white blood cell count of 7.53 x10$^9$/L (range, 1.29-278.5 x10$^9$/L), and a median platelet count of 252 x10$^9$/L (range, 16-695 x10$^9$/L). The median uric acid level was 5.7 mg/dL (range: 1.6-46 mg/dL), and the median LDH level was 310.5 U/L (range, 121-14,050 U/L). Based on the international prognostic index (IPI) scores for risk classification, 38% of cases were low risk, 40% were low to intermediate, 20% were high to intermediate, and 2% were high.

After dividing the patients in two groups (< 65 years vs. ≥ 65 years), no statistically significant difference was found in the groups' baseline characteristics or initial laboratory findings. However, the younger group displayed good ECOG-PS scores (0 and 1) and a higher proportion of low IPI scores than the elderly group (Table 1).

**Treatment and response outcomes**

More than one half of patients received the CHOP-based regimen (9.1% of R-CHOP regimen and 49.1% of CHOP regimen), followed by CVP regimen (12.7%) and mini-CHOP regimen (4.5%), respectively. The treatment responses comprised CR (33.7%), partial remission (6.5%), stable disease (4.7%), and progressive disease (6.5%). An insignificant difference was observed in the CR rates of the younger and elderly groups (59.2% vs. 49.2%; p = 0.199; OR 2.07; 95%CI: 0.68-6.36). All of the approximately 10% of cases that did not require immediate treatment comprised the indolent lymphoma subtype.

**Long term survival outcomes**

The median OS was 36.2 months (range, 22.3–50.1 months; Figure 1), and the 1- and 3-year OS rates were 73% and 51%, respectively (Table 2).The younger group had a median OS of 49.2 months (range, 0.2-55.9 months), whereas that of the elderly group was half as much, at 24.2 months (range 2.1–49.5 months; p = 0.024; Figure 2). Likewise, the 3-year OS rate of the younger patients was higher than that of the elderly patients, with 57% and 35%, respectively.

**Table 1** Comparison of the demographic data and laboratory findings of the younger and older age groups

| | NHL in younger age group (n = 72) Positive results (n, %) | NHL in elderly age group (n = 33) Positive results (n, %) | p-value |
|---|---|---|---|
| Age (years), mean ± SD | 50 ± 10 | 74 ± 8 | NA |
| Gender | | | 0.395 |
| - Male | 44 (61%) | 23 (70%) | |
| B symptom | | | |
| - Fever | 8 (11%) | 2 (6%) | 0.396 |
| - Night sweating | 4 (4%) | 1 (1%) | 0.557 |
| - Significant weight loss | 16 (22%) | 5 (15%) | 0.400 |
| Laboratory findings | | | |
| Complete blood count | | | |
| Mean Hb level (g/dL) | 11.8 ± 2.6 | 11.3 ± 1.8 | 0.351 |
| - Median WBC count (X $10^9$/L) | 7.18 (1.29-41.45) | 8.21 (4.26-278.5) | |
| - Median Serum creatinine (mg/dL) | 0.82 (0.45-9.4) | 0.98 (0.50-7.61) | |
| - Mean serum albumin (g/dL) | 3.6 ± 0.7 | 3.5 ± 0.6 | 0.363 |
| - Mean serum globulin (g/dL) | 4.1 ± 1.6 | 4.1 ± 0.9 | 0.924 |
| - Median serum uric acid (mg/dL) | 5.3 (2.3-46) | 6.0 (1.6-10) | |
| - Median serum LDH (U/L) | 318 (121-14,050) | 301 (134-914) | |
| - Median percentatge of Ki 67 | 40 (5-90) | 70 (5-95) | |
| Pathology | | | 0.123 |
| - Diffuse large B-cell lymphoma | 44 (61%) | 20 (60%) | |
| - Follicular lymphoma | 10 (14 %) | 3 (9%) | |
| - Extranodal marginal zone B-cell lymphoma | 8 (11 %) | 0 (0%) | |
| - Nodal marginal zone B-cell lymphoma | 4 (6%) | 1 (3%) | |
| - Chronic lymphocytic leukemia | 1 (1%) | 1 (3%) | |
| - Mantle cell lymphoma | 1 (1%) | 4 (12%) | |
| - Burkitt lymphoma | 1 (1%) | 1 (3%) | |
| - Lymphoplasmablastic lymphoma | 1 (1%) | 1 (3%) | |
| - Peripheral T-cell lymphoma | 2 (3%) | 1 (3%) | |
| Ann arbor stage | | | 0.717 |
| - Stage I | 5 (7%) | 4 (12%) | |
| - Stage II | 26 (36%) | 10 (30%) | |
| - Stage III | 26 (36%) | 10 (30%) | |
| - Stage IV | 18 (25%) | 8 (24%) | |
| ECOG performance status | | | 0.002 |
| - 0 | 45 (63%) | 10 (30%) | |
| - 1 | 21 (29%) | 21(64%) | |
| - 2 | 6 (8%) | 1 (1%) | |
| International prognostic index | | | < 0.0001 |
| - Low risk (0-1 scores) | 28 (39%) | 10 (30%) | |
| - Low intermediate risk (2 scores) | 34 (47%) | 6 (18%) | |
| - High intermediate risk (3 scores) | 6 (8%) | 14 (42%) | |
| - High risk (4-5 scores) | 1 (1%) | 1 (3%) | |

Abbreviations: ECOG, Eastern Cooperative Oncology Group;  Hb, Hemoglobin;  LDH, Lactate dehydrogenase;

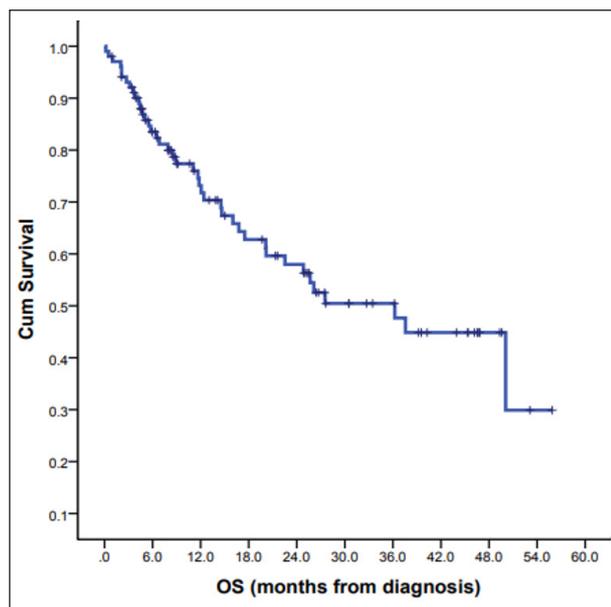NA, Not applicable;  NHL, Non-Hodgkin lymphoma;  SD, standard deviation;  WBC, White Blood Cell

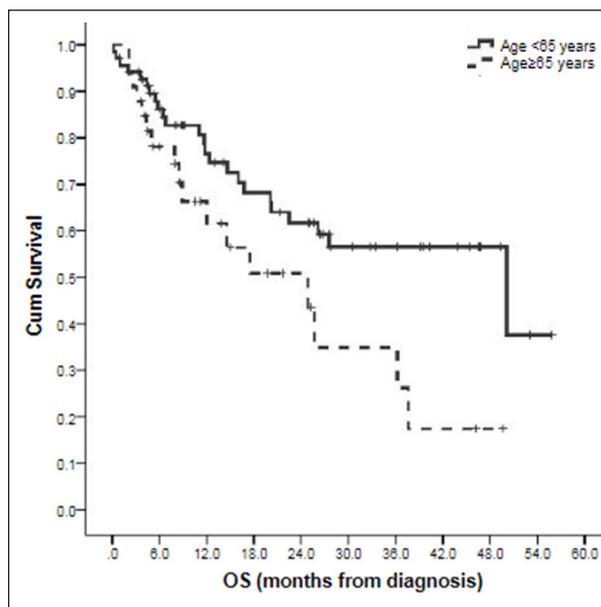**Figure 1** Kaplan-Meier overall survival for non-Hodgkin lymphoma patients



**Figure 2** Kaplan-Meier overall survival for patients aged < 65 years and ≥ 65 years (p = 0.024)

**Table 2** Treatment responses and clinical outcomes of the non-Hodgkin lymphoma patients

|  | NHL in younger age group (n = 72) Positive results (%) | NHL in elderly age group (n = 33) Positive results (%) | p-value |
|---|---|---|---|
| Complete remission rate | 59.2% | 41.2% | 0.199 |
| Cumulative mortality rate during follow-up | 18/69 (26.1%) | 12/33 (36.4%) |  |
| Causes of death (n = cases) |  |  |  |
|   - Treatment related complication | 4 | 4 | - |
|   - Disease progression | 9 | 1 | - |
|   - Other comorbidity related | 2 | 4 | - |
|   - Unknown cause | 3 | 3 | - |
| Median overall survival (months) | 49.2 (0.2-55.9) | 24.2 (2.1-49.5) | 0.024 |
| 1-year overall survival (%) | 77% | 66% | NA |
| 3-year overall survival (%) | 57% | 35% | NA |

Abbreviations: NA, Not applicable; NHL, Non-Hodgkin lymphoma

## Discussion

This single-center, retrospective, observational study focused on the clinical characteristics and outcomes of elderly lymphoma patients relative to younger patients. Those patients with NHL patients aged 65 or more accounted for one third of the Thai patients with NHL in the study, which was similar to findings of related reports[4,9]. The most common lymphoma subtype was DLBCL, which also corresponded with the results of other reports[10-14].

One prior international study found that developing countries had a significantly lower frequency of B-cell lymphoma (86.6%) and a higher frequency of T-cell and natural killer-cell lymphomas (13.4%) than developed countries (90.7% and 9.3%, respectively)[15]. However, in the current study's cohort, T-cell lymphoma accounted for only 3% of cases. Interestingly, the proportion of mantle cell lymphomas in the elderly group was dramatically higher than the corresponding figure for the younger age group (12.1% vs. 1.4%, respectively).

The 3-year OS in this study totaled 51%, which was lower than the rates found by other studies[16-18]. A possible reason for the unfavorable survival outcome in the present study was that only 10% of patients with

B-lymphoma could afford the rituximab needed for their treatment. Fortunately, Thailand's Universal Health Care Coverage Scheme has recently begun providing rituximab for all Thai patients with DLBCL. A prospective study is currently underway to determine the outcomes for patients receiving rituximab.

A prior study reported that a lymphoma patient's survival declined with every 10-year increase in age group, and each age group above age 39 had a significantly higher risk ratio than the reference group[4]. That result corresponded with our finding that the elderly group had a significantly inferior long term survival outcome than the younger patients. As the primary differences between the two groups were their ECOG-PS and IPI scores, we believe that poor PS and high IPI scores may lead to dismal outcomes for elderly patients.

This study had some limitations. As this comprised a retrospective, observational study, some important data were missing due to a lack of documentation. Moreover, because it was a single-center study, the number of included cases was limited. This meant that some factors to determine survival outcomes were insignificant due to insufficient power for statistical analysis.

### Conclusion

Although the distribution of the lymphoma subtypes among the younger and older patients was quite similar, the survival outcome of the elderly group was poor.

**Compliance with Ethics Standards**

**Acknowledgements**

Acknowledgements are not applicable.

**Disclosure of potential conflicts of interest**

The authors declare that they have no conflicts of interest.

**Ethics approval and consent to participate**

This study was approved by the Ethics Committee for Research in Human Subjects at the hospital.

**Consent for publication**

A copy of the consent document is available for review from the Editor-in-Chief of Siriraj Medical Journal.

**Availability of data and materials**

The datasets used for the current study are available from the corresponding author upon reasonable request.

**Authors' contributions**

Both authors designed the study. SS collected the data, drafted the manuscript and revised the final manuscript. WO performed the statistical analyses and made critical revisions. Both authors read and approved the final manuscript.

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