Original article

Impact of active pulmonary tuberculosis on overall survival among adult patients with B-cell non-Hodgkin lymphoma

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Abstract:

Introduction: *Patients with B-cell non-Hodgkin lymphoma (B-cell NHL) have an increased risk of developing active tuberculosis (TB) during treatment. Active pulmonary TB among patients with B-cell NHL often leads to poor outcomes.* ***Objective****: The primary objective was to compare the 3-year overall survival (OS) of patients with B-cell NHL and active pulmonary TB to those without active pulmonary TB. The secondary objective was to investigate the association of active pulmonary TB with mortality risk among patients with B-cell NHL.* ***Materials and Methods:*** *A retrospective cohort was conducted on patients with newly diagnosed B-cell NHL at Chiangrai Prachanukroh Hospital from January 2016 to December 2023. OS rates were estimated using the Kaplan-Meier method and compared between groups using the two-sided log-rank test. Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for risk factors associated with mortality.* ***Results:*** *A total of 415 patients were enrolled, with a mean age of 58.96 years. Among them, 19 (4.58%) developed active pulmonary TB after their B-cell NHL diagnosis and during treatment. Patients with active pulmonary TB had significantly worse 3-year OS compared to those without active pulmonary TB (22.39% vs. 55.11%, p < 0.001). The median follow-up time was 89 weeks. Active pulmonary TB was associated with an increased risk of mortality (HR, 1.80, 95%CI: 1.01-3.21).* ***Conclusion:*** *Active pulmonary TB among adult patients with B-cell NHL is associated with worse survival outcomes and represents an independent risk factor for mortality.*

Keywords : ● *Pulmonary tuberculosis* ● *Overall survival* ● *B-cell non-Hodgkin lymphoma* ● *Risk factor*

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นิพนธ์ต้นฉบับ

ผลกระทบของวัณโรคปอดต่ออัตราการอยู่รอดโดยรวมในผู้ป่วยมะเร็งต่อมน้ำเหลืองชนิด B-cell non-Hodgkin

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บทคัดย่อ

บทนำ *ผู้ป่วยมะเร็งต่อมน้ำเหลืองชนิด B-cell non-Hodgkin lymphoma (B-cell NHL) มีความเสี่ยงสูงที่จะเป็นวัณโรคปอดระหว่างการรักษา ทำให้ผลลัพธ์ของการรักษาแย่ลง* ***วัตถุประสงค์*** *เปรียบเทียบอัตราการอยู่รอดโดยรวมที่ 3 ปี ของผู้ป่วย B-cell NHL ที่เป็นวัณโรคปอดกับไม่เป็นวัณโรคปอด และความสัมพันธ์ระหว่างวัณโรคปอดกับความเสี่ยงต่อการเสียชีวิตในผู้ป่วย B-cell NHL* ***วัสดุและวิธีการ*** *ศึกษาย้อนหลัง ในโรงพยาบาลเชียงรายประชานุเคราะห์ ตั้งแต่เดือนมกราคม 2559 ถึงเดือนธันวาคม 2566 เพื่อวิเคราะห์อัตราการอยู่รอดโดยรวมที่ 3 ปีด้วย Kaplan-Meier method วิเคราะห์ความสัมพันธ์ระหว่างวัณโรคปอดกับความเสี่ยงต่อการเสียชีวิตด้วย cox proportional hazards models* ***ผลการศึกษา****: ผู้ป่วย B-cell NHL 415 ราย อายุเฉลี่ย 58.96 ปี พบ เป็นวัณโรคปอด 19 ราย คิดเป็นร้อยละ 4.58 หลังการวินิจฉัยและระหว่างการรักษา ผู้ป่วย B-cell NHL ที่เป็นวัณโรคปอดมีอัตราการอยู่รอดโดยรวมที่ 3 ปี แย่กว่าผู้ป่วยที่ไม่เป็นวัณโรคปอด (ร้อยละ 22.39 เทียบกับ ร้อยละ 55.11, $p < 0.001$) วัณโรคปอดเพิ่มความเสี่ยงต่อการเสียชีวิต 1.80 เท่า (HR, 1.80, 95%CI: 1.01-3.21)* ***สรุป*** *วัณโรคปอดในผู้ป่วยมะเร็งต่อมน้ำเหลืองชนิด B-cell NHL สัมพันธ์กับอัตราการอยู่รอดที่แย่ลง และเป็นปัจจัยเสี่ยงต่อการเสียชีวิตอย่างมีนัยสำคัญ*

คำสำคัญ : ● *วัณโรคปอด* ● *อัตราการอยู่รอดโดยรวม* ● *มะเร็งต่อมน้ำเหลืองชนิด B-cell non-Hodgkin lymphoma* ● *ปัจจัยเสี่ยง*

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Introduction

Tuberculosis (TB) is a communicable disease and a major global health threat, leading to significant morbidity and mortality.[1,2] Approximately one in three people worldwide--representing 2 to 3 billion individuals--are infected with *Mycobacterium tuberculosis* (*M. tuberculosis*), with 5% to 10% likely to develop active TB during their lifetime.[3] In 2022, 7.5 million people were newly diagnosed with TB, and 1.3 million died from the disease.[4] Globally, TB is the 13th leading cause of death and the second leading infectious killer after COVID-19.[5] According to the World Health Organization (WHO), Thailand is considered a high-incidence country for TB, with an estimated TB incidence rate of 157 per 100,000 population in 2023.[6,7] The risk of developing active pulmonary TB is increased among individuals with immunocompromising conditions such as human immunodeficiency virus (HIV) infection,[8] chronic kidney disease (CKD),[9] diabetes mellitus[10] and among those receiving immunosuppressive medications,[11,12] particularly patients with B-cell non-Hodgkin lymphoma (B-cell NHL).[13,14]

B-cell NHL can lead to malnutrition and immune dysfunction, both directly due to the malignancy and as a result of chemotherapy.[15,16] Therefore, it is reasonable to assume that patients with B-cell NHL are at risk of developing active pulmonary TB or acquiring new TB infections during their clinical course.[17] Active pulmonary TB in patients with cancer--particularly those with Hodgkin lymphoma (HL) and upper aerodigestive cancers--often results in poor prognosis. The coexistence of TB and cancers complicates treatment and may lead to worse outcomes.[18,19] However, no studies to date have specifically investigated the impact of active pulmonary TB on survival outcomes inpatients with B-cell NHL.

This study aims to address this gap by conducting a retrospective cohort analysis to determine the impact of active pulmonary TB on survival and its association with mortality risk among patients with B-cell NHL.

Materials and Methods

Study design

This retrospective study included patients with newly diagnosed B-cell NHL at Chiangrai Prachanukroh Hospital from January 2016 to December 2023. We evaluated the three-year overall survival (OS) of adult patients with B-cell NHL and active pulmonary TB. This study protocol was approved by the Ethics Committee of Chiangrai Prachanukroh Hospital (EC CRH 098/67) and was carried out in accordance with the Declaration of Helsinki.

Participants

This study included patients aged 18 years or older having newly diagnosed B-cell according to the 2016 of the WHO classification of lymphoid neoplasms criteria.[20] All patients were admitted to or attended the outpatient clinic in Chiangrai Prachanukroh Hospital, Thailand. Patients who had been diagnosed with TB before their B-cell NHL diagnosis were excluded from the study. Data were acquired from the Chiangrai Prachanukroh Hospital databases. Adult patients with B-cell NHL who developed active pulmonary TB during the course of B-cell NHL treatment were defined as patients with B-cell NHL and active pulmonary TB. Active pulmonary TB was defined as follows: (I) isolation of *M. tuberculosis* using any mycobacterial culture method; (II) isolation of *M. tuberculosis* using any molecular methods; (III) histopathologic examination; or (IV) a diagnosis of pulmonary TB by a pulmonary physician or infectious disease physician (ICD-10 codes A15, A16 and A19) and prescription of anti-TB medications, such as isoniazid, rifampicin, ethambutol, pyrazinamide, streptomycin, kanamycin or amikacin.

Objectives

The primary outcome of this study was the three-year OS of patients with B-cell NHL and active pulmonary TB compared to those without active pulmonary TB. The OS was measured from the date of B-cell NHL diagnosis to the date of death from any cause. The secondary

outcome was the association of active pulmonary TB with mortality risk among patients with B-cell NHL.

Statistical analysis

Statistical analyses were performed using STATA, version 14 (StataCorp LLC, College Station, TX, USA). Descriptive statistics were used to present the data, with numbers and percentages for categorical variables. The mean and standard deviation (SD) were used to describe normally distributed continuous variables, while the median and interquartile range (IQR) were used to describe non-normally distributed continuous variables. Categorical variables were compared using the exact probability test as appropriate. The t-test was used to compare normally distributed data, and the Wilcoxon rank-sum (Mann-Whitney) test was used to compare non-normally distributed data. The OS rates were estimated using the Kaplan-Meier method and compared between risk groups using the two-sided log-rank test. The multivariate Cox proportional hazards regression model was used to calculate the hazard ratio (HR) and its 95% confidence interval (CI) for risk factors associated with all-cause mortality among patients with newly diagnosed B-cell NHL. A *p-value* of < 0.05 was considered statistically significant.

Results

The study included 415 patients with a mean age of 58.96 years who were newly diagnosed with B-cell NHL between 2016 and 2023, without prior pulmonary TB. Most cases were diffuse large B-cell lymphoma (DLBCL), accounting for 265 patients (63.86%). Nineteen patients (4.58%) developed active pulmonary TB after their B-cell NHL diagnosis and during treatment. Among these, 13 were diagnosed with DLBCL. Table 1 summarizes the clinical characteristics of patients with B-cell NHL with and without active pulmonary TB. No differences were noted regarding age, sex, B-cell NHL subtype, Ann Arbor stage of lymphoma and comorbidities (including diabetes mellitus, HIV and CKD) between the groups.

Patients with B-cell NHL and active pulmonary TB exhibited poorer performance status according to Eastern Cooperative Oncology Group (ECOG) scores (II-IV) compared to those without active pulmonary TB (15 [78.95%] vs. 185 [46.72%], $p = 0.008$). Moreover, patients with B-cell NHL without active pulmonary TB had a lower International Prognostic Index (IPI) score (0-I) compared to those with active pulmonary TB (132 [33.33%] vs. 2 [10.53%], $p = 0.044$).

In terms of B-cell NHL treatment, no differences were noted regarding the use of rituximab-based therapy, radiation therapy and surgery between the groups. According to complete blood count results, no significant differences were observed concerning mean hemoglobin (Hb) levels, median white blood cell (WBC) count, median absolute neutrophil count and mean platelet count between the groups.

In the survival analysis using a multivariate Cox regression model, Table 2 shows that the following variables were independent risk factors for mortality: active pulmonary TB (HR 1.80, 95%CI: 1.01-3.21), high IPI score (4-5) (HR 1.32, 95%CI: 1.09-1.60), HIV (HR 1.87, 95%CI: 1.03-3.40) and CKD (HR 1.51, 95%CI: 1.00-2.56). Additionally, Figure 1 reveals significantly worse survival among patients with B-NHL and active pulmonary TB compared to those without active pulmonary TB. Patients with B-cell NHL and active pulmonary TB demonstrated a notably lower three-year OS rate compared to those without active pulmonary TB (22.39% vs 55.11%, $p < 0.001$). The median follow-up time for this analysis was 89 weeks.

Discussion

This study highlights that the coexistence of active pulmonary TB among adult patients with B-cell NHL is associated with worse survival rates. Patients with B-cell NHL may carry latent tuberculosis infection (LTBI), where the bacteria remain dormant in the body without causing active disease. However, if the immune system becomes compromised due to the disease itself or as

Table 1 Clinical characteristics of newly diagnosed B-cell nonHodgin lymphoma (NHL) patients with and without active pulmonary tuberculosis (TB)

Factors	Patients with B-cell NHL 415 (100 %)	Patients with B-cell NHL with active TB 19 (4.58 %)	Patients with B-cell NHL without TB 396 (95.42 %)	*p*-value
Age (years) mean (±SD)	58.96 (±13.18)	60.32 (±20.48)	58.90 (±12.77)	0.647
Male	183 (44.10)	10 (52.63)	173 (43.69)	0.484
B-cell NHL subtype				
- Diffuse large B-cell lymphoma (DLBCL)	265 (63.86)	13 (68.42)	252 (63.64)	0.809
- Marginal zone lymphoma	49 (11.81)	2 (10.53)	47 (11.87)	1.000
- Follicular lymphoma	33 (7.95)	0	33 (8.33)	0.385
- Primary DLBCL of the CNS	18 (4.34)	2 (10.53)	16 (4.04)	0.196
- Small lymphocytic lymphoma	15 (3.61)	1 (5.26)	14 (3.54)	0.511
- Mantle cell lymphoma	8 (1.93)	0	8 (2.02)	1.000
- Burkitt's lymphoma	8 (1.93)	1 (5.26)	7 (1.77)	0.315
- Another subtype	19 (4.58)	0	19 (4.80)	1.000
Ann Arbor stage				
- I-II	178 (42.89)	7 (36.84)	171 (43.18)	0.383
- III-IV	237 (57.11)	12 (63.16)	225 (56.82)	0.642
ECOG performance status				
- 0-I	215 (51.81)	4 (21.05)	211 (53.28)	0.005
- II-IV	200 (48.19)	15 (78.95)	185 (46.72)	0.008
International Prognostic Index score				
- Low (0-1score)	134 (32.29)	2 (10.53)	132 (33.33)	0.044
- Low intermediate (2 score)	93 (22.41)	5 (26.32)	88 (22.22)	0.778
- High intermediate (3 score)	116 (27.95)	6 (31.58)	110 (27.78)	0.817
- High (4-5 score)	72 (17.35)	6 (31.58)	66 (16.67)	0.116
Comorbidity				
- Diabetes mellitus	50 (12.05)	4 (21.05)	46 (11.62)	0.267
- HIV	28 (6.75)	2 (10.53)	26 (6.57)	0.372
- Chronic kidney disease	81 (19.52)	7 (36.84)	74 (18.69)	0.071
B-cell NHL treatment				
- Rituximab-based therapy	150 (36.14)	5 (26.32)	145 (36.62)	0.467
- Radiation therapy	73 (17.59)	4 (21.05)	69 (17.42)	0.756
- Surgery	38 (9.41)	3 (16.67)	35 (9.07)	0.234
Hemoglobin (g/dl) mean (±SD)	11.14 (±2.23)	10.66 (±2.15)	11.16 (±2.23)	0.338
White blood cell ($x10^9$/L) median (IQR)	7.80 (6.00-10.60)	6.10 (5.60-9.50)	7.95 (6.1-10.60)	0.172
Absolute neutrophil count ($x10^9$/L) median (IQR)	4.89 (3.15-6.91)	4.26 (2.40-5.70)	4.90 (3.19-6.95)	0.205
Platelet ($x10^9$/L) mean (±SD)	276.24 (±121.83)	266.74 (±119.70)	276.69 (±122.06)	0.728

B cell NHL; B-cell nonHodgin lymphoma; CNS, Central nervous system; other subtypes of B-cell NHL include primary mediastinal B-cell lymphoma, lymphoplasmacytic lymphoma, High-grade B-cell lymphoma and B-cell lymphoma, unclassifiable with features intermediate between DLBCL and classical HL; IPI, International Prognostic Index score includes age more than 60 years, performance status assessment using ECOG scores 2-4, Ann Arbor stages III-IV, extranodal involvement more than 1 site and serum lactate dehydrogenase (LDH) more than upper normal limit; HIV, Human immunodeficiency virus

Table 2 Survival analysis between patients with newly diagnosed B-cell nonHodgin lymphoma (NHL) with and without active pulmonary tuberculosis (TB)

	Univariate		Multivariate	
	HR	**95%CI**	**HR**	**95%CI**
Active pulmonary TB	2.52	1.43-4.46	1.80	1.01-3.21
Age				
< 40 years	1.00	0.99-1.01		
40-49 years (reference)	1	-	1	-
50-59 years	1.01	1.00-1.01	1.00	0.99-1.01
> 60 years	0.99	0.98-1.00		
Male	1.44	1.05-1.99	1.32	0.94-1.83
International Prognostic Index (IPI) score				
- Low (0-1score) (reference)	1	-	1	-
- Low intermediate (2 score)	1.41	1.27-1.55	1.46	0.96-1.37
- High intermediate (3 score)	1.32	1.20-1.46	1.20	0.99-1.44
- High (4-5 score)	1.45	1.26-1.66	1.32	1.09-1.60
Comorbidity				
- Diabetes mellitus	1.21	0.78-1.89		
- HIV	1.81	1.04-3.13	1.87	1.03-3.40
- Chronic kidney disease	2.11	1.47-3.05	1.51	1.00-2.56
B-cell NHL Treatment				
- Rituximab-based therapy	0.73	0.51-1.06		
- Radiation therapy	0.66	0.42-1.03		
- Surgery	0.96	0.56-1.67		

HR, hazard ratio; CI, confidence interval; TB, tuberculosis; IPI, International Prognostic Index scores include age more than 60 years, performance status assessment using Eastern Cooperative Oncology Group (ECOG) scores 2-4, Ann Arbor stage III-IV, extranodal involvement more than 1 site and serum lactate dehydrogenase (LDH) more than upper normal limit; HIV, Human immunodeficiency virus; B cell NHL; B-cell non-Hodgin lymphoma

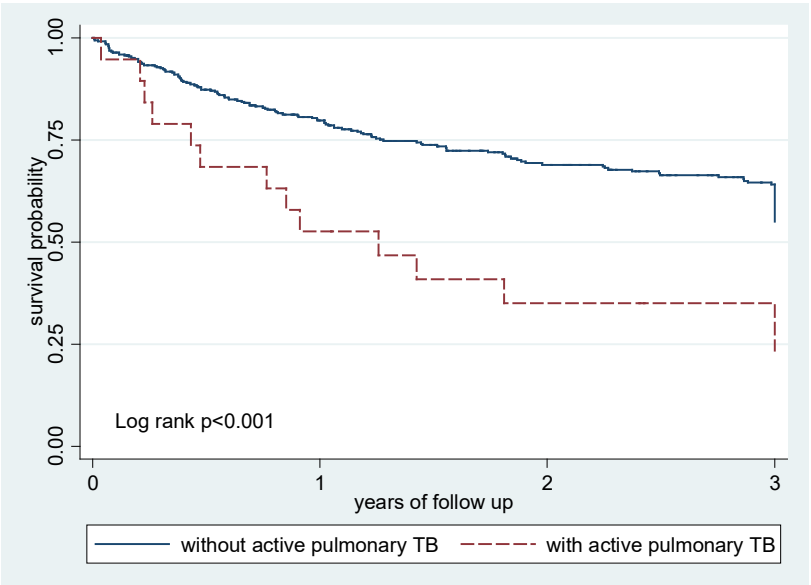

Figure 1 Kaplan-Meier survival analysis for patients with B-cell nonHodgin lymphoma (NHL) and active pulmonary tuberculosis (TB) and matched cohort without active pulmonary TB.

a consequence of chemotherapy, LTBI can reactivate, leading to active TB.[21,22] In this study, 4.58% of patients with B-cell NHL developed active pulmonary TB during the course of B-cell NHL treatment, consistent with previous reports indicating that 2% to 4% of lymphoma patients develop TB.[23,24] Patients with hematologic malignancies possess a higher risk of active pulmonary TB compared to the general population[25-28] due to underlying immunological deficiencies that facilitate the emergence of infections.[29-31] Alterations in the T-helper 1 cell response or those caused by chemotherapy, often associated with high dose corticosteroids or hematopoietic stem cell transplantation, lead to an impaired immune response that particularly promotes the progression from LTBI to active pulmonary TB.[32-34]

Patients with B-cell NHL exhibiting poorer performance status are often debilitated due to the disease process, coexisting comorbidities or the cumulative effects of prior treatments. This deterioration reflects a reduction in metabolic and reparative reserves essential for effective host defense and recovery from infections and cellular stress, as well as compromised cellular immunity, which increases their susceptibility to active pulmonary TB.[35-37] A higher IPI score indicates an adverse prognosis driven by aggressive disease biology, frequently leading to the secretion of immunosuppressive cytokines such as transforming growth factor-beta (TGF-β) and interleukin-10 (IL-10). These cytokines suppress immune surveillance, impairing the ability to respond effectively to both tumors and opportunistic infections such as active pulmonary TB.[38-40]

The survival rates of patients with B-cell NHL can vary based on several factors including WHO subtypes,[41] IPI scores,[42] initial chemotherapy regimens[43] and comorbidities such as HIV and CKD.[8,9,44] In our study, we found that the majority of cases comprised patients with DLBCL stages III to IV without active pulmonary TB. Among all patients, the three-year OS rate of 55.11% was consistent with previous studies reporting the three-year OS rates for DLBCL ranging from 50 to 85%, depending on IPI scores.[45,46] Patients with B-cell NHL and active pulmonary TB had a three-year OS rate of only 22.39%, significantly shorter than those without active pulmonary TB. Active pulmonary TB increased mortality risk (HR 1.8, 95%CI: 1.01-3.21) compared to those without active pulmonary TB. Few studies have investigated the survival rate of patients with lymphoma and active pulmonary TB. However, our results aligned with previous studies, indicating that active TB in patients with NHL or with HL increased mortality rates and resulted in poor survival.[18,24] Similarly, previous studies have reported that the survival of cancer patients, especially those with aerodigestive cancer, lung cancer and hematologic malignancies, was significantly shorter among those with active pulmonary TB compared to those without.[19,47,48] Moreover, a high IPI score of 4 to 5, HIV and CKD also increased mortality risk in B-cell NHL. The IPI is a scoring system used to predict the prognosis, especially in DLBCL, which is the most common subtype of B-cell NHL. A high IPI score (4-5) indicates a worse prognosis.[49,50] CKD can worsen prognosis and increase mortality risk among patients with B-cell NHL due to several factors, such as impaired immune function. CKD can also limit treatment options, affecting efficacy, and leading to additional complications such as cardiovascular disease, electrolyte imbalances and anemia.[51,52] Additionally, HIV can increase mortality risk among patients with B-cell NHL due to several reasons, including impaired immune function, a higher risk of opportunistic infections and drug interactions between antiretroviral therapy and chemotherapy that complicate treatment plans.[53,54]

Thus, active pulmonary TB among adult patients with B-cell NHL is associated with worse survival rates and constitutes an independent risk factor for mortality. These results emphasize the importance of monitoring and early diagnosis of pulmonary TB in patients with B-cell NHL, particularly in regions with high TB prevalence. Targeted LTBI screening and treatment in these patients could potentially improve outcomes by preventing the reactivation of TB during immunosuppressive therapies.[55-57]

Conclusion

Active pulmonary TB among adult patients with B-cell NHL was associated with worse survival rates and constitutes an independent risk factor for mortality.

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