


Prognostic Factors for Clinical Outcomes in Patients with Newly Diagnosed Advanced-stage Hodgkin Lymphoma: A Nationwide Retrospective Study

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Abstract

Introduction: While Hodgkin lymphoma (HL) is mostly curable, outcomes for advanced-stage HL remain unsatisfactory. The International Prognostic Score and its modifications were developed to predict HL prognosis; however, more straightforward prognostic factors are needed. This study aimed to identify simpler prognostic factors for advanced-stage newly diagnosed HL (NDHL).

Methods: This retrospective study used the Taiwan National Health Insurance Research Database and the Taiwan Cancer Registry. Patients with advanced-stage NDHL receiving ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) or ABVD-like regimens between 2009 and 2016 were enrolled. Cox proportional hazards models were used to identify prognostic factors for the time to next treatment (TTNT) and overall survival (OS). We used the time-dependent area under the receiver operating characteristic curve (AUROC) to evaluate model performance.

Results: The study included 459 patients with advanced-stage NDHL. A bimodal age distribution (peaks 20–44 and >65 years) was observed. Over a median follow-up of 4.7 years, the complete remission and OS rates were 52% and 76%, respectively. Age ≥ 60 years (adjusted hazard ratio [aHR]: 1.73, 95% confidence interval [CI]: 1.23–2.43), extranodal involvement (1.40, 1.05–1.87), B symptoms (1.53, 1.13–2.06), and Charlson Comorbidity Index (CCI) ≥ 1 (1.49, 1.08–2.06) were significantly associated with a shorter TTNT. The time-dependent AUROC was .65. With a time-dependent AUROC of .81, age ≥ 60 years (4.55, 2.90–7.15) and CCI ≥ 1 (1.86, 1.18–2.91) were risk factors for worse OS.

Conclusion: Older age and more comorbidities were risk factors for an inferior OS in advanced-stage NDHL, while older age, extranodal involvement, B-symptoms, and higher CCI were significantly associated with disease relapse.

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Keywords

hodgkin lymphoma, prognostic factor, overall survival, time to next treatment

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Introduction

Hodgkin lymphoma (HL) is a rare hematologic malignancy that originates from germinal center B cells. Sequential lymphadenopathy is a typical presentation of this condition. According to the 2017 Taiwan Cancer Registry (TCR) Annual Report, the annual incidence rate of HL is .2% among all malignancies and 6.3% among malignant lymphomas.¹ The age at diagnosis has a bimodal distribution, with peaks between 20 and 30 years and >50 years.²

Currently, ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) is the standard of care for newly diagnosed HL (NDHL). For patients with stage I/II NDHL, the long-term overall survival (OS) rate can be as high as 90% after four cycles of ABVD, followed by 30 Gy of involved-field radiotherapy.³ However, the treatment of advanced HL remains challenging. Approximately 40% of patients with advanced HL eventually relapse,^{4,5} with poor outcomes and this is likely worse in the real-world setting.⁶

It is crucial to identify adverse prognostic factors for advanced HL. Hasenclever and Diehl developed the International Prognostic Score (IPS-7) in 1998 to predict freedom from progression (FFP) of advanced HL. Albumin <4 g/dL, hemoglobin <10.5 g/dL, male sex, age \geq 45 years, stage IV, white blood cell count \geq 15,000/mm³, and lymphocyte count <600/mm³ are the parameters of IPS-7.⁷ However, the utility of IPS-7 in the modern era has been decreasing because therapeutic and imaging modalities for HL have greatly improved over the past decades. The survival of HL has also improved, and the differences across risk groups have diminished.⁸⁻¹⁰ One example comes from the report of the Spanish study group, showing Stage IV and age >45 years were the only prognostic factors of the IPS for the outcome of advanced HL.¹¹ To improve the predictive ability of IPS-7, Diefenbach et al proposed IPS-3, which comprises age, stage, and hemoglobin level. Compared to IPS-7, IPS-3 provides a more accurate outcome prediction.⁹

However, it is unclear how to further predict the outcome of advanced-stage NDHL easily and precisely. The present study aimed to analyze the clinical characteristics of advanced-stage NDHL to identify more specific prognostic factors using Taiwanese nationwide databases.

Material and Methods

Data Source

This is a nationwide population-based retrospective study. We used linked data from the TCR (2008-2016), the National Health

Insurance Research Database (NHIRD) (2008-2017), the Catastrophic Illness Patient Registry (CIPR), and the Cause of Death Data of Taiwan to conduct this study. The Research Ethics Committee of the National Taiwan University Hospital approved the study and agreed to waive the patient's informed consent owing to the retrospective nature of the study and de-identified data used (No. 201901097RIND).

Study Population

Patients with stage III and IV advanced-stage NDHL (ICD-O-3 codes: 9650-9667) diagnosed between January 1, 2009, and December 31, 2016, were identified using the TCR (n = 1309). The TCR provided information on patient demographics, date of cancer diagnosis, cancer-specific profiles, and first course of treatment. We used the CIPR to validate the diagnosis of HL (ICD-9-CM: 201.x; ICD-10-CM: C81.x). This study excluded NDHL patients with a history of other malignancies (n = 46). Patients without intent-to-cure treatment were also excluded (n = 107; Figure 1, Supplementary Table S1). Considering the heterogeneity of patients, we only analyzed patients with advanced-stage NDHL who received ABVD or ABVD-like regimens (containing three of four ABVD drugs or regimens with an ABVD backbone). To avoid lead-time bias, the date of the first prescription of HL treatment was defined as the index date. The frontline regimen was determined based on all HL medications prescribed within 60 days of the index date.

Patient Characteristics and Covariates

We used the NHIRD to identify the patients' medical history. The NHIRD claims data on outpatient visits, inpatient visits, and medication records includes more than 99.6% of the Taiwanese population.¹² Data regarding age, sex, presence or absence of extranodal involvement, B symptoms, and the Charlson Comorbidity Index (CCI) were collected within 1 year prior to the first HL diagnosis.

Clinical Outcomes

The time to next treatment (TTNT) and overall survival (OS) were the outcome measures in the current study. TTNT, a progression proxy, was defined as the time period between the index date and the date of receiving new HL treatments other than ABVD or ABVD-like regimens, autologous hematopoietic stem cell transplantation (ASCT), or death. Follow-up was censored at December 31, 2017 if none of the aforementioned events occurred. We used the conditioning regimen employed before ASCT to

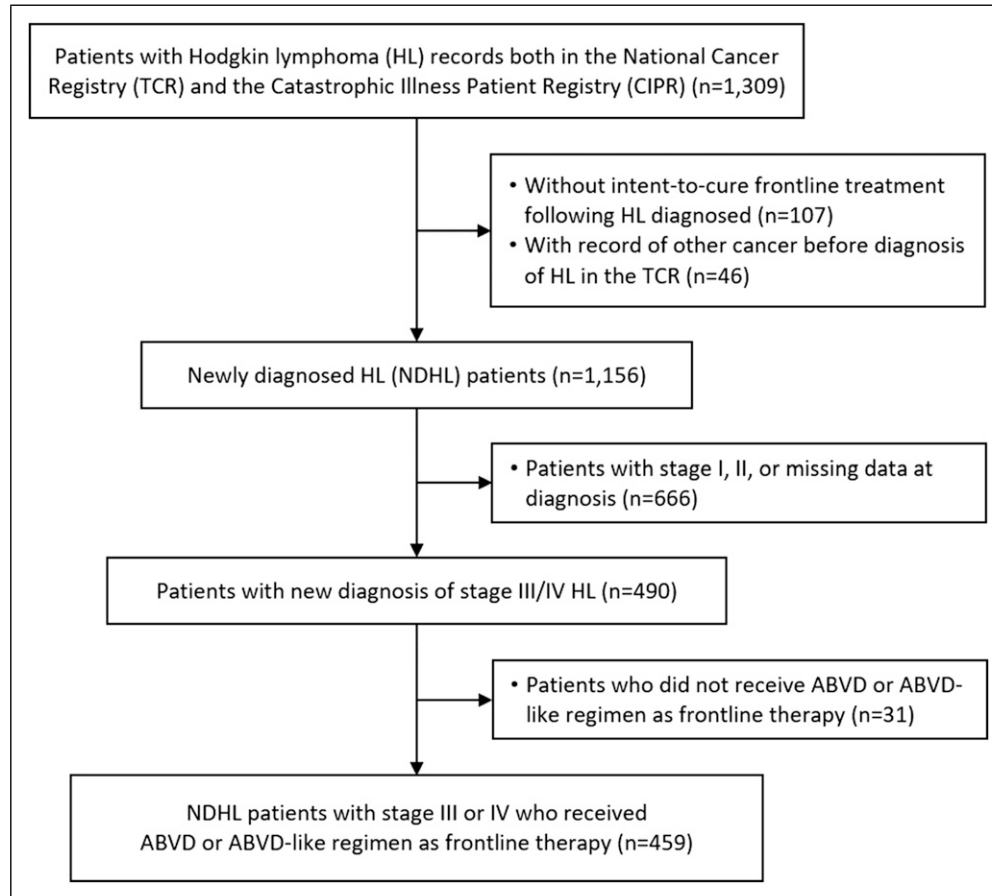


Figure 1. Patient enrollment diagram.

Table 1. Characteristics of patients with advanced-stage NDHL receiving ABVD or ABVD-like regimen (n = 459).

Characteristics	n (%)
Age at Diagnosis	
Median, min-max (years)	34, 5-87
Mean \pm SD	40.17 \pm 20.20
<45	285 (62.1)
45-59	77 (16.8)
60-64	16 (3.5)
\geq 65	81 (17.7)
Male	286 (62.3)
Extranodal involvement	267 (58.2)
B-symptoms	
Yes	185 (40.3)
No	167 (36.4)
Unknown	107 (23.3)
Charlson comorbidity index	
0	333 (72.6)
1	80 (17.4)
\geq 2	46 (10.0)

ABVD: doxorubicin, bleomycin, vinblastine, dacarbazine; NDHL: newly diagnosed Hodgkin lymphoma.

ascertain whether ASCT was performed. OS was defined as the time from the index date to all-cause death, and patients were censored at December 31, 2017 if still alive. We obtained the date of death by using the Cause of Death Data.

Statistical Analysis

Categorical variables are presented as numbers with percentages. Continuous characteristics are presented as medians with ranges. Kaplan-Meier methods were used to determine TTNT and OS. We used the Cox proportional hazards model to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) in order to evaluate potential factors associated with OS and TTNT. These factors included age, sex, extranodal involvement, B symptoms, and CCI. Age was dichotomized using a cutoff of 60 years according to the subgroup analysis of the ECHELON-1 trial (age <60 and \geq 60 years) so that the results of patient outcomes could be compared.^{13,14} Considering that extranodal involvement could have been undercoded in the TCR, the presence of extranodal involvement was defined as extranodal involvement or stage IV at diagnosis. Since 23% of the information on B symptoms was unknown, we

used the multiple imputation method to address the missing values. The multiple imputation method for handling missing data maintains the sample size and considers the variability of missing data.¹⁵ CCI was categorized into 0 and ≥ 1 based on the distribution, and $CCI \geq 1$ indicates having at least one comorbidity. The proportional hazards assumption was assessed graphically. We used the time-dependent area under the receiver operating characteristic curve (AUROC) to determine the discrimination of the multivariable regression analysis.¹⁶ Statistical significance was set at $P < .05$. All statistical analyses were performed using SAS (version 9.4; SAS Institute Inc., Cary, NC, USA).

Results

Study Population and Baseline Characteristics

Between January 1, 2009, and December 31, 2016, 1156 patients with NDHL with intent-to-cure treatment were enrolled, of whom 490 were in the advanced stage (Figure 1). Among these 490 patients with advanced NDHL, ABVD was the primary frontline regimen and was used in 78.8% of the study population (386/490). In addition, 14.9% (73/490) of the patients received

ABVD-like regimens (AVD or BVD). Because the current study only included patients undergoing ABVD or ABVD-like regimens, only data from 459 patients were finally analyzed. In our study cohort, the median age of the patients was 34 years. Male

Table 2. Factors associated with an inferior time to next treatment.

	Univariable Analysis		Multivariable Analysis	
	HR (95% CI)	P-value	Adjusted HR (95% CI)	P-value
Age, years				
<60	Reference		Reference	
≥ 60	2.08 (1.55-2.79)	<.001	1.73 (1.23-2.43)	.002
Sex				
Female	Reference		Reference	
Male	1.24 (.94-1.65)	.130	1.11 (.84-1.48)	.465
Extranodal involvement				
No	Reference		Reference	
Yes	1.39 (1.06-1.84)	.019	1.40 (1.05-1.87)	.021
B-symptoms				
No	Reference		Reference	
Yes	1.67 (1.24-2.25)	<.001	1.53 (1.13-2.06)	.006
Charlson comorbidity index				
0	Reference		Reference	
≥ 1	1.87 (1.42-2.48)	<.001	1.49 (1.08-2.06)	.016

CI: confidence interval; HR: hazard ratio.

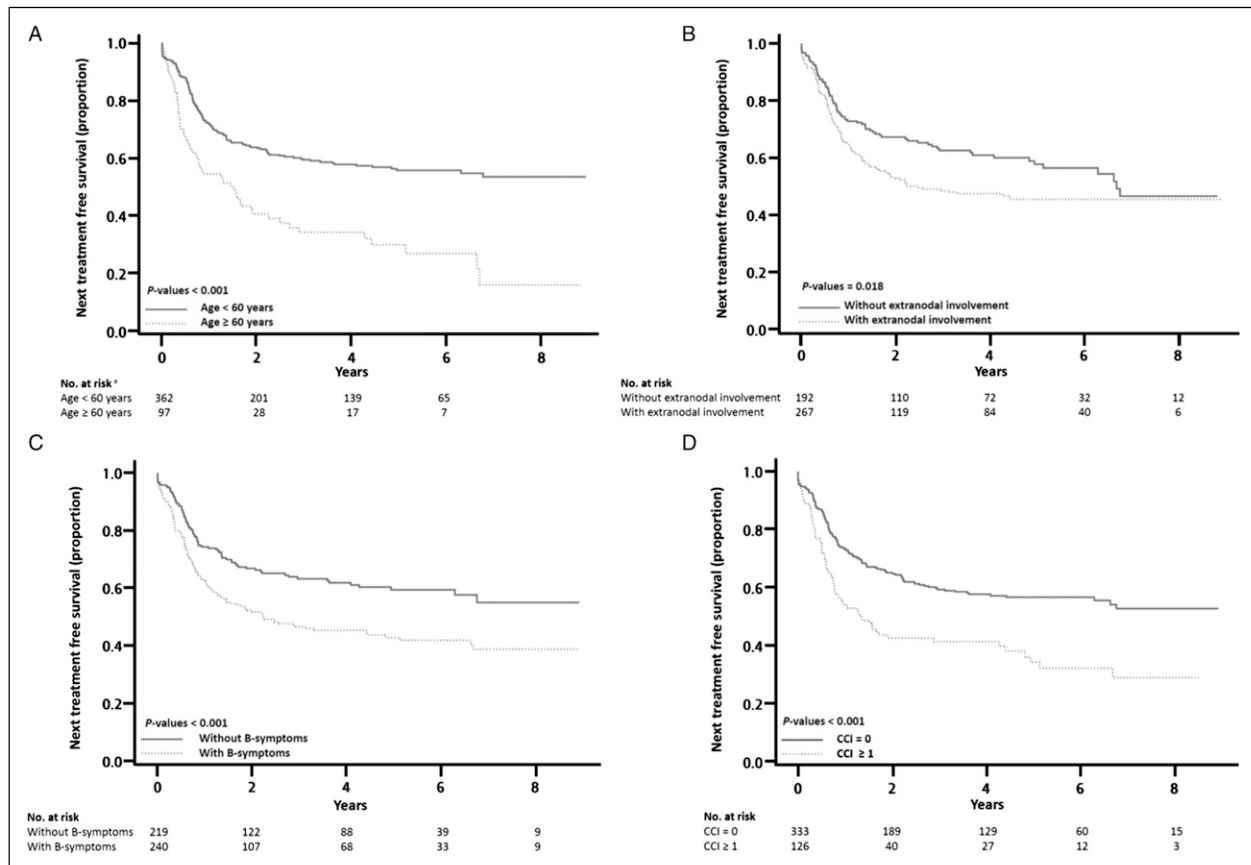


Figure 2. Time to next treatment (TTNT) compared by (A) age, (B) extranodal involvement, (C) B symptoms, and (D) Charlson Comorbidity Index (CCI).^a The exact number at 8 years of follow-up is less than 3 and cannot be provided according to the data privacy regulations.

patients accounted for 62.3% of the population. Extranodal involvement was observed in 58.2% of the patients. Furthermore, B symptoms were identified in 56.6% of patients with available information (Table 1).

Clinical Outcomes

In this real-world, population-based study, 76% of patients remained alive, and 52% were in complete remission after a median follow-up of 4.7 years. The median TTNT was 5.1 years, and the median OS was not reached (Supplementary Figure S1).

Factors Associated With TTNT and OS

In the univariable regression analysis, age ≥ 60 years (HR: 2.08; 95% CI: 1.55-2.79), extranodal involvement (HR: 1.39; 95% CI: 1.06-1.84), B symptoms (HR: 1.67; 95% CI: 1.24-2.25), and CCI ≥ 1 (HR 1.87; 95%CI: 1.42-2.48) were significantly associated with a shorter TTNT. Multivariable regression analysis further validated these results, showing that age ≥ 60 years (adjusted HR [aHR]: 1.73; 95% CI: 1.23-2.43), extranodal involvement (aHR: 1.40; 95% CI: 1.05-1.87), B symptoms (aHR: 1.53; 95% CI: 1.13-2.06), and CCI ≥ 1 (aHR: 1.49; 95% CI: 1.08-2.06) were significantly associated with a shorter TTNT (Table 2). The time-dependent AUROC of the multivariable regression analysis was .65 (Supplementary Figure S2(a)). Figure 2 shows the Kaplan-Meier curves for patients grouped by age, extranodal involvement, B symptoms, and CCI. Patients with age ≥ 60 years ($P < .001$), extranodal involvement ($P = .018$), B symptoms ($P < .001$), and CCI ≥ 1 ($P < .001$) had an inferior TTNT than patients without these factors.

Regarding OS, significant factors in the univariable regression analysis were age ≥ 60 years (HR: 6.06; 95% CI: 4.11-8.95), male sex (HR: 1.59; 95% CI: 1.04-2.44), B

symptoms (HR: 1.75; 95% CI: 1.08-2.83), and CCI ≥ 1 (HR: 3.49; 95%CI: 2.37-5.13). In the multivariable regression analysis, patients with age ≥ 60 years (aHR: 4.55; 95% CI: 2.90-7.15) and CCI ≥ 1 (aHR: 1.86; 95% CI: 1.18-2.91) had a significantly inferior OS (Table 3). The time-dependent AUROC of the multivariable regression analysis was .81 (Supplementary Figure S2(b)). Figure 3 shows the Kaplan-Meier curves for patients grouped by age and CCI. Patients with age ≥ 60 years ($P < .001$) and CCI ≥ 1 ($P < .001$) had a significantly inferior OS compared to patients without these criteria.

Discussion

The present study demonstrated that age ≥ 60 years, extranodal involvement, B symptoms, and CCI ≥ 1 were significant factors

Table 3. Factors associated with an inferior overall survival.

	Univariable Analysis		Multivariable Analysis	
	HR (95% CI)	P-value	Adjusted HR (95% CI)	P-value
Age, years				
<60	Reference		Reference	
≥ 60	6.06 (4.11-8.95)	<.001	4.55 (2.90-7.15)	<.001
Sex				
Female	Reference		Reference	
Male	1.59 (1.04-2.44)	.031	1.24 (.80-1.91)	.330
Extranodal involvement				
No	Reference		Reference	
Yes	1.12 (.76-1.67)	.560	1.30 (.87-1.96)	.205
B-symptoms				
No	Reference		Reference	
Yes	1.75 (1.08-2.83)	.023	1.60 (.99-2.57)	.056
Charlson comorbidity index				
0	Reference		Reference	
≥ 1	3.49 (2.37-5.13)	<.001	1.86 (1.18-2.91)	.007

CI, confidence interval; HR: hazard ratio.

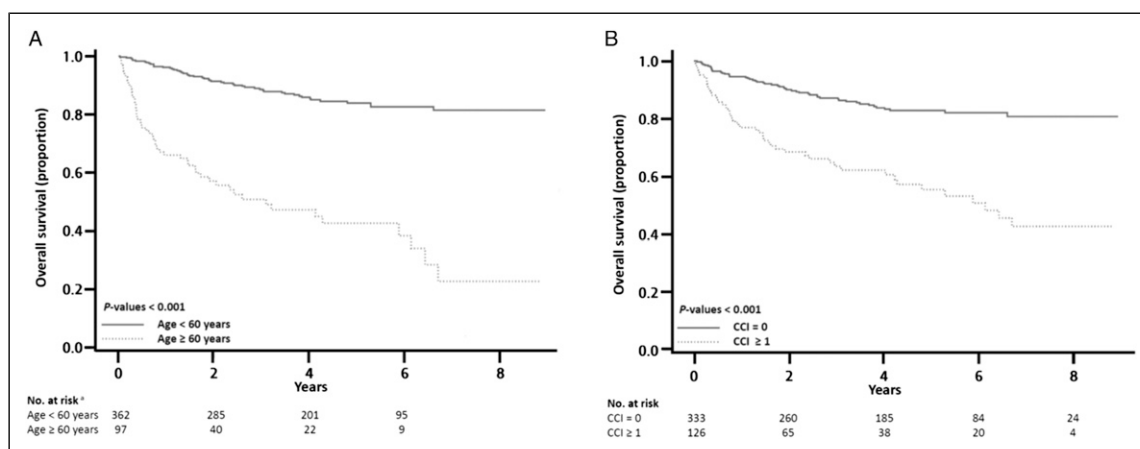


Figure 3. Overall survival (OS) compared by (A) age and (B) Charlson Comorbidity Index (CCI).^a The exact number at 8 years of follow-up is less than 3 and cannot be provided according to the data privacy regulations.

for a shorter TTNT in patients with advanced-stage NDHL who received ABVD or ABVD-like chemotherapies. Importantly, older age and the presence of more comorbidities were substantially associated with an inferior OS in these patients.

Currently, the IPS-3 is widely used to stratify the risks of NDHL.⁹ Besides IPS-3, risk stratification systems containing immune and inflammatory parameters have also been applied to NDHL.¹⁷⁻¹⁹ Different studies have demonstrated the application of CCI for predicting outcomes in various hematologic malignancies. An observational population-based study by Wieringa et al²⁰ showed that CCI ≥ 2 was an independent risk indicator for worse OS in patients with advanced diffuse large B-cell lymphoma undergoing R-CHOP treatment. Because HL is more curable than diffuse large B-cell lymphoma, it is unclear whether CCI could be a prognostic factor for advanced HL treated with ABVD. The current study partially answered this unsolved question, that CCI ≥ 1 was an independent risk factor for an inferior OS in advanced-stage HL.

In addition to CCI scores, our study also showed that age was a dominant factor affecting TTNT and OS in advanced-stage HL. This result was partially supported by a study by Diefenbach et al,⁹ which showed that older age was significantly related to worse OS in HL. However, the data from two Chinese cohorts did not reveal a comparable conclusion, where younger patients with HL did not necessarily have better FFP than elderly patients.^{10,21} Diverse age distribution among different study cohorts could be one explanation for this data discrepancy. Approximately 20% of patients were aged ≥ 60 years in the current study. However, 25% of patients in the study cohort of Yu et al. were aged ≥ 45 years, suggesting that our study cohort comprised more elderly patients than other study populations. Importantly, our study also identified that extranodal involvement was significantly associated with a shorter TTNT. Because of coding issues, our study considered stage IV as extranodal involvement. This could explain our results, which were further validated by other analyses, showing that stage IV was related to worse FFP and OS.^{9,10}

In the past decade, the ECHELON-1 study demonstrated that brentuximab vedotin increased the progression-free survival of advanced-stage NDHL.¹³ In the ECHELON-1 study, the 5-year progression-free survival rate of patients receiving ABVD was as high as 75.3%.¹⁴ However, with a median follow-up of 4.7 years, only 52% of patients in the current study had FFP, revealing that data from clinical trials are usually different to those in real-world settings. This result further raised the hypothesis that patients with advanced-stage NDHL who were older age and had more comorbidities might have benefited from brentuximab vedotin as well, which needs more pieces of evidence to support.

Nevertheless, there were some limitations to this study. First, since we used the nationwide claims database and included all the eligible patients, we did not determine the required sample size before conducting the analysis. A significant limitation was the lack of information regarding

patients' performance status, bulky disease, objective treatment responses, and laboratory results. In addition, missing data on B symptoms were imputed in the present study. Because we could not obtain the laboratory data from the database we used, we could not obtain the IPS-7 and IPS-3 scores. This drawback made a direct comparison of model performance between our model and IPS-7 or IPS-3 impossible. However, the indirect comparison indicated that the significance of our prognostic factors for both TTNT and OS might not be inferior to those of IPS-3. More studies are needed to establish an outcome prediction model for advanced HL that is better than IPS-7 and IPS-3.

Conclusion

In summary, the characteristics and treatment patterns of advanced NDHL in Taiwan were comparable to those in Western countries. Older age, extranodal involvement, B symptoms, and higher CCI were significant factors for a shorter TTNT. Moreover, older age and comorbidities were significantly associated with an inferior OS in patients with advanced-stage NDHL undergoing ABVD or ABVD-like therapy. Patients with these criteria might achieve more clinical benefits with the addition of brentuximab vedotin. However, more pieces of evidence from randomized controlled studies are needed to support this hypothesis.

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Declaration of Conflicting Interests

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Ethical Approval

This study was conducted in accordance with the current version of the Declaration of Helsinki. The Research Ethics Committee of the National Taiwan University Hospital approved the study and agreed to waive the patient informed consent due to its retrospective nature (No. 201901097RIND).

Disclaimer

The interpretation and conclusions contained herein do not represent those of the National Health Insurance Administration or Health and Welfare Data Science Center.

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Supplemental Material

Supplemental material for this article is available online.

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