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Original Article

Prognostic Impact of Age at the Time of Diagnosis in Korean Patients with Diffuse Large B-cell Lymphoma in the Rituximab Era: A Single Institution Study

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Purpose In contrast to the Western diffuse large B-cell lymphoma (DLBCL), prognostic impact of age in a Korean population with DLBCL has not been fully evaluated.

Materials and Methods Six hundred and eight DLBCL patients treated with rituximab-containing chemotherapeutic regimens from January 2002 to March 2012 in Asan Medical Center were enrolled. Survival models using the restricted cubic spine–transformed age variable were constructed to evaluate non-linear relationships between age and survival outcome. Finally, age was categorized according to the conventional international prognostic index (IPI), National Comprehensive Cancer Network (NCCN)-IPI, and Grupo Español de Linfomas/Trasplante Autólogo de Médula Ósea (GELTAMO)-IPI schemes and the prognostic implications were evaluated.

Results The relative hazard did not change significantly during the first to fifth decades, but began to increase exponentially in patients aged over 62 years. This pattern or relationship was also retained in a multivariate model fitted to the age-adjusted IPI and relative dose intensity. Multivariate survival analysis revealed that age > 75 years, but not age > 60 years, was associated independently with poor overall and progression-free survival when the relative dose intensity and age-adjusted IPI were taken into account.

Conclusion The outcome of DLBCL in Korean populations may deteriorate rapidly as age exceeds 62 years. Therefore, a consensus cutoff value for age in Korean DLBCL patients should be determined to better predict prognosis.

Key words Diffuse large B-cell lymphoma, Age, Prognosis, Statistical model

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of aggressive non-Hodgkin lymphoma, accounting for about 30% of cases world-wide [1]. Predicting treatment outcomes at the time of initial treatment is one of the important issues in DLBCL [2]. The conventional international prognostic index (IPI) of DLBCL [3] is widely accepted as a universal prognostic factor. However, because rituximab has led to a marked improvement in outcome for patients with DLBCL [4-6], other prognostic classifiers based on DLBCL populations treated with rituximab (e.g., the NCCN [National Comprehensive Cancer Network]–IPI [7] and GELTAMO [Grupo Español de Linfomas/Trasplante Autólogo de Médula Ósea]–IPI [8]) have been proposed. Although conventional IPI is valid in the rituximab era [9], the validity of these other prognostic systems has not been evaluated fully in Eastern DLBCL populations.

Patient age at the time of diagnosis is a traditional prognostic factor for DLBCL. The conventional IPI classifies patients aged ≥ 60 years as a "poor prognostic group"; however, the cutoff values for the recently proposed classifiers [7,8] are different (Table 1). This may cause confusion when classifying patients as high-risk. Furthermore, the clinical utility of these age cutoffs has not been validated fully in Eastern DLBCL populations. In addition, in spite of the biologic and socioeconomic differences between Eastern and Western populations of patients with DLBCL [10], the relationship between patient age and survival outcome has not been evaluated in Eastern DLBCL populations.

Here, we evaluated the relationship between patient age and the survival outcomes in a single center Korean DLBCL cohort treated with rituximab-containing chemotherapeutic regimens. We also examined the prognostic impact of known age cutoff values.

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Materials and Methods

1. Patients

A total of 613 DLBCL patients treated with rituximab-containing regimens between January 2002 and March 2012 (a dataset identical to that presented in a previous study) [11] were enrolled. In contrast to the previous study, cases with DLBCL variants or those showing DLBCL transformed from low-grade B-cell lymphomas were not excluded. However, of these, five cases with insufficient clinical information, particularly factors related to the IPI or dose of chemotherapeutic agents, were excluded. Finally, 608 cases were enrolled in the study. The medical records of all enrolled patients were reviewed to obtain data related to birth date, sex, Eastern Cooperative Oncology Group performance score, presence B symptoms, involved anatomic site, initial serum lactate dehydrogenase (LDH) titer, and Hans cell-of-origin subgroup [12] evaluated at the time of initial diagnosis. Cases were staged according to Ann Arbor stage [13] and classified according to age-adjusted IPI risk group [3], which could serve as a prognostic group free from the patient age. Patient age was re-calculated based on birth date. The relative dose intensity (RDI) of each chemotherapeutic agent (cyclophosphamide, doxorubicin, or vincristine) was calculated by dividing the actual dose over the actual treatment duration by the standard dose over the standard treatment duration [14]. The average RDI (ARDI) of each patient was then calculated; patients with an ARDI < 85% were assigned as the low-dose intensity group [15].

2. Statistical analysis

The impact of age at the time of diagnosis on survival outcome was estimated using scatterplot smoothing curves between the Martingale residual of the null Cox proportional hazard (PH) model and age (as a continuous variable) [16]. The Cox PH model fitted with the age-adjusted IPI and ARDI < 85% variables was used as a null model for the multivariate setting. These estimates were confirmed using a Cox PH model fitted with the transformed age variable using the restricted cubic spline function [17]. The prognostic significance of age variables categorized according to known cutoff values (such as the conventional IPI [3], NCCN-IPI [7], and GELTAMO-IPI [8]) (Table 1) were evaluated using both univariate Kaplan-Meier survival analysis and multivariate Cox PH models. The statistical procedures described above were also carried out for the DLBCL-NOS (not otherwise indicated) subgroup. All statistical analysis was performed using R ver. 3.6.1 (R foundation for statistical computing, Vienna, Austria). Two-sided p-values < 0.05 were considered statistically significant.

Table 1. Age cutoffs for the conventional IPI, NCCN-IPI, and GELTAMO-IPI

Score	Conventional IPI	NCCN-IPI	GELTAMO-IPI
0	≤ 60	≤ 40	< 65
1	> 60	41-60	65-79
2	-	61-75	≥ 80
3	-	> 75	-

GELTAMO, Grupo Español de. Linfomas/Trasplante Autólogo de Médula Ósea; IPI, International Prognostic Index; NCCN, National Comprehensive Cancer Network.

Results

1. Clinical characteristics of the enrolled patients

The clinical characteristics of the enrolled patients are summarized in Table 2. The mean age was 53.3 years. About one third (32.7%) of patients were aged > 60 years, and 15 (2.5%) were elderly (> 75 years). Only six patients (1.0%) were aged > 80 years. More than 90% (91.9%) of patients were diagnosed with DLBCL-NOS histologically; 26 cases (4.1%) had variants of large B-cell lymphoma, including Epstein-Barr virus–positive large B-cell lymphoma (12 cases), T-cell/histiocyte-rich B-cell lymphoma (seven cases), primary mediastinal B-cell lymphoma (four cases), primary cutaneous large B-cell lymphoma (two cases), and lymphomatoid granulomatosis (one case). Another 23 cases were DLBCL with concurrent low-grade B-cell lymphomas, including extranodal marginal zone B-cell lymphoma (14 cases), high-grade (four cases) or low-grade (three cases) follicular lymphoma, and marginal zone B-cell lymphoma (two cases). About half (49.3%) of cases had advanced disease (Ann Arbor stage III-IV) at the time of the diagnosis, and 47.2% of cases had elevated serum LDH titers. Multiple extranodal site involvement was identified in about one third of patients (31.4%). More than half of cases (50.7%) were classified as low IPI risk. About two thirds of the tumors were classified as non–germinal center B-cell-like subgroup by the Hans immunohistochemical algorithm in available patients (n=402). Almost all patients were treated with an R-CHOP (rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone) regimen; only three patients (0.5%) were treated with an R-CVP (rituximab with cyclophosphamide, vincristine and prednisone) regimen. Due to dose reduction during treatment, about 30% of patients received chemotherapeutic treatment with low ARDI levels (< 85%). Nevertheless, 88.8% of patients achieved complete remission after cessation of initial treatment, and 83.6% attained 3-year survival. On univariate survival analyses, all of the components of the conventional IPI system, pres-

Table 2. Clinical characteristics of the enrolled patients

Characteristic	No. (%) (n=608)	KM p-value (OS)	KM p-value (PFS)
Age, mean±SD (yr)	53.3±14.1	-	-
Age (yr) (conventional IPI)			
≤ 60	409 (67.3)	0.030	0.025
> 60	199 (32.7)		
Age (yr) (NCCN-IPI)			
≤ 40	118 (19.4)	< 0.001	0.002
41-60	291 (47.9)		
61-75	184 (30.3)		
> 75	15 (2.5)		
Age (yr) (GELTAMO-IPI)			
< 65	455 (74.8)	< 0.001	< 0.001
≥ 65 and < 80	147 (24.2)		
≥ 80	6 (1.0)		
Sex			
Male	335 (55.1)	0.915	0.137
Female	273 (44.9)		
Pathologic diagnosis			
DLBCL-NOS	559 (91.9)	0.781	0.558
Variant of DLBCL	26 (4.3)		
DLBCL arising from LGBCL	23 (3.8)		
ECOG PS >1	40 (6.6)	0.004	0.001
Ann Arbor stage III-IV	300 (49.3)	< 0.001	< 0.001
Extranodal involvement > 1 site	191 (31.4)	< 0.001	< 0.001
Serum LDH elevation	287 (47.2)	< 0.001	< 0.001
IPI risk group			
Low	308 (50.7)	< 0.001	< 0.001
Low-intermediate	19 (17.9)		
High-intermediate	121 (19.9)		
High	70 (11.5)		
Age-adjusted IPI risk group			
Low	230 (37.8)	< 0.001	< 0.001
Low-intermediate	164 (27.0)		
High-intermediate	179 (29.4)		
High	35 (5.8)		
Presence of B symptoms	127 (20.9)	< 0.001	< 0.001
Chemotherapy regimen			
R-CHOP	605 (99.5)	0.040	0.153
R-CVP	3 (0.5)		
ARDI < 85%	179 (29.4)	0.017	0.010
Hans cell-of-origin			
GCB	133/402 (33.1)	0.381	0.089
ABC	269/402 (66.9)		
Complete remission	540 (88.8)	-	-
Median follow-up length (mo)	46	-	-
3-Year survival rate	508 (83.6)	-	-

ABC, activated B-cell-like; ARDI, average relative dose intensity; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; GCB, germinal center B-cell-like; GELTAMO, Grupo Español de. Linfomas/Trasplante Autólogo de Médula Ósea; IPI, International Prognostic Index; KM, Kaplan-Meier survival analysis; LDH, lactate dehydrogenase; LGBCL, low-grade B-cell lymphoma; NCCN, National Comprehensive Cancer Network; NOS, not otherwise specified; OS, overall survival; PFS, progression-free survival; PS, performance score; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone; R-CVP, rituximab with cyclophosphamide, vincristine and prednisone; SD, standard deviation.

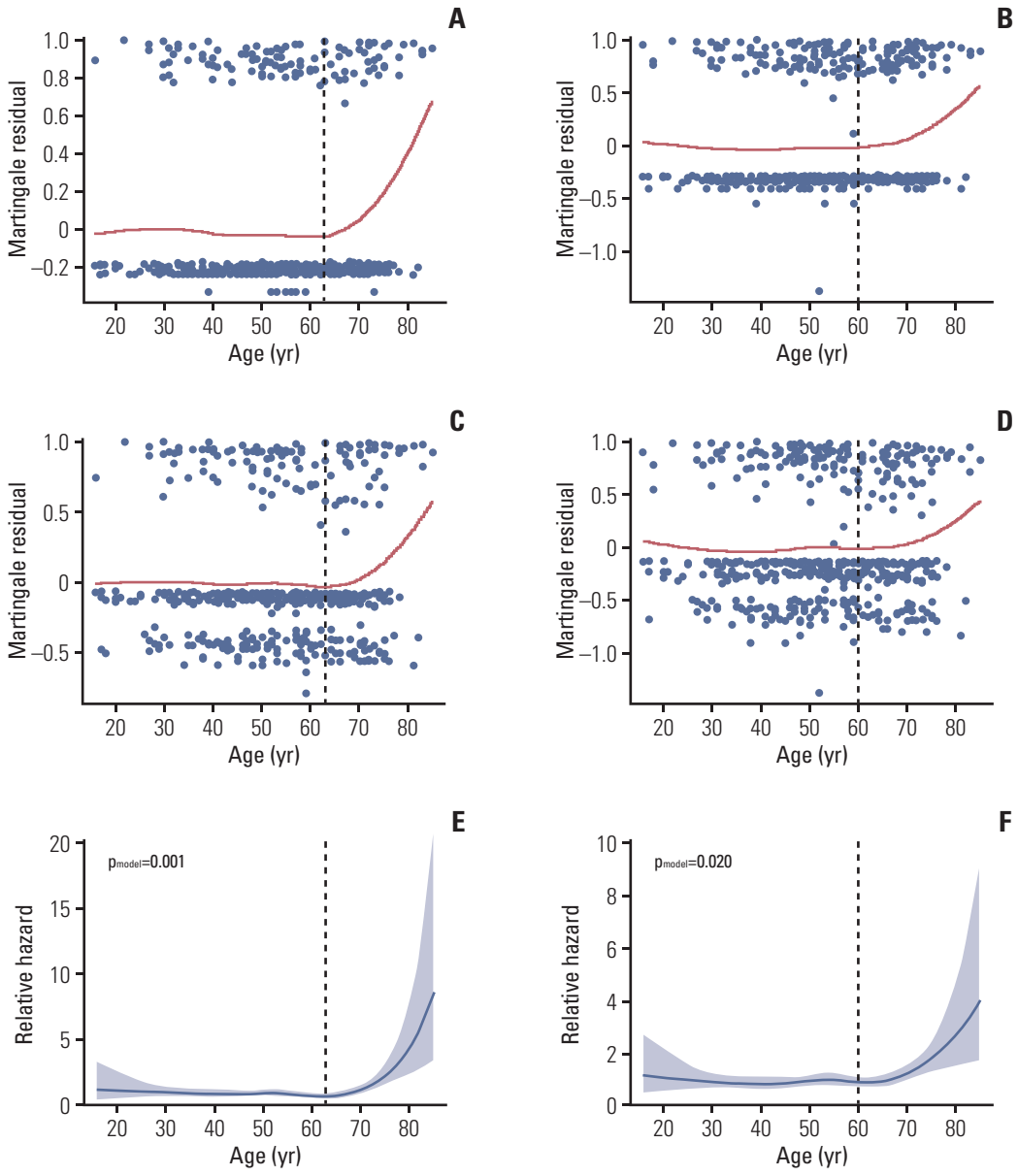

Fig. 1. Relationship between patient age and survival outcome. (A, B) Martingale residual plots from null Cox proportional hazard (PH) models for overall survival (OS) (A) and progression-free survival (PFS) (B), with scatterplot smoothing lines showing a rapid increasing pattern of smoothened Martingale residuals (indicating relative hazards) as age exceeded 62 years. (C, D) Martingale residual plots for multivariate Cox PH models fitted according to age-adjusted international prognostic index, presence of B symptoms, and average relative dose intensity for OS (C) and PFS (D). Plots show scatterplot smoothing lines with similar patterns to those in (A) and (B). (E, F) Univariate relative hazard plots for restricted cubic spline–transformed age variables for OS (E) and PFS (F) displaying the patterns identical to those of the scatterplot smoothing lines shown in (A) and (B). The gray areas denote 95% confidence intervals, and the interrupted vertical lines indicate age of 62 years.

ence of B symptoms, and low ARDI level showed statistically significance. However, the Hans cell-of-origin subgroup did not significantly correlate with survival outcome ($p > 0.05$) (Table 1).

2. Non-linear relationship between patient age and survival outcome

First, we examined the relationship between the age and survival outcome using the Martingale residuals from both null (no predictor included) and multivariate Cox PH mod-

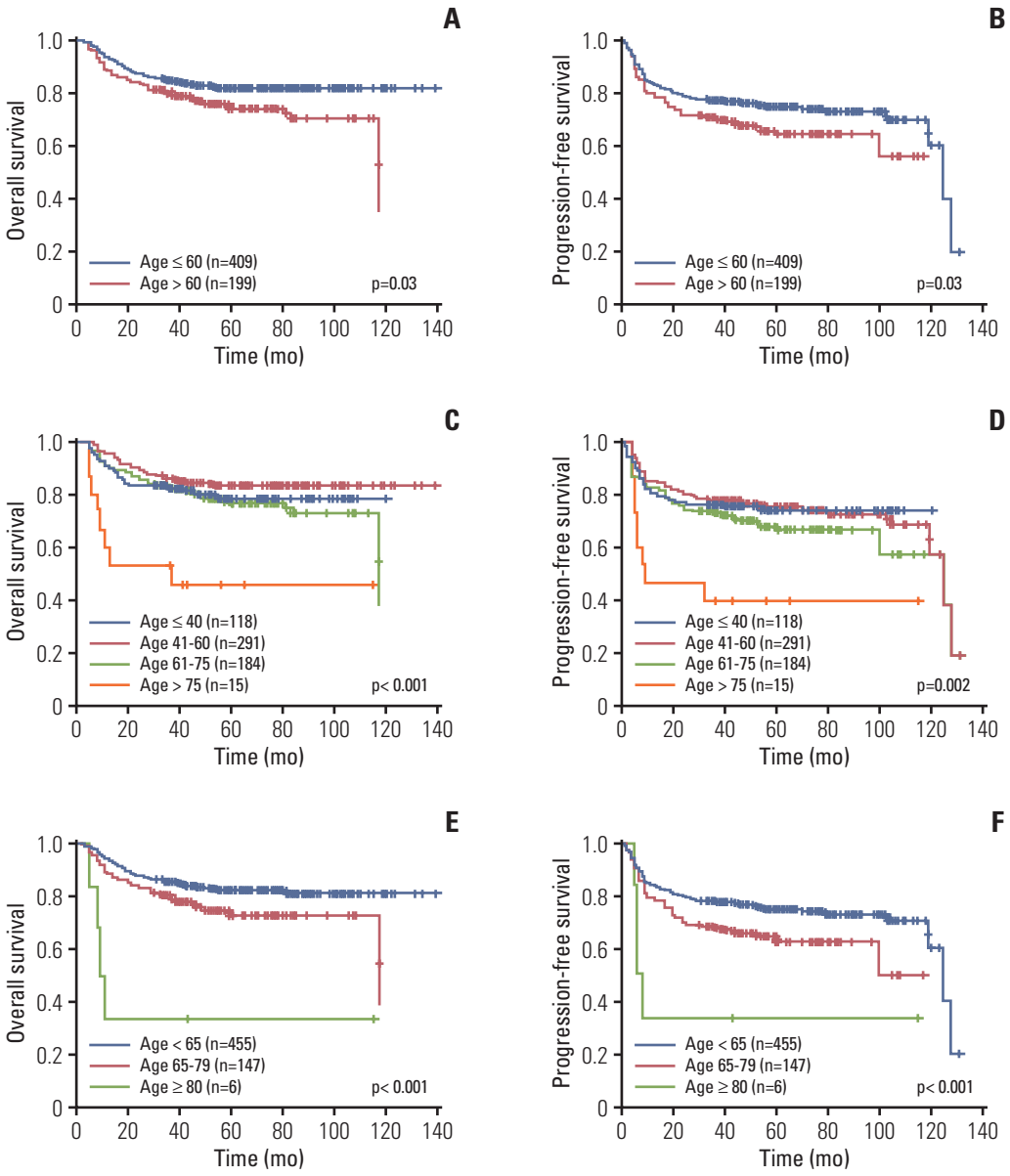

Fig. 2. Kaplan-Meier survival analyses for age variables categorized according to known cutoff criteria. (A, B) Age variables for the conventional IPI. (C, D) Age variables for the NCCN-IPI. (E, F) Age variables for the GELTAMO-IPI. GELTAMO, Grupo Español de Linfomas/Trasplante Autólogo de Médula Ósea; IPI, International Prognostic Index; NCCN, National Comprehensive Cancer Network.

els (Fig. 1A and B). Age-adjusted IPI risk, presence of B symptom, and categorized ARDI variables (less or more than 85%) were included as predictor variables in the multivariate Cox PH models. Scatterplot smoothing lines between the Martingale residuals of the null Cox models and age variables were not significantly different between patients aged up to 62 years. However, when age exceeded 62 years, the Martingale residuals started to increase rapidly and exponentially; which is apparent in the models for overall survival (OS) and progression-free survival (PFS). These relationships were maintained when data was examined using a multivariate Cox model (Fig. 1C and D) and the DLBCL-NOS group (S1A-D Fig.). These findings suggest that the relative hazard increases only for patients aged > 62 years.

The non-linear relationship between the age variable and relative hazard was also evaluated using variable transformation models. The shape of the predicted relative hazard curves (Fig. 1E and F) calculated from the selected models was similar to that of the smoothened curve of the Martingale residual plot (Fig. 1A and B). Also, these relationships were

Table 3. Results of multivariate Cox PH analysis of age variables categorized according to the NCCN-IPI criterion

Parameter	OS			PFS		
	HR	95% CI	p-value	HR	95% CI	p-value
Age-adjusted IPI risk						
Low	1	-	-	1	-	-
Low-intermediate	1.44	0.77-2.71	0.252	1.72	1.08-2.73	0.022
High-intermediate	4.38	2.59-7.43	< 0.001	3.37	2.21-5.15	< 0.001
High	3.67	1.69-7.97	0.001	3.36	1.78-6.33	< 0.001
ARDI < 85%	1.07	0.72-1.61	0.728	1.06	0.75-1.50	0.729
Presence of B symptoms	1.61	1.07-2.41	0.022	1.47	1.04-2.09	0.031
Age (yr)						
≤ 40	1	-	-	1	-	-
41-60	0.76	0.46-1.24	0.271	0.95	0.62-1.45	0.804
61-75	1.00	0.60-1.69	0.989	1.19	0.75-1.87	0.463
> 75	3.11	1.36-7.12	0.007	2.74	1.27-5.92	0.010

ARDI, average relative dose intensity; CI, confidence interval; HR, hazard ratio; IPI, International Prognostic Index; NCCN, National Comprehensive Cancer Network; OS, overall survival; PFS, progression-free survival; PH, proportional hazard.

Table 4. Results of multivariate Cox PH analysis of age variables categorized according to the conventional IPI criterion

Parameter	OS			PFS		
	HR	95% CI	p-value	HR	95% CI	p-value
Age-adjusted IPI risk						
Low	1	-	-	1	-	-
Low-intermediate	1.44	0.77-2.70	0.255	1.71	1.08-2.71	0.023
High-intermediate	4.55	2.68-7.72	< 0.001	3.44	2.25-5.25	< 0.001
High	3.66	1.69-7.94	0.001	3.33	1.77-6.28	0.0002
ARDI						
< 85%	1.10	0.74-1.64	0.650	1.09	0.78-1.53	0.621
Presence of B symptoms	1.54	1.03-2.31	0.037	1.45	1.02-2.06	0.040
Age (yr)						
> 60	1.36	0.92-2.00	0.121	1.33	0.95-1.84	0.092

ARDI, average relative dose intensity; CI, confidence interval; HR, hazard ratio; IPI, International Prognostic Index; OS, overall survival; PFS, progression-free survival; PH, proportional hazard.

reproduced identically in subgroup analysis of the DLBCL-NOS group (S1E and S1F Fig.). Therefore, it can be concluded that the age variable and survival outcome are not linearly correlated; the relative hazard was not significantly different for those aged younger than 62 years, but increased rapidly when the age variable exceeded 62 years.

3. Prognostic significance of categorized age variables according to known cutoff criteria

Finally, we examined the prognostic significance of three known cutoff criteria for age variables: the conventional IPI, the NCCN-IPI, and the GELTAMO-IPI (Table 1). Although all univariate survival analyses of age variables categorized according to the conventional IPI, the NCCN-IPI, and the GELTAMO-IPI schemes were statistically significant both for OS and PFS, only the elderly patient groups (age > 75 or ≥ 80 years) showed markedly inferior survival outcomes (Table 1, Fig. 2A-F), which was also observed in the DLBCL-NOS subgroup (data not shown). In line with this trend, only the patients aged > 75, classified according to the NCCN-IPI criterion, displayed an independently poor survival outcome in multivariate analysis adjusted for age-adjusted IPI and ARDI variables (Table 3). Age variables divided by the cutoffs of conventional IPI and 62 years were non-significant in multivariate analyses; nevertheless, some of the significance levels were borderline (Table 4, S2 Table). In addition, multivariate analysis revealed that age > 80 years, classified according to the GELTAMO-IPI criterion, was statistically significant only

Table 5. Results of multivariate Cox PH analysis of age variables categorized according to the GELTAMO-IPI criterion

Parameter	OS			PFS		
	HR	95% CI	p-value	HR	95% CI	p-value
Age-adjusted IPI risk						
Low	1	-	-	1	-	-
Low-intermediate	1.42	0.76-2.66	0.276	1.68	1.06-2.67	0.028
High-intermediate	4.30	2.53-7.32	< 0.001	3.31	2.16-5.07	< 0.001
High	3.65	1.68-7.91	0.001	3.31	1.76-6.24	< 0.001
ARDI						
< 85%	1.04	0.69-1.57	0.839	1.04	0.74-1.47	0.811
Presence of B symptoms	1.60	1.06-2.41	0.024	1.48	1.04-2.11	0.029
Age (yr)						
< 65	1	-	-	1	-	-
65-79	1.45	0.95-2.21	0.082	1.45	1.02-2.06	0.041
≥ 80	4.14	1.47-11.65	0.007	2.50	0.90-6.92	0.078

ARDI, average relative dose intensity; CI, confidence interval; GELTAMO, Grupo Español de. Linfomas/Trasplante Autólogo de Médula Ósea; HR, hazard ratio; IPI, international prognostic index; OS, overall survival; PFS, progression-free survival; PH, proportional hazard.

for OS but significantly borderline for PFS, which could be attributable to the small number of the patients with > 80 years old (n=6). Interestingly, age 65 to < 80 was statistically significant for PFS, but was significantly borderline for OS (Table 5). These results of multivariate analyses were also recapitulated when the DLBCL-NOS subgroup was subjected to the same analysis (S3-S5 Tables), except that patients > 80 years old were borderline significant for PFS (p=0.086) (S4 Table). Further analyses of the Hans cell-of-origin-available subgroup revealed a significantly poor OS outcome only for patients > 75 years old (p=0.045) (data not shown).

Discussion

In the present study, we showed that the age variable correlated with patient survival in a non-linear fashion in Korean DLBCL patients. The relative hazards for both OS and PFS did not change significantly for patients younger than 62 years; however, they increased rapidly in patients older than 62 years. This pattern was maintained in the multivariate Cox PH model. Accordingly, the age variable categorized according to the conventional IPI cutoff was non-significant in the multivariate Cox PH model. Only age > 75 years, the last-tier category according to the NCCN-IPI, was statistically significant for both OS and PFS in the multivariate Cox model. We found that age ≥ 80 years, the last-tier according to the GELTAMO-IPI, was not significantly associated with PFS in multivariate analysis; this could be attributable to the small sample size of the group (n=6). In other words, known age cutoff values may be of limited value for predicting prognosis in Korean DLBCL patients treated with rituximab-containing agents. These cutoff values need to be re-established taking into account the above non-linear relationship.

Previous Western population-based studies show that survival outcomes for patients with DLBCL deteriorate proportionally as age of onset increases [18,19]. Also, a NCCN-IPI study based on data from large Western multicenter DLBCL cohorts reveals that age of onset is linearly associated with survival outcome [7]. By contrast, a GELTAMO-IPI study based on a large-scale Spanish DLBCL population reported a non-linear relationship between age and patient survival, with changes in the relative hazard noted after age 65 and 79 years [8]. In addition, a previous Korean multicenter study based on a prospective R-CHOP–treated DLBCL cohort showed a proportional increase in the hazard ratio when comparing the four NCCN-IPI age groups; however, the increase in the hazard ratio was significant only for groups aged > 60 years [20], which suggests a non-linear relationship between patient age and survival outcome. Further multicenter studies based on large-scale Korean cohorts will be needed to validate this relationship and establish the appropriate risk stratification criterion for DLBCL patients treated with rituximab.

Patient age is a prognostic factor for various cancers [21-23]. Elderly patients are more likely to encounter adverse drug effects [24]; thus dose adjustment during treatment is more common in older patients with DLBCL [25]. In addition, several biologic features associated with poor prognosis, such as activated B-cell-like subtype [26], BCL2 expression, or cytogenetic complexity [27], are more common in older age groups with DLBCL, which may also contribute to the inferior prognosis for elderly patients. Here, we demonstrated that the relationship between patient age and survival may

be different between Western and Eastern populations with DLBCL. This suggests socioeconomic, pharmacodynamic, and biologic differences between these populations, which will be characterized in further studies.

The present study has several limitations. First, it is based on a retrospective single center cohort; this increases the risk of selection bias and may affect the difference in the prognostic impacts of the variables between the present study and previous studies. Furthermore, patients were not evenly distributed according to decade of age, which could also increase the risk of selection bias. In addition, the study does not reflect the biologic heterogeneity of DLBCL, which could skew the survival outcomes of the different age groups. Nevertheless, the study did take into account the prognostic effects of chemotherapy dose adjustments, which could worsen survival outcomes of elderly patients with DLBCL [28]. Therefore, we believe that the results of the present study help to explain the prognostic effects of patient age on outcomes for DLBCL patients treated with R-CHOP.

In conclusion, the age of Korean DLBCL patients in the rituximab era may correlate with the survival outcome in a non-linear fashion with the rapid increase of relative hazard only in patients aged > 62 years. Because known criteria for classifying age groups may not efficiently reflect this relationship, further large-scale studies will be required to validate the trend and establish an efficient age-based prognostic criterion.

Electronic Supplementary Material

Supplementary materials are available at Cancer Research and Treatment website (https://www.e-crt.org).

Ethical Statement

The study was approved by the Institutional Review Board of Asan Medical Center (2009-0098) with waiver of the informed consent.

Author Contributions

Conceived and designed the analysis: Park CS, Suh C, Huh J, Go H.
Collected the data: Yoon DH, Hwang HS.
Contributed data or analysis tools: Yoon DH, Suh C.
Performed the analysis: Hwang HS, Kim M.
Wrote the paper: Hwang HS.

Conflicts of Interest

Conflicts of interest relevant to this article was not reported.

References

1. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al. WHO classification of tumours of haematopoietic and lymphoid tissues. Revised 4th ed. Lyon: IARC Press; 2017.
2. Vaidya R, Witzig TE. Prognostic factors for diffuse large B-cell lymphoma in the R(X)CHOP era. Ann Oncol. 2014;25:2124-33.
3. International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphoma. N Engl J Med. 1993;329:987-94.
4. Coiffier B, Lepage E, Briere J, Herbrecht R, Tilly H, Bouabdallah R, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med. 2002;346:235-42.
5. Coiffier B, Thieblemont C, Van Den Neste E, Lepeu G, Plantier I, Castaigne S, et al. Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: a study by the Groupe d'Etudes des Lymphomes de l'Adulte. Blood. 2010;116:2040-5.
6. Horvat M, Zadnik V, Juznic Setina T, Boltezar L, Pahole Golicnik J, Novakovic S, et al. Diffuse large B-cell lymphoma: 10 years' real-world clinical experience with rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisolone. Oncol Lett. 2018;15:3602-9.
7. Zhou Z, Sehn LH, Rademaker AW, Gordon LI, Lacasce AS, Crosby-Thompson A, et al. An enhanced International Prognostic Index (NCCN-IPI) for patients with diffuse large B-cell lymphoma treated in the rituximab era. Blood. 2014;123:837-42.
8. Montalban C, Diaz-Lopez A, Dlouhy I, Rovira J, Lopez-Guillermo A, Alonso S, et al. Validation of the NCCN-IPI for diffuse large B-cell lymphoma (DLBCL): the addition of beta2 -microglobulin yields a more accurate GELTAMO-IPI. Br J Haematol. 2017;176:918-28.
9. Sehn LH, Berry B, Chhanabhai M, Fitzgerald C, Gill K, Hoskins P, et al. The revised International Prognostic Index (R-IPI) is a better predictor of outcome than the standard IPI for patients with diffuse large B-cell lymphoma treated with R-CHOP. Blood. 2007;109:1857-61.
10. Chen Y, Han T, Iqbal J, Irons R, Chan WC, Zhu X, et al. Diffuse large B-cell lymphoma in Chinese patients: immunophenotypic and cytogenetic analyses of 124 cases. Am J Clin Pathol. 2010;133:305-13.
11. Hwang HS, Yoon DH, Suh C, Huh J. Body mass index as a prognostic factor in Asian patients treated with chemoimmunotherapy for diffuse large B cell lymphoma, not otherwise specified. Ann Hematol. 2015;94:1655-65.
12. Hans CP, Weisenburger DD, Greiner TC, Gascoyne RD, Delabie J, Ott G, et al. Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. Blood. 2004;103:275-82.

13. Lister TA, Crowther D, Sutcliffe SB, Glatstein E, Canellos GP, Young RC, et al. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. J Clin Oncol. 1989;7:1630-6.
14. Kwak LW, Halpern J, Olshen RA, Horning SJ. Prognostic significance of actual dose intensity in diffuse large-cell lymphoma: results of a tree-structured survival analysis. J Clin Oncol. 1990;8:963-77.
15. Lyman GH, Dale DC, Friedberg J, Crawford J, Fisher RI. Incidence and predictors of low chemotherapy dose-intensity in aggressive non-Hodgkin's lymphoma: a nationwide study. J Clin Oncol. 2004;22:4302-11.
16. Therneau TM, Grambsch PM, Fleming TR. Martingale-based residuals for survival models. Biometrika. 1990;77:147-60.
17. Harrell FE Jr. Regression modeling strategies: with applications to linear models, logistic and ordinal regression, and survival analysis. 2nd ed. New York: Springer; 2015.
18. Castillo JJ, Winer ES, Olszewski AJ. Sites of extranodal involvement are prognostic in patients with diffuse large B-cell lymphoma in the rituximab era: an analysis of the Surveillance, Epidemiology and End Results database. Am J Hematol. 2014;89:310-4.
19. Hedstrom G, Hagberg O, Jerkeman M, Enblad G, Swedish Lymphoma Study G. The impact of age on survival of diffuse large B-cell lymphoma: a population-based study. Acta Oncol. 2015;54:916-23.
20. Hong J, Kim SJ, Chang MH, Kim JA, Kwak JY, Kim JS, et al. Improved prognostic stratification using NCCN- and GELTA-MO-international prognostic index in patients with diffuse large B-cell lymphoma. Oncotarget. 2017;8:92171-82.
21. Chen HL, Zhou MQ, Tian W, Meng KX, He HF. Effect of age on breast cancer patient prognoses: a population-based study using the SEER 18 database. PLoS One. 2016;11:e0165409.
22. Lu CH, Lee SH, Liu KH, Hung YS, Wang CH, Lin YC, et al. Older age impacts on survival outcome in patients receiving curative surgery for solid cancer. Asian J Surg. 2018;41:333-40.
23. Tas F, Ciftci R, Kilic L, Karabulut S. Age is a prognostic factor affecting survival in lung cancer patients. Oncol Lett. 2013;6:1507-13.
24. Balducci L. Pharmacology of antineoplastic medications in older cancer patients. Oncology (Williston Park). 2009;23:78-85.
25. Thieblemont C, Coiffier B. Lymphoma in older patients. J Clin Oncol. 2007;25:1916-23.
26. Mareschal S, Lanic H, Ruminy P, Bastard C, Tilly H, Jardin F. The proportion of activated B-cell like subtype among de novo diffuse large B-cell lymphoma increases with age. Haematologica. 2011;96:1888-90.
27. Klapper W, Kreuz M, Kohler CW, Burkhardt B, Szczepanowski M, Salaverria I, et al. Patient age at diagnosis is associated with the molecular characteristics of diffuse large B-cell lymphoma. Blood. 2012;119:1882-7.
28. Juul MB, Jensen PH, Engberg H, Wehberg S, Dessau-Arp A, Haziri D, et al. Treatment strategies and outcomes in diffuse large B-cell lymphoma among 1011 patients aged 75 years or older: A Danish population-based cohort study. Eur J Cancer. 2018;99:86-96.