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Nomogram model and risk score predicting overall survival and guiding clinical decision in patients with Hodgkin's lymphoma: an observational study using SEER population-based data

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ABSTRACT

Introduction This study developed a prognostic nomogram of Hodgkin lymphoma (HL) for purpose of discussing independent risk factors for HL patients with Surveillance, Epidemiology and End Results (SEER) database.

Methods We collected data of HL patients from 2010 to 2015 from the SEER database and divided it into two cohorts: the training and the verification cohort. Then the univariate and the multivariate Cox regression analyses were conducted in the training, the verification as well as the total cohort, after which the intersection of variables with statistical significance was taken as independent risk factors to establish the nomogram. The predictive ability of the nomogram was validated by the Concordance Index. Additionally, the calibration curve and receiver operating characteristic curve were implemented to evaluate the accuracy and discrimination. Finally, we obtained 1-year, 3-year and 5-year survival rates of HL patients.

Results 10 912 patients were eligible for the study. We discovered that Derived American Joint Committee on Cancer (AJCC) Stage Group, lymphoma subtype, radiotherapy and chemotherapy were four independent risk factors affecting the prognosis of HL patients. The 1-year, 3-year and 5-year survival rates for high-risk patients were 85.4%, 79.9% and 76.0%, respectively. It was confirmed that patients with stage I or II had a better prognosis. Radiotherapy and chemotherapy had a positive impact on HL outcomes. However, patients with lymphocyte-depleted HL were of poor prognosis.

Conclusions The nomogram we constructed could better predict the prognosis of patients with HL. Patients with HL had good long-term outcomes but novel therapies are still in need for fewer complications.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ To find exactly independent risk factors for the prognosis of patients with Hodgkin lymphoma, we conducted univariate and multivariate Cox regression analyses, respectively, in the training cohort, the verification cohort and the total cohort. The intersection of variables with statistical significance of three cohorts was taken as independent risk factors.
⇒ The predictive ability of the nomogram was evaluated by concordance index, calibration curve and receiver operating characteristic curve.
⇒ Though the study was a large-sample observational research based on the Surveillance, Epidemiology and End Results database, the lack of clinical information like details on radiotherapy and chemotherapy caused biases.

INTRODUCTION

Hodgkin lymphoma (HL) is a haematological tumour that originates from B lymphocytes and accounts for merely 10% of lymphoma.[1] According to the American Cancer Society, it is reported that 8480 patients are new cases with HL (4690 males and 3790 females) and 970 of them are dead (570 males and 3790 females).[2] It is common among people aged between 15 and 35 and over 55 years old, which shows a bimodal distribution.[3] HL includes two main subtypes: the more commonly diagnosed classical HL (cHL) and the rare nodular lymphocyte predominant HL. The cHL is subclassified into lymphocyte-rich, lymphocyte-depleted (LD), mixed cellularity (MC) and nodular sclerosis (NS).[4]

In recent decades, advances in HL treatment have remarkably increased the cure rate as well as improved the therapeutic efficacy. Along with the enhancement in survival is the concerns focused on side effects and toxicities of regimens. In order to balance the risks and benefits of various factors for

survival of HL patients, we developed a nomogram with Surveillance, Epidemiology and End Results (SEER) data in this study and compared the predictive ability of it to that of American Joint Committee on Cancer (AJCC) staging system.

METHODS

Data sources

SEER is an authorised database set up by the National Cancer Institute.[5] It records the morbidity and mortality of millions of malignant tumour patients in America, providing abundant data for researchers to carry out studies on cancers in order to spare a large number of patients from the burden of tumours.

Patient selection

58 238 patients diagnosed with HL during 1975–2016 were initially extracted from the SEER database in this study. The codes used to qualify HL patients with subtypes were 9650–9667 according to International Classification of Diseases for Oncology-3. We investigated demographic, pathological and treatment-related variables in SEER, including age, race, sex, site, lymphoma subtype, Derived AJCC Stage Group, RX Summ—Surg Prim Site, RX Summ—Surg Oth Reg/Dis, radiation sequence with surgery, reason no cancer-directed surgery, radiation, chemotherapy, SEER cause-specific death classification, SEER other cause of death classification, sequence number, total number of in situ/malignant tumours for patient, total number of benign/borderline tumours for patient, age at diagnosis and marital status at diagnosis. Survival months and vital status were taken as the outcome variables and collected as well. To predict the prognosis of patients more accurately, we excluded patients with invalid information on all the above variables, and those whose HL was not the first tumour. Finally, 10 912 eligible patients with HL from 2010 to 2015 were included in the total cohort of this study (figure 1).

Statistical analysis

After data cleaning, we randomly divided all the data into two cohorts: the training cohort (n=6004) and the verification cohort (n=4908). Clinical, pathological and therapeutical variables were compared using Pearson χ^2 test between these two cohorts.

In the training cohort, we performed univariate Cox proportional hazards regression analysis on all the candidate variables mentioned above. Significant variables ($p<0.05$) were selected for multivariate Cox proportional hazards regression analysis. The same methods were conducted on the verification cohort and the total cohort respectively. We also got HRs with 95% CIs. In order to obtain variables that affected prognosis of HL patients more probably, we took the common variables with significance of three cohorts in multivariable analysis as independent risk factors.

Based on identified independent risk factors, a nomogram for predicting 1-year, 3-year and 5-year survival rates was constructed in the total cohort. To evaluate the discrimination ability of the nomogram, we recorded the receiver operating characteristic (ROC) curve with the area under ROC curve (AUC)[6] and Harrell's

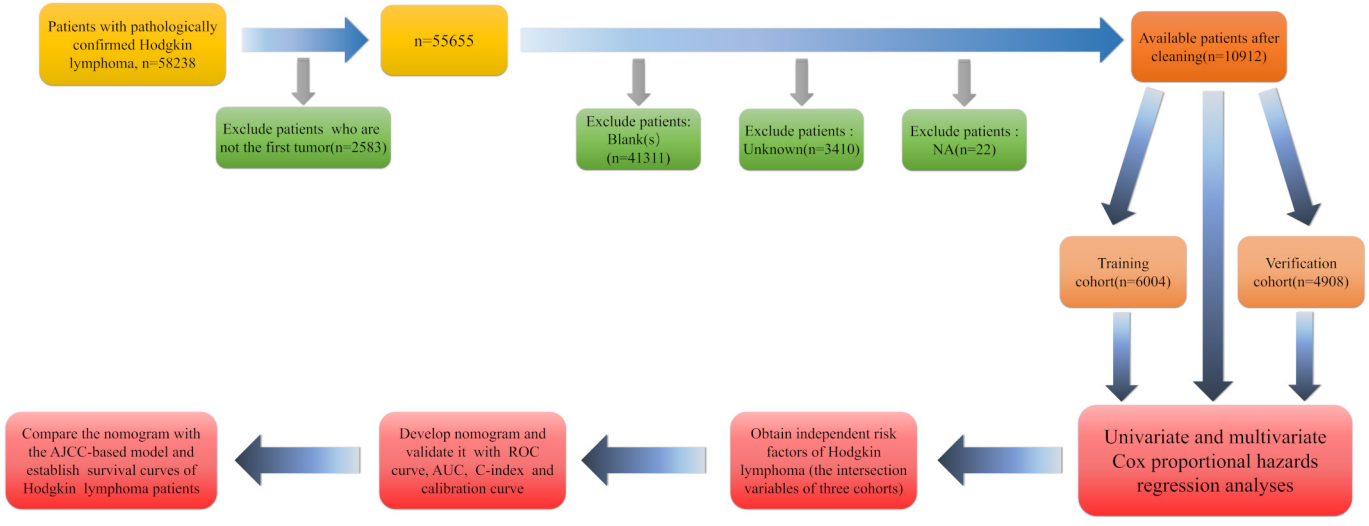

Figure 1 The flow chart of patient selection and statistical analysis. The patients pathologically diagnosed with Hodgkin lymphoma (HL) were extracted from the SEER database. The exclusion criteria were as follows: (1) Hodgkin lymphoma was not the first tumour. (2) Incomplete information on all the variables (blanks, unknown, NA). After patient selection, the remaining part of patients was divided into two cohorts randomly. We conducted the univariate and the multivariate Cox regression analyses in the training cohort, the verification cohort and the total cohort, respectively. The independent risk factors were the intersection of statistically significant variables of three cohorts and a nomogram based on these factors was established to predict the prognosis for Hodgkin lymphoma patients. We validated the new model and compared it with the AJCC-based one. The survival curves were drawn by Kaplan-Meier method. AJCC, American Joint Committee on Cancer; AUC, area under the curve; ROC, receiver operating characteristic; SEER, Surveillance, Epidemiology and End Results.

Table 1 Patient characteristics of Hodgkin lymphoma after data cleaning: SEER 2010–2015

Variable	Total cohort, n=10912				Training cohort, n=6004	Verification cohort, n=4908	P value
	All patients, n=10912	Alive, n=9454	Dead due to Hodgkin lymphoma, n=1024	Dead of other causes, n=434			
Age							0.727
1–14	528 (4.8)	522 (5.5)	6 (0.6)	0 (0.0)	296 (4.9)	232 (4.7)	
15–24	2343 (21.5)	2260 (23.9)	66 (6.4)	17 (3.9)	1322 (22.0)	1021 (20.8)	
25–34	2312 (21.2)	2206 (23.3)	82 (8.0)	24 (5.5)	1246 (20.8)	1066 (21.7)	
35–44	1600 (14.7)	1486 (15.7)	79 (7.7)	35 (8.1)	883 (14.7)	717 (14.6)	
45–54	1418 (13.0)	1227 (13.0)	134 (13.1)	57 (13.1)	780 (13.0)	638 (13.0)	
55–64	1199 (11.0)	943 (10.0)	165 (16.1)	91 (21.0)	652 (10.9)	547 (11.1)	
65+	1512 (13.9)	810 (8.6)	492 (48.0)	210 (48.4)	825 (13.7)	687 (14.0)	
Race							0.283
Black	1455 (13.3)	1235 (13.1)	168 (16.4)	52 (12.0)	773 (12.9)	682 (13.9)	
White	8775 (80.4)	7623 (80.6)	791 (77.2)	361 (83.2)	4850 (80.8)	3925 (80.0)	
Others*	682 (6.3)	596 (6.3)	65 (6.3)	21 (4.8)	381 (6.3)	301 (6.1)	
Sex							0.804
Female	4837 (44.3)	4255 (45.0)	416 (40.6)	166 (38.2)	2655 (44.2)	2182 (44.5)	
Male	6075 (55.7)	5199 (55.0)	608 (59.4)	268 (61.8)	3349 (55.8)	2726 (55.5)	
Site recode ICD-O-3/WHO 2008							0.414
Hodgkin-extra nodal	204 (1.9)	163 (1.7)	29 (2.8)	12 (2.8)	118 (2.0)	86 (1.8)	
Hodgkin-nodal	10708 (98.1)	9291 (98.3)	995 (97.2)	422 (97.2)	5886 (98.0)	4822 (98.2)	
Lymphoma subtype recode/WHO 2008							0.857
Lymphocyte-rich	328 (3.0)	292 (3.1)	25 (2.4)	11 (2.5)	185 (3.1)	143 (2.9)	
Mixed cellularity	1137 (10.4)	931 (9.8)	150 (14.6)	56 (12.9)	643 (10.7)	494 (10.1)	
Lymphocyte-depleted	101 (0.9)	56 (0.6)	32 (3.1)	13 (3.0)	55 (0.9)	46 (0.9)	
Nodular sclerosis	5781 (53.0)	5272 (55.8)	338 (33.0)	171 (39.4)	3159 (52.6)	2622 (53.4)	
Classical HL, NOS	2806 (25.7)	2186 (23.1)	457 (44.6)	163 (37.6)	1538 (25.6)	1268 (25.8)	
Nodular lymphocyte predominant HL	759 (7.0)	717 (7.6)	22 (2.1)	20 (4.6)	424 (7.1)	335 (6.8)	
Derived AJCC Stage Group, seventh ed							0.824
I	1642 (15.0)	1483 (15.7)	86 (8.4)	73 (16.8)	908 (15.1)	734 (15.0)	
II	4471 (41.0)	4164 (44.0)	190 (18.6)	117 (27.0)	2437 (40.6)	2034 (41.4)	
III	2514 (23.0)	2088 (22.1)	309 (30.2)	117 (27.0)	1398 (23.3)	1116 (22.7)	
IV	2285 (20.9)	1719 (18.2)	439 (42.9)	127 (29.3)	1261 (21.0)	1024 (20.9)	
RX Summ—Surg Prim Site (1998+)							0.414
0	8343 (76.5)	7179 (75.9)	832 (81.3)	332 (76.5)	4569 (76.1)	3774 (76.9)	
15–24	37 (0.3)	31 (0.3)	3 (0.3)	3 (0.7)	19 (0.3)	18 (0.4)	
25–29	2104 (19.3)	1876 (19.8)	149 (14.6)	79 (18.2)	1163 (19.4)	941 (19.2)	
30–39	362 (3.3)	322 (3.4)	27 (2.6)	13 (3.0)	213 (3.5)	149 (3.0)	
40–49	19 (0.2)	16 (0.2)	1 (0.1)	2 (0.5)	12 (0.2)	7 (0.1)	
50–59	19 (0.2)	13 (0.1)	4 (0.4)	2 (0.5)	14 (0.2)	5 (0.1)	
60–89,98	28 (0.3)	17 (0.2)	8 (0.8)	3 (0.7)	14 (0.2)	14 (0.3)	
RX Summ—Scope Reg LN Sur (2003+)							0.341
No surgical procedure	10805 (99.0)	9360 (99.0)	1015 (99.1)	430 (99.1)	5950 (99.1)	4855 (98.9)	
Surgical procedure	107 (1.0)	94 (1.0)	9 (0.9)	4 (0.9)	54 (0.9)	53 (1.1)	
Radiation sequence with surgery							0.941
No radiation	10025 (91.9)	8604 (91.0)	1003 (97.9)	418 (96.3)	5517 (91.9)	4508 (91.9)	
Radiation and surgery	887 (8.1)	850 (9.0)	21 (2.1)	16 (3.7)	487 (8.1)	400 (8.1)	
Reason no cancer-directed surgery							0.503
Not recommended	8253 (75.6)	7095 (75.0)	829 (81.0)	329 (75.8)	4515 (75.2)	3738 (76.2)	

Continued

Table 1 Continued

Variable	Total cohort, n=10912						
	All patients, n=10912	Alive, n=9454	Dead due to Hodgkin lymphoma, n=1024	Dead of other causes, n=434	Training cohort, n=6004	Verification cohort, n=4908	P value
Recommended but not performed	113 (1.0)	97 (1.0)	10 (1.0)	6 (1.4)	64 (1.1)	49 (1.0)	
Surgery performed	2546 (23.3)	2262 (23.9)	185 (18.1)	99 (22.8)	1425 (23.7)	1121 (22.8)	
Radiation recode							0.545
No radiation	7689 (70.5))	6386 (67.5)	931 (90.9)	372 (85.7)	4245 (70.7)	3444 (70.2)	
Radiation	3223 (29.5)	3068 (32.5)	93 (9.1)	62 (14.3)	1759 (29.3)	1464 (29.8)	
Chemotherapy recode							0.350
No/unknown	1408 (12.9)	991 (10.5)	308 (30.1)	109 (25.1)	791 (13.2)	617 (12.6)	
Yes	9504 (87.1)	8463 (89.5)	716 (69.9)	325 (74.9)	5213 (86.8)	4291 (87.4)	
SEER cause-specific death classification							0.720
Alive or dead of other cause	9888 (90.6)	/	/	/	5446 (90.7)	4442 (90.5)	
Dead (attributable to this cancer dx)	1024 (9.4)	/	/	/	558 (9.3)	466 (9.5)	
SEER other cause of death classification							0.679
Alive or dead due to cancer	10478 (96.0)	/	/	/	5761 (96.0)	4717 (96.1)	
Dead (attributable to causes other than this cancer dx)	434 (4.0)	/	/	/	243 (4.0)	191 (3.9)	
Sequence no							0.181
One primary only	10461 (95.9)	9108 (96.3)	966 (94.3)	387 (89.2)	5742 (95.6)	4719 (96.1)	
First of two or more primaries	451 (4.1)	346 (3.7)	58 (5.7)	47 (10.8)	262 (4.4)	189 (3.9)	
Total no of in situ/malignant tumours for patient							0.559
1	10526 (96.5)	9168 (97.0)	968 (94.5)	390 (89.9)	5786 (96.4)	4740 (96.6)	
>1	386 (3.5)	286 (3.0)	56 (5.5)	44 (10.1)	218 (3.6)	168 (3.4)	
Total no of benign/borderline tumours for patient							0.856
0	10882 (99.7)	9432 (99.8)	1019 (99.5)	431 (99.3)	5987 (99.7)	4895 (99.7)	
≥1	30 (0.3)	22 (0.2)	5 (0.5)	3 (0.7)	17 (0.3)	13 (0.3)	
Age at diagnosis							0.727
1–14	528 (4.8)	522 (5.5)	6 (0.6)	0 (0.0)	296 (4.9)	232 (4.7)	
15–24	2343 (21.5)	2260 (23.9)	66 (6.4)	17 (3.9)	1322 (22.0)	1021 (20.8)	
25–34	2312 (21.2)	2206 (23.3)	82 (8.0)	24 (5.5)	1246 (20.8)	1066 (21.7)	
35–44	1600 (14.7)	1486 (15.7)	79 (7.7)	35 (8.1)	883 (14.7)	717 (14.6)	
45–54	1418 (13.0)	1227 (13.0)	134 (13.1)	57 (13.1)	780 (13.0)	638 (13.0)	
55–64	1199 (11.0)	943 (10.0)	165 (16.1)	91 (21.0)	652 (10.9)	547 (11.1)	
65+	1512 (13.9)	810 (8.6)	492 (48.0)	210 (48.4)	825 (13.7)	687 (14.0)	
Marital status at diagnosis							0.426
Single	5294 (48.5)	4849 (51.3)	328 (32.0)	117 (27.0)	2905 (48.4)	2389 (48.7)	
Married or partner	4540 (41.6)	3861 (40.8)	482 (47.1)	197 (45.4)	2523 (42.0)	2017 (41.1)	
Separated, divorced or widowed	1078 (9.9)	744 (7.9)	214 (20.9)	120 (27.6)	576 (9.6)	502 (10.2)	

* signifies Asians, Pacific Islanders, and Hispanics
AJCC, American Joint Committee on Cancer; SEER, Surveillance, Epidemiology and End Results.

Concordance Index (C-index). AUC ranged from 0.5 to 1.0. The closer it got to 1.0, the better the nomogram was. We made a comparison between the predictive value of the new model and the one of the AJCC staging model by C-index and the ROC curve. Internal validation was performed under 1000 bootstrap resamples[7] and the calibration curve was generated to compare the predicted outcomes with the observed ones.[8]

Survival curves were generated with Kaplan-Meier (KM) method in the total cohort, followed by the log-rank test. The primary outcome of the study was the overall survival (OS) which was defined as time from diagnosis with HL

Table 2 Univariate and multivariate analysis of factors associated with overall survival in patients with Hodgkin lymphoma in the total cohort

	Univariate analysis				Multivariate analysis		
Variable	**HR**	**95% CI**	**P value**	**SE**	**HR**	**95% CI**	**P value**
Age				0.006			
1–14	1	Reference			1	Reference	
15–24	3.07	1.34 to 7.04	**0.008**		0.48	0.20 to 1.16	0.103
25–34	4.05	1.78 to 9.23	**0.001**		0.48	0.20 to 1.14	0.096
35–44	6.46	2.84 to 14.67	**<0.001**		0.57	0.24 to 1.38	0.213
45–54	12.67	5.62 to 28.55	**<0.001**		0.63	0.26 to 1.50	0.293
55–64	21.11	9.40 to 47.42	**<0.001**		0.64	0.27 to 1.52	0.313
65+	56.01	25.07 to 125.10	**<0.001**		0.65	0.25 to 1.54	0.330
Race				0.006			
Black	1	Reference			1	Reference	
White	0.86	0.75 to 1.00	**0.046**		1.04	0.89 to 1.22	0.589
Others*	0.85	0.66 to 1.08	0.186		1.22	0.94 to 1.58	0.127
Sex				0.007			
Female	1	Reference			1	Reference	
Male	1.22	1.10 to 1.36	**<0.001**		1.02	0.91 to 1.14	0.755
Site recode ICD-O-3/WHO 2008				**0.002**			
Hodgkin-extra nodal	1	Reference			1	Reference	
Hodgkin-nodal	0.62	0.46 to 0.85	**0.003**		0.87	0.59 to 1.28	0.470
Lymphoma subtype recode/WHO 2008				0.007			
Lymphocyte-rich	1	Reference			1	Reference	
Mixed cellularity	1.73	1.21 to 2.46	**0.002**		1.77	1.23 to 2.54	**0.002**
Lymphocyte-depleted	5.17	3.34 to 8.02	**<0.001**		2.18	1.39 to 3.42	**0.001**
Nodular sclerosis	0.80	0.57 to 1.12	0.188		1.33	0.94 to 1.89	0.108
Classical HL, NOS	2.29	1.64 to 3.21	**<0.001**		1.71	1.21 to 2.42	**0.002**
Nodular lymphocyte predominant HL	0.51	0.32 to 0.79	**0.003**		1.36	0.86 to 2.16	0.191
Derived AJCC Stage Group, seventh edition				0.007			
I	1	Reference			1	Reference	
II	0.69	0.57 to 0.84	**0.000**		1.21	0.99 to 1.49	0.060
III	1.85	1.54 to 2.22	**<0.001**		1.47	1.21 to 1.80	**<0.001**
IV	2.91	2.44 to 3.47	**<0.001**		1.53	1.26 to 1.85	**<0.001**
RX Summ—Surg Prim Site (1998+)				0.005			
0	1	Reference			1	Reference	
15–24	1.09	0.49 to 2.44	0.828		0.93	0.09 to 9.18	0.948

Continued

Table 2 Continued

Variable	Univariate analysis				Multivariate analysis		
	HR	95% CI	P value	SE	HR	95% CI	P value
25–29	0.74	0.64 to 0.85	**<0.001**		1.17	0.14 to 9.76	0.883
30–39	0.76	0.55 to 1.04	0.083		0.92	0.11 to 7.94	0.942
40–49	1.19	0.38 to 3.69	0.765		1.18	0.10 to 14.04	0.895
50–59	2.35	1.05 to 5.24	**0.037**		1.51	0.16 to 14.60	0.720
60–89,98	3.43	1.89 to 6.21	**<0.001**		1.49	0.71 to 3.18	0.291
RX Summ–Scope Reg LN Sur (2003+)				0.001			
No surgical procedure	1	Reference			/	/	/
Surgical procedure	0.89	0.51 to 1.53	0.663		/	/	/
Radiation sequence with surgery				0.002			
No radiation	1	Reference			1	Reference	
Radiation and surgery	0.26	0.19 to 0.36	**<0.001**		1.14	0.76 to 1.72	0.521
Reason no cancer-directed surgery				0.005			
Not recommended	1	Reference			1	Reference	
Recommended but not performed	0.89	0.54 to 1.46	0.641		0.65	0.39 to 1.09	0.103
Surgery performed	0.75	0.66 to 0.86	**<0.001**		0.86	0.10 to 7.14	0.889
Radiation recode				0.004			
No radiation	1	Reference			1	Reference	
Radiation	0.25	0.21 to 0.29	**<0.001**		0.51	0.42 to 0.63	**<0.001**
Chemotherapy recode				0.006			
No/unknown	1	Reference			1	Reference	
Yes	0.30	0.27 to 0.34	**<0.001**		0.39	0.34 to 0.44	**<0.001**
SEER cause-specific death classification				0.006			
Alive or dead of other cause	1	Reference			1	Reference	
Dead (attributable to this cancer dx)	63.54	56.36 to 71.64	**<0.001**		1.37×10^{10}	0.00-Inf	0.973
SEER other cause of death classification				0.006			
Alive or dead due to cancer	1	Reference			1	Reference	
Dead (attributable to causes other than this cancer dx)	16.17	14.43 to 18.12	**<0.001**		9.33×10^{9}	0.00-Inf	0.974
Sequence no				0.003			
One primary only	1	Reference			1	Reference	
First of two or more primaries	1.67	1.37 to 2.03	**<0.001**		0.38	0.15 to 0.92	**0.033**
Total no of in situ/malignant tumours for patient				0.003			
1	1	Reference			1	Reference	
>1	1.85	1.51 to 2.27	**<0.001**		1.26	0.50 to 3.15	0.620

Continued

Table 2 Continued

Variable	Univariate analysis				Multivariate analysis		
	HR	95% CI	P value	SE	HR	95% CI	P value
Total no of benign/borderline tumours for patient				0.001			
0	1	Reference			1	Reference	
≥1	2.43	1.21 to 4.87	**0.012**		2.60	1.27 to 5.31	**0.009**
Age at diagnosis				0.006			
1–14	1	Reference			1	Reference	
15–24	3.07	1.34 to 7.04	**0.008**		NA	NA	NA
25–34	4.05	1.78 to 9.23	**0.001**		NA	NA	NA
35–44	6.46	2.84 to 14.67	**<0.001**		NA	NA	NA
45–54	12.67	5.62 to 28.55	**<0.001**		NA	NA	NA
55–64	21.11	9.40 to 47.42	**<0.001**		NA	NA	NA
65+	56.01	25.07 to 125.10	**<0.001**		NA	NA	NA
Marital status at diagnosis				**0.007**			
Single	1	Reference			1	Reference	
Married or partner	1.85	1.64 to 2.08	**<0.001**		0.99	0.86 to 1.14	0.904
Separated, divorced or widowed	4.27	3.70 to 4.92	**<0.001**		0.93	0.78 to 1.10	0.375

* signifies Asians, Pacific Islanders, and Hispanics.
The bold values mean the values < 0.05.
AJCC, American Joint Committee on Cancer; HL, Hodgkin lymphoma; ICD-O-3, International Classification of Diseases for Oncology; NA, not available; NOS, not otherwise specified; SEER, Surveillance, Epidemiology and End Results.

to death due to any cause. We assumed the cause of death was related to HL, so the cause-specific survival (CSS) was time from diagnosis to death of the assumed cause. Patients who were dead of other causes or still alive at the end of the study, were censored at the time of death or the end of follow-up.

All statistical analyses were performed using 'R' software (V.3.5.3) and IBM SPSS statistics V.26. All p values were binary, and p values<0.05 were believed to be statistically significant.

RESULTS

Patient characteristics

The study cohort included 10 912 HL patients diagnosed during 2010–2015 and 9454 of them survived. In the total cohort, HL mostly occurred in young people aged between 15 and 34, accounting for 42.7% in the total cohort. The majority of patients were white (80.4%) and male (55.7%). In addition, single patients (48.5%) were a bit more than married or partnered ones (41.6%), but were about five times more than the divorced, separated or partner-dead (9.9%). Only 204 patients (1.9%) had extranodal diseases. NS was the most common histological type (53.0%), while LD was the least (0.9%). In addition, most cases were diagnosed with AJCC stage II (41.0%), followed by patients of stage III (22.1%). Over half of patients (76.5%) had no surgery of the primary site. 95.9% of HL patients had only one malignant or in situ primary tumour. As for treatment, HL patients hardly underwent regional lymph node surgery (99.0%). Chemotherapy receivers (87.1%) were much more than the radiation ones (29.5%). Radiotherapy combined with surgery was merely applied for a small part of patients (8.1%). About three-quarters (75.6%) did not accept cancer-directed surgery on the grounds that doctors did not recommend it. 1024 (9.4%) deaths were HL-specific and 434 (4.0%) were attributable to other causes, which indicated that the vast majority stayed alive during the follow-up. Other details of clinical and pathological characteristics of the training and verification cohorts were listed in table 1.

Independent risk factors for survival prognosis

Using the univariate and multivariate analyses, we identified statistically significant variables respectively in every cohort. In the training cohort, they were age, lymphoma subtype, Derived AJCC Stage Group, radiation, chemotherapy and sequence number (online supplemental table S1). In the verification cohort, lymphoma subtype, AJCC Stage, RX Summ—Surg Prim Site (1998+), radiation, chemotherapy and total number of in situ/malignant tumours for patient were associated with OS of HL patients (online supplemental table S2). In the total cohort, the significant variables included lymphoma subtype, Derived AJCC Stage Group, radiation, chemotherapy, sequence number, total number of benign/borderline tumours for patient (table 2). The

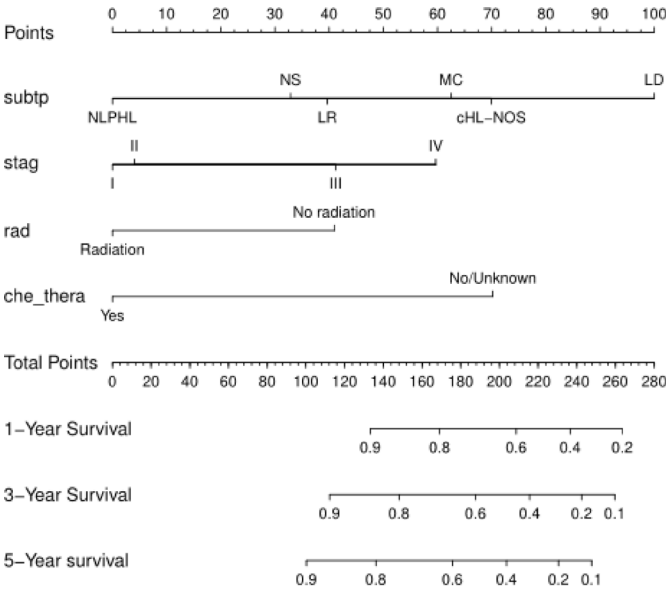

Figure 2 Nomogram for prediction of 1-year, 3-year, 5-year overall survival based on independent risk factors for HL patients. In the nomogram, each level of each variable means a score on the 'points' scale. Add up each score and draw a straight line down to the '1-year survival', '3-year survival', '5-year survival' scale to get corresponding overall survival. cHL-NOS, classical Hodgkin lymphoma not otherwise specified; HL, Hodgkin lymphoma; LR, lymphocyte-rich; LD, lymphocyte-depleted; MC, mixed cellularity; NLPHL, nodular lymphocyte predominant Hodgkin lymphoma; NS, nodular sclerosis.

intersected variables, including lymphoma subtype, Derived AJCC Stage Group, radiation and chemotherapy, were considered as independent risk factors. LD cHL was at the highest risk (HR 2.18, 95% CI 1.39 to 3.42, p=0.001), followed by MC (HR 1.77, 95% CI 1.23 to 2.54, p=0.002) and the cHL not otherwise specified (HR 1.71, 95% CI 1.21 to 2.42, p=0.002). Patients with more advanced AJCC stage had worse OS (stage III: HR 1.47, 95% CI 1.21 to 1.80, p<0.001; stage IV: HR 1.53, 95% CI 1.26 to 1.85, p<0.001). Moreover, radiotherapy (HR 0.51, 95% CI 0.42 to 0.63, p<0.001) and chemotherapy (HR 0.39, 95% CI 0.34 to 0.44, p<0.001) exerted great influences on the improvement of OS in patients with HL (table 2).

The development and validation of the nomogram

Figure 2 presents the nomogram of the total cohort. In the nomogram, each level of variables meant a different score on the 'Points' scale. After getting the sum of each score for each selected variable, we located the total score on the 'Total points' scale and obtained the 1-year, 3-year and 5-year survival rates by drawing a straight line down to the corresponding survival scales.

The C-index of the nomogram was 0.769, higher than that of the AJCC staging model of 0.671. The 1-year, 3-year, 5-year AUC based on our model was 0.778, 0.741, 0.714, proving that it had a better discriminative ability than the traditional model based on AJCC stage (1 year

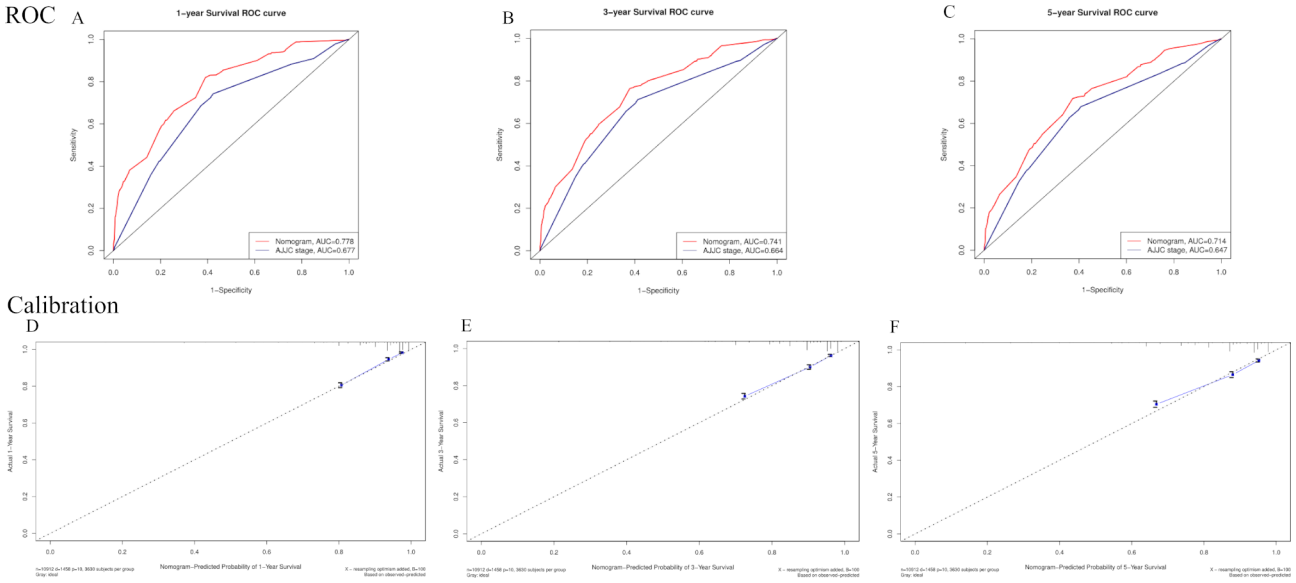

Figure 3 Calibration curves and ROC curves of the total cohort. (A–C) Calibration curves for prediction of 1-year (A), 3-year (B) and 5-year (C) overall survival. The grey dotted line is the standard line and the blue solid line is the calibration line. (D–F) ROC curves of the nomogram and the AJCC staging model for 1-year (D), 3-year (E) and 5-year (F) overall survival. AUC, area under the curve; ROC, receiver operating characteristic curve.

AUC: 0.677, 3year AUC: 0.664, 5year AUC: 0.647) (figure 3A–C). Furthermore, good agreement between the predicted OS and the observed outcomes was showed by the calibration curves of the nomogram (figure 3D–F).

The OS analysis and prognosis

According to the nomogram, KM curves of four independent risk factors (figure 4A–D) and risk score were exhibited (figure 5), respectively. The 1-year, 3-year and 5-year survival rates of the high-risk curve for the total cohort were 85.4%, 79.9% and 76.0%, and the ones of the low-risk curve were 97.5%, 94.9% and 92.5%. LD HL patients had the worst prognosis (figure 4A), whose median survival time was only 71.9 months. The survival time shortened with stage advancing (figure 4B). The 5-year survival rates of stage I, II, III and IV were 88.0%, 91.6%, 80.3% and 71.6% (online supplemental table S3). Patients treated with chemotherapy had a better 5-year survival rate of 86.8% than those without (67.2%) (online supplemental table S3). Patients who underwent radiotherapy (RT) and didn't had 5year OS differences of 86.8% and 80.3% (online supplemental table S3). Other details on 1-year, 3-year and 5-year survival rates of these independent risk factors were showed in online supplemental table S3.

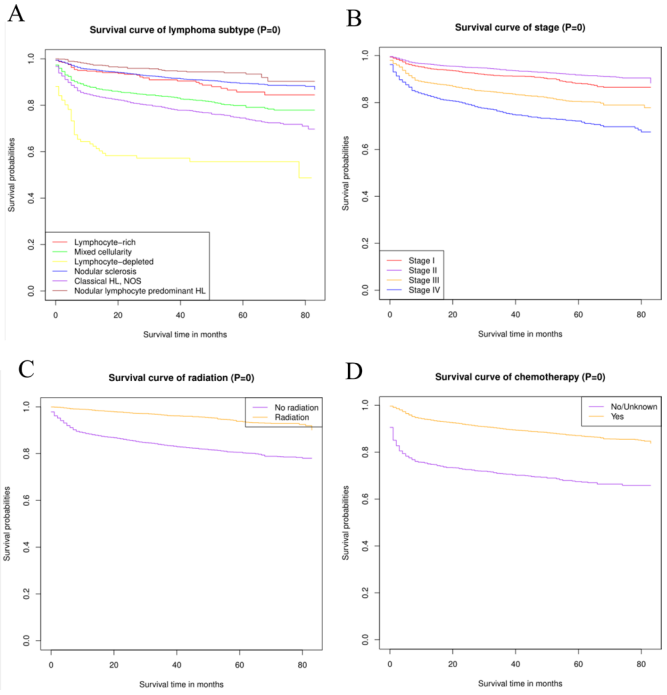

Figure 4 Kaplan-Meier survival curves of the independent risk factors of HL in the total cohort. (A) The survival curve concerning lymphoma subtype and their 1-year, 3-year, 5-year survival rates. (B) The survival curve associated with Derived AJCC Stage Group and their 1-year, 3-year, 5-year survival rates. (C) The radiotherapy-related survival curve and their 1-year, 3-year, 5-year survival rates. (D) The survival curve in relationship with chemotherapy and their 1-year, 3-year, 5-year survival rates. HL, Hodgkin lymphoma; NOS, not otherwise specified.

DISCUSSION

HL is an uncommon type of lymphoma, also one of the most prevalent malignant tumours in the young.[9 10] With enhanced modern therapy these years, the cure rate of HL has exceeded 80%. Though the AJCC staging system is of great use in evaluating the prognosis in HL patients, it is not so comprehensive

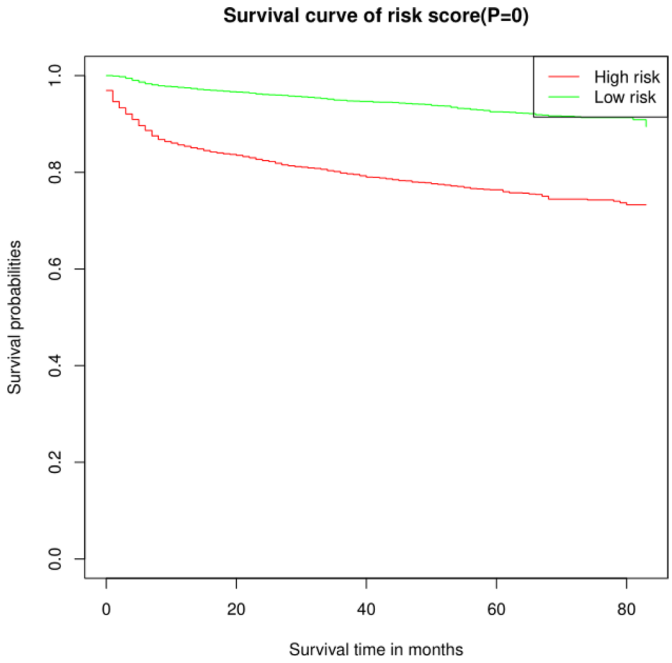

Figure 5 Kaplan-Meier survival curves of risk score of the total cohort. The survival curve of the risk score of the total cohort. The 1-year, 3-year, 5-year survival rates of high risk are respectively 86.3%, 81.0%, 77.3% and the low-risk survival rates are 97.9%, 95.6%, 93.3%, respectively.

for neglecting some factors, such as sex, race, histological subtypes. In our study, we investigated a variety of factors and lymphoma subtype, Derived AJCC Stage Group, radiation and chemotherapy were found to be predictive for OS of HL patients. The nomogram based on these independent risk factors were confirmed to make more accurate predictions compared with the AJCC staging-based model.

The demographics in our study were similar with other previous reports.[11] The incidence pattern was bimodal with the first peak in adolescents and young adults aged 15–34 and the second one in the elderly over 65 years old.[12 13] But elderly patients tend to have a higher morality than the young,[14 15] which is associated with increased comorbidities and reduced tolerance with full chemotherapy treatment. Son *et al* found that age was in connection with treatments, indicating that factors such as hospice care as well as shared decision-making played a role in treating older patients.[16] There was little difference between male and female patients in our study, but male sex was considered as one risk factor in International Prognostic Score (IPS) system.

Among all subtypes of HL, lymphocyte depletion patients in our study cohort had the worst prognosis with the lowest incidence, whereas NS patients had a higher incidence but a better survival. It is reported that lymphocyte depletion is mostly found in the elderly and the HIV infected with an association to their weak immune system, while NS is more frequent in adolescents and young adults.[17]

Up to now, HL subtypes has not translated into verified treatments. In most cases, it is the stage of this disease that determines what therapy patients will receive. Derived AJCC Stage Group is derived from Ann Arbour staging but with more details about involved areas. We observed that advanced AJCC staging led to worse OS, which was expected as stage III extended binary lymph nodes of diaphragm or the spleen and stage IV disseminated extranodal areas.[12]

With an increasing cure rate, people begin to centre their concerns around the treatment-associated toxicity. How to balance the benefit and risk of treatments is a critical problem. In our study cohort, both RT and chemotherapy benefited patients as they increased 5 year OS by 10% at least. Most early-stage patients are treated with chemotherapy combined with involved-field RT (IFRT), while those with advanced HL receive chemotherapy only, which is the general rule in HL therapy. It has been widely accepted that the standard treatment for low-risk patients with early-stage disease is two-cycle ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) followed by 20 Gy IFRT.[18 19] It is based on the favourable prognosis for the HD10 trial performed by the GHSG. The study divided patients into four groups, and each group was given either two or four cycles of ABVD and 20 or 30 Gy IFRT. It showed little difference between the groups with their progression-free survival (PFS) and OS.[20] Both EORTC H10 trial[21] and British RAPID trial[22] found that omitting RT for I/II cHL with negative PET findings led to increased recurrence rate within 2 years. In the GHSG HD16 trial, among patients with negative PET scans, the 5 years PFS of the radiotherapy given was 93.4%, while the one of those without RT was 86.1%, which showed inferiority of RT omission.[23] Consistent with these trials, the latest NCCN clinical practice guidelines recommend the combined modality therapy to early stage favourable HL.[24] With more widespread use of PET scans, response-adapted therapy has developed soon, bringing challenges to the role of RT. Totadri *et al* found that PET-CT guided regimen improved OS of early-stage cHL patients under 18 years old and suggested that those who achieved metabolic remission on interim PET had no need to receive RT.[25] In all of these trials, patients with early-stage favourable HL did have excellent outcomes regardless of RT, so it seemed that OS were not so easily affected by some small reduction in treatment. Physicians can optimise the therapy according to treatment goals and individual characteristics of patients.

For stage I/II with high risk, HD14 proved that patients could reduce recurrence when receiving 2-cycle escalated BEACOPP (eBEACOPP) (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone) combined with two-cycle ABVD compared with four-cycle ABVD.[26] But it caused more adverse effects at the same time. Advanced HL can choose ABVD or BEACOPP as their first-line treatment. HD9 found that the eBEACOPP was significantly more effective than chronic obstructive pulmonary disease (COPP) or adriamycin,

bleomycin, vinblastine, dacarbazine (ABVD) in OS and in the control of early progression, but it induced more long-term complications such as haematology diseases and infection.[27] Such results were also approved by SWOG S0816.[28 29] RT is seldom included in the advanced treatment and its efficacy in advanced HL is in debate. A seer analysis reported that RT improved 5-year OS (5 year OS 87.5% with RT vs 69.6% without RT) and CSS (5-year CSS 92.8% with RT compared with 83.7% without RT) for stage III patients, which disagreed with RT omission for all advanced patients.[11] Another study also supported the role of consolidative RT for those with advanced disease as an improved OS was observed in patients receiving RT at 25 years after diagnosis (60.8% with RT vs 53.2% without RT).[15] Opposite with the former, Italian HD0607 noted that IIB-IVB patients had no PFS benefit from six-cycle ABVD followed by 30 Gy RT compared with those given chemotherapy (97% vs 93%).[30]

In summary, chemotherapy acts as an essential part of treatment in all stage favourable or unfavourable HL, while the role of RT, including its dose and field sizes, still needs ongoing researches for different stage HL. Up to now, interim positron emission tomography (PET) scan has been a good predictor for therapy adjustment to gain as much survival benefit as possible.[31]

Nevertheless, both RT and chemotherapy result in complications. Not only does RT cause damage to reproductive system[32] but also cardiovascular diseases[33] and radiation enteritis.[34] Chemotherapy often leads to pulmonary toxicity[35] and haematological diseases. The risk of secondary malignancies rises as well.[36 37] Therefore, new tactics with less long-term complications and side effects are quite in need. The checkpoint inhibitor PD-1, a monoclonal antibody, has opened a new chapter for the first-line treatment of HL. NIVAHL trial indicated that nivolumab combined with AVD (bleomycin omitted) made early stage HL patients with unfavourable prognosis gain a better complete response rate of 90%.[38] Nivolumab combined with AVD utilised in CheckMate 205 exhibited good efficacy in advanced cHL with an objective response rate of 86% and complete metabolic response (CMR) rate of 76%.[39] Brentuximab vedotin (BV) is an antibody-drug conjugate targeted at CD30.[40] The latest follow-up results of ECHELON-1 suggested that compared with ABVD, the six-cycle BV-AVD (doxorubicin, vinblastine and dacarbazine in combination with BV) enhanced the 3-year PFS for III/IV patients, decreasing the pulmonary toxicity of chemotherapy.[41 42] The subgroup results showed that BV-AVD was also recommended to adolescents and young adults.[43] Another phase II trial conducted by GHSG developed two new regimens based on the combination of escalated BEACOPP with BV. One was BrECADD (BV, etoposide, cyclophosphamide, doxorubicin, procarbazine, prednisone) and the other was BrECAPP (BV, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone). Both were feasible.[44]

Researches on incorporation of new agents are underway now. Relapsed or refractory cHL patients aged 5–30 years old received Nivolumab plus BV and Bendamustine in CheckMate 744 (NCT02927769). The CMR was 88%. Such favourable outcome was observed among high-risk HL patients after first relapse.[45] However, phase II BRAPP2 (NCT02298283) illustrated that the use of BV in consolidation therapy induced more adverse events. In general, immunotherapy is promising and powerful in the future.

The traditional prognostic model based on the AJCC stage has been widely accepted for many years, but it is limited for not taking some significant risk factors such as age, sex and marital status into consideration. Different with it, the nomogram is based on a variety of risk factors, trying to better understand the influence of each factor and prognosis for HL. The new model indeed has a proven discrimination by the C-index and ROC analysis with AUC.

Though this study is population based, defects are inevitable. First, details on treatment and prognosis are unavailable in the SEER database, such as dose, fractionation, field size and location of RT, specifics of chemotherapy administration, erythrocyte sedimentation rate, bulky disease. IPS is not available as well, which is critical and widely used for predictions of advanced HL. Moreover, relevant imaging examination information like PET scans is not in record. If information regarding to patients' performance and tumour burden can be combined with the interim assessment reflecting treatment insensitivity, it is more likely to predict exact OS for HL patients. Second, the investigated variables are uncorrelated with this disease from molecular level, which are not so sensitive as baseline metabolic tumour volume,[46] circulating tumour DNA,[47 48] tumour-associated macrophages[49 50] and other characteristics of tumours. Third, it is possible to miss truly predictive variables by the univariate Cox regression analysis prior to the multivariate analysis, because the univariate analysis is unable to eliminate the effect of confounding factors. Besides, the nomogram is only validated internally but not externally due to lack of data extracted from other databases.

Given the discussion above, early-stage HL is now highly curable in most patients. According to the results of our study, histological subtypes, AJCC stage and the utilisation of chemotherapy and RT are concerned with the OS benefit. Compared with the traditional AJCC staging model, the nomogram constructed in this study is more comprehensive and discriminative despite of some limitations. The aim in the future includes reduction of long-term toxicity as well as individualisation of treatments. To achieve this goal, it is essential to find more representative and easily monitored markers combined with conventional factors for therapeutic risk stratification as well as refinement of patient selection. A dynamic prognosis system based on combination of these factors and mutation characteristics of tumour cells will be of great help as well.

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Ethics approval This study involves human participants and was approved by The work was approved by the Guangdong Medical University Ethics committee, and in accordance with the Declaration of Helsinki of the World Medical Association. Informed consent forms are not required for patient data extracted from the SEER database. Participants gave informed consent to participate in the study before taking part.

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