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Risk and outcome of second primary malignancy in patients with classical Hodgkin lymphoma

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Abstract

Background: Hodgkin lymphoma survivors demonstrated increased risk of secondary primary malignancies (SPMs), but comprehensive analysis of the risk and outcome of SPMs in classical Hodgkin lymphoma (cHL) patients has not yet been reported.

Methods: Patients with cHL from 1975 to 2017 were identified from the Surveillance, Epidemiology and End Results (SEER) database. Standardized incidence ratios were calculated for the risk of solid and hematologic SPMs in cHL patients compared to the general population. The outcome of cHL patients developing SPMs were assessed by performing survival, competing risks regression, and cox proportional regression analyses.

Results: In a follow-up of 26,493 cHL survivors for 365,156 person years, 3866 (14.59%) secondary cancers were identified, with an standardized incidence ratio of 2.09 (95% CI: 2.02–2.15). The increased risk was still notable after follow-up of 10 years or more, and the risk is more pronounced for patients with female gender, younger age, advanced stage, chemotherapy, and radiation therapy. The overall survival is worse for cHL patients with SPMs after 11 years of follow-up ($P < .0001$). The main cause of death for cHL patients with SPMs is not cHL but other causes including SPMs. Multivariate Cox regression analysis confirmed SPMs as an independently adverse prognostic factor for cHL survivors (hazard ratio, 1.13; 95% CI, 1.05–1.21, $P = .001$).

Conclusions: There is a significantly increased risk of developing SPMs for cHL survivors. The overall survival is worse for cHL patients and SPMs is an independent prognostic factor for cHL.

Abbreviations: AER = absolute excess risk, cHL = classical Hodgkin Lymphoma, CI = confidence interval, HR = hazards ratio; MP-SIR = multiple primary standardized incidence ratio, PSM = propensity score matching, SEER = Surveillance, Epidemiology, and End Results, SIR = standardized incidence ratio, SPMs = second primary malignancies.

Keywords: classical Hodgkin lymphoma, outcome, second primary malignancies, SEER, SIR

1. Introduction

Classical Hodgkin lymphoma (cHL) is a relatively rare type of malignancy with an incidence of 2 to 3 cases per 100,000 people per year in western populations,[1] but it is one of the more frequent lymphomas that accounts for 15% to 25% of all lymphomas and approximately 95% of Hodgkin lymphoma.[2] Some studies have shown that Epstein–Barr virus infection could be related to 25 to 40% of cHL cases; however, there are no clearly defined risk factors for the cause and development of cHL.[3] The pathologic hallmark of cHL is the presence of the characteristic multinucleated giant Hodgkin and Reed-Sternberg cells within the inflammatory including B lymphocytes, T lymphocytes, eosinophils, and macrophages.[4] Epidemiology research showed that cHL has a bimodal age distribution with a first peak in patients at the age of 20 to 30 years and a second peak in patients older than 55 years.[5,6] cHLs are histologically heterogenous and are generally subclassified into 4 subgroups: lymphocyte-rich, lymphocyte-depleted classical Hodgkin lymphoma, nodular sclerosis classical Hodgkin lymphoma, and mixed cellularity classical Hodgkin lymphoma.[7] Nodular sclerosis classical Hodgkin lymphoma is the most common histological subtype of cHL, comprising up to 70% of all cHL cases and is mostly frequent in young adults with the peak incidence at 15 to 35 years of age.[8] Lymphocyte-depleted classical Hodgkin lymphoma is the rarest subtype, comprising less than 1% of cHL cases.[9] Mixed cellularity classical Hodgkin lymphoma accounts for about 15 to 30% of cHL cases and is mostly found in adult patients older than 55 years of age, and it is reported with an association to infection of Epstein–Barr virus.[10] Lymphocyte-rich classical Hodgkin lymphoma is an uncommon subtype of cHL, making up about 5% of all CHL cases.[9]

cHL is generally viewed as a highly curable cancer with standard first-line chemotherapy and radiotherapy in some

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The datasets generated during and/or analyzed during the current study are publicly available.

The data analyzed in this study are from the SEER database (https://seer.cancer.gov/) that are available to the public.

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cases.[11] Advances in therapeutic armamentarium for patients with cHL has significantly increased the cure rates, reaching 90%.[12] Long-term follow-up of Hodgkin lymphoma survivors demonstrated increased risk of secondary primary malignancies (SPMs), which now stand for one of the most important late morbidity.[13–15] To our knowledge, however, comprehensive analysis of the risk of SPMs in cHL survivors has not yet been reported. Furthermore, there is a lack of information on the outcome of SPMs diagnosed in patients with cHL. In this study, we investigated the risk of SPMs development specifically in cHL patients as compared to the general population using the national Cancer Institute's Surveillance, Epidemiology and End Results (SEER) database. We also evaluated the SPMs incidence based on age, gender, race, stage, and subtype of cHL cases. Furthermore, we explored the impact of SPMs occurrence on the prognosis of cHL patients.

2. Materials and Methods

2.1. Data source

The SEER Program of the National Cancer Institute (NCI) is a reliable source of cancer incidence and survival data that covers around 35% of the population in the United States.[16] The SEER*Stat software (version 8.3.9.1; NCI, Bethesda, MD) was used to obtain the data.[17] Using the US population-based SEER 9 Registry Custom Data, Nov 2019 Sub (1975–2017), which covers approximately 9.4% of the US population (based on 2010 census) from 5 states (Connecticut, Hawaii, Iowa, New Mexico, and Utah) and 4 metropolitan areas (Detroit, Atlanta, San Francisco-Oakland, and Seattle-Puget Sound), cHL patients diagnosed from January 1975 to December 2017 were selected. The cHL cases were identified according to the Lymphoma Subtype Recode/WHO 2008, which is updated for Hematopoietic codes on the basis of the World Health Organization (WHO) International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3), and the WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues (2008). The cHL pathologic subtypes include lymphocyte-rich cHL, mixed cellularity cHL, lymphocyte depleted cHL, nodular sclerosing cHL, and cHL not otherwise specified. Cases diagnosed during an autopsy and those who were lost to follow-up were excluded. Cases with only known age (censored at age 89 years) and only malignant behavior were selected. SPMs was defined as a metachronous malignancy that developed at least 6 months after diagnosis of cHL. The multiple primary standardized incidence ratio (MP-SIR) session with the statistic of "SIR Tables" of in the SEER*Stat software was used to calculate the SIR of SPMs for cHL survivors, which is a commonly used methodology recommended by the SEER rules to ascertain SPMs.[18,19] SIR measures the relative risk of 2 cancers, it was calculated as the ratio of the observed (O) number of second cancer cases in the study group and the expected (E) number of second cancer cases in the general population.[20] Absolute excess risk (AER) is an absolute measure of the clinical burden of the additional cancer occurrence in the study population.[20] It is reported as the number of excess events per 10,000 person per year, and is calculated as: ((Observed count – Expected count) * 10,000)/Person years at risk. Kruskal–Wallis and Wilcoxon rank sum tests were used to compare the differences in the time to the development of a SPMs based on the different cancer types. The confidence intervals (CIs) at the 95% level for SIRs were calculated with the exact method. We also calculated SIRs for solid tumors and hematologic malignancies with respect to the latency from the index cHL diagnosis (6-11, 12-59, 60–119, and 120 + months). Using the same population, the "MP-SIR session" with the statistic of "Case Listing" in the SEER*Stat software was applied to extract the case-level data on patients' demographic profile including age, gender, race, year of diagnosis, subtype, Ann Arbor Stage, vital status, survival months, cause-specific death classification, cause of death to site, primary site, sequence number, first malignant primary indicator, total number of in situ/malignant tumors for patient, chemotherapy recode, and radiation recode. The first primary cHL was determined by using the SEER variable "First Malignant Primary Indicator" with "Yes." Then cHL with SPMs was defined by using the variable "Sequence number" with "1st of 2 or more primaries," and cHL without SPMs was defined by using the variable "Sequence number" with "One primary only." The factor of age was categorized into 3 groups: < 20 years old, 20–59 years old, and 60 + years old. The stage information for cHL is according to the Ann Arbor staging system,[21] the Ann Arbor Stage I and II were combined as "Stage Early," and the Ann Arbor Stage III and Stage IV were combined as "Stage Advanced." Cause-of-death information was taken from the "SEER cause-specific death classification" field in the SEER data. Overall survival time was calculated from date of cHL diagnosis to death or last follow up. The final data was summarized in Supplemental Digital Content (Table S1, http://links.lww.com/MD/H999). The requirement of ethical approval was not needed since all the SEER data used in the present study are publicly available, and it had not any interaction with human participants or reidentification of individuals.

2.2. Propensity score matching

To minimize the bias effect of potential confounders on selection bias, propensity score matching (PSM) was carried out by using the R "MatchIt" package v4.1.0,[22] the "nearest neighbor matching" method and "glm (generalized linear model)" distance without replacement were chosen. Since the Ann Arbor Stage is blank if the "Year of diagnosis" is prior to 1983 or after 2015 in the SEER database, which will bias the results, the stage of "Blank(s)" were excluded. The covariates of age, race, sex, stage, subtype, chemotherapy, and radiotherapy for cHL were incorporated into matching analysis with the ration of 1:2 to balance differences in baseline clinical characteristics between cHL cases with or without SPMs, yielding a group of 2327 cHL subjects with SPMs and a group of 4654 subjects without SPMs. The characteristics of the matched variables between the 2 groups were comparable (Table 3). Covariate balance was assessed using the method of standardized differences, which is a preferred method of hypothesis testing as the standardized difference does not depend on sample size and a value of the standardized difference < 10% is desirable.[23] As shown in Supplemental Digital Content (Figure S1, http://links.lww.com/MD/H1000), the standardized mean differences of the matched variables in the matched groups were less than 0.1, meaning all the covariables were well balanced among the groups in this study. In the matched cohort after PSM, survival analysis was performed. To compare the overall survival between cHL patients with SPMs and without SPMs, the "survival" package (version 3.2.7)[24] in R was used for survival analysis with log-rank tests and the "survminer" package (version 0.4.8)[25] was used for drawing the Kaplan–Meier survival curve. Moreover, the cumulative incidence function of cancer death from the initial cHL diagnosis was measured with a competing-risk Fine-Gray model, treating death of other causes instead of cHL as a competing risk. The cumulative incidence function analysis was performed by using the "cmprsk" package (version 2.2.10)[26] in R, and the differences in incidence across strata were compared with the Gray test.[27] To identify the potential independent risk factors for overall survival of cHL mortality, univariate and multivariate Cox proportional regression analyses were also further performed by using the "survival" package as well, the hazards ratio (HR) estimates and 95% CIs were reported.

2.3. Statistical analysis

All statistical analysis of the present study was carried out using the R program language (http://www.r-project.org/, version 4.0.4; R Foundation for Statistical Computing, Vienna, Austria). Comparisons between the 2 groups of continuous data and categorical data were performed using independent *t*-test and Chi-squared test, respectively. The Fisher exact method was applied when the smallest expected value is less than 5. All *P* values were 2-sided and a *P* value < 0.05 was considered to be statistically significant.

3. Results

3.1. Observed risk of SPMs in cHL versus the general population

In total 26,493 patients were diagnosed with cHL as a primary malignancy in the SEER 9 registry, Nov 2019 Sub (1975–2017) from January 1975 to December 2017. Among these patients, 3866 (14.59%) patients with second cancers were identified, with a SIR of 2.09 (95% CI: 2.02–2.15, *P* < .05), and an AER of 55.16. There was a significantly higher risk of malignancies in the following sites when compared with the general population: oral cavity and pharynx, digestive system (esophagus, stomach, liver, anus, etc.), respiratory system, bone and joints, soft tissue, skin, breasts, female genital system, and endocrine system. Additionally, leukemia, lymphoma, and mesothelioma occurred more frequently than in the general population (Table 1). Among hematological malignancies, leukemia and lymphoma were significantly increased with an SIR of 4.41 (*P* < .05, AER = 4.68) and 4.74 (*P* < .05, AER = 9.42), respectively. The risk of developing a non-Hodgkin lymphoma was greater than 5 times higher in cHL survivors than in the general population (NHL, SIR = 5.35, *P* < .05, AER = 9.40). Acute myeloid leukemia (SIR = 10.06, *P* < .05, AER = 3.50) and acute lymphocytic leukemia (SIR = 5.21, *P* < .05, AER = 0.33) were the most commonly occurring types of leukemia after primary cHL. Additionally, the incidence of chronic myeloid leukemia (SIR = 2.06, *P* < .05, AER = 0.21) was significantly increased in patients previously diagnosed with cHL. However, the incidence of chronic lymphocytic leukemia was significantly decreased in cHL survivors than in general population (SIR = 0.55, *P* < .05, AER = 0.24). Moreover, no significant increased risk of Kaposi Sarcoma was observed in cHL survivors.

3.2. Relative risk of SPMs in cHL patients according to latency period

Exploring the latency of developing SPMs after the diagnosis cHL, the risk compared to the US general population was increased across all latency periods. The risk for all sites was elevated and almost stable from 6 to 119 months, however, the SIR was obviously increased after 120 months (Table 2, SIR 2.34; 95% CI 2.25–2.43, *P* < .05). Furthermore, based on cancer types, the risk of developing second solid tumors was variable within all the follow-up period, and the maximum risk was observed after 120 months (Table 2, SIR 2.26; 95% CI 2.16–2.35, *P* < .05); the risk of developing the second hematological malignancies was maximum within 12 to 59 months after diagnosis of cHL (Table 2, SIR 6.26; 95% CI 5.44–7.17, *P* < .05). The risk for the development of an extranodal cHL was relatively high within 6 to 11 months (Table 2, SIR 102.13; 95% CI 2.59–569.02, *P* < .05), however, the risk was not significantly elevated compared to the general population after 1 year. The risk for the development of non-Hodgkin Lymphoma was increased within 6–11 months and was steadily decreased in the subsequent periods (Table 2), while the risk for the development of Acute Lymphoblastic

Table 1

Risk of second primary malignancies in patients with cHL reported in the SEER database between January 1975 and December 2017.

	Observed cases	Expected cases	SIR	*P* value	CI lower	CI upper	AER
All sites	3866.00	1851.66	2.09	<.05	2.02	2.15	55.16
Oral cavity and pharynx	138.00	52.15	2.65	<.05	2.22	3.13	2.35
Lip	13.00	4.10	3.17	<.05	1.69	5.43	0.24
Tongue	42.00	15.11	2.78	<.05	2.00	3.76	0.74
Salivary gland	37.00	5.10	7.26	<.05	5.11	10.01	0.87
Digestive system	552.00	318.60	1.73	<.05	1.59	1.88	6.39
Esophagus	47.00	19.19	2.45	<.05	1.80	3.26	0.76
Stomach	71.00	27.28	2.60	<.05	2.03	3.28	1.20
Anus, anal canal, and anorectum	32.00	7.19	4.45	<.05	3.05	6.29	0.68
Liver, Gallbladder, Intrahep bile duct, and other biliary	57.00	36.53	1.56	<.05	1.18	2.02	0.56
Respiratory system	680.00	238.86	2.85	<.05	2.64	3.07	12.08
Bones and joints	17.00	3.38	5.03	<.05	2.93	8.05	0.37
Soft tissue including heart	71.00	12.19	5.82	<.05	4.55	7.34	1.61
Skin excluding basal and squamous	157.00	111.12	1.41	<.05	1.20	1.65	1.26
Breast	622.00	265.03	2.35	<.05	2.17	2.54	9.78
Female genital system	138.00	102.85	1.34	<.05	1.13	1.59	0.96
Male genital system	289.00	311.50	0.93	1.30	0.82	1.04	0.62
Urinary system	197.00	142.56	1.38	<.05	1.20	1.59	1.49
Endocrine system	188.00	55.27	3.40	<.05	2.93	3.92	3.63
Mesothelioma	15.00	3.73	4.02	<.05	2.25	6.63	0.31
All lymphatic and hematopoietic diseases	684.00	165.43	4.13	<.05	3.83	4.46	14.20
Lymphoma	436.00	91.98	4.74	<.05	4.31	5.21	9.42
Hodgkin lymphoma	14.00	13.10	1.07	.83	0.58	1.79	0.02
Non-Hodgkin lymphoma	422.00	78.89	5.35	<.05	4.85	5.89	9.40
Leukemia	221.00	50.06	4.41	<.05	3.85	5.04	4.68
Acute lymphocytic leukemia	15.00	2.88	5.21	<.05	2.92	8.60	0.33
Chronic lymphocytic leukemia	11.00	19.92	0.55	<.05	0.28	0.99	0.24
Acute myeloid leukemia	142.00	14.12	10.06	<.05	8.47	11.85	3.50
Chronic myeloid leukemia	15.00	7.29	2.06	<.05	1.15	3.39	0.21
Kaposi sarcoma	14	8.21	1.7	.06	0.93	2.86	0.16

AER = absolute excess risk, cHL = classical Hodgkin lymphoma; CI = confidence interval, SIR = standardized incidence ratio.

Table 2

Risk of second primary malignancies in patients with cHL by latency period between January 1975 and December 2017.

	6–11 months		12–59 months		60–119 months		120 + months	
	SIR	95% CI	SIR	95% CI	SIR	95% CI	SIR	95% CI
All sites	1.86*	1.52–2.27	1.69*	1.56–1.83	1.77*	1.64–1.91	2.34*	2.25–2.43
All solid tumors	1.43*	1.11–1.82	1.22*	1.1–1.35	1.50*	1.37–1.63	2.26*	2.16–2.35
All hematological malignancies	6.12*	4.13–8.73	6.26*	5.44–7.17	4.40*	3.72–5.17	3.18*	2.83–3.56
Oral cavity and pharynx	0.67	0.02–3.75	2.31*	1.47–3.47	3.58*	2.51–4.96	2.54*	2.01–3.17
Esophagus	0	0–6.64	0.81	0.17–2.36	1.61	0.59–3.49	3.40*	2.4–4.66
Stomach	0	0–3.93	1.34	0.58–2.64	0.88	0.29–2.06	3.94*	3–5.1
Colon, rectum and anus	1.19	0.48–2.45	0.74	0.49–1.07	1.26	0.92–1.68	1.94*	1.67–2.23
Lung and bronchus	2.51*	1.49–3.96	1.82*	1.45–2.25	2.58*	2.13–3.09	3.56*	3.23–3.91
Female breast	0.48	0.1–1.41	0.67*	0.45–0.96	1.46*	1.14–1.84	3.12*	2.86–3.4
Hodgkin extranodal	102.13*	2.59–569.02	0	0–53.09	0	0–50.02	0	0–21.65
Non-Hodgkin lymphoma	11.84*	7.74–17.36	7.81*	6.46–9.35	4.71*	3.71–5.9	4.45*	3.86–5.1
Acute lymphocytic leukemia	0	0–34.38	4.29	0.88–12.53	7.83*	2.54–18.26	4.89*	1.97–10.08
Acute myeloid leukemia	0	0–8.63	19.47*	14.71–25.28	15.23*	11.06–20.44	5.30*	3.82–7.16
Chronic myeloid leukemia	4.55	0.12–25.37	1.35	0.16–4.86	3.95*	1.45–8.59	1.47	0.54–3.21

CI = confidence interval, cHL = classical Hodgkin lymphoma; SIR = standardized incidence ratio.

*$P < .05$.

Table 3

Characteristics of cHL Patients with SPMs matched patients without SPMs after Propensity Score Matching.

	SPMs		
Characteristics	Yes (N = 2327) n (%)	No (N = 4654) n (%)	*P* value*
Sex			
Male	1192 (51.2%)	2368 (50.9%)	.806
Female	1135 (48.8%)	2286 (49.1%)	
Age			
<20	160 (6.9%)	315 (6.8%)	.795
20–59	1677 (72.1%)	3389 (72.8%)	
60+	490 (21.1%)	950 (20.4%)	
Race			
White	2029 (87.2%)	4100 (88.1%)	.456
African-American	218 (9.4%)	416 (8.9%)	
Other	80 (3.4%)	138 (3.0%)	
Stages†			
Early	1427 (61.3%)	2827 (60.7%)	.879
Advanced	794 (34.1%)	1607 (34.5%)	
Unknown	106 (4.6%)	220 (4.7%)	
Subtype			
Lymphocyte rich	121 (5.2%)	230 (4.9%)	.875
Mixed cellularity	467 (20.1%)	949 (20.4%)	
Lymphocyte depleted	30 (1.3%)	48 (1.0%)	
Nodular sclerosis	1407 (60.5%)	2823 (60.7%)	
NOS	302 (13.0%)	604 (13.0%)	
Chemotherapy			
Yes	1439 (61.8%)	2886 (62.0%)	.910
No	888 (38.2%)	1768 (38.0%)	
RT			
Yes	1152 (49.5%)	2303 (49.5%)	1.000
No	1175 (50.5%)	2351 (50.5%)	

cHL = classical Hodgkin lymphoma, NOS = not otherwise specified, RT = radiation therapy, SPMs = second primary malignancies.

* Chi-squared test.

† Ann Arbor Stage I and II were combined as Stage Early, while Ann Arbor Stage III and Stage IV were combined as Stage Advanced.

Leukemia and Acute Myeloid Leukemia were increased within 12 to 59 months and was steadily decreased after 60 months (Table 2). The significantly elevated risk for the development of Chronic Myeloid Leukemia was only observed within 60 to 119 months (Table 2, SIR 3.95; 95% CI 1.45–8.59, $P < .05$).

3.3. Risk of SPMs by clinical and demographic factors

A further analysis was performed to investigate the relationship of clinical and demographic factors and SPMs. A forest plot of SPMs incidence in cHL patients was shown in Fig. 1. Analysis based on gender revealed that the risk of SPMs was higher in women than in men either for aggregate SPMs or for the solid/hematological categories (Fig. 1). Additionally, the risk of SPMs in different age groups was explored. For young cHL patients (< 20 years old), the relative risk of aggregate SPMs was quite high (SIR, 5.21; 95% CI, 4.71–5.75; Fig. 1A), the risk decreased in patients aged between 20 and 59 years (SIR, 2.18; 95% CI, 2.10–2.26; Figure 1A) and aged over 60 years (SIR, 1.37; 95% CI, 1.27–1.47; Fig. 1A). For the second hematological

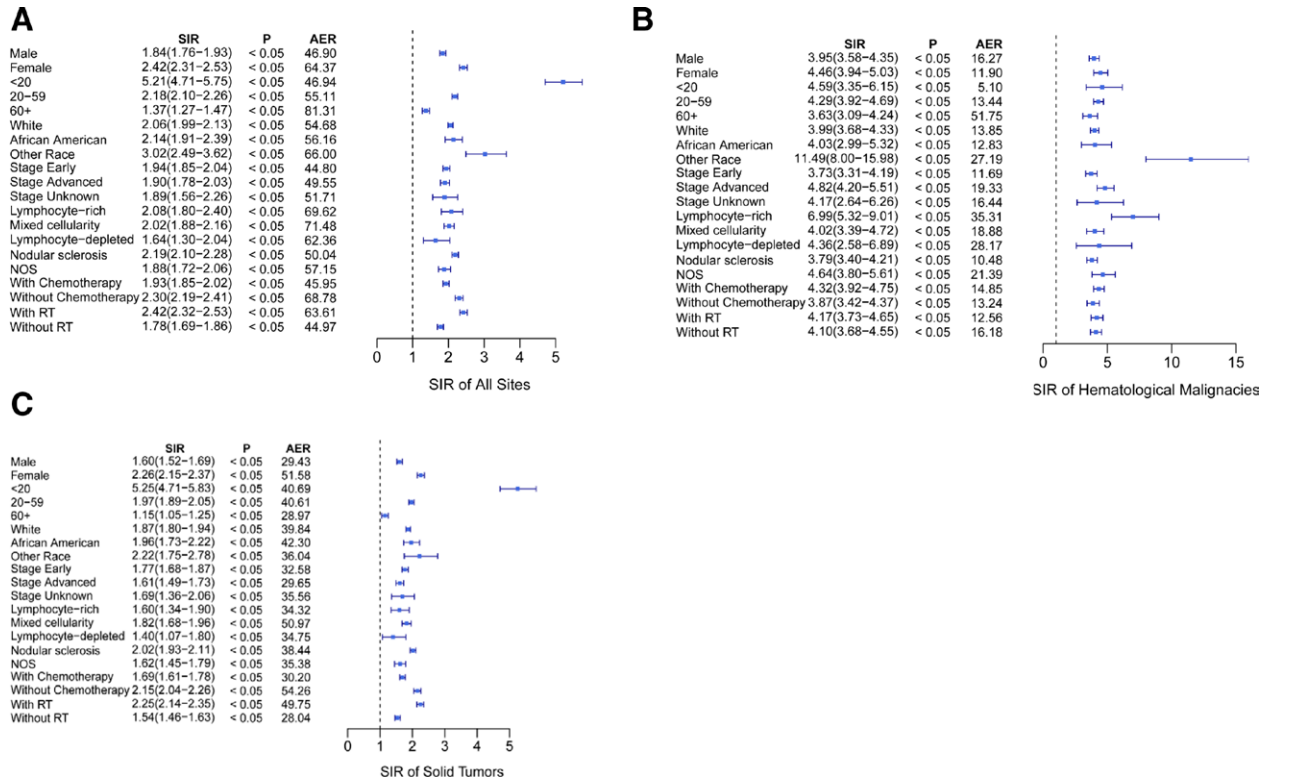

Figure 1. Forest plot of the standardized incidence ratios of secondary malignancies according to clinical and demographic factors in patients with classical Hodgkin Lymphoma from the SEER database between January 1975 and December 2017. (A), (B) and (C) indicates SIR analysis of all sites, hematological malignancies, and solid tumors, respectively. $P < .05$, compared to the general population. Ann Arbor Stage I and II were combined as Stage Early, while Ann Arbor Stage III and Stage IV were combined as Stage Advanced. AER = absolute excess risk; cHL = classical Hodgkin lymphoma; RT = radiation therapy; SIR = standardized incidence ratio.

malignancies, young cHL group showed similar risk with 20 to 59-year-old group (SIR, 4.59; 95% CI, 3.35–6.15; SIR, 4.29; 95% CI, 3.92–4.69; respectively. Fig. 1B), while the risk was slightly decreased in group aged over 60 years (SIR, 3.63; 95% CI, 3.09–4.24; Fig. 1B). However, for the second solid tumors, although the risk was still quite high for young cHL patients (SIR, 5.25; 95% CI, 4.71–5.83; Fig. 1C), the risk for patients aged over 60 years was only 15% higher than general population (SIR, 1.15; 95% CI, 1.05–1.25; Fig. 1C). For the analysis by race, the risk of developing SPMs (especially the secondary hematological malignancies) was higher among "other race (Asians, American Indians, Native Americans, and Pacific Islanders)" as compared to African Americans and the Whites, while African Americans and the Whites showed similar risk of developing SPMs (Fig. 1). Based on the stages of cHL, it was noted that the early stage and advanced stage subgroup of cHL patients had the similar risk of developing aggregate SPMs and solid tumors (Fig. 1A and 1C), however, the advanced stage subgroup had comparatively much higher risk of developing a secondary hematological malignancy (SIR, 4.82; 95% CI, 4.20–5.51; Fig. 1B). According of the classification cHL, the nodular sclerosis subgroup of cHL patients had the highest risk of developing aggregate SPMs and solid tumors (Fig. 1A and 1C), while the lymphocyte-rich subgroup had the highest risk of developing a secondary hematological malignancy (SIR, 6.99; 95% CI, 5.32–9.01; Fig. 1B). Compared to patients without chemotherapy, the chemotherapy group had higher risk to develop secondary hematological malignancies (Fig. 1B), but less risk of secondary solid tumors (Fig. 1C). Patients with radiation therapy had much higher risk of secondary solid tumors (Fig. 1C), but slightly increased risk of secondary hematological malignancies in relative to those without radiation therapy (Fig. 1B).

3.4. Outcome of cHL patients developing SPMs

To exclude the bias effect of demographic factors, PSM was employed to minimize confounding effects between groups with or without SPMs. The baseline characteristics (age, race, sex, stage, subtype for cHL) were incorporated into matching analysis with the ration of 1:2. For each comparison, all the characteristics were well matched (Figure S1, Supplemental Digital Content, http://links.lww.com/MD/H1000), Table 3). The overall survival was not significantly different between the cHL only group and the group with SPMs before 11 years of follow-up ($P = .14$, Fig. 2A). However, the cHL with SPMs group showed significantly worse overall survival versus the cHL only group after 11 years of follow-up ($P < .0001$; Fig. 2B). By applying the competing risk analysis, it is evident that the cumulative incidence of death from cHL is significantly higher in the cHL only group compared to the group with SPMs ($P < .001$; Fig. 2C), and the cumulative incidence of death from other causes rather than directly from cHL was significantly lower in the cHL only group ($P < .001$; Fig. 2D).

3.5. Cox regression analysis of risk factors for overall survival of cHL patients

For the propensity score matched cohort, overall survival analysis showed that there were significant differences within the covariates of age, sex, race, subtype, stage, chemotherapy, and radiotherapy (Figure S2, Supplemental Digital Content, http://links.lww.com/MD/I2), A–G). Univariate Cox proportional hazard regression analysis suggested that older age ($P < .001$, Fig. 3A), male gender (HR 1.51; $P < .001$, Fig. 3A), Ethnicity of African American and other (Asians, American Indians, Native Americans, and Pacific Islanders) ($P < .001$ and $P = .025$,

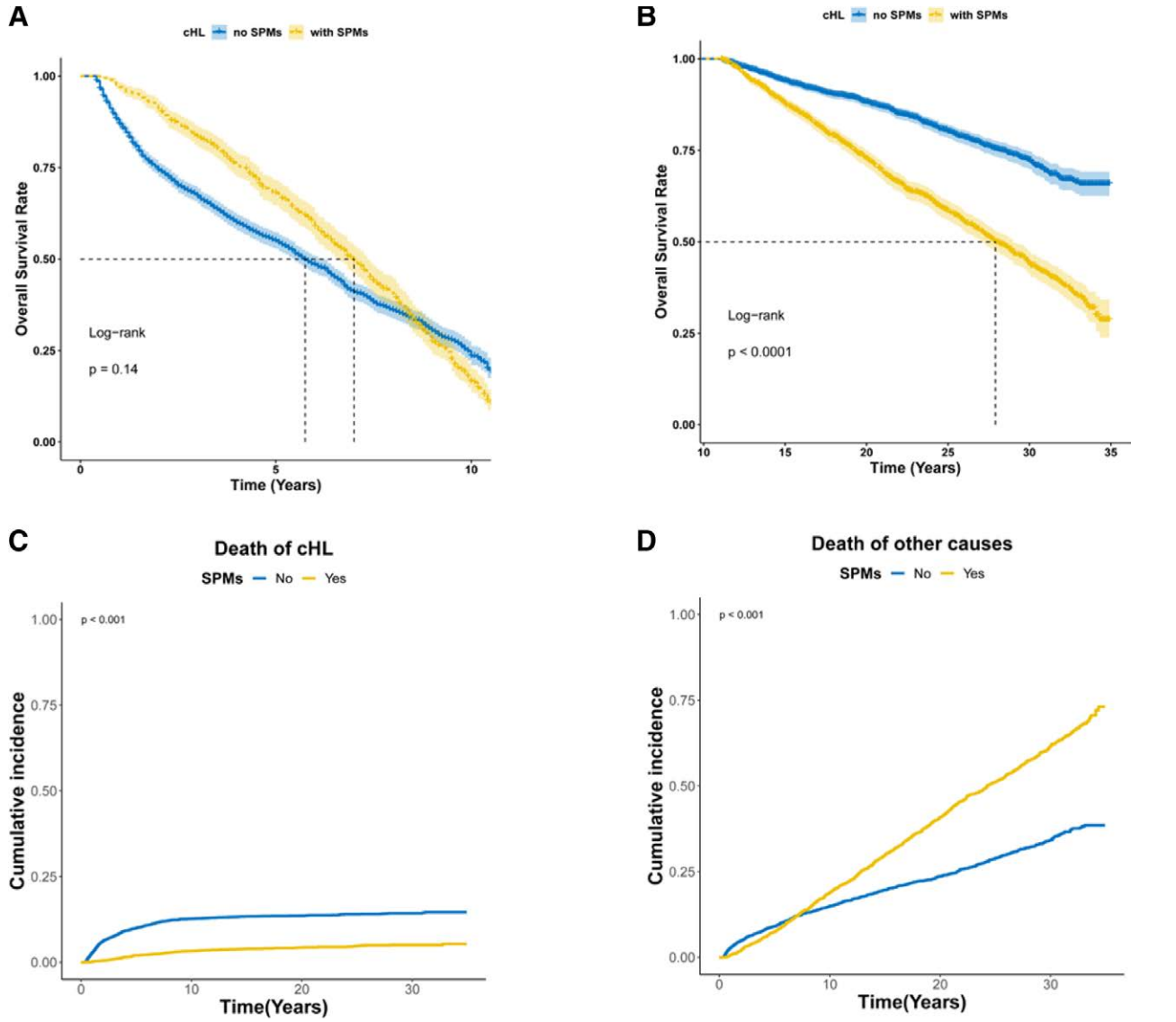

Figure 2. Outcome of cHL patients developing SPMs. Overall survival of cHL patients in cHL only group compared to the group with SPMs before (A) and after (B) 11 years of follow-up was shown, respectively. The cumulative incidence of death from cHL (C) and other causes (D) with the 2 groups was also shown, respectively. cHL = classical Hodgkin lymphoma; SPMs = second primary malignancies.

respectively; Fig. 3A), subtypes except nodular sclerosis (Fig. 3A), advanced stage (HR 1.51; $P < .001$, Fig. 3A), with SPMs (HR 1.25; $P < .001$, Fig. 3A), and chemotherapy (HR 1.26; $P < .001$, Fig. 3A) were associated with worse overall survival, while radiation therapy (HR 0.58; $P < .001$, Fig. 3A) and the subtype of nodular sclerosis (HR 0.69; $P < .001$, Fig. 3A) were associated with better overall survival. Similar results were obtained with the multivariate logistic regression analysis except little differences: For the variable subtypes, only the subtype of lymphocyte-depleted (HR 1.39; $P = .036$, Fig. 3B) was an independent worse prognostic factors of cHL; For the variable race, the ethnicity of other (Asians, American Indians, Native Americans, and Pacific Islanders) was not significantly associated with worse prognosis anymore (HR 1.22; $P = .053$, Fig. 3B); Chemotherapy was not associated with worse prognosis as well ($P = .395$, Fig. 3B). Multivariate analysis indicated that SPMs was still a worse prognostic factor for cHL (HR 1.13; $P = .001$, Fig. 3B).

4. Discussion

Some studies have shown that Hodgkin lymphoma patients are at high risk for developing SPMs.[15] Nevertheless, systematical studies regarding SPMs among cHL patients has not been reported. In the current study, 26,493 patients with cHL as primary malignancies were identified in the SEER 9 registry, Nov 2019 Sub (1975–2017) from January 1975 to December 2017. Among the cHL survivors, we found there was a significantly increased risks of secondary hematological malignancies and solid tumors, such as acute myeloid leukemia, acute lymphocytic leukemia, chronic myeloid leukemia, non-Hodgkin lymphoma, bone and soft tissue tumors, oral cavity and pharynx cancer, digestive system cancer, skin cancer, endocrine tumors, respiratory system cancer, and breast cancer, which is similar to some previous studies showed that survivors of Hodgkin Lymphoma had an increased risk of second cancer, but our study has a larger study population and longer span of observation period.[15,28,29] Moreover, increased SIR of SPMs was observed among cHL patients throughout all the latency periods (6–120 months), even after 120 months. Specifically, the risk of developing second solid tumors such as breast cancer was maximum after 120 months, while the risk of developing the second hematological malignancies was maximum within 12 to 59 months after diagnosis of cHL. The risk for the development of non-Hodgkin

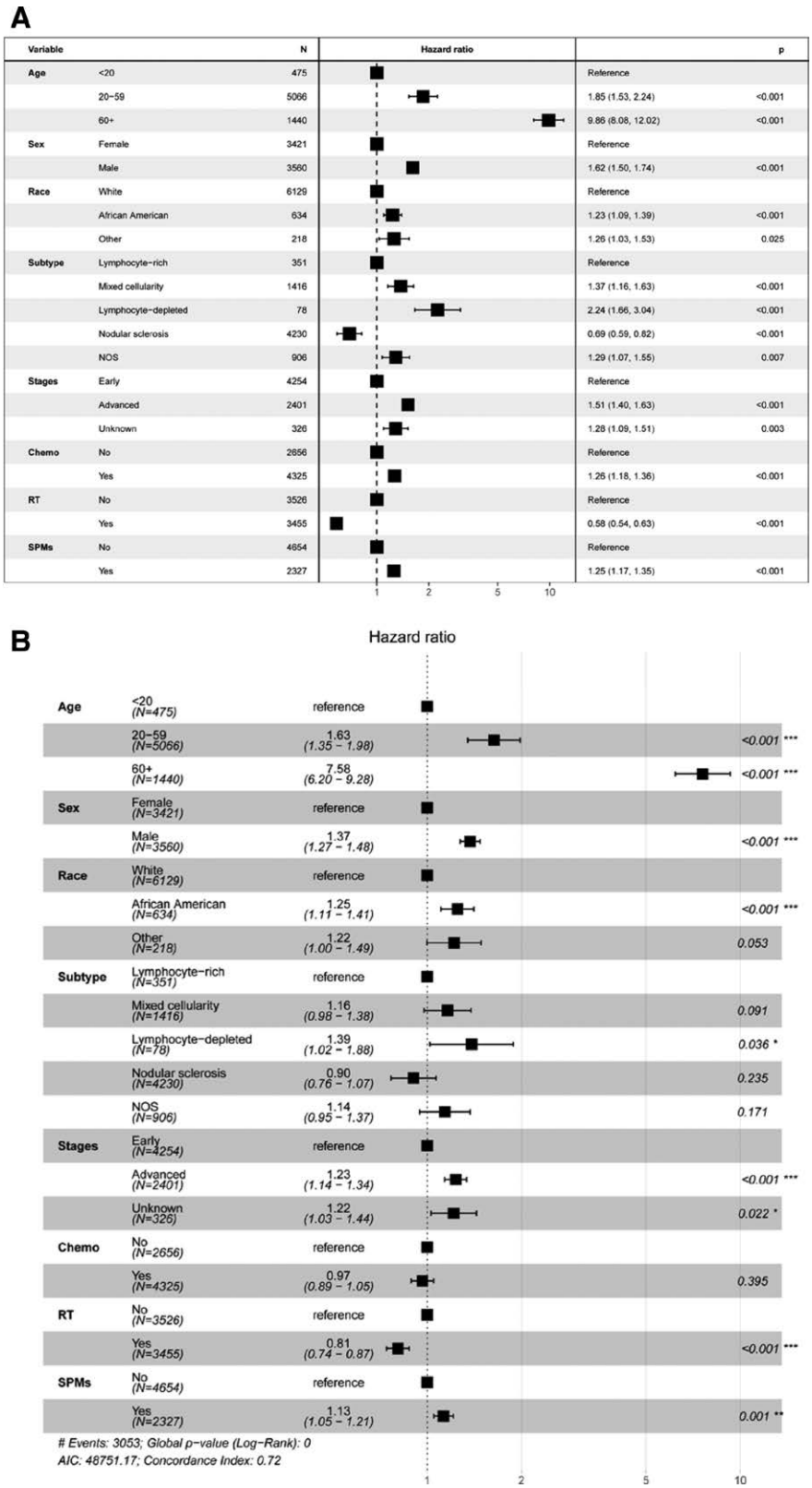

Figure 3. Univariate (A) and multivariate (B) logistic regression analyses for predictors of overall survival in cHL patients after propensity score matching. * Ann Arbor Stage I and II were combined as Stage Early, while Ann Arbor Stage III and Stage IV were combined as Stage Advanced; Race (other): Asians, American Indians, Native Americans, and Pacific Islanders; cHL = classical Hodgkin lymphoma; NOS = not otherwise specified; SPMs = second primary malignancies.

Lymphoma was increased within 6 to 11 months and was steadily decreased thereafter. Thus, it is essential to increase awareness of the incurrence of SPMs during short-term and long-term follow-ups of cHL survivors. To our knowledge, this is the first systematical study about SPMs among cHL patients.

In this study, we found female survivors of cHL had higher risk of SPMs, which was also noted by a meta-analysis.[30]

Furthermore, we found that increased risk of SPMs (especially solid tumors) was associated with younger age (< 20 years old) that may be related with more aggressive and multiple courses of chemotherapy and radiation therapy regime applied in the younger patients, since some previous studies have shown chemotherapy was followed by substantial risk of hematological malignancies such as leukemia and NHL[31] and the risk of developing a solid tumor after radiation therapy increased as the radiation dose went up.[32] For the analysis by race, the risk of developing SPMs, especially the secondary hematological malignancies, was highest in "other race (Asians, American Indians, Native Americans, and Pacific Islanders)" in relative to African Americans and the Whites, while African Americans and the Whites showed similar risk of developing SPMs. The disparities may be due to the genetic background and socioeconomic status of different ethnicity group. Compared to patients with early stage of cHL, the advanced stage group demonstrated an increased risk of secondary hematological malignancies instead of secondary solid tumors, this may also be due to the fact that the advanced stage of cHL patients tend to receive escalated chemotherapy regimen with potentially more toxicity, which was supported by the reports that acute myeloid leukemia or myelodysplastic syndrome were more frequently observed in patients treated with the dose escalated chemotherapy regime such as BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone).[33] Additionally, SPMs risks were strikingly different based on cHL subtypes: the nodular sclerosis subgroup of cHL patients had the highest risk of developing solid tumors, while the lymphocyte-rich subgroup had the highest risk of developing a secondary hematological malignancy. The basis for the differences of SPMs risks in histologic cHL subtypes is unknown but may reflect a nodular sclerosis subtype being more greatly associated with younger age and being apt to undergo more intensified chemotherapy.[5]

Over past several decades, advances in chemotherapy and the combination of radiation therapy have significantly increased the cure rate of patients with cHL.[5] However, concerns over the possible late side effects after chemotherapy or radiation therapy, particularly SPMs need to be considered when planning an optimal treatment regime for a given patient. ABVD (adriamycin, bleomycin, vinblastine, and dacarbazine) is considered as the standard chemotherapy regimen for HL patients because of its efficacy and lower toxicity.[34] Some more intensive chemotherapy regimens such as BEACOPP and escalated BEACOPP (eBEACOPP) were developed for HL with unfavorable risk factors[35] and advanced-stage Hodgkin lymphoma,[36,37] respectively. Studies had shown that ABVD can induce leukemia[38] and BEACOPP increased the incidence secondary leukemia as compared to ABVD,[39] which may be associated with the use of alkylating agents and topoisomerase II inhibitors used in the chemotherapy regime.[40–42] For solid tumors, chemotherapy alone showed reduced risk of secondary breast cancer.[31] In the present study, we found that the chemotherapy group had higher risk to develop secondary hematological malignancies, but less risk of secondary solid tumors, which is consistent with previous studies. In a study of cHL survivors treated with radiation therapy, the 5-year survival after development of SPMs was 38%, and the excess risk of SPMs continues to be elevated after 15 to 20 years of completing therapy without an appearing plateau.[14] We also found patients with radiation therapy had slightly increased risk of secondary hematological malignancies, and higher risk of secondary solid tumors in relative to those without radiation therapy. Thus, survivors of cHL patients treated with radiation therapy represent a high-risk population for secondary solid tumors, optimal screening strategies for those secondary solid tumors should be developed. Nowadays, cHL patients normally received radiation therapy at lower doses and with smaller fields than previous courses, however, its impact on the long-term side-effects such as SPMs still needs further investigation.

A previous study demonstrated that adolescents and young adults with SPMs were more probable to experience worse survival compared to those with the same primary malignant neoplasms.[43] In this study, the outcomes of cHL patients who developed SPMs were compared with the propensity score-matched controls, which will minimize the bias effect of potential confounders, it is interested to find that the overall survival was worse for cHL patients with SPMs as to those without SPMs after 11 years of follow-up. Although worse overall survival among survivors of HL with second primary head and neck cancer,[44] breast,[45] and lung cancer[46] had previously been described, to our knowledge, the present study is the largest population-based analysis (365,156 patient-years of follow-up) to systematically investigate the outcomes of SPMs for patients with cHL. Moreover, the results of the current study showed that the cumulative incidence of death from cHL was significantly higher in cHL patients without SPMs than those with SPMs, while the cumulative incidence of death from other causes was significantly higher in cHL patients with SPMs than those without SPMs. It indicates that for cHL patients with SPMs, the main risk of death is not cHL itself directly but other causes such as the second primary cancers, diseases of heart, diabetes mellitus, pneumonia, and so on, and our finding is well supported by a large retrospective study showed that the main cause of death among young HL patients was SPMs and cardiovascular diseases instead of HL after 20 years of follow-up.[47] Furthermore, in this study, multivariate cox regression analysis confirmed SPMs as an independently prognostic factor for cHL survivors, which had not been reported by other studies.

Although the SEER data has the advantage of including a good deal of patients with long period of follow-up covering a comparatively large geographic area, there are still some limitations. Firstly, the SEER registry lacks information including social economic status, carcinogens exposure, family history, alcohol/smoking consumption history, Epstein-Barr virus status, human immunodeficiency virus status, human papillomavirus status, which might potentially affect SPMs risk. Secondly, details concerning therapy for cHL such as immunotherapy (such as PD-1 antibody), chemotherapy regime are not noted in the SEER database, thus the analysis on different treatment regimen is impossible. Additionally, data about radiation dose and fields, and underreporting radiotherapy are also missing, which will attenuate the generalizability of our findings. Thirdly, there are possibilities of under-ascertainment of SPMs risks due to patient migration outside of SEER program areas. Finally, this study is a retrospective study based on SEER database, which is prone to selection bias, recall bias or misclassification bias just as other retrospective cohort studies did.

5. Conclusions

In conclusion, our large population-based study indicates that cHL survivors have an increased risk of developing SPMs versus the general population, and the increase in risk is more pronounced for patients with the characteristics of female gender, younger age, advanced stage, chemotherapy, and radiation therapy. Additionally, SPMs risks were strikingly different based on cHL subtypes. Moreover, the overall survival is worse for cHL patients with SPMs as to those without SPMs after 11 years of follow-up, the main cause of death for cHL patients with SPMs is other causes including SPMs, and SPMs is an independently prognostic factor for cHL survivors.

These findings suggest that awareness of the increased risk of secondary SPMs remains crucial for cHL survivors, and ongoing monitoring and management of SPMs during and after therapy for cHL is paramount to improve the survival of cHL patients.

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Author contributions

F.W. came up with the conception, design, data analysis, and manuscript preparation.

Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing—original draft, Writing—review and editing: Fan Wang.

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