JAMA Network Open

Research Letter | Hematology

Mortality Outcomes Among Long-Term Hodgkin Lymphoma Survivors

Bryan Valcarcel, MD, MPH; Javier Retamales, MD; Michelle A. T. Hildebrandt, PhD; Veronica Leautaud, PhD; Hun Ju Lee, MD; Sairah Ahmed, MD; Maria Alma Rodriguez, MD; Christopher R. Flowers, MD; Luis Malpica, MD

Introduction

Treatment advances in Hodgkin lymphoma (HL) have driven 5-year relative survival rates close to 90% in the United States,[1] resulting in a growing population of long-term survivors at risk for late effects that contribute substantially to mortality.[2-5] Although previous studies have reported increased all-cause mortality among HL survivors,[4] these estimates are largely derived from populations that do not adequately represent contemporary long-term survivors diagnosed during adulthood.[3-8] Most prior reports have focused on childhood cancer survivors,[6] patients evaluated during early follow-up,[7] or those treated before the widespread adoption of contemporary strategies such as positron emission tomography–adapted therapy or involved-field radiation.[6-8] As a result, existing mortality estimates have limited applicability for informing survivorship care among adults. To address this gap, we conducted a population-based analysis to quantify excess all-cause mortality among 5-year HL survivors diagnosed during adulthood compared with the general US population.

Methods

We conducted a retrospective cohort study using data from 16 population-based registries of the Surveillance, Epidemiology, and End Results (SEER) program. Eligible patients were aged 20 years or older at diagnosis with first-primary HL diagnosed during 2000 to 2017, received chemotherapy with or without radiotherapy, and survived at least 5 years after diagnosis. Follow-up was available up to December 2023. Race and ethnicity was obtained from the SEER database variable to identify demographic groups at higher risk of all-cause mortality. This study was deemed exempt from review and the requirement for informed consent due to the use of publicly available deidentified data by University of Texas MD Anderson Cancer Center Institutional Review Board. This research follows the STROBE reporting guideline.

Standardized mortality ratios (SMRs) and excess absolute risks (EARs) per 10 000 patient-years were estimated using expected deaths from US population mortality rates matched by age, sex, race and ethnicity, and calendar period, assuming a Poisson distribution. Follow-up was censored 5 years after the index date to ensure comparable estimates across broad diagnostic periods (2000-2007 vs 2008-2017). SMR heterogeneity across subgroups was assessed using likelihood ratio tests comparing a null model with those adjusted for the variable. Cumulative incidence of mortality was estimated using competing-risks methods. Two-sided $P < .05$ was considered statistically significant. Analyses were conducted in R version 4.5.2 (R Project for Statistical Computing).

Results

Among 20 057 HL survivors, the median (IQR) age was 36 (27-50) years (53.7% male; 15.0% Hispanic, 10.3% non-Hispanic Black, and 69.2% non-Hispanic White; 63.4% with nodular sclerosis) (**Table**). Mortality was significantly higher among HL survivors compared with the general US population (2899 observed vs 1480.8 expected deaths; SMR, 1.96; 95% CI, 1.89-2.03), corresponding to an EAR of 81.9 (95% CI, 75.8-88.0) per 10 000 patient-years. Relative mortality

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

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Table. Patient Characteristics, Standardized Mortality Ratios, and Absolute Excess Risk Per 10 000 by Patient Factors From 16 SEER Registries, 2000-2017

Characteristic	All patients, No. (%)	Deaths, No.		Person-years	SMR (95% CI)	*P* for heterogeneity	EAR (95% CI)
		Observed	Expected				
Overall	20 057 (100)	2899	1480.8	173 243.1	1.96 (1.89-2.03)	NA	81.9 (75.8-88.0)
Age at diagnosis, y							
Median (range)	36 (20-89)	NA	NA	NA	NA	NA	NA
20-39	11 497 (57)	676	268.2	106 887.3	2.52 (2.34-2.72)	<.001	38.2 (33.4-42.9)
40-59	6005 (30)	1026	521.6	51 735.3	1.97 (1.85-2.09)		97.5 (85.4-109.6)
60-89	2555 (13)	1197	691.0	14 620.5	1.73 (1.64-1.83)		346.1 (299.7-392.5)
Sex							
Female	9480 (47)	1072	576.6	83 831.7	1.86 (1.75-1.97)	.03	59.1 (51.4-66.7)
Male	10 577 (53)	1827	904.1	89 411.4	2.02 (1.93-2.12)		103.2 (93.8-112.6)
Race and ethnicity							
Hispanic	3001 (15)	384	146.8	23 444.8	2.62 (2.37-2.89)	<.001	101.2 (84.8-117.6)
Non-Hispanic American Indian or Alaska Native	87 (<1)	21	6.3	697.1	3.31 (2.16-5.08)		210.4 (81.5-339.2)
Non-Hispanic Asian or Pacific Islander	1029 (5)	102	28.8	8273.4	3.54 (2.91-4.29)		88.4 (64.5-112.3)
Non-Hispanic Black	2061 (10)	330	162.1	17 292.6	2.04 (1.83-2.27)		97.1 (76.5-117.7)
Non-Hispanic White	13 879 (69)	2062	1136.7	123 535.2	1.81 (1.74-1.89)		74.9 (67.7-82.1)
Year of diagnosis[a]							
2000-2007	8578 (43)	683	263.7	40 707.4	2.59 (2.4-2.79)	<.001	103.0 (90.4-115.6)
2008-2017	11479 (57)	755	392.8	45 770.1	1.92 (1.79-2.06)		79.1 (67.4-90.9)
Hodgkin lymphoma subtype							
NSHL	12 711 (63)	1446	761.8	116 979.2	1.90 (1.80-2.00)	.03	58.5 (52.1-64.9)
MCHL	2287 (11)	564	269.6	19 624.3	2.09 (1.93-2.27)		150 (126.3-173.7)
LRHL	553 (3)	99	62.6	4670.4	1.58 (1.30-1.93)		77.9 (36.2-119.7)
LDHL	145 (1)	38	21.4	1334.7	1.77 (1.29-2.44)		124.1 (33.6-214.6)
cHL-NOS	4361 (22)	752	365.3	30 634.4	2.06 (1.92-2.21)		126.2 (108.7-143.8)
Cancer stage							
I-II	11 870 (59)	1400	815.2	108 308.6	1.72 (1.63-1.81)	<.001	54 (47.2-60.8)
III-IV	7650 (38)	1405	620.1	60 134.7	2.27 (2.15-2.39)		130.5 (118.3-142.8)
Unknown	537 (3)	94	45.5	4799.8	2.06 (1.69-2.53)		101 (61.4-140.6)
Radiotherapy							
No	12 483 (62)	2028	954.8	98 572.7	2.12 (2.03-2.22)	<.001	108.9 (99.9-117.8)
Yes	7574 (38)	871	526.1	74 670.4	1.66 (1.55-1.77)		46.2 (38.5-54.0)
Radiotherapy in cancer stage I-II							
No	5771 (49)	750	387.1	47 980.8	1.94 (1.8-2.08)	<.001	75.6 (64.4-86.8)
Yes	6099 (51)	650	428.1	60 327.8	1.52 (1.4-1.64)		36.8 (28.5-45.1)
Radiotherapy in cancer stage III-IV							
No	6313 (83)	1214	535.3	47 242.6	2.27 (2.14-2.4)	.95	143.7 (129.2-158.1)
Yes	1337 (17)	191	84.7	12 892	2.26 (1.95-2.59)		82.5 (61.5-103.5)
Cause of death[b]							
Solid malignant neoplasm	NA	391	273.4	NA	1.43 (1.29-1.58)	NA	6.8 (4.6-9.0)
Digestive system	NA	112	91.5	NA	1.22 (1.01-1.46)	NA	1.2 (0-2.4)
Respiratory system	NA	154	80.7	NA	1.91 (1.62-2.23)	NA	4.2 (2.8-5.6)
Skin excluding basal and squamous	NA	27	7.4	NA	3.63 (2.43-5.18)	NA	1.1 (0.5-1.7)
Lymphoma	NA	653	11.2	NA	58.15 (53.8-62.73)	NA	37.0 (34.2-39.9)
Hodgkin lymphoma	NA	417	0.7	NA	638.65 (579.3-701.93)	NA	24.0 (21.7-26.3)
Non-Hodgkin lymphoma	NA	236	10.6	NA	22.31 (19.59-25.28)	NA	13.0 (11.3-14.8)
Other hematologic malignant neoplasms	NA	47	18.2	NA	2.59 (1.92-3.4)	NA	1.7 (0.9-2.4)

(continued)

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Table. Patient Characteristics, Standardized Mortality Ratios, and Absolute Excess Risk Per 10 000 by Patient Factors From 16 SEER Registries, 2000-2017 (continued)

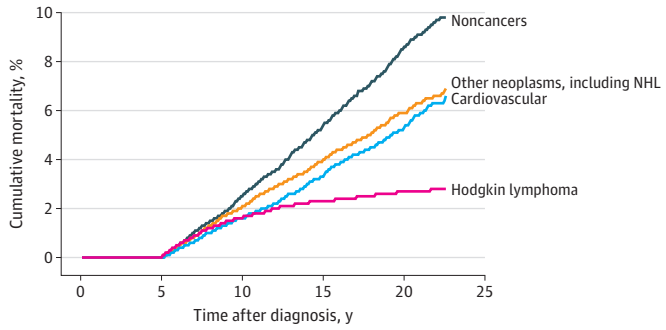
Characteristic	All patients, No. (%)	Deaths, No.		Person-years	SMR (95% CI)	*P* for heterogeneity	EAR (95% CI)
		Observed	Expected				
Unspecified cancer	NA	92	32.0	NA	2.87 (2.33-3.5)	NA	3.5 (2.4-4.5)
Cardiovascular	NA	670	410.8	NA	1.63 (1.51-1.76)	NA	15.0 (12.0-17.9)
Diseases of heart	NA	554	316.7	NA	1.75 (1.61-1.9)	NA	13.7 (11.0-16.4)
Other cardiovascular diseases	NA	116	94.1	NA	1.23 (1.02-1.47)	NA	1.3 (0-2.5)
Other noncancer	NA	1046	735.1	NA	1.42 (1.34-1.51)	NA	17.9 (14.3-21.6)
Infections	NA	91	48.3	NA	1.88 (1.52-2.3)	NA	2.5 (1.4-3.5)
Other chronic conditions	NA	298	221.5	NA	1.35 (1.2-1.5)	NA	4.4 (2.5-6.4)
Other or ill-defined	NA	657	465.3	NA	1.41 (1.31-1.52)	NA	11.1 (8.2-14.0)

Abbreviations: cHL-NOS, classic Hodgkin lymphoma, not otherwise specified; EAR, excess absolute risk; LDHL, lymphocyte-depleted Hodgkin lymphoma; LRHL, lymphocyte-rich Hodgkin lymphoma; MCHL, mixed cellularity Hodgkin lymphoma; NA, not applicable; NSHL, nodular sclerosis Hodgkin lymphoma; SEER, Surveillance, Epidemiology, and End Results; SMR, standardized mortality ratio.

[a] Median (IQR) follow-up after index date was 174 (151-200) months for the 2000 to 2007 period and 69 (39-100) months for the 2008 to 2017 period.

[b] Cause of death grouping is based on the variable "SEER Cause of Death Recode 1969+ (03/01/2018)" which is based on the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* codes for solid malignant neoplasms (C15-C22.4, C22.7, C22.9, C23-C25, C26.0, C26.8-C26.9, C45.1, C48.0-C48.2, C48.8 [digestive system], C30-C34, C38.1-C38.4, C38.8, C39, C45.0 [respiratory system], C43-C44, C46 [skin excluding basal and squamous], C00-C14, C37-C38.0, C40-C41, C45.2, C47, C49-C58, C60-C75); lymphoma (C81 [Hodgkin lymphoma], C82-86 and C96.3 [non-Hodgkin lymphoma]); other hematologic malignant neoplasms (C90.0, C90.2, C90.3 [myeloma], C90.1, C91.0-C92.9, C93.0-C93.3, C93.7, C93.9, C94.0-C94.5, C94.7, C95.0-C95.2, C95.7, C95.9 [leukemia]); unspecified cancer (C26.1, C45.7+, C45.9+, C76-C80, C88, C94.6, C96.0-C96.2, C96.4-C97, D00-D48); cardiovascular (I00-I09, I11, I13, I20-I51 [diseases of the heart], I10, I12, I60-I69, I70, I71, I72-I78 [other cardiovascular diseases]); other noncancer (A15-A19, A40-A41, A50-A53, J09-J18 [infections], A34, E10-E14, G30, J40-J47, K25-K28, K70, K73-K74, N00-N07, N17-N19, N25-N27, O00-O95, O98-O99, P00-P96, Q00-Q99 [other chronic conditions]; R00-R99, U01-U03, V01-Y09, Y35, Y85-Y87.1, Y89.0 [other or ill-defined], remaining codes per SEER documentation).

Figure. Line Graph of Cumulative Mortality Among 5-Year Hodgkin Lymphoma Survivors From 16 Surveillance, Epidemiology, and End Results Registries, 2000-2017



No. at risk					
Patients	0	20057	13906	7943	2974
Events, No.					
Noncancers	0	7	461	806	1008
Other neoplasms, including NHL	0	11	383	616	739
Cardiovascular	0	3	295	508	634
Hodgkin lymphoma	0	13	307	392	413

NHL indicates non-Hodgkin lymphoma.

risk was higher for all major causes of death, primarily from malignant conditions. However, the largest absolute number of excess deaths was attributable to other noncancer and cardiovascular causes (Table).

Excess mortality varied across subgroups. Hispanic patients, non-Hispanic American Indian or Alaska Native patients, non-Hispanic Asian or Pacific Islander patients, and those diagnosed at ages 20 to 39 years had SMRs greater than 2.50. However, the highest EARs were observed among adults aged 60 to 89 years, non-Hispanic American Indian or Alaska Native patients, and those diagnosed with mixed cellularity HL. SMRs and EARs were lower in 2008 to 2017 than in 2000 to 2007. Radiotherapy was associated with lower SMR and EAR only among patients with stage I or II disease (Table).

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With a median (IQR) follow-up of 173 (120-226) months since diagnosis, the overall 10-year cumulative mortality was 8.0% (95% CI, 7.6%-8.4%), increasing to 15.0% (95% CI, 15.0%-16.0%) at 15 years. At 10 years, mortality form noncancer causes was highest at 2.5% (95% CI, 2.3%-2.8%), followed by other neoplasms at 2.1% (95% CI, 1.9%-2.3%), cardiovascular conditions at 1.6% (95% CI, 1.5%-1.8%), and HL at 1.6% (95% CI, 1.5%-1.8%). HL-related deaths plateaued over time, while mortality from other causes continued to increase (**Figure**).

Discussion

In this retrospective population-based cohort study, 5-year HL survivors diagnosed during adulthood experienced nearly 2-fold higher all-cause mortality than the general US population, with varying estimates across demographic and clinical subgroups. Previous studies among childhood survivors have reported higher SMRs of 4 to 8,[4,6,7] possibly reflecting differences in age at diagnosis, treatment protocols, background comorbidity, and lack of conditioning on 5-year survival. Notably, the long-term predominance of noncancer and cardiovascular mortality supports integrated survivorship care beyond lymphoma recurrence surveillance. Our estimates quantify population-based disparities and excess mortality among adults diagnosed in the era of risk-adapted therapy, suggesting the need for continued improvement in survivorship care. The SEER registries lack detailed clinical and socioeconomic information, limiting adjustment for potential confounding; therefore, associations with radiotherapy should not be interpreted as causal. Furthermore, follow-up may be insufficient to detect late radiation-associated outcomes, including second primary malignant neoplasms and cardiovascular disease, often emerging decades after treatment.

These findings may inform patient counseling and support the development of risk-based survivorship approaches, as previously suggested,[9] focusing on strengthening screening and management practices for cardiovascular disease, subsequent neoplasms, and noncancer conditions. Future studies are needed to identify modifiable clinical factors and social determinants of health associated with overall and subgroup-specific excess mortality to support their integration into survivorship care. Continued population-based surveillance is warranted to assess how novel immunotherapies, including brentuximab-vedotin and nivolumab,[10] may shape long-term mortality patterns.

ARTICLE INFORMATION

Accepted for Publication: June 27, 2026.

Published: August 18, 2026. doi:10.1001/jamanetworkopen.2026.29775

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Corresponding Author: Luis Malpica, MD, Department of Lymphoma & Myeloma, The University of Texas MD Anderson Cancer Center, 515 Holcombe Blvd, Unit 429, Houston, TX 77030-4009 (LEMalpica@mdanderson.org).

Author Affiliations: Department of Lymphoma and Myeloma, The University of Texas MD Anderson Cancer Center, Houston (Valcarcel, Hildebrandt, Leautaud, Lee, Ahmed, Rodriguez, Flowers, Malpica); Hospital Sotero del Rio, Region Metropolitana, Chile (Retamales).

Author Contributions: Dr Valcarcel had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Valcarcel, Hildebrandt, Flowers, Malpica Castillo.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Valcarcel, Retamales, Lee, Malpica Castillo.

Critical review of the manuscript for important intellectual content: Valcarcel, Hildebrandt, Leautaud, Ahmed, Rodriguez, Flowers, Malpica Castillo.

Statistical analysis: Valcarcel.

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Obtained funding: Flowers, Malpica Castillo.

Administrative, technical, or material support: Retamales, Leautaud, Ahmed, Rodriguez, Flowers.

Supervision: Hildebrandt, Lee, Flowers, Malpica Castillo.

Conflict of Interest Disclosures: Dr Retamales reported receiving grants to the institution from Pfizer and Sanofi outside the submitted work. Dr Ahmed reported receiving research support to the institution from Kite/Gilead, Janssen, Caribou, Bristol-Myers Squibb, and Avencell Therapeutics and serving as a consultant or advisor to ADC Therapeutics, Kite/Gilead, Genmab/Abbvie, Janssen, Avencell Therapeutics, and Bristol-Myers Squibb outside the submitted work. Dr Flowers reported having consulting agreements with BeOne; Foresight Diagnostics, a wholly-owned subsidiary of Natera Inc; Genentech, a member of the Roche Group; Genmab US Inc; and N-Power Medicine; conducting contracted research for 4D Pharma PLC; Acerta Pharma, a member of the AstraZeneca Group; Adaptimmune; Alaunos Therapeutics; Allogene Therapeutics; Amgen Inc; BostonGene; Cellectis; EMD Serono Inc; Genentech, a member of the Roche Group; Guardant Health; Iovance Biotherapeutics; Kite, a Gilead Company; MorphoSys; Nektar Therapeutics; Novartis; Pfizer Inc; Sanofi; Takeda Pharmaceuticals USA Inc; TG Therapeutics Inc; and Xencor; holding stock or stock options in Foresight Diagnostics, a wholly-owned subsidiary of Natera Inc, and N-Power Medicine; and receiving grants from the Burroughs Wellcome Fund, Cancer Prevention and Research Institute of Texas (CPRIT Scholar in Cancer Research RR190079), Eastern Cooperative Oncology Group, the National Cancer Institute, and The V Foundation for Cancer Research. No other disclosures were reported.

Funding/Support: This research was funded by the American Society of Hematology Amos Medical Faculty Development Program, the Birdies Fore Logan Foundation, and the Robert A. Winn Clinical Investigator Leadership Award.

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Meeting Presentation: This study was presented as a poster presentation at the 2025 American Society of Hematology meeting; December 6 to 9, 2025; Orlando, Florida.

Data Sharing Statement: See the Supplement.

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SUPPLEMENT.

Data Sharing Statement

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