HHS Public Access

Author manuscript

Cancer. Author manuscript; available in PMC 2022 December 15.

Published in final edited form as:

Cancer. 2021 December 15; 127(24): 4613–4619. doi:10.1002/cncr.33868.

Initial cancer treatment and survival in children, adolescents and young adults with Hodgkin lymphoma: A population-based study

Justine M. Kahn, MD, MS[1], **Frances B. Maguire, PhD, MPH**[2], **Qian Li, MS**[3], **Renata Abrahão, MD MSc PhD**[3,4], **Jamie E. Flerlage, MD**[4,5], **Elysia Alvarez, MD**[3,6], **Theresa H.M. Keegan, PhD, MS**[3]

[1]Department of Pediatrics, Columbia University Irving Medical Center, New York, NY

[2]California Cancer Reporting and Epidemiologic Surveillance Program, University of California Davis Comprehensive Cancer Center Sacramento, CA

[3]Center for Oncology Hematology Outcomes Research and Training (COHORT) and Division of Hematology and Oncology, University of California Davis School of Medicine, Sacramento, CA

[4]Center for Healthcare Policy and Research, University of California Davis School of Medicine, Sacramento-CA

[5]Department of Oncology, St Jude Children's Research Hospital, Memphis, TN

[6]Department of Pediatrics, University of California Davis School of Medicine, Sacramento, CA

Abstract

Background: Hodgkin lymphoma (HL) is a treatable tumor affecting children, adolescents, and young adults (AYA; 15 – 39 years). Population-based studies report worse survival in non-White children and AYAs but have limited data on individual therapeutic exposures. We examined overall and HL-specific survival in a population-based cohort of patients while adjusting for sociodemographic factors and treatment.

Methods: Data for 4,807 patients <40 years with HL (2007 – 2017) were obtained from the California Cancer Registry. Individual treatment information was extracted from text fields; chemotherapy regimens were defined by standard approaches for pediatric and adult HL. Multivariable Cox models examined the influence of patient and treatment factors on survival.

Results: At median follow-up of 4.4 years, 95% of patients were alive. Chemotherapy differed by age, with 70% of 22–39 vs. 41% of <22-year-olds receiving ABVD (p<0.001). In multivariable

Corresponding Author: Justine M. Kahn, MD MS, Assistant Professor of Pediatrics, Division of Pediatric Hematology/Oncology/ Stem Cell Transplantation, 161 Fort Washington Avenue, IP7, New York, NY 10032, jk2034@cumc.columbia.edu, Phone: 212-305-9770 | fax: 212-305-5848.

Contributions: **Justine M. Kahn:** Conceptualization, investigation, interpretation, writing original draft, and writing–review and editing; **Frances B. Maguire**: Conceptualization, methodology, investigation, writing– review and resources. **Qian Li**: Conceptualization, methodology, analysis, writing–review and editing; **Jamie E. Flerlage**: Investigation, writing–review and editing; **Renata Abrahão**: Methodology, interpretation and writing–review and editing; **Elysia Alvarez**: Investigation, writing–review and editing; **Theresa H. M. Keegan**: Conceptualization, investigation, methodology, writing-original draft, writing– review and editing, resources, and supervision.

Conflict of interest: The authors have no conflicts of interest to declare

models, older (22 – 39 vs. <22y; hazard ratio (HR): 1.52, 95% confidence interval (CI): 1.10, 2.09), Black (vs. White; HR: 1.90, 95%CI 1.25, 2.88) and Hispanic (HR: 1.48, 95%CI: 1.07, 2.03) patients experienced worse survival; among those <22 years, older age (15 – 21) was associated with 1.2-fold increased risk of death (HR: 1.22, 95%CI 1.02, 1.46) and Black race was associated with 3.6-fold increased risk of death (HR: 3.64, 95%CI 1.48, 8.95).

Conclusion: In children and AYAs with HL, older age and non-White race/ethnicity predicted worse survival after adjusting for treatment data. Further work is needed to identify biologic and non-biologic factors driving disparities in these at-risk populations.

Précis:

Adjusting for chemotherapy regimen and treatment details in this population-based cohort did not mitigate survival differences by age, with AYAs being more likely to die than children with Hodgkin Lymphoma. In Black (vs. White) children, the risk of death from Hodgkin Lymphoma was up to 5-fold increased even after adjusting for detailed treatment data.

Keywords

pediatric; adolescent; adolescent and young adult (AYA); disparities; Hodgkin lymphoma; registry; outcomes

Introduction

Hodgkin lymphoma (HL) accounts for 20% of annual cancer diagnoses in children, adolescents, and young adults (AYA; 15 – 39 years) in the United States (U.S.).[1] While 5-year overall survival (OS) rates in HL are generally excellent (94 – 96%),[1] older (vs. younger) age and non-White (vs. White) race/ethnicity are consistently associated with worse outcomes.[2–4] Proposed hypotheses for these disparities broadly include racial/ethnic and age-related differences in access to high-quality cancer care, variations in disease or host biology and treatment-related toxicities, and long-term follow-up care. [4,5] Disentangling the influence of these factors on clinical cancer outcomes has been a long-time challenge, particularly in population-based cohorts where individual-level treatment information is limited. In a California Cancer Registry (CCR) analysis of AYA cancer outcomes, we reported that Black and Hispanic race/ethnicity, low neighborhood socioeconomic status (SES) and public or no health insurance predicted worse HL-specific and OS.[5] Because treatment data were unavailable for analysis, whether differences in therapy contributed to observed disparities could not be assessed. In the present study we address this limitation by incorporating detailed patient-level treatment information into analyses of OS and disease-specific survival (DSS) in a large registry cohort of children and AYAs with HL.

Materials and Methods

Setting and Patients

We included all patients <40 years residing in California when diagnosed with classical HL between 2007 and 2017, and reported to the CCR. From the CCR, which operates under a state cancer reporting law and comprises three National Cancer Institute (NCI) Surveillance

Epidemiology and End Results (SEER) program registries, we obtained information from the medical record at diagnosis for each patient on age, sex, race/ethnicity, insurance, American Joint Committee on Cancer (AJCC) stage, B-symptoms, histologic subtype, initial treatment (chemotherapy, radiotherapy [RT]), hospital providing initial care (NCI-designated cancer center [NCI-CC] or not) and census-block group of residence. Hematopoietic cell transplantation (HCT) was determined from the CCR and by linking to hospital admission data from California's Office of Statewide Health Planning and Development. Patients diagnosed by death certificate or autopsy and patients with incomplete information or inconsistent survival time were also excluded (Figure 1).

Age categories were defined as ≤21 vs. 22 – 39 years based on the American Academy of Pediatrics[6] definitions.[7] For sub-analyses within age groups, age <15 years defined pediatric vs. adolescent according to the NCI definition of AYA (15 – 39). Racial/ethnic categories were White, Black, Hispanic, Asian/Pacific Islander (A/PI) or other/mixed race. We used a multi-component index of SES based on patients' residential census-block group at diagnosis.[8] Vital status (determined by the CCR through hospital follow-up and external linkages) as of December 31, 2017 was obtained. For the deceased, underlying cause of death as coded by state vital statistics personnel was included and defined as lymphoma, other cancer, cardiovascular or other/unknown.

Chemotherapy regimens: Detailed data about chemotherapy drugs and administration dates were extracted from unstructured free-text fields in the CCR; first-line regimen was defined by initial combination of drugs and were based on standard pediatric and adult approaches in HL.[9] These included ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine), BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone), ABVE-PC (doxorubicin, bleomycin, vincristine, etoposide, prednisone, cyclophosphamide), and the Stanford V regimen (doxorubicin, vinblastine, nitrogen mustard, etoposide, vincristine, bleomycin, prednisone). Regimens were considered modified if they omitted one drug from a standard protocol but were otherwise administered according to expected dosing schedules, as in the German Hodgkin Study Group trial HD13[10] or as is done in the setting of toxicities or drug shortages.

Statistical analyses

Descriptive statistics characterized the study population. Chi-squared tests assessed whether sociodemographic and clinical characteristics varied by age and/or race/ethnicity. Outcomes included OS, which considers death from all causes, and DSS, which considers death from HL. For deceased patients, survival time was measured in days from diagnosis date to date of death from any cause for OS, and to date of death from HL for DSS. Patients who died from other causes were censored at the time of death in analyses of DSS. Patients alive at study completion were censored at that time or at the date of last known contact.

Multivariable Cox proportional hazards regression models were used to examine the influence of sociodemographic and clinical variables on survival outcomes overall and by age group, and are presented as adjusted hazard ratios (HRs) with corresponding 95% confidence intervals (CI). Final models were adjusted for race/ethnicity, sex, insurance, SES,

HL histology, stage at diagnosis, presence of B symptoms, chemotherapy regimen, RT, and receipt of HCT. Receipt of HCT was included in the models as a time-dependent variable to avoid "immortal time" bias. Location-of-care was not significantly associated with outcome in univariate models and was thus omitted from final models. The proportional hazards assumption was assessed numerically based on cumulative sums of Martingale residuals and visually based on inspection of the survival curves [log (−log) of the survival distribution function by log (months)]; no variable violated this assumption. Statistical analyses were performed using SAS statistical software (version 9.4), and a 2-sided P value < 0.05 was considered statistically significant. Analyses were overseen by University of California, Davis Institutional Review Board.

Results

Of 4,807 patients, 33% were ≤21 years (N= 1,605) and 67% were 22–39 years (N= 3,202) (Table 1). Compared with patients 22–39 years, a higher proportion of those ≤21 years were Hispanic (39% vs. 31%, p<0.001), and had public (vs. private) insurance (36% vs. 27% p<0.001). Baseline characteristics by race/ethnicity and age (<15, 15 – 21) are in Supplementary Tables 1 and 2. In brief, 44% and 46% of Black and Hispanic patients, respectively, had public or no insurance vs. 20% of White patients (p<0.001). A higher proportion of Black (vs. White) patients had B symptoms (53% vs. 41%, p< 0.001), and fewer Hispanic (vs. White) patients had nodular sclerosis histology (63% vs. 71%, p<0.001).

Treatment:

In total, 41% of patients ≤21 years and 70% of patients 22 – 39 years received ABVD (p<0.001) (Table 1); 39% of patients ≤21 years received RT vs. 26% of those 22–39 (p<0.001). Among all patients, fewer Black and Hispanic (vs. White) patients received RT (26 – 27% vs. 32%, p<0.001) (Supplemental Table 1).

Survival:

Median follow-up was 4.4 years. Pooled OS was 95% and did not differ significantly between patients ≤21 years and 22 – 39 (96% vs. 94%, p= 0.070) in unadjusted analyses (Table 1). In adjusted models, ages 22 – 39 years (vs. ≤21) conferred worse OS (HR: 1.53, 95% CI: 1.11, 2.10) (Table 2). Unadjusted survival probabilities differed significantly by race/ethnicity with OS rates of 96% in White patients vs. 90% in Black patients (p<0.001) (Supplemental Table 1). In multivariable analyses, these differences remained significant with Black (vs. White) patients having worse OS (HR: 1.90, 95% CI: 1.25, 2.88) and worse DSS (HR: 1.80, 95% CI: 1.04, 3.14). Similarly, Hispanic (vs. White) patients had worse OS and DSS (OS: HR: 1.45, 95% CI: 1.06, 1.99; DSS: 1.55, CI: 1.03, 2.33). Among all patients, having public/no vs. private insurance conferred worse OS (HR: 1.75, 95% CI: 1.32, 2.31), however neighborhood SES was not significantly associated with either OS or DSS (Table 2). Chemotherapy regimen was not significantly associated with survival in those receiving standard regimens, however chemotherapy regimen NOS was associated with worse OS (HR: 2.10, CI 1.04, 4.25). Lastly, RT was not associated with survival and undergoing HCT predicted up to 8-fold increased risk of death from HL (HR: 8.59, CI: 5.84, 12.64) (Table 2).

Among patients ≤21 years, Black (vs. White) patients had significantly worse OS (HR: 3.26, CI: 1.43, 7.42) and DSS (HR: 5.59, CI: 1.93, 16.20) (Table 3). Among patients 22–39 years, survival additionally differed by age with those 30–39 (vs. 22 – 29) having worse OS (HR: 1.51, CI: 1.12, 2.05) (Table 3); for every one-year increase in age (modeled continuously), HRs for OS and DSS increased by 2% and 4%, respectively (Supplemental Table 3). In this 22 – 39-year age group, Black (vs. White) race/ethnicity predicted worse OS (HR: 1.65, 95% CI: 1.00, 2.71), but was not associated with DSS (Table 3). In contrast to observations in the younger patients, receipt of BEACOPP was associated with worse OS (HR: 2.54, CI: 1.01, 6.40) and DSS (HR: 3.50, CI:1.35, 9.10).

Discussion

In this registry cohort of 4,807 children and AYAs with HL, we report findings consistent with previous population-basesd [4,5,11] and cooperative group studies[12,13] demonstrating inferior survival in older (vs. younger), and in Black and Hispanic[2] (vs. White) patients.[14] Of significant concern are Black patients <22 years who were 5-times more likely to die than White patients after adjusting for insurance, SES, and initial therapy. These findings suggest that factors other than chemotherapy, including access, clinical trial participation, treatment-related toxicities, and long-term survivorship care likely also contribute.[15]

As expected, initial treatment regimen differed by age, with AYAs being more likely than children to receive ABVD, and less likely to receive RT by design.[16] After adjusting for treatment, older age remained associated with worse OS in patients 22 – 39 years. This finding is consistent with observations from recent clinical trials,[16] where adjusting for therapy did not change the effect of age on survival, raising the possibility of differences in treatment tolerability, toxicities and post-therapy follow-up across the age spectrum.[12] Patients 22 – 39 years who received BEACOPP (vs. ABVD) experienced worse OS. Given known toxicities associated with this regimen, it is possible that older patients may have experienced more treatment-related mortality, however additional work is needed to explore this further. [17]

This study builds on our prior CCR analyses demonstrating worse survival in Black and Hispanic (vs. White) patients, with the addition of detailed chemotherapy regimen in multivariable models. These findings are consistent with analyses from Grubb and colleagues who reported worse outcomes in Black vs. White children using Florida Cancer Registry data.[11] As they were unable to adjust for treatment in this analysis, differences in therapy remained a potential explanation for these findings.[14] Potential drivers of disparities in our cohort may relate to differences in toxicities, drug metabolism, chemotherapy sensitivity and/or access to care. In a recent analysis of clinical trials data from the Children's Oncology Group (COG), event-free survival did not differ by race. Adjusted OS, however, was worse in Black and Hispanic children, a finding largely driven by inferior post-relapse outcomes in these groups.[2] Authors hypothesized that post-relapse disparities may have resulted from racial/ethnic differences in access to novel salvage regimens, under-enrollment on early phases clinical trials, and variable receipt of HCT in the non-White group, as has been reported in other analyses.[1819] These factors may also have contributed to

the findings of the present analyses, thus further analyses to identify un-measured variables impacting access and survival in the non-White patients are urgently needed.[18]

Public insurance conferred worse OS across all patients and, among those 22 – 39 years, worse DSS. Our previous study in California revealed that AYA age and public insurance were associated with advanced stage HL.[20] In a separate analysis of AYA outcomes, those with Medicaid insurance (vs. private) had worse cancer-specific survival. Those who were continuously insured fared better than those with breaks in coverage.[21] These findings are relevant for policy interventions to improve cancer prevention, treatment and long-term care in AYAs. Of relevance to our cohort, while recent studies examining the impact of the Affordable Care Act-Dependent Coverage Expansion demonstrate fewer uninsured AYAs with cancer,[22,23] this benefit has not been observed among Black patients or patients from low SES neighborhoods in California.

This study has limitations. While drugs and chemotherapy regimens were defined for each patient, we considered only the first course of therapy, and data on dose modifications were not available, nor were data on RT doses and fields. We could not adjust for differences in biology beyond histology, and could not incorporate bulky disease or interim treatment response into models. As median follow up was <5 years, differences in late effects by age and race/ethnicity[19] are largely unaccounted for in this analysis, as are potential differences in treatment-related mortality.

This study, which is the largest of its kind to date, adds to the growing body of evidence demonstrating that outcome disparities by age and race/ethnicity persist in our most treatable tumors, and that variations in up-front chemotherapy are insufficient to explain these differences. Work is now needed to determine the extent to which other components of care such as clinical trial enrollment, salvage therapy, early and late toxicities, and patterns of long-term follow-up contribute to these disparities so that targeted interventions to improve the survival of these patients can be expeditiously developed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding:

This work is supported in part by The Lymphoma Research Foundation and a KL2 Mentored Career Development Award Grant No. KL2-TR001874 from the Irving Institute for Clinical and Translational Research at Columbia University Irving Medical Center (J.M.K.); The Health Resources and Services Administration (HRSA) of the U.S. Department of Health and Human Services (HHS) under grant number T32HP30037 for Research in Primary Care (R.A).; The California Department of Public Health as part of the statewide cancer reporting program mandated by California Health and Safety Code Section 103885; the National Cancer Institute's Surveillance, Epidemiology and End Results Program under contracts awarded to the Cancer Prevention Institute of California, the University of Southern California, and the Public Health Institute; and the Centers for Disease Control and Prevention's National Program of Cancer Registries, under agreement awarded to the California Department of Public Health. (F.B.M.; Q.L.).

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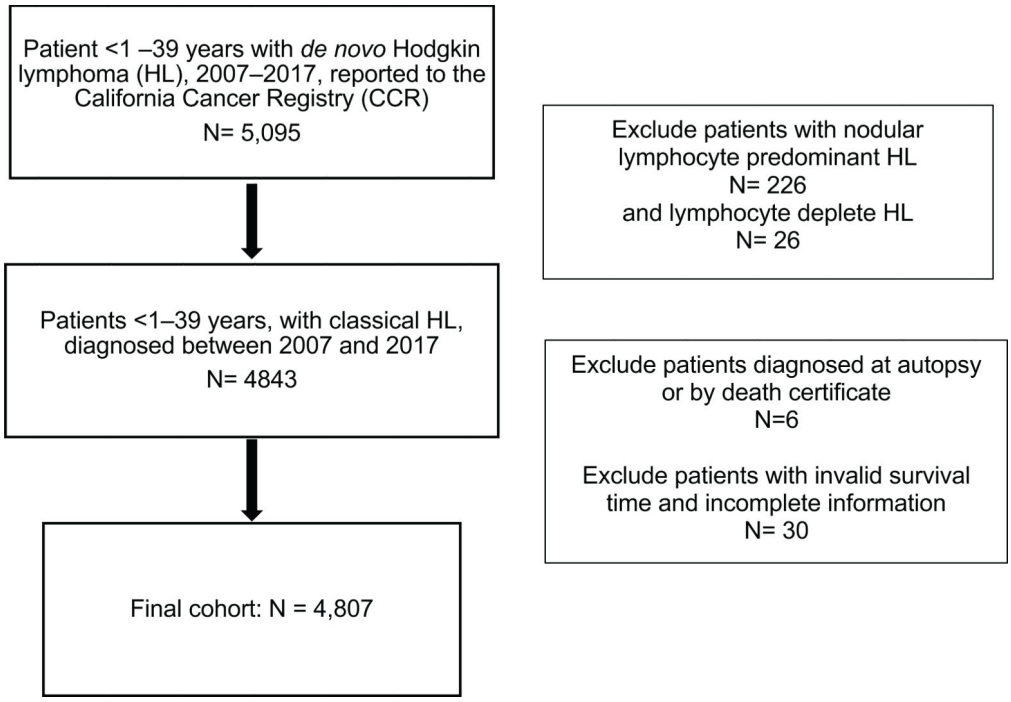

Figure 1:
Study cohort

Table 1.

Characteristics of 4,807 patient ages ≤39 years with classical Hodgkin lymphoma overall, and by age group, California, 2007 – 2017.

		≤21 years	22 – 39 years	p-value*
	N (%)	N (%)	N (%)	
Total	**N= 4807 (100)**	**N= 1605 (33)**	**N= 3202 (67)**	
Race/ethnicity				
White	2298 (48)	689 (43)	1609 (50)	
Black	336 (7)	110 (7)	226 (7)	
Hispanic	1611 (34)	628 (39)	983 (31)	
NH Asian/PI	480 (10)	153 (10)	327 (10)	
Other/Unknown	82 (2)	25 (2)	57 (2)	**<0.001**
Sex				
Male	2474 (51)	808 (50)	1666 (52)	
Female	2333 (49)	797 (50)	1536 (48)	0.269
Health insurance				
Private	3214 (67)	993 (62)	2221 (69)	
Public/none	1446 (30)	575 (36)	871 (27)	
Unknown	147 (3)	37 (2)	110 (3)	**<0.001**
Neighborhood SES				
Low SES	1467 (31)	527 (33)	940 (29)	
Middle SES	1689 (35)	530 (33)	1159 (36)	
High SES	1651 (34)	548 (34)	1103 (34)	**0.026**
Stage				
Stage I	420 (9)	104 (6)	316 (10)	
Stage II	2340 (49)	779 (49)	1561 (49)	
Stage III	950 (20)	337 (21)	613 (19)	
Stage IV	855 (18)	309 (19)	546 (17)	
Unknown	242 (5)	76 (5)	166 (5)	**0.007**
B symptoms				
No	2265 (47)	814 (51)	1451 (45)	
Yes	2075 (43)	676 (42)	1399 (44)	
Unknown	467 (10)	115 (7)	352 (11)	**<0.001**
Histology				
Classical HL, NOS	1136 (24)	368 (23)	768 (24)	
Mixed cellularity	406 (8)	136 (8)	270 (8)	
Nodular sclerosis	3265 (68)	1101 (69)	2164 (68)	0.716
NCI Cancer Center				
No	3505 (73)	991 (62)	2514 (79)	
Yes	1302 (27)	614 (38)	688 (21)	**<0.001**
Radiation therapy				

		≤21 years	22 – 39 years	p-value*
Total	**N (%) N= 4807 (100)**	**N (%) N= 1605 (33)**	**N (%) N= 3202 (67)**	
No radiation/unknown	3341 (70)	983 (61)	2358 (74)	
Radiation	1466 (30)	622 (39)	844 (26)	**<0.001**
Chemotherapy regimen				
ABVD	2913 (61)	665 (41)	2248 (70)	
ABVE-PC	159 (3)	158 (10)	~	
BEACOPP	98 (2)	68 (4)	30 (1)	
Stanford V	234 (5)	96 (6)	138 (4)	
Modified regimen	661 (14)	383 (24)	278 (9)	
Standard regimen, other	160 (3)	97 (6)	63 (2)	
Unknown treatment	420 (9)	101 (6)	319 (10)	
Chemo, NOS	162 (3)	37 (2)	125 (4)	**<0.001**
Hematopoietic cell transplantation				
Yes	460 (10)	128 (8)	332 (10)	
No	4347 (90)	1477 (92)	2870 (90)	**0.008**
Cause of death				
Alive	4566 (95)	1543 (96)	3023 (94)	
Death from lymphoma (HL+NHL)	167 (3)	42 (3)	125(4)	
Death from other cancer	~	~	~	
Death from heart/cerebrovascular	7(<1)	~	5 (<1)	
Death from other cause	45(1)	10 (1)	35 (1)	
Death from unknown cause	19(<1)	6 (<1)	13 (<1)	0.089

Abbreviations: SES: socioeconomic status; NCI: National Cancer Institute; NOS: not-otherwise specified; ABVD: doxorubicin, bleomycin, vinblastine, dacarbazine ABVE-PC: doxorubicin, bleomycin, vincristine, etoposide, prednisone, cyclophosphamide; BEACOPP: bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone Stanford V: doxorubicin, vinblastine, nitrogen mustard, etoposide, vincristine, bleomycin, prednisone

~Data not shown due to too few (<5) patients

Table 2.

Multivariable* adjusted hazard ratio (HR) and 95% confidence interval (CI) estimates for overall survival and disease-specific survival (DSS) in children and adolescent and young adult patients with classical Hodgkin lymphoma, California, 2007– 2017. **Significant HRs are in bold.**

	Overall survival HR (95% CI)	Disease-specific survival HR (95% CI)
Age at diagnosis (years; R: < 21)		
22 – 39	**1.53 (1.11, 2.10)**	1.50 (0.99, 2.27)
Sex (R: Male)		
Female	0.86 (0.66, 1.13)	0.85 (0.60, 1.21)
Race/ethnicity (R: NH White)		
Black	**1.90 (1.25, 2.88)**	**1.80 (1.04, 3.14)**
Hispanic	**1.45 (1.06, 1.99)**	**1.55 (1.03, 2.33)**
Asian/PI	1.17 (0.74, 1.86)	1.07 (0.59, 1.94)
Health insurance (R: Private)		
Public/none	**1.75 (1.32, 2.31)**	1.41 (0.97, 2.05)
Unknown	**2.12 (1.08, 4.13)**	**2.82 (1.33, 6.00)**
Neighborhood SES (R: High)		
Low	0.86 (0.60, 1.24)	0.79 (0.49, 1.28)
Middle	1.05 (0.76, 1.45)	1.11 (0.74, 1.68)
Stage (R: Stage I)		
Stage II	1.30 (0.68, 2.48)	1.52 (0.60, 3.89)
Stage III	1.78 (0.91, 3.47)	1.71 (0.65, 4.54)
Stage IV	**2.07 (1.06, 4.02)**	2.52 (0.97, 6.56)
B-symptoms (R: No)		
Yes	**2.33 (1.68, 3.22)**	**2.24 (1.48, 3.41)**
Unknown	1.56 (0.87, 2.78)	2.08 (0.97, 4.44)
Radiation therapy (R: Yes)		
No/unknown	1.11 (0.80, 1.52)	0.79 (0.54, 1.17)
Histology (R: Nodular sclerosing)		
Classical HL, NOS	**1.65 (1.24, 2.21)**	**1.50 (1.02, 2.21)**
Mixed cellularity	0.92 (0.57, 1.50)	0.86 (0.44, 1.67)
Chemotherapy regimen (R: ABVD)		
ABVE-PC	0.75 (0.23, 2.46)	0.30 (0.04, 2.25)
BEACOPP	1.13 (0.49, 2.62)	1.64 (0.69, 3.91)
Stanford V	1.06 (0.54, 2.07)	0.50 (0.18, 1.40)
Modified regimens	1.43 (0.97, 2.10)	1.01 (0.59, 1.73)
Unknown chemotherapy	1.45 (0.81, 2.57)	0.53 (0.18, 1.57)
Chemo, NOS	**2.10 (1.04, 4.25)**	0.68 (0.16, 2.86)
Hematopoietic cell transplantation (R: No)		

	Overall survival HR (95% CI)	Disease-specific survival HR (95% CI)
Yes	**7.75 (5.65, 10.62)**	**8.59 (5.84, 12.64)**

Abbreviations: R: reference group; SES: socioeconomic status; NOS: not-otherwise specified;

ABVD: doxorubicin, bleomycin, vinblastine, dacarbazine ABVE-PC: doxorubicin, bleomycin, vincristine, etoposide, prednisone, cyclophosphamide; BEACOPP: bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone Stanford V: doxorubicin, vinblastine, nitrogen mustard, etoposide, vincristine, bleomycin, prednisone

Table 3.

Multivariable * adjusted hazard ratio (HR) and 95% confidence interval (CI) estimates for overall survival (OS) and disease-specific survival (DSS) in children and adolescent/young adult patients with classical HL, by age group, California, 2007– 2017. **Significant HRs are in bold.**

	Ages ≤21 years		Ages 22–39 years	
	OS HR (95% CI)	**DSS HR (95% CI)**	**OS HR (95% CI)**	**DSS HR (95% CI)**
Age				
15– 21 (R: ≤14)	2.15 (0.94, 4.95)	2.56 (0.80, 8.19)		
30 – 39 (R: 22 – 29y)			**1.51 (1.12, 2.05)**	1.30 (0.88, 1.93)
Sex (R: Male)				
Female	0.81 (0.47, 1.38)	0.65 (0.32, 1.31)	0.88 (0.64, 1.21)	0.97 (0.64, 1.46)
Race/ethnicity (R: White)				
Hispanic	1.75 (0.87, 3.49)	2.13 (0.83, 5.44)	1.31 (0.91, 1.88)	1.36 (0.86, 2.17)
Black	**3.26 (1.43, 7.42)**	**5.59 (1.93, 16.20)**	**1.65 (1.00, 2.71)**	1.22 (0.60, 2.47)
Asian/PI	1.21 (0.46, 3.17)	1.87 (0.55, 6.41)	1.15 (0.68, 1.97)	0.94 (0.47, 1.87)
Health insurance (R: private)				
Public/none	**1.84 (1.03, 3.28)**	1.21 (0.57, 2.59)	1.77 (1.27, 2.46)	1.60 (1.04, 2.48)
Unknown	2.80 (0.78, 10.12)	4.36 (1.12, 16.93)	1.94 (0.87, 4.32)	2.56 (0.99, 6.63)
Neighborhood SES (R: high)				
Low SES	1.03 (0.50, 2.14)	1.33 (0.51, 3.47)	0.91 (0.59, 1.40)	0.72 (0.41, 1.26)
Middle SES	0.93 (0.47, 1.86)	1.28 (0.51, 3.23)	1.16 (0.80, 1.69)	1.13 (0.70, 1.80)
Stage at diagnosis (R: I)				
Stage II	1.03 (0.30, 3.58)	1.92 (0.24, 15.50)	1.44 (0.67, 3.09)	1.46 (0.51, 4.21)
Stage III	0.77 (0.20, 3.01)	1.33 (0.15, 12.11)	**2.48 (1.14, 5.41)**	2.04 (0.68, 6.12)
Stage IV	1.70 (0.47, 6.15)	2.94 (0.36, 24.19)	**2.35 (1.07, 5.13)**	2.54 (0.86, 7.48)
B-symptoms (R: No)				
Yes	1.55 (0.84, 2.86)	1.27 (0.59, 2.75)	**2.67 (1.81, 3.95)**	**2.84 (1.70, 4.73)**
Unknown	1.73 (0.53, 5.59)	1.45 (0.27, 7.72)	1.65 (0.84, 3.25)	**2.58 (1.08, 6.15)**
Histology (R: NS)				
Classical HL, NOS	1.31 (0.69, 2.45)	1.07 (0.45, 2.54)	**1.85 (1.33, 2.58)**	**1.72 (1.11, 2.68)**
Mixed cellularity	0.48 (0.14, 1.63)	0.70 (0.15, 3.20)	1.04 (0.60, 1.78)	0.93 (0.44, 1.98)
Chemotherapy regimen (R: ABVD)				
ABVE-PC	0.70 (0.19, 2.56)	0.25 (0.03, 2.21)		
BEACOPP	0.28 (0.04, 2.09)	0.46 (0.06, 3.69)	**2.54 (1.01, 6.40)**	**3.50 (1.35, 9.10)**
Stanford V	1.93 (0.66, 5.68)	1.09 (0.22, 5.33)	0.82 (0.32, 2.07)	0.34 (0.08, 1.41)
Modified regimens	0.89 (0.43, 1.84)	0.62 (0.23, 1.66)	**2.18 (1.40, 3.40)**	1.68 (0.90, 3.15)
No/unknown chemo treatment	0.37 (0.04, 3.03)	0.45 (0.04, 4.56)	**1.90 (1.04, 3.48)**	0.59 (0.17, 2.01)
Chemo, NOS	2.92 (0.63, 13.52)		1.98 (0.89, 4.45)	0.87 (0.20, 3.73)
Radiation therapy (R: Yes)				

	Ages ≤21 years		Ages 22–39 years	
	OS HR (95% CI)	**DSS HR (95% CI)**	**OS HR (95% CI)**	**DSS HR (95% CI)**
No/unknown	1.15 (0.64, 2.06)	0.98 (0.47, 2.08)	1.03 (0.69, 1.53)	0.68 (0.43, 1.09)
Hematopoietic cell transplantation (R: No)				
Yes	**8.87 (4.75, 16.58)**	**8.36 (3.71, 18.86)**	**7.56 (5.20, 10.97)**	**8.71 (5.57, 13.61)**

*Models adjusted for all variables in the table. *Abbreviations:* R: reference group; NH: non-Hispanic; SES: socioeconomic status; NOS: not-otherwise specified; ABVD: doxorubicin, bleomycin, vinblastine, dacarbazine ABVE-PC: doxorubicin, bleomycin, vincristine, etoposide, prednisone, cyclophosphamide; BEACOPP: bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone Stanford V: doxorubicin, vinblastine, nitrogen mustard, etoposide, vincristine, bleomycin, prednisone