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Survival After Diagnosis of Cardiovascular Disease in Survivors of Adolescent and Young Adult Lymphoma

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ABSTRACT

Cardiac dysfunction is a major morbidity among survivors of adolescent and young adult (AYA) lymphoma. Although high mortality after cardiovascular disease (CVD) diagnosis has been shown in other cancer survivor populations, this has not been investigated in a diverse population of survivors of AYA lymphoma. Therefore, in this study we evaluated survival after a diagnosis of CVD and investigated differences in the CVD-survival relationship. Demographics, treatment variables, and CVD diagnoses occurring at least 3 months after their lymphoma diagnosis were collected in a diverse population of AYA lymphoma survivors ($N = 825$; race/ethnicity: 58.5% White, 26.9% Hispanic, 14.5% Black). Nearly 25% (23.6%; $N = 195$) had a CVD diagnosis during the median follow-up time of 9.8 years with the median age at CVD diagnosis being 33.0 years. In Cox models with CVD as a time-varying covariate, the development of a CVD was highly associated with inferior survival (HR: 7.11, 95% CI: [4.03–12.5]). This adverse CVD-survival relationship was consistently observed among patient subpopulations; however, the magnitudes of the adverse effect of CVD on survival were most pronounced (HR > 7) among Black and Hispanic patients, NHL survivors, and those with a healthy baseline BMI. Together these findings underscore the need for cardiovascular health surveillance among survivors of AYA lymphoma to potentially mitigate this adverse effect of CVD on survival in this at-risk population.

1 | Introduction

In the United States, the incidence of cancer among adolescents and young adults (AYA, defined as having a cancer diagnosis between the ages of 15–39) has reached an estimated 89 500 new diagnoses per year [1]. Although treatment advances have led to improved 5-year survival rates for AYAs, treatment exposures in a population that is living decades after diagnosis have led to an increased burden of chronic disease comorbidity compared to the general population [2–6].

Modalities commonly used in the treatment of AYA malignancies are often cardiotoxic [1, 7–9]. Exposure to anthracyclines and radiation has previously been shown to lead to a higher rate of cardiac comorbid conditions such as congestive heart failure, pericardial disease, and valvular abnormalities [10, 11].

Common chronic conditions in AYA cancer survivors include dyslipidemia, hypertension, cardiovascular disease (CVD), and diabetes, often with multiple comorbidities present [2]. Previous studies have also shown increased mortality and hospitalization risk after major CVD events in childhood and early adolescent survivors of cancer compared to their similarly-aged peers in the general population [4, 12–14].

These cardiotoxic treatment regimens are the mainstay for AYA lymphoma patients, including anthracycline and mediastinal radiation. Few previous studies have examined the risk of mortality after CVD events in AYAs treated for lymphoma. Furthermore, prior studies in AYAs with lymphoma have been limited by size, focused on only children and/or primarily homogenous populations, with limited racial and ethnic diversity [12, 13, 15]. Knowledge regarding outcomes following a CVD event could improve clinical decision-making through risk-guided surveillance of cardiovascular health and function among AYA lymphoma survivors. Therefore, the objective of this retrospective cohort study is to evaluate overall survival in survivors of AYA Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) after a diagnosis of CVD and to investigate differences in the CVD-survival relationship by racial/ethnic subpopulation.

2 | Methods

2.1 | Study Population

Participants included in this analysis were selected from the Project DANCES (Discovery in AYA Cancer Survivors) retrospectively ascertained AYA cancer patient cohort. Project DANCES includes patients seen at MD Anderson Cancer Center (MDACC) who were diagnosed with a primary cancer within the AYA age range (15–39 years) between 2000 and 2016. A total of 837 lymphoma (HL and NHL) survivors were included in the current analysis. Patient demographics, including race/ethnicity, sex, cancer diagnosis, vital status at last follow-up, and last follow-up date, were obtained from the MDACC Cancer Registry. Data abstracted from a comprehensive medical record review included anthropometric characteristics, cancer diagnosis information (age at diagnosis, date of diagnosis), treatment variables (chemotherapy, radiation therapy, transplant status), and CVD diagnoses occurring at least 3 months after diagnosis of lymphoma. CVD diagnoses included coronary artery disease, myocardial infarction, congestive heart failure, pericardial effusion, pericarditis or myocarditis, valvular heart disease, arrhythmia, angina pectoris, transient ischemic attack, and cardiomyopathy. CVD diagnoses were ascertained via clinical documentation noted in the medical record at any timepoint following their lymphoma diagnosis. Due to low patient numbers for AYAs of Asian and other/unknown race/ethnicity ($n = 12$), the analysis was restricted to White, Hispanic, and Black patients generating the final population of 825 AYA cancer patients. This study was conducted under approval from the MDACC Institutional Review Board.

2.2 | Statistical Methods

Overall survival (OS) was defined as the time from diagnosis to death or last follow-up. To account for CVD occurring during follow-up, CVD was modeled as a time-varying covariate in Cox proportional hazards models, with patients contributing person-time before and after CVD onset. Twenty-five survivors who developed a CVD but did not have a recorded date of CVD diagnosis, were excluded from the time-varying Cox analysis. All patients were retained for descriptive analyses. Multivariable models were adjusted for age at diagnosis, cancer type, sex, race/ethnicity, anthracycline dose $> 300\,\text{mg/m}^2$, chest radiation exposure, transplant status, and baseline BMI based on CDC categories of underweight, healthy, overweight, and obese. Baseline BMI collected at time of presentation to MD Anderson, which was a median of 21 days from date of diagnosis (IQR: 0–56 days). Robust standard errors were used to account for within-patient correlation. The proportional hazards assumption was assessed using Schoenfeld residuals, with no major deviations observed. Survival curves by time-varying CVD status were visualized using a Simon–Makuch approach. Five-year survival rates were estimated using a 2-year landmark analysis and should be interpreted as survival probabilities over 5 years following the landmark (i.e., 7 years from diagnosis). Subgroup analyses were conducted according to cancer diagnosis, race/ethnicity, and BMI categories. All analyses were performed using R 4.4.1 (R Core Team, 2024).

3 | Results

3.1 | Study Population

Of the 825 patients included in the analysis (Table 1), 73.7% ($N = 608$) were diagnosed with HL and 26.3% ($N = 217$) with NHL. The most common subtype of NHL was diffuse large B-cell lymphoma (69.6%). The median age at diagnosis was 28.0 years. The population was diverse in terms of self-identified race/ethnicity with 58.5% White, 26.9% Hispanic, and 14.5% Black patients. Hypertension and hyperlipidemia were present in 16.1% ($N = 132$) and 20.0% ($N = 164$) of the survivors. About one quarter (23.6%; $N = 195$) had a CVD diagnosis subsequent to their cancer diagnosis during the median follow-up time of 9.8 years with the median age at CVD diagnosis being 33.0 years. The most frequent CVD diagnoses observed were arrythmias (20.2%) and pericardial effusions (9.2%) with 3.8% experiencing cardiomyopathy and 3.5% diagnosed with congestive heart failure (Table S1). There were differing rates of CVD events by race, with 35.0% of Black survivors, 31.1% of Hispanic survivors, and 17.4% of White survivors experiencing a CVD event after their lymphoma diagnosis ($p < 0.001$).

3.2 | Overall Survival by CVD Status

OS was detrimentally impacted by the development of CVD subsequent to being diagnosed with lymphoma (Figure 1). In the time-varying Cox model, CVD was associated with a more than 7-fold increased risk of death due to any cause (Table 2; HR: 7.11, 95% CI: 4.03–12.5, $p < 0.0001$). As a sensitivity analysis, a 2-year landmark analysis was performed to estimate 5-year survival rates by CVD events (Table 3). The development of CVD by the landmark resulted in a 17.6% reduction in 5-year survival ($p < 0.001$).

TABLE 1 | Characteristics of AYA lymphoma survivors.

	Overall	HL	NHL
N	825	608 (73.7%)	217 (26.3%)
Sex, *N* (%)			
Male	405 (49.1)	298 (49.0)	107 (49.3)
Female	420 (50.9)	310 (51.0)	110 (50.7)
Age at diagnosis [median (IQR)]	28 (21–34)	26 (21–32)	33 (27–36)
Race/ethnicity, *N* (%)			
Black	120 (14.5)	73 (12.0)	47 (21.7)
Hispanic	222 (26.9)	142 (23.4)	80 (36.9)
White	483 (58.5)	393 (64.6)	90 (41.5)
Anthracycline dose > 300 mg/m^2, *N* (%)	68 (8.2)	43 (7.1)	25 (11.5)
Chest radiation, *N* (%)	318 (40.1)	282 (48.5)	36 (17.0)
Transplant, *N* (%)	196 (23.9)	151 (24.9)	45 (21.1)
Baseline BMI category, *N* (%)			
Underweight	29 (4.2)	23 (4.5)	6 (3.4)
Healthy weight	243 (35.0)	192 (37.2)	51 (28.5)
Overweight	199 (28.6)	145 (28.1)	54 (30.2)
Obese	224 (32.2)	156 (30.2)	68 (38.0)
CVD diagnosis, *N* (%)	195 (23.6)	146 (24.0)	49 (22.6)
Age at CVD diagnosis, median (IQR)	33 (26–39)	31 (26–38)	38 (30–39)
Hypertension, *N* (%)	164 (20.0)	103 (17.0)	61 (28.4)
Hyperlipidemia, *N* (%)	132 (16.1)	93 (15.3)	39 (18.2)
Vital status, *N* (%)			
Alive	692 (83.9)	523 (86.0)	169 (77.9)
Deceased	133 (16.1)	85 (14.0)	48 (22.1)
Follow-up time (years), median (IQR)	9.8 (6.3–14.5)	9.8 (6.4–14.6)	9.7 (6.0–14.3)

3.3 | Differences in Survival After CVD Onset by Sociodemographic Factors

We next explored the potential for differences in this relationship with survival by patient subpopulations. The detrimental effect of CVD on survival was consistently evident across sociodemographic variables, although the magnitude of the effect did vary across subpopulations (Table 2). Although CVD was significantly associated with reduced overall survival for both HL and NHL patients (Figure 2A), the adverse effect of CVD among HL patients (HR: 5.68, 95% CI: 2.87–11.2) was nearly half the risk due to CVD observed for NHL patients (HR: 11.6, 95% CI: 4.02–33.6). Similarly, CVD conferred an adverse impact on survival within each of the subpopulations defined by race/ethnicity (Figure 2B). However, the magnitude of the effect of CVD on survival appeared greater among Black (HR: 8.75, 95% CI: 2.49–30.8) and Hispanic (HR: 11.6, 95% CI: 3.82–35.1) survivors. Patients who were overweight or obese had an approximately 6-fold increased risk of death associated with CVD (Figure 2C). This risk of poor survival among normal weight individuals due to CVD increased to over 11-fold (HR: 11.7, 95% CI: 3.49–39.4). Due to the limited number of underweight patients in the dataset, survival analysis was not conducted for this subgroup. Confidence intervals were wider in subgroup analyses, reflecting smaller sample sizes within strata.

4 | Discussion

This study underscores the adverse impact of CVD on long-term survival outcomes in a large, diverse cohort of survivors of AYAs diagnosed with lymphoma. This negative association between a CVD diagnosis after cancer and survival was consistent and universal, regardless of lymphoma diagnosis, race/ethnicity, and baseline BMI—although the magnitude of the adverse effect of CVD did vary by subgroup. These findings, in a young

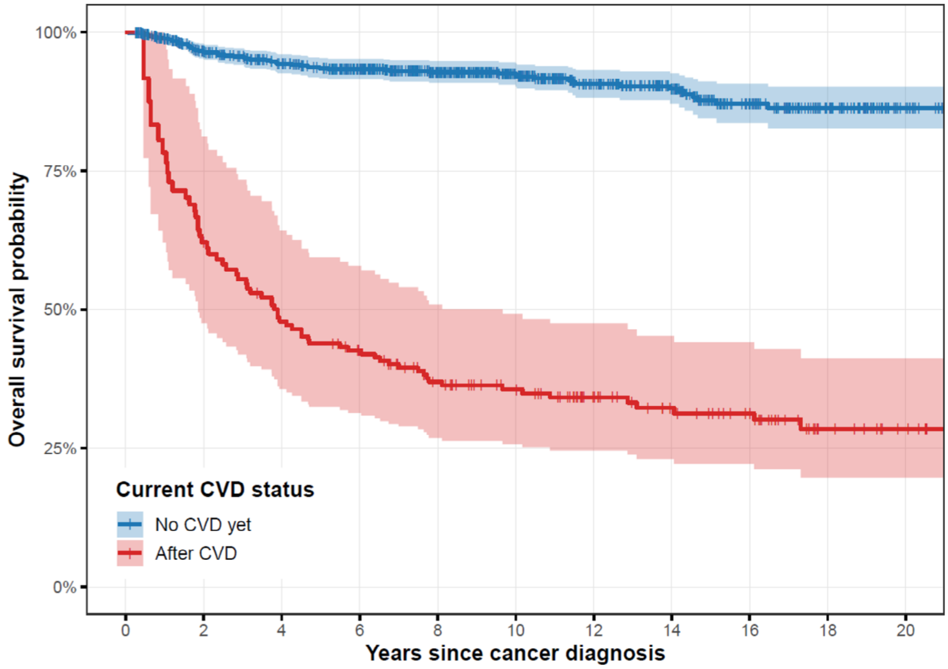

FIGURE 1 | Survival by time-varying CVD status among AYA lymphoma survivors. Survival curves were visualized using the Simon–Makuch approach, in which patients contribute person-time to the non-CVD group prior to CVD onset and to the CVD group thereafter. Shaded areas represent 95% confidence intervals.

TABLE 2 | Risk of dying associated with time-varying CVD status among AYA lymphoma survivors.

	CVD development, *N* (%)	HR[a]	95% CI	*p*
Overall	195 (19.1)	7.11	4.03–12.5	< 0.0001
Cancer diagnosis: HL	146 (19.4)	5.68	2.87–11.2	< 0.001
NHL	49 (18.4)	11.6	4.02–33.6	< 0.001
Race/ethnicity: Black	42 (25.9)	8.75	2.49–30.8	< 0.001
Hispanic	69 (23.7)	11.6	3.82–35.1	< 0.001
White	84 (14.8)	5.10	2.27–11.4	< 0.001
Baseline BMI: Healthy weight	39 (19.5)	11.7	3.49–39.4	< 0.001
Overweight	42 (17.4)	6.14	2.10–17.9	< 0.001
Obese	63 (22.0)	6.12	2.57–14.5	< 0.001

[a]CVD modeled as a time-varying covariate in Cox proportional hazard models adjusted for age at diagnosis, cancer type, sex, race/ethnicity, anthracycline dose > 300 mg/m^2, chest radiation exposure, transplant status, and baseline BMI. The stratified variable was not included as an adjustment covariate in the corresponding subgroup analyses.

TABLE 3 | Five-year overall survival from a 2-year landmark among AYA lymphoma survivors.

		N	5-year survival rate (95% CI)[a]	*p*
Overall	No CVD	541	93.8 (92–95.6)	< 0.001
	CVD	36	76.2 (65.7–88.5)	

[a]Five-year survival rates were estimated using Kaplan–Meier methods from a 2-year landmark. *p* values are based on log-rank tests comparing groups for all samples.

patient population within a follow-up time of approximately 10 years, indicate that, despite increasing lymphoma cure rates, the development of CVD increases the risk of early mortality.

Although cardiac morbidity associated with cancer treatment has been well described [4, 16–18], there is a gap of the impact of a cardiovascular disease diagnosis on mortality in survivors of AYA cancer. An analysis of over 5600 individuals from the Kaiser Permanente AYA Cancer Survivors Study with a 10:1 matched comparison group reported a greater than 10-fold increased mortality risk for those with a CVD than survivors without CVD, with an average follow-up time of 6.4 years after cancer diagnosis [19]. That magnitude of risk is over 1.5 times that observed in this study. However, there are differences in our patient populations that may be influencing this difference in effect, including differences in health care systems, the inclusion of all AYA cancer diagnoses, and differences in the racial/ethnic composition of the study populations. Due to the limited

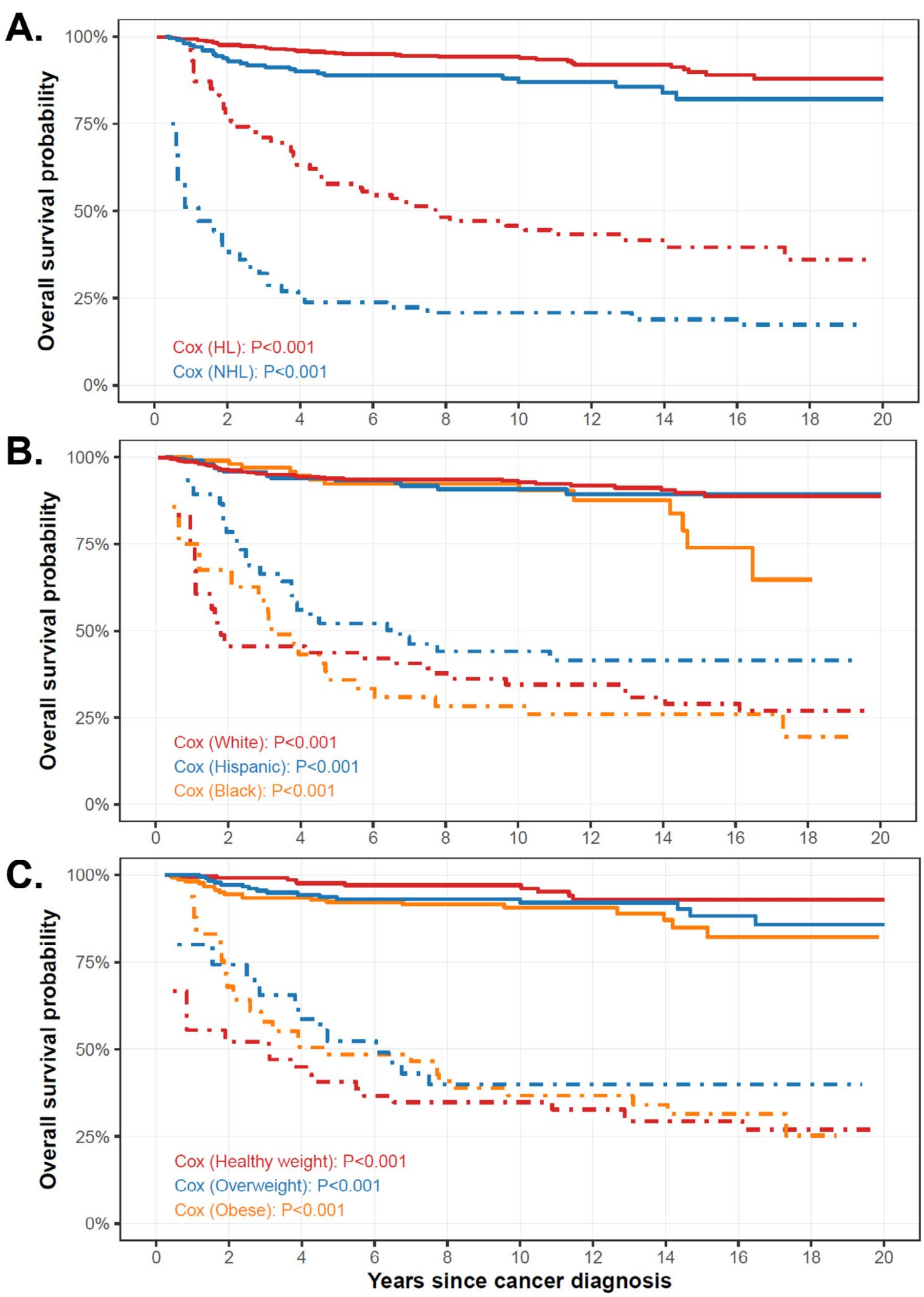

FIGURE 2 | Survival by time-varying CVD status among AYA lymphoma survivors by subpopulation. (A) By lymphoma diagnosis; (B) by race/ethnicity; (C) by baseline BMI. Survival curves were visualized using the Simon–Makuch approach, in which patients transition from the non-CVD group to the CVD group over time. Dotted lines representing survival after CVD onset.

number of individual CVD diagnoses currently present in this cohort, the analyses were conducted on a summary CVD endpoint. With increased follow-up time it is anticipated that the number of CVD diagnoses will increase, facilitating future studies focusing on the impact of specific CVD diagnosis (i.e., myocardial infarction, cardiomyopathy). These analyses would be of great interest to further define the CVD-survival relationships.

Hispanic and Black patients have a higher risk of CVD and CVD-related mortality in the general population [20, 21]. Similarly, previous studies by our group have identified a magnified risk of chronic health conditions among Hispanic and Black survivors of AYA cancer leveraging population-based datasets [22–24]. In this study, we were able to extend these findings to identify disparities in the CVD-survival relationship. Although CVD had a negative impact on survival across all race/ethnic subgroups, Hispanic and Black patients had an elevated risk of death after a CVD diagnosis than the risk observed for White patients after a CVD. However, the number of Hispanic and Black patients included in this analysis is limited and the findings should be viewed with this in mind. Continued expansion of inclusive survivorship studies is needed to fully evaluate outcomes in understudied populations. Yet, even with the limited sample size, these findings mirror the underlying increased burden of CVD-related mortality among minoritized populations. Future studies exploring the potential drivers of disparities would be important to potentially intervene and mitigate these survival differences.

Obesity is an established risk factor for CVD and CVD-related mortality [25–27]. In our analysis, the impact of CVD diagnosis on survival for normal weight patients was greater than the magnitudes of risks observed for overweight and obese patients with CVD compared to their matched cohorts without CVD. This seemingly paradoxical CVD-survival link with patients having lower BMI experiencing the highest risk of death following CVD may be explained, in part, by the obesity paradox and the complex relationship between energy reserves and survival after a disease diagnosis. Previous studies in HL and non-Hodgkin lymphoma patients have observed improved cancer-specific survival among patients with higher adiposity [28–30]. Non-obese HL patients also had increased risk of hospital and ER admissions due to chemotherapy-related complications compared to obese patients [31]. The combined effect of cancer and CVD diagnoses may overwhelm the relatively limited nutrient and energy reserves in lean survivors of AYA cancer. Rapid weight loss due to a lymphoma diagnosis, particularly for HL patients, may also have an impact on these findings as the baseline weight may not be indicative of the patient's normal weight and energy reserves. Of note, we had only a few survivors who were classified as underweight at baseline ($N=29$), thus they were excluded from the survival risk analyses reported in Table 3. Future studies in this population would be of interest to determine if the impact of CVD on survival among underweight survivors mirrors that of normal weight survivors or of that overweight/obese survivors. It should be noted that, given the limited number of events within subgroups, the findings from the subgroup analyses should be interpreted cautiously and viewed as hypothesis-generating.

This study's main strength lies in the large number of AYA lymphoma survivors included with a relatively long follow-up time to conduct robust statistical analysis with CVD diagnosis ascertained by in-depth abstraction from medical records. In addition, the diversity of the population included in this study is more representative of the current United States racial and ethnic makeup as compared to other AYA cancer survivor studies, which is important in understanding generalizable trends within the inequities of cancer survivorship. A potential limitation of this study is that the participant population comes from a large, tertiary comprehensive cancer center, which does not encompass a patient population that is fully generalizable to other cancer care settings, such as community oncology clinics, as these patients may not have had access to sub-specialized cancer care or clinical trials. Studies that incorporate cause-specific survival, which was lacking in this survivor cohort, would be valuable in understanding if deaths subsequent to the development of CVD are due to the lymphoma or the CVD, which may help to illuminate the underlying cause of these findings. However, the long-term survival trajectory for AYAs with lymphoma is favorable, suggesting that these deaths are likely not due to the cancer and the findings of the landmark analysis at 2 years were consistent with this pattern. Finally, studies are needed to understand how CVD development and subsequent impact on survival is changing with current treatment approaches. As this was a retrospective analysis of patients diagnosed between 2000 and 2016, patients who received newer therapies, such as checkpoint inhibitors [32], are limited in this cohort. Chemotherapy-based regimens are also evolving to minimize exposure to cardiotoxic therapies. For example, a study done in the Netherlands showed that survival outcomes were comparable in lymphoma patients treated with R-CEOP, which substitutes etoposide for the anthracycline in R-CHOP [33]. However, despite the new advances in lymphoma care, anthracyclines and radiation remain a backbone of many upfront chemotherapy regimens for AYA lymphoma.

In conclusion, survival outcomes were inferior for survivors of AYA lymphoma diagnosed with CVD subsequent to their cancer diagnosis. Our analysis suggests that this burden may not be shared equally based on sociodemographic and patient characteristics. These findings are of particular concern as this study encompasses a young population of cancer survivors who are likely to live many decades beyond their cancer diagnosis and it is anticipated that the adverse impact of CVD on survival in this population will become further magnified with extended follow-up. Together, these findings provide strong support for screening and cardiovascular follow-up care of AYA lymphoma survivors to mitigate the adverse impact of CVD on survival, especially due to CVD diagnoses appearing at younger ages among this survivor population.

Author Contributions

Conceptualization: K.G., M.E.R., and M.A.T.H. Acquisition of data: K.G., M.G., A.A., C.C., A.W., and E.R.R. Analysis: K.G., J.W., and M.A.T.H. Interpretation of the findings: K.G., S.A., B.C., J.M., D.R.F., K.A.M., G.A., D.E.-K., K.A., E.K., M.E.R., J.W., and M.A.T.H. Writing draft of manuscript: K.G., J.W., and M.A.T.H. Final review and approval of manuscript: All authors.

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Disclosure

The authors have nothing to report.

Ethics Statement

The IRB of the University of Texas MD Anderson Cancer Center provided approval for this study.

Conflicts of Interest

S.A. reports serving as a consultant for ADC therapeutics, KITE/Gilead, Genmab, and BMS. The other authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Cardiovascular disease (CVD) diagnoses in study population.