Survival outcomes in diffuse large B-cell lymphoma patients with and without HIV in the United States from 2001 to 2016: a population-based analysis

People living with human immunodeficiency virus (HIV) are at an increased risk of developing diffuse large B-cell lymphoma (DLBCL) compared to the general population.[1] Although European-based cohort studies suggest similar outcomes between DLBCL patients with and without HIV after the introduction of antiretroviral therapy (ART),[2-4] United States (US) population-based studies up to 2009 reported that DLBCL patients with HIV still experience inferior survival.[5,6] Previous studies have not investigated whether survival differences in the US persist within demographic subgroups and for more recent ART regimens, which have fewer toxicities and drug-drug interactions.[7] We compared the overall survival (OS) in a contemporary cohort (2008-2016) and assessed temporal changes, reflecting changes in ART, between DLBCL patients with and without HIV overall and within demographic subgroups.

We conducted a population-based retrospective cohort study using 13 registries with available HIV status from the Surveillance, Epidemiology, and End Results (SEER) database during 2001-2016, with follow-up through 2019. We included patients newly diagnosed with DLBCL at 20-79 years of age. The following International Classification of Diseases for Oncology, 3rd edition, codes were used: 9680/3, 9684/3 (2001-2009 period), 9688/3, 9712/3, 9735/3 (2010-2016 period), 9737/3, 9738/3. Exclusion criteria were diagnosis through autopsy/death certificate (N=115), no survival time (N=181), unknown race and ethnicity (N=299), and no reported first course of chemotherapy or immunotherapy (N=10,811). This study is not considered human subjects research and did not require the exemption or approval from an Institutional Review Board or Ethics Committee.

The calendar year of DLBCL diagnosis was grouped corresponding to ART approval periods for proxy of ART availability as 2001-2003 (non-nucleoside reverse transcriptase inhibitors era), 2004-2007 (first entry inhibitors), 2008-2012 (1st generation integrase inhibitors), and 2013-2016 (2nd generation integrase inhibitors).[7] We classified patients as young adults (20-39 years) and adults (40-79 years). HIV status was identified at DLBCL diagnosis. Because of the low counts of DLBCL among non-Hispanic Asian / Pacific Islander (N=63) and non-Hispanic American Indian / Alaska Native (N<20) patients with HIV, we grouped these patients as Other.

The primary endpoint was overall survival (OS), defined from diagnosis to death of any cause, end of follow-up, or end of the study. Subgroup analyses involved estimating OS differences within demographic groups (i.e., sex, age, and race and ethnicity).

Diffuse large B-cell lymphoma patients with HIV were propensity matched to DLBCL patients without HIV using the nearest neighborhood method and a 1:3 ratio based on age group, race and ethnicity, cancer registry, sex, year of diagnosis, primary site grouping, and cancer stage. All matching variables were successfully balanced with standard mean differences <0.1. Changes in demographic features across periods were evaluated with a χ^2 test for trend or Kruskal-Wallis test, as appropriate. We used the Kaplan-Meier method and Log-rank test to estimate and compare OS. Median follow-up was calculated using the reverse Kaplan-Meier method. Given the matched design, we used univariable Cox regression analysis and reported the findings with Hazard Ratios (HR) and 95% Confidence Intervals (CI). We fitted interaction models and compared them to models without the interaction terms using a likelihood ratio test to evaluate the impact of ART regimen periods and demographic subgroups on OS. $P \leq 0.05$ was considered statistically significant. We used the R software (v4.3.2) for analysis.

We included 8,624 DLBCL patients diagnosed during 2001-2016 after propensity score matching (2,156 with HIV and 6,468 without HIV). The demographic features of DLBCL patients with HIV changed over time (*Online Supplementary Table S1*). The median age at diagnosis increased from 43 years in 2001-2003 to 48 years in 2013-2016 ($P<0.001$), and the proportion of non-Hispanic Black (NHB) patients rose from 21% in 2001-2003 to 34% in 2013-2016 ($P<0.001$). The male predominance remained consistent across periods, ranging from 83% to 90% ($P=0.079$), as well as the proportion of Hispanic patients (range: 21-27%). Advanced stage at diagnosis was consistent across calendar years (range: 68-69%; $P=0.498$).

With a median follow-up of 59 months (95% CI: 58-61 months) in the latest period (2013-2016), DLBCL patients with HIV had consistently worse 5-year OS rates and an increased risk of all-cause mortality (HR: 1.47-1.86) compared to DLBCL patients without HIV across all ART periods (Figure 1, *Online Supplementary Table S2*). This mortality risk was attenuated in 2013-2016 (from $HR_{2001-2003}$: 1.85, 95% CI: 1.58-2.16 to $HR_{2013-2016}$: 1.47, 95% CI: 1.26-1.73; $P_{trend}=0.021$). Subgroup analyses revealed that this overall attenuation in the HR across calendar periods was limited to males (from $HR_{2001-2003}$: 1.85, 95% CI: 1.57-2.18 to $HR_{2013-2016}$: 1.43, 95% CI: 1.21-1.69; $P_{trend}=0.011$) and non-Hispanic White (NHW) patients (from $HR_{2001-2003}$: 2.04, 95% CI: 1.63-2.55 to $HR_{2013-2016}$: 1.38,

95% CI: 1.05-1.80; P_{trend}=0.010). HR remained elevated and constant over time for females (P_{trend}=0.900), young adults (P_{trend}=0.572), older adults (P_{trend}=0.107), Hispanic patients (P_{trend}=0.216), and NHB patients (P_{trend}=0.938).

In the contemporary cohort (2008-2016) (*Online Supplementary Table S3*), the median age among patients with HIV was 47 years at diagnosis. Most patients were male (85%), were diagnosed at advanced stages (65%), and had primary nodal disease at presentation (62%). With a median follow-up of 88 months (95% CI: 86-89 months) during 2008-2016, the overall 5-year OS rate for DLBCL patients with HIV was 53% (95% CI: 50-56%) and 65% for DLBCL patients without known HIV (95% CI: 63-67%; *P*<0.0001; HR: 1.56, 95% CI: 1.41-1.73) (Table 1, Figure 2). The 5-year OS rates for DLBCL young adults with HIV were notably lower than patients without known HIV (56% *vs.* 81%; HR: 2.84, 95% CI: 2.24-3.59). Similarly, the 5-year OS rates for older, male, female, NHB, NHW, and Hispanic patients were lower among patients with HIV (Table 1).

This population-based study identified persistent survival differences overall and within demographic subgroups for DLBCL patients with HIV compared to those without HIV in the US. Our study expands the observation period of previous US studies (up to 2009)[5,6,8] and indicates that mortality remains higher among DLBCL patients with HIV. Our findings contrast with European studies in academic centers suggesting that HIV status is not associated with poor outcomes among those treated with immunochem-

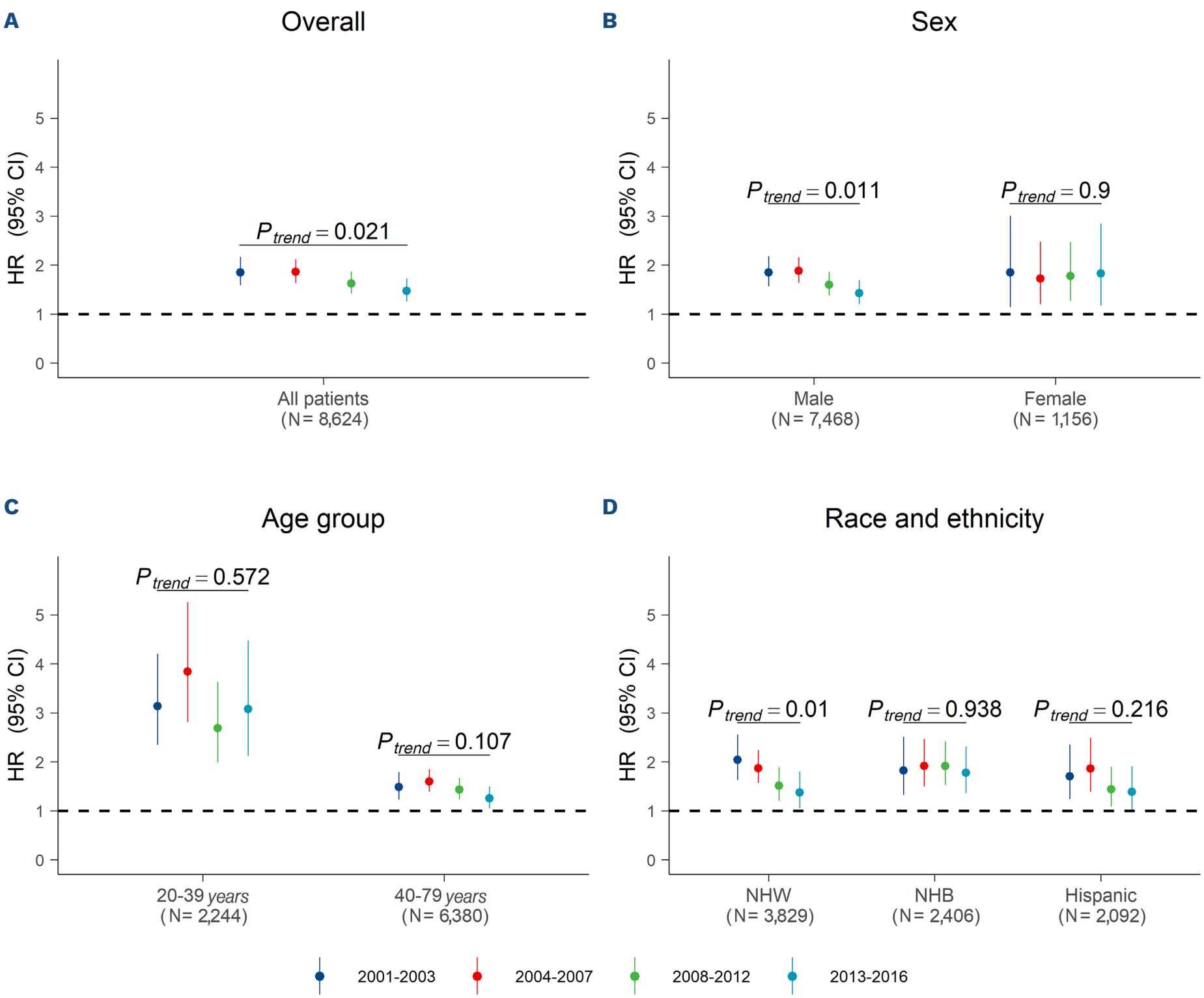

Figure 1. Hazard ratios for overall survival across antiretroviral therapy periods (2001-2016) in a matched cohort (A) and subgroup analyses within demographic groups (B-D). Estimates for Other race and ethnicity are not shown. *P* values reflect the likelihood ratio test comparing model fit with and without the interaction term of HIV and calendar year. CI: Confidence Interval; HR: Hazard Ratio; NHB: Non-Hispanic Black; NHW: Non-Hispanic White. Derived from 13 Surveillance, Epidemiology, and End Results registries.

otherapy while on ART.[2-4] However, our report aligns with previous US population-based studies reporting inferior 5-year OS ranging from 41-44% among DLBCL patients with HIV compared to 54-61% among the general DLBCL population in the ART era.[5,6,8] The worse OS among patients with HIV in the US may be associated with several factors, including differences in management between academic *versus* community centers, healthcare access, challenges of managing HIV while receiving cancer-directed therapy, and differences in treatment approaches.[5,9-11]

Notable results were identified within demographic groups. Only males and NHW patients with HIV appeared to have a reduction in the survival gap, indicating that further efforts to improve access to care and disease control should reach all demographic subgroups. Historically, under-represented racial and ethnic groups have been excluded from pivotal clinical trials, and HIV status has been suggested as an unnecessary exclusion criterion.[12] Our findings may indicate persistent challenges in providing cancer care for DLBCL patients with HIV, even in the era after the Affordable Care Act was implemented in 2010,[13] suggesting barriers to receiving optimal care remain. Additionally, the recent approval of chimeric antigen receptor T-cell therapy for relapsed / refractory disease based on trials excluding patients with HIV could potentially exacerbate the observed survival difference. Future analyses should evaluate whether the receipt of novel therapies and standard of care for DLBCL is similar across demographic subgroups in the HIV setting. Remarkably, young adult patients with HIV had the most significant survival difference (HR: 2.84), and OS was similar to their older counterparts with HIV, in contrast to the typical higher survival outcomes among DLBCL young adults without HIV. Although our results are exploratory, this similar OS across age groups may align with previous

Table 1. Kaplan-Meier and Cox regression analyses evaluating the effect of human immunodeficiency virus status on overall survival among patients with diffuse large B-cell lymphoma in the contemporary matched cohort (2008-2016). Derived from 13 Surveillance, Epidemiology, and End Results registries.

Characteristics	Events	N	5-year OS, % (95% CI)	Log-rank *P* values	HR (95% CI)	*P* values for interaction
All patients						
HIV$^-$ / unknown	1,165	3,429	65 (63-67)	<0.0001	Ref	-
HIV$^+$	526	1,143	53 (50-56)		1.56 (1.41-1.73)	
Sex						
Female						
HIV$^-$ / unknown	159	486	66 (62-71)	<0.0001	Ref	0.259
HIV$^+$	84	174	51 (44-59)		1.79 (1.37-2.35)	
Male						
HIV$^-$ / unknown	1,006	2,943	65 (63-67)	<0.0001	Ref	
HIV$^+$	442	969	53 (50-57)		1.52 (1.36-1.71)	
Age at diagnosis in years						
20-39						
HIV$^-$ / unknown	162	864	81 (78-83)	<0.0001	Ref	< 0.0001[a]
HIV$^+$	124	288	56 (50-62)		2.84 (2.24-3.59)	
40-79						
HIV$^-$ / unknown	1,003	2,565	60 (58-62)	<0.0001	Ref	
HIV$^+$	402	855	52 (49-56)		1.35 (1.2-1.52)	
Race and ethnicity						
Non-Hispanic White						
HIV$^-$ / unknown	451	1,341	66 (63-68)	<0.0001	Ref	
HIV$^+$	185	422	56 (51-60)		1.46 (1.22-1.73)	
Non-Hispanic Black						
HIV$^-$ / unknown	370	1,077	65 (62-68)	<0.0001	Ref	0.092
HIV$^+$	199	381	47 (42-52)		1.86 (1.56-2.21)	
Hispanic						
HIV$^-$ / unknown	300	887	64 (61-68)	0.001	Ref	
HIV$^+$	126	297	56 (51-62)		1.42 (1.15-1.75)	
Other[b]						
HIV$^-$ / unknown	44	124	63 (55-72)	0.666	Ref	
HIV$^+$	<20	43	62 (49-78)		1.14 (0.64-2.03)	

Counts <20 were suppressed. [a]Likelihood ratio test suggests a statistically significant interaction between human immunodeficiency virus (HIV) status and age based on comparing model fit with and without the interaction term. [b]'Other' race and ethnicity includes non-Hispanic Asian / Pacific Islander and non-Hispanic American Indian / Alaska Native. N: number; OS: overall survival; HR: Hazard Ratio; CI: Confidence Interval; Ref: reference values.

descriptions of less heterogeneous disease biology arising in the HIV setting, irrespective of age.[11,14] Additionally, young adults have been recognized as an underserved group in whom few dedicated trials have been conducted.[15] It is likely that the described difficulties in accessing timely cancer care and lack of supportive networks for this population may explain the observed poor survival. Identifying factors associated with this higher mortality risk is warranted.

The findings of this study should be interpreted within the limitations of its retrospective design. We did not have detailed information on cancer-directed therapy, ART regimens, HIV-related factors (e.g., CD4 count, HIV viremia, HIV transmission groups), treatment-related adverse events, type of center (academic *vs.* community), or social determinants of health. The small sample size for certain race and ethnicity subgroups precluded meaningful comparisons.

In conclusion, US DLBCL patients with HIV continue to experience a higher mortality risk compared to those without HIV. This increased mortality risk suggests that changes and improvements in DLBCL management, HIV control, and supportive care have not fully reached this vulnerable population in the US. Although we observed an overall

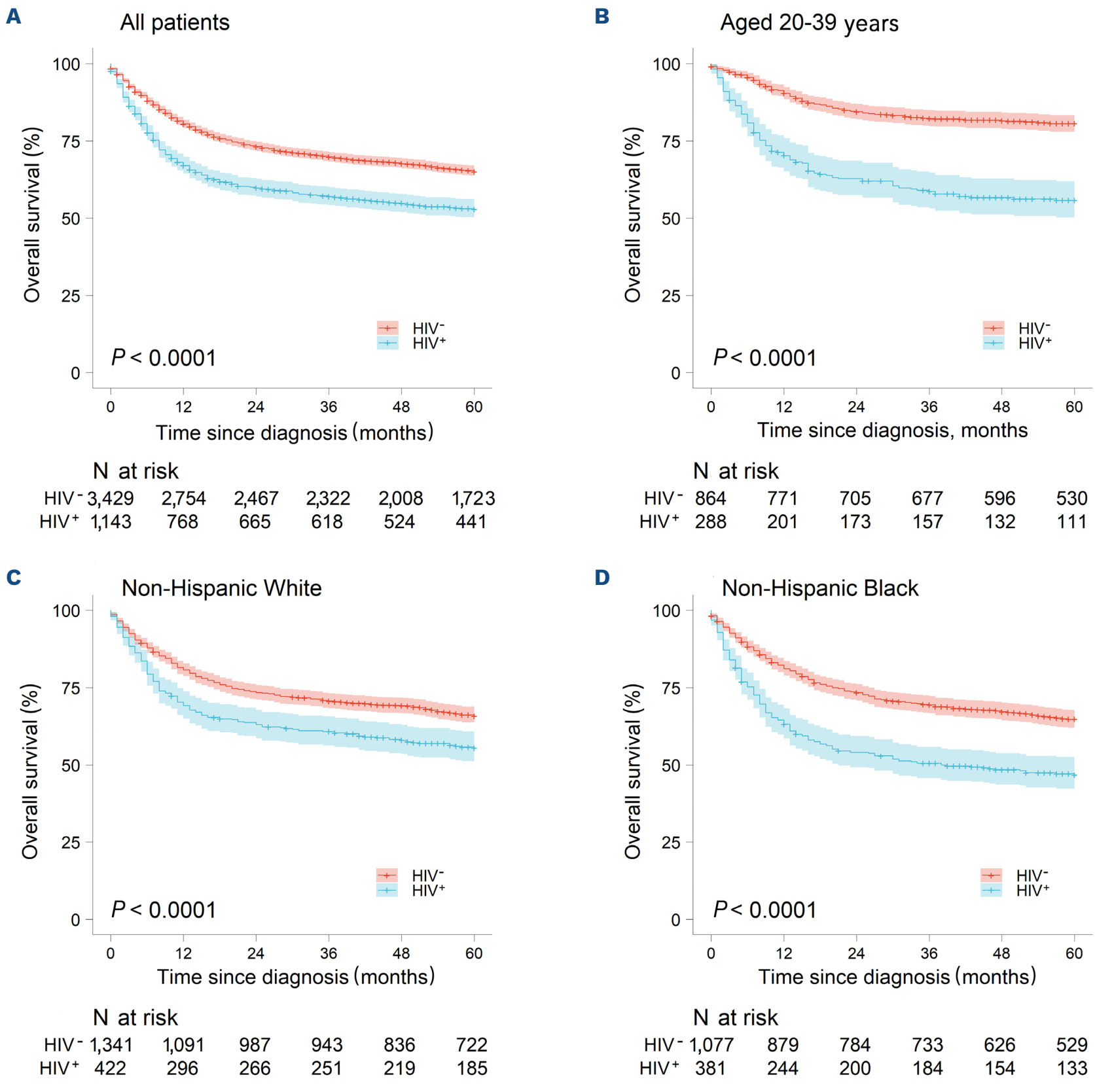

Figure 2. Kaplan-Meier curves evaluating the effect of human immunodeficiency virus status on overall survival among all included patients (A) and selected demographic groups (B-D). Remarkable survival differences are shown, with diffuse large B-cell lymphoma in the contemporary matched cohort (2008-2016). HIV: human immunodeficiency virus. Derived from 13 Surveillance, Epidemiology, and End Results registries.

decrease in mortality risk over time, stratified analyses revealed that this mortality gap reduction was restricted to males and NHW patients, suggesting the need to improve care delivery with particular attention to other demographic subgroups. Notably, young adults aged 20-39 experienced the most significant survival difference. Identifying social determinants of health, age-related demographic, biological, or healthcare system factors mediating survival outcomes and receipt of treatment is warranted to further design interventions and mitigate differences in mortality risk.

Authors

Bryan Valcarcel,[1] Sara J. Schonfeld,[1] Meredith S. Shiels,[2] Jorge J. Castillo[3] and Lindsay M. Morton[1]

[1]Radiation Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda; [2]Infections and Immunoepidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda and [3]Division of Hematological Malignancies, Dana-Farber Cancer Institute, Boston, MA, USA

B. VALCARCEL - BSValcarcel@mdanderson.org

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Contributions

BV, SJS and LMM conceptualized and designed the study. BV performed the analysis. BV, SJS and LMM drafted the manuscript. SJS and LMM contributed to data acquisition and acquired funding. LMM supervised and administered the study. SJS, MSS, JJC and LMM provided valuable edits to the manuscript and approved the final version for publication.

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Data-sharing statement

Deidentified data are available at https://seer.cancer.gov/

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