Original Article

Population-Based Prognostic Factors for Survival in Patients With Burkitt Lymphoma

An Analysis From the Surveillance, Epidemiology, and End Results Database

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BACKGROUND: Burkitt lymphoma (BL) is an aggressive but potentially curable lymphoma, previously described in small, single-institution studies. This study evaluated prognostic factors for survival in adult patients with BL and a potential outcome improvement over the past decade in a population-based cohort. **METHODS:** Adult patients with BL diagnosed between 1998 and 2009 were selected from the Surveillance, Epidemiology, and End Results (SEER) database. Prognostic factors were identified in a multivariate model for relative survival (RS), and trends in survival were evaluated using period analysis. **RESULTS:** The study cohort included 2284 patients, with a median age of 49 years and male predominance (2.6:1). Gastrointestinal tract and the head and neck were the most common sites of extranodal disease. Older age, black race/ethnicity, and advanced stage were associated with a worse survival. In the period analysis, trends in improved survival between 1998 and 2009 were seen, except for patients older than 60 years and black patients, whose survival did not improve. A prognostic score divided patients into 4 groups: low-risk (5-year RS: 71%), low-intermediate (5-year RS: 55%), high-intermediate (5-year RS: 41%), and high-risk (5-year RS: 29%; $P < .001$). **CONCLUSIONS:** The outcome of patients younger than 60 years with BL improved over the past decade. Age, race, and stage have a prognostic role for survival. The proposed score can help inform prognosis in newly diagnosed patients and stratify participants in future trials. ***Cancer* 2013;119:3672-9**. © *2013 American Cancer Society.*

KEYWORDS: Burkitt lymphoma; prognostic factors; SEER; epidemiology; race; rituximab.

INTRODUCTION

Burkitt lymphoma (BL) is a highly aggressive but also curable subtype of non-Hodgkin lymphoma (NHL). BL is characterized by a translocation involving the *MYC* oncogene located in chromosome 8 and genes associated with transcription of immunoglobulin heavy and light chains.[1] Such translocations in the *MYC* oncogene promote cell cycle deregulation characterized by increased proliferation rates close to 100% in pathological samples.

The treatment of BL usually requires intensive multiagent chemotherapeutic regimens with central nervous system penetrance.[2-4] Many of the protocols were adapted for adults based on the improved outcomes seen in pediatric patients.[5,6] With the addition of rituximab to chemotherapy, an improvement in response and survival rates in patients with BL is expected, although it had been difficult to conclusively demonstrate in small single-arm, single-institution studies.[7,8] In addition, little is known about prognostic factors for survival in patients with BL in the rituximab era, which makes patient counseling and stratification in contemporary treatment studies difficult. Current guidelines are limited to recommending uniform, aggressive therapy for all patients without risk categorization based on stage or other validated factors.

The aims of this study were to identify population-based prognostic factors for survival in patients with a diagnosis of BL from the Surveillance, Epidemiology, and End Results (SEER) database, and to evaluate a potential improvement in outcomes over years, possibly associated with the addition of rituximab to chemotherapy.

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We acknowledge the efforts of the Applied Research Program, National Cancer Institute; Information Management Services, Inc.; and the SEER program tumor registries in the maintenance of the database as a research resource.

DOI: 10.1002/cncr.28264, **Received:** March 6, 2013; **Revised:** May 17, 2013; **Accepted:** June 7, 2013, **Published online** July 30, 2013 in Wiley Online Library (wileyonlinelibrary.com)

MATERIALS AND METHODS

Data Source and Cohort Selection

Our study was based on data from the SEER program database.[9] SEER collects cancer incidence (with a mandated case ascertainment of 98%), characteristics, treatment, and outcome information from 18 geographic areas in the United States, representing 28% of the population. We used direct case listings extracted by SEER*Stat software.[10] Our query included all patients with BL diagnosis based on the International Classification of Diseases for Oncology, Third Edition (ICD-O-3) histology code 9687 (Burkitt lymphoma), recorded between 1998 and 2007, who were older than 20 years of age at diagnosis, and in whom BL was the first malignancy. We excluded patients with an unrecorded primary site of disease (n = 9). Expected mortality rates, stratified by attained age, sex, race, and calendar year, were obtained by the SEER program from life tables published by the National Center for Health Statistics (Hyattsville, Md).

Definition of Variables

The database contained variables indicating age at diagnosis, year of diagnosis, sex, race/ethnicity, clinical stage, primary anatomical site of involvement, outcome, survival time, and cause of death. Age was categorized into age groups of 20 to 39 years, 40 to 59 years, 60 to 79 years, and $\geq$ 80 years. Race/ethnicity was categorized as white, black, and other, with an additional category for Hispanic patients (of any race), assigned according to the North American Association of Central Cancer Registries Hispanic Identification Algorithm.[11] Stage was based on the Ann Arbor system. Primary anatomical sites were categorized according to the ICD-O-3 topography code reported by SEER: lymph nodes, head and neck, gastrointestinal tract, and other extranodal sites. Socioeconomic status was approximated as quintiles of percentage of persons living under the poverty level by county of residence. Survival time was calculated between the date of diagnosis and the date of death, date last known to be alive, or date of the study cutoff (December 31, 2009).

Relative survival (RS), the method of choice for estimating estimate in population-based studies was the primary endpoint of interest.[12] It is defined as the ratio of observed (overall) divided by expected survival and reflects excess mortality from cancer compared with individuals of the same age, sex, and race in the general population in a specific calendar year. The associated measures of population-based survival include crude mortality from cancer (or competing causes, also known as cumulative incidence) and conditional survival (RS restricted to subjects surviving beyond a specified initial interval). Where appropriate, we used measures of overall survival (OS).

Statistical Analysis

Descriptive statistics were used to report population characteristics. Multivariate flexible parametric model (with direct modeling of RS using individual data) on a proportional-hazard scale was fitted to evaluate the prognostic variables (ie, age, sex, race, stage, and site of involvement).[13] We evaluated and excluded interactions between the variables, and we assessed the proportional hazard assumption by studying interaction of all variables with time.

For the benefit of patients and clinicians, we provided estimates of cumulative incidence of lymphoma-related death accounting for presence of competing causes. Such estimates are particularly important for older patients, in whom competing risks may lead to significant bias in the Kaplan-Meier method.[14] Cumulative incidence function was calculated based on expected survival rather than death certificate records, using the method of Cronin and Feuer.[15] We additionally fitted a flexible parametric cure model to estimate statistical cure rates in each prognostic category.[16] Trends in survival were studied using the SEER period survival methodology, which is a modification of the method proposed by Brenner et al.[17,18] Outcomes are reported as percentages or hazard ratios (HR) with 95% confidence interval (CI). *P* values $<$ .05 were considered statistically significant. Calculations and graphs were obtained using Stata, version 12.1 (StataCorp LP, College Station, Tex).

RESULTS

Our study cohort included 2284 adult patients with the BL diagnosis recorded in the SEER database between 1998 and 2009. The median age at diagnosis was 49 years (range, 20-99 years) with a male-to-female ratio of 2.6:1. The most common extranodal sites of involvement were gastrointestinal tract (43%) and head and neck (15%). Other extranodal sites accounted for 42% of cases. The main clinical characteristics in the study cohort are shown in Table 1. The median follow-up for surviving patients was 3.7 years.

The majority of lymphoma-related deaths occurred within the first year from diagnosis and the excess mortality rate after 3 years was close to zero, indicating a level equal to mortality expected in general population (Fig. 1A). The cumulative incidence of death from BL at 3 years was 37.4% (95% CI = 33.4%-41.4%) for patients aged 20 to 39 years at diagnosis, 48.4% (95%

TABLE 1. Main Characteristics of 2284 Patients With Burkitt Lymphoma From the SEER Database, 1998-2009

Characteristic	No.	Percentage
Age		
20-39 y	649	28.4
40-59 y	934	40.9
60-79 y	532	23.3
≥80 y	169	7.4
Sex		
Female	641	28.1
Male	1643	71.9
Race		
White	1476	64.6
Black	219	9.6
Hispanic	411	18.0
Other	169	7.4
Unrecorded	10	0.4
Ann Arbor stage		
I	434	19.0
II	342	15.0
III	237	10.4
IV	1172	51.3
Unrecorded	99	4.3
Primary site		
Lymph node	1639	71.8
Gastrointestinal tract	279	12.2
Head and neck	99	4.3
Central nervous system	40	1.8
Other extranodal	227	9.9
Year of diagnosis		
1998-2000	315	13.8
2001-2003	583	25.5
2004-2006	645	28.2
2007-2009	741	32.4
Outcome		
Alive	1074	47.0
Dead	1210	53.0
Dead at 6 mo	787	65.0
Dead at 12 mo	1011	83.6
Dead at 24 mo	1106	91.4
Cause of death		
Lymphoma	734	60.7
Infections	307	25.4
Other causes	169	13.9

CI = 44.8%-51.9%) for those aged 40 to 59 years, 55.3% (95% CI = 50.2-60.0%) for those aged 60 to 79 years, and 70.7% (95% CI = 61.3%-78.1%) for those aged ≥ 80 years. The respective values at 5 years were only 2% to 3% higher, consistent with the aggressive but curable nature of BL. Moreover, the conditional 5-year RS in patients who survived beyond 12 months from diagnosis was 83.4% (95% CI = 80.3%-86.0%), without significant difference in age subgroups except for patients ≥ 80, in whom the 5-year RS in patients surviving beyond 12 months was 60% (95% CI = 29.0%-81.0%). The median OS was 35 months with 5- and 10-year OS rates of 46% and 40%, respectively (Fig. 1B).

We evaluated age, sex, race/ethnicity, clinical stage, and primary anatomical site in univariate and multivariate models as potential prognostic factors. In the univariate survival analysis, older age categories, black race, and advanced stage were associated with worse outcomes (Fig. 2). The extranodal sites, particularly head and neck, exhibited a seemingly better outcome, but this association was confounded by stage distribution and disappeared upon multivariate adjustment. In the multivariate model, older age, black race, and advanced stage were associated with a significantly worse outcome (Table 2). Some variables showed departure from the proportional hazard assumption, but the estimates and measures of fit were not substantially different in the model with or without time interactions (data not shown). We additionally investigated interaction of race with socioeconomic status and found that black race was a poor prognostic factor, independent of poverty level (test for interaction $P = .84$).

Based on the results from the multivariate model, we generated a prognostic score assigning 1 point for age 40 to 59 years or black race, 2 points for age 60 to 79 years or stage III/IV disease, and 4 points for age ≥ 80 years. The patients were then classified into 4 risk groups according to their score: 0 or 1 points, low risk; 2 points, low-intermediate risk; 3 points, high-intermediate risk; and ≥ 4 points, high risk. The prognostic score was significantly associated with RS (Fig. 3) and OS ($P < .0001$ on log-rank test for trend). By fitting a cure model, we estimated the proportion of patients who were cured from the lymphoma in each risk category, ranging from 26% to 72%. There was very little difference in the survival of uncured patients (Table 3). The scoring model was internally validated using a nonparametric bootstrap method with 2000 replications. In sensitivity analyses, the model remained prognostic when removing patients ≥ 80 years and ≥ 60 years, who could be less likely to be treated with a curative intent, and in each calendar period of diagnosis (data not shown).

For a delineation of the survival trends, we estimated 3-year RS in the categories of age and race/ethnicity, for yearly periods of 1995 to 2009 (Fig. 4). In the 1990s, the survival was similar for all age groups (34.7% in all age groups combined in 1998, 95% CI = 27.4%-42.0%), but there was evidence of a rapid rise soon after and ongoing improvement in the youngest group with the estimated survival of 62.1% (95% CI = 54.8%-68.5%) by 2007. Conversely, patients ≥ 60 years continued to have a relatively flat survival trend with the 2007 5-year estimate of 43.5% (95% CI = 34.5%-52.1%). We did not find evidence of stage migration, with 65% of patients presenting with stage III/IV disease in all periods (κ^2 test of proportions, $P = .88$). The age distribution was also consistent between the periods ($P = .24$). In race/ethnicity

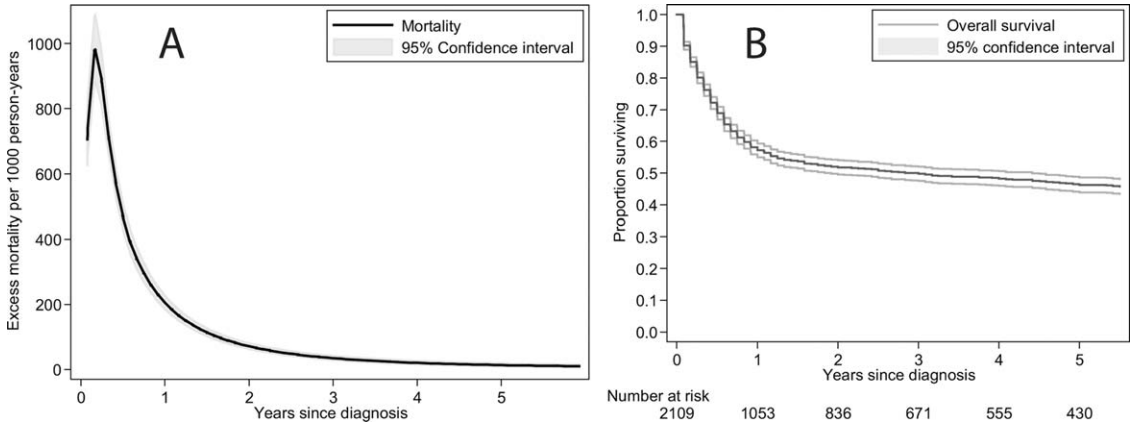

Figure 1. Excess mortality rate (per 1000 person-years, A) and overall survival (B) in Burkitt lymphoma patients are shown. The excess mortality rate was predicted from the relative survival flexible parametric model; the rate of zero indicates mortality rate equal to the rate in the general population.

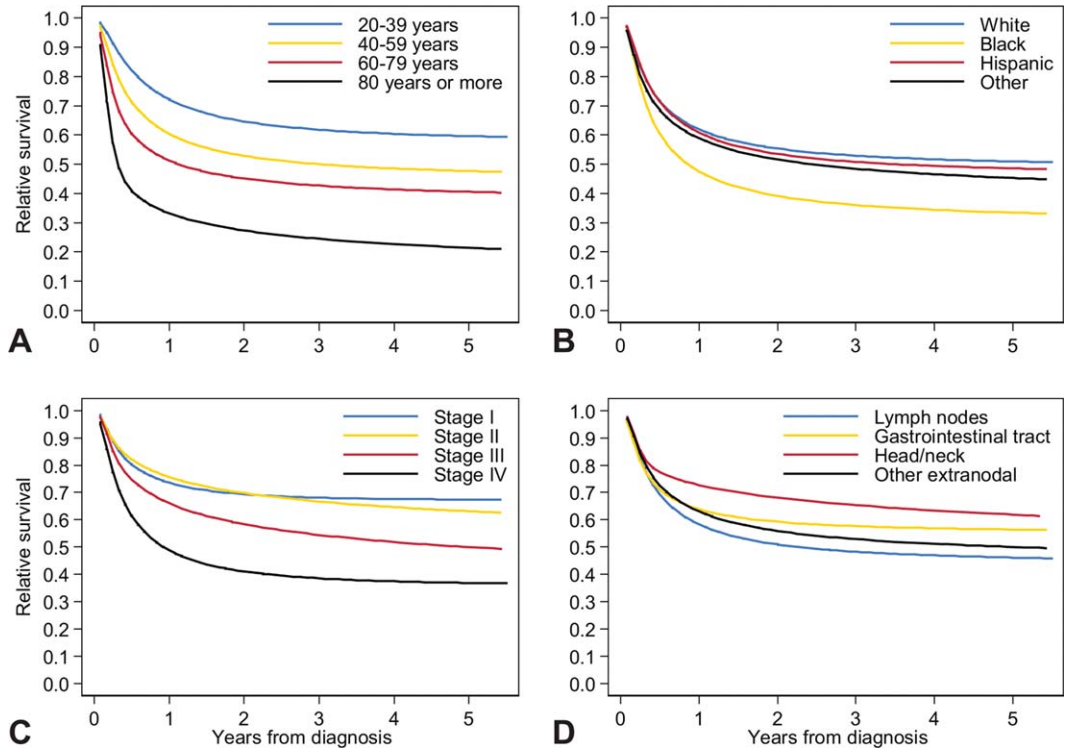

Figure 2. Relative survival of Burkitt lymphoma patients stratified by age, race, stage, and primary anatomical site is shown.

groups, the point estimates between 1998 and 2007 steadily increased and were significantly different for white non-Hispanic (from 31.7% [95% CI = 25.5%-38.0%] to 50.9% [95% CI = 47.2%-54.4%]) and Hispanic individuals (from 22.7% [95% CI = 12.3%-35.1%] to 47.1% [95% CI = 40.2%-23.7%]). Conversely, there was no significant change in black patients (from 28.8% [95% CI = 14.6%-44.8%] to 29.9% [95% CI = 21.8%-38.3%]), with a resulting increasing disparity compared with other groups over the past decade. For other races, the trend was favorable, but not statistically significant, possibly due to small number of patients (from 36.5% [95%

TABLE 2. Multivariate Prognostic Model in 2013 Patients With Burkitt Lymphoma From the SEER Database, 1998-2009

Characteristic	% Patients	HR (95% CI)	*P*
Age category			
20-39 years	29.5%	1.00 (Ref)	
40-59 years	41.4%	1.46 (1.23-1.73)	<.0001
60-79 years	22.6%	2.07 (1.71-2.50)	<.0001
≥80 years	6.5%	4.92 (3.79-6.40)	<.0001
Sex			
Female	28.4%	1.00 (Ref)	
Male	71.6%	1.15 (0.99-1.33)	.07
Race/ethnicity			
White	64.9%	1.00 (Ref)	.
Black	9.3%	1.60 (1.30-1.97)	<.0001
Hispanic	17.9%	1.08 (0.90-1.29)	.40
Other	7.9%	1.17 (0.92-1.49)	.19
Ann Arbor stage			
I	20.7%	1.00 (Ref)	
II	16.1%	1.06 (0.81-1.38)	.69
III	11.0%	1.48 (1.12-1.94)	.005
IV	52.3%	2.43 (1.99-2.97)	<.0001
Primary site			
Nodal	71.2%	1.00 (Ref)	
Gastrointestinal tract	12.3%	0.91 (0.73-1.12)	.37
Head and neck	4.7%	0.82 (0.56-1.19)	.29
Central nervous system	1.8%	0.97 (0.58-1.63)	.91
Other extranodal	10.0%	0.98 (0.79-1.23)	.88

Abbreviations: CI, confidence interval; HR, hazard ratio; Ref, reference value.

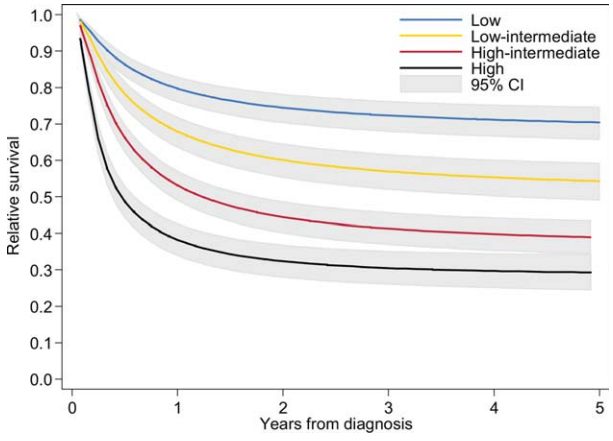

Figure 3. Relative survival of Burkitt lymphoma patients stratified by the prognostic score categories is shown.

CI = 18.8%-54.4%] to 48.2% [95% CI = 37.4%-58.2%]).

DISCUSSION

We presented a large population-based study aimed at identifying prognostic factors and trends in outcomes of patients with BL. The data demonstrate improvement in the survival of patients younger than 60 years over the past decade, not explained by stage migration. Although the addition of rituximab to chemotherapy has increased the response and survival rates in several randomized trials in diffuse large B-cell lymphoma (DLBCL), only observational studies comparing outcomes with historical controls have been published in BL.[19-21] Thomas and colleagues showed similar complete response after hyper-CVAD with or without rituximab (85% and 86%, respectively) in 79 adult patients with BL, although the 3-year survival was better with the monoclonal antibody (89% and 53%, respectively).[8] In another retrospective study evaluating the effects of adding rituximab to CODOX-M/IVAC regimen in 80 adult patients with BL, the complete response rate was 90% with rituximab (n = 40) and 85% without it (n = 40), whereas the 3-year OS rates were 77% and 66%, respectively ($P = .43$).[7] None of the patients in those 2 series was older than 80 years. Recently, a randomized study including 26% of patients older than 60 years demonstrated an improved 3-year OS with a multiagent regimen including rituximab (82% versus 71% in the non-rituximab comparator arm, $P = .016$), without increased toxicity.[22] Another prospective phase 2 trial showed a 2-year survival of 86% with rituximab-CODOX-M/IVAC combination.[23] The significantly lower OS in our study can be explained by the inclusion of older patients, who are evidently underrepresented in clinical trials and may have received much lower intensity treatments, or just palliative care. One systematic review of BL series found that only 42% of patients in prior reports were over the age of 40 years, whereas this proportion was 70% in our analysis.[24] A significant number of infection-related deaths reported in SEER may also suggest high toxicity of intensive chemotherapy when it is administered in the community, although investigation of this hypothesis would require access to individual treatment records unavailable in the database. Although one could indirectly assume that the use of rituximab in BL increased in the early 2000s, the survival benefit was only realized in the younger age group (20-39 years). Patients aged 40 to 59 years achieved a smaller, although still notable, improvement in survival, but there was no evident trend in older patients. Further research of supportive care and tailored chemotherapy regimens is urgently needed in this group. Other factors such as improved supportive therapies (ie, antibiotic prophylaxis and growth factor support) and advances in bone marrow transplantation likely complemented the observed survival improvement.

We identified clinical prognostic factors for inferior survival in adult patients with BL, which included older age, black race, and advanced stage. Previous studies have

TABLE 3. Survival and Cure Outcomes in the 4 Risk Categories of Patients With Burkitt Lymphoma

			Overall Survival (months)	5-y Relative Survival	Percent Cured	Overall Survival of the Uncured (months)
Risk Score[a]	*N*	%	Median (95% CI)	Proportion (95% CI)	Proportion (95% CI)	Median (95% CI)
Low	514	23.6	NR	71% (66-75)	72% (68-76)	6.0 (5.4-6.5)
Low-intermediate	504	23.2	86 (48-108)	55% (50-60)	57% (52-62)	5.5 (4.9-6.0)
High-intermediate	604	27.8	12 (9-19)	41% (36-45)	41% (37-45)	4.8 (4.3-5.4)
High	554	25.5	6 (5-7)	29% (24-35)	26% (22-30)	4.0 (3.6-4.5)

Abbreviations: CI, confidence interval; NR, not reached.

[a] The risk score was calculated by assigning: 1 point for age 40-59 years or black race, 2 points for age ≥60 years or stage III/IV, 4 points for age ≥80 years. The risk categories were designated as: low (0-1 points), low-intermediate (2 points), high-intermediate (3 points), high (≥4 points).

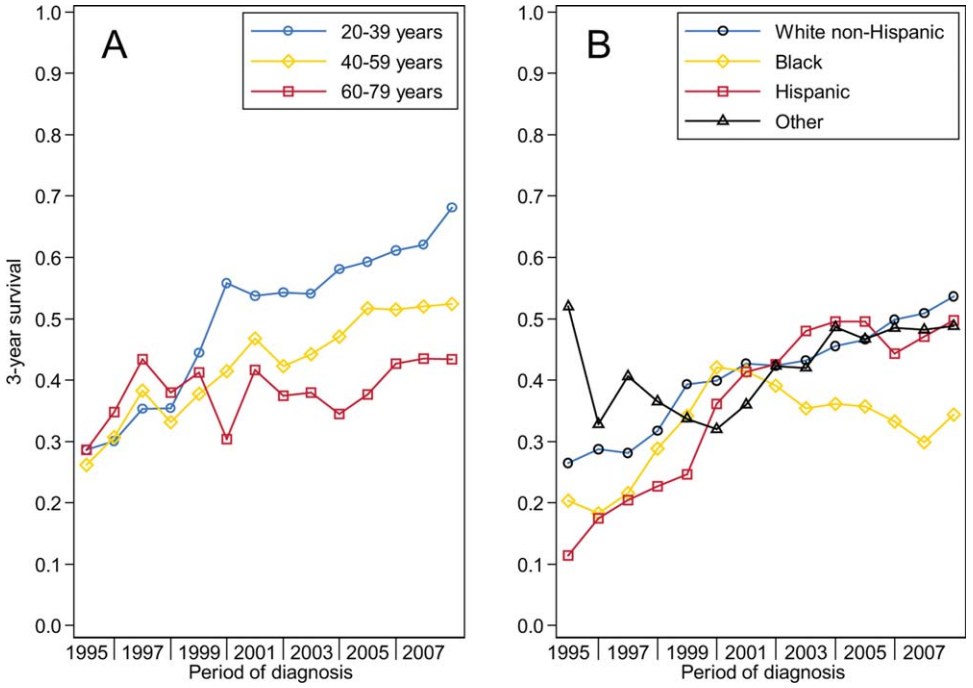

Figure 4. Trends in 3-year relative survival of Burkitt lymphoma patients in age (A) and race/ethnicity (B) groups are shown. The cumulative 3-year relative survival was estimated using period analysis for each yearly cohort between 1995 and 2008. The improvement in point estimates between 1998 and 2007 was statistically significant for the 20- to 39-year and 40- to 59-year age groups, white non-Hispanic and Hispanic patients.

reported age as a factor closely related to prognosis in BL, with divergent outcomes even between children and adolescents.[25] Younger adults are more likely to receive and tolerate potentially curative intensive treatments such as hyper-CVAD and CODOX-M/IVAC. Advanced stage was also associated with a worse outcome. However, the Ann Arbor staging system used in the SEER database might be inadequate for BL, because it does not fully describe the extent of extranodal involvement. Based on our results, advanced stage seems to be the second most important prognostic factor in BL after age, whereas the observed difference between stage III and IV disease may underscore the prognostic value of disseminated extranodal involvement.

Our study distinctly shows worse outcomes in BL in black Americans when compared to other races, with a consideration of Hispanic ethnicity. Our choice of RS endpoint assured adjustment for baseline mortality differences between races and sexes. Black patients presented with a somewhat higher proportion of stage IV disease, as

has also been reported in DLBCL, but their outcomes in our study were consistently inferior regardless of stage.[26] A recent cohort study showed that black patients with DLBCL are less likely to receive chemotherapy or rituximab.[27] Disadvantaged socioeconomic status is associated with worse disease-specific survival in Hodgkin and non-Hodgkin lymphoma and might confound the association with race/ethnicity.[28,29] However, we found that the unfavorable association of black race and survival in BL was independent of socioeconomic status, and the outcomes in Hispanic patients with a similar distribution of the poverty levels were not inferior. We could not assess the impact of access to care, because information on insurance and treatment was not available. Another hypothetical reason for this disparity is a host susceptibility factor such as seen in the endemic BL subtype prevalent in Africa in association with Epstein-Barr virus and malarial infection. We also observed a notable increase in the survival discrepancy between black patients and other racial/ethnic groups in most recent years in the period analysis.

Similar to our results, a recent analysis from the SEER database evaluating pediatric and adult patients with BL identified a lack of improvement in survival in blacks and elderly patients.[30] Our study, however, provided an additional opportunity to generate population-based survival predictors for general use, rather than those derived from highly selective studies in tertiary centers. Our risk assessment score stratified the BL cohort into groups with long-term cure rates ranging from 26% to 72%. Of further value for clinicians and patients is the reassuring finding that the 5-year survival conditional on surviving the first year after diagnosis exceeds 80% for all age groups except the oldest. The score was equally valid for the most recent group diagnosed between 2007 and 2009.

Our study carries weaknesses inherent to the limitations of the SEER database. The most prominent difficulty is the lack of central pathological confirmation, which could have introduced classification bias. An unknown portion of cases could be potentially reclassified as BL-like or aggressive B-cell lymphoma with features intermediate between DLBCL and BL. The only previous study of lymphoma subtype validation in the SEER data unfortunately predates the modern ICD-O-3 and World Health Organization classification, and reported low concordance in BL (46%), but a satisfactory agreement for combined high-grade lymphomas (74%).[31] An excellent agreement (85%), however, was found between the computerized recoding of BL diagnosis from the 1998 to 2000 era and a manual pathology report review in order to assign the ICD-O-3 histology code.[32] Patients with disseminated BL of particularly poor prognosis may have been recorded as acute lymphoblastic leukemia, a diagnosis that was not included in our study. We were also unable to evaluate the prevalence or significance of laboratory abnormalities or poor performance status. A Swedish population-based study of 156 adult patients with BL found age over 40 years, poor performance status, and abnormal lactate dehydrogenase to be of prognostic value.[33] In the United Kingdom Lymphoma Group LY06 study, which predated rituximab, the value of the International Prognostic Index (IPI) in BL was limited to crude dichotomous classification of low-risk (IPI = 0) and high-risk (IPI $\geq$ 1) groups.[3] The lack of detailed therapy information is another weakness of our study, because SEER does not provide data on chemotherapy or immunotherapy. Our sensitivity analysis in patients younger than 60 years, who would be most likely to receive curative regimens, showed a sustained discriminating value of the prognostic score. The lack of information on human immunodeficiency virus (HIV) status is another potential source of bias, since the immunodeficiency-related BL may have a distinct clinical profile. However, recent studies show no difference in outcome between HIV-positive and HIV-negative patients with BL.[34,35]

Conclusions

Our study indicates an improvement in the survival outcomes of younger patients with BL in recent years, which may be partially explained by the addition of rituximab to intensive chemotherapy regimens. The evidently worse outcome in black patients will require further study. Finally, we generated a simple prognostic scale using age, stage, and race, which, with appropriate external validation, could help quantify the curative potential in newly diagnosed patients and stratify participants in future clinical trials.

FUNDING SOURCES

No specific funding was disclosed.

CONFLICT OF INTEREST DISCLOSURE

The authors made no disclosure.

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