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Original Article

Cancer-Specific Mortality, Cure Fraction, and Noncancer Causes of Death Among Diffuse Large B-Cell Lymphoma Patients in the Immunochemotherapy Era

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BACKGROUND: Survival after the diagnosis of diffuse large B-cell lymphoma (DLBCL) has been increasing since 2002 because of improved therapies; however, long-term outcomes for these patients in the modern treatment era are still unknown. **METHODS:** Using Surveillance, Epidemiology, and End Results data, this study first assessed factors associated with DLBCL-specific mortality during 2002-2012. An epidemiologic risk profile, based on clinical and demographic characteristics, was used to stratify DLBCL cases into low-, medium-, and high-risk groups. The proportions of DLBCL cases that might be considered cured in these 3 risk groups was estimated. Risks of death due to various noncancer causes among DLBCL cases versus the general population were also calculated with standardized mortality ratios (SMRs). **RESULTS:** Overall, 8274 deaths were recorded among 18,047 DLBCL cases; 76% of the total deaths were attributed to DLBCL, and 24% were attributed to noncancer causes. The 10-year survival rates for the low-, medium-, and high-risk groups were 80%, 60%, and 36%, respectively. The estimated cure proportions for the low-, medium-, and high-risk groups were 73%, 49%, and 27%, respectively; however, these cure estimates were uncertain because of the need to extrapolate the survival curves beyond the follow-up time. Mortality risks calculated with SMRs were elevated for conditions including vascular diseases (SMR, 1.3), infections (SMR, 3.1), gastrointestinal diseases (SMR, 2.5), and blood diseases (SMR, 4.6). These mortality risks were especially high within the initial 5 years after the diagnosis and declined after 5 years. **CONCLUSIONS:** Some DLBCL patients may be cured of their cancer, but they continue to experience excess mortality from lymphoma and other noncancer causes. ***Cancer* 2017;000:000-000**. © *2017 American Cancer Society.*

KEYWORDS: cancer-specific survival, causes of death, cure, diffuse large B-cell lymphoma, noncancer causes of death, rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), standardized mortality ratio, Surveillance, Epidemiology, and End Results (SEER).

INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma (NHL) in the United States and represents approximately a fourth of NHL cases.[1] Since 2002, standard therapy has involved immunochemotherapy (ie, rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone [R-CHOP]).[2-5] In particular, with the advent of rituximab in 2002, survival has improved dramatically for DLBCL patients, especially among those with advanced-stage disease.[2,6-9] Although the majority of DLBCL patients treated with R-CHOP respond to treatment, approximately 20% to 40% of patients either will fail to achieve remission or will relapse.[3,10,11] Many DLBCL patients can be long-term survivors of their disease in the R-CHOP era.[12]

Nonetheless, it is often difficult to determine whether an individual patient is cured when he or she becomes free of symptoms and other signs of lymphoma. On the other hand, at the population level, cure occurs when DLBCL patients as a whole do not experience any excess mortality due to lymphoma after some time has passed since the diagnosis. This can be evaluated with 2 approaches: 1) determining when risk of death reaches the same level as mortality in the general population

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Additional supporting information may be found in the online version of this article.
See editorial on pages 000-000, this issue.

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(ie, with a relative survival approach) and 2) identifying when there is no risk of death from DLBCL itself, which can be determined from the underlying causes of death (CODs) reported on the death certificate (ie, with a cause-specific survival approach).[13] Under either approach, cure is defined as the point when the survival curve reaches a plateau; in other words, the excess risk of death from DLBCL appears to be zero.

DLBCL patients are at risk of dying of conditions other than their malignancy, which may arise from treatment side effects or comorbidities associated with DLBCL. Some notable medical issues that lymphoma patients face include immunosuppression, venous thromboembolism, and complications of treatment such as cardiovascular disease, diabetes mellitus, and gastric ulcers.[14-17] Information about long-term survival among DLBCL patients with respect to these conditions, based on population-based data in the R-CHOP era, is lacking.

To address these issues, we used population-based data from the US Surveillance, Epidemiology, and End Results (SEER) program. We first assessed factors associated with DLBCL cancer-specific mortality in the R-CHOP era (ie, DLBCL cases diagnosed from 2002 onward). We created an epidemiologic risk profile for DLBCL cases that incorporated important demographic and clinical characteristics at the time of diagnosis. Using the risk profile, we stratified DLBCL cases into low-, medium-, and high-risk groups. We then estimated the proportion of DLBCL cases who could be considered cured of their malignancy. Finally, we assessed the risk of death from main noncancer causes among the DLBCL cases in comparison with the general population.

MATERIALS AND METHODS

Data Source

All adult (age $\geq$ 20 years) DLBCL cases diagnosed during 2002-2011 in the SEER-13 registries were identified with the SEER lymphoma subtype recode variable.[18] These 13 registries cover approximately 14% of the US population. Patients with a first or only cancer diagnosis of DLBCL were included (4398 patients who had a prior cancer before they were diagnosed with DLBCL were excluded from the analysis). Cases with primary mediastinal large B-cell lymphoma (histology code 9679; n = 177) were excluded because these cases typically do not receive R-CHOP. We also excluded human immunodeficiency virus (HIV)–infected DLBCL cases (determined with the SEER HIV flag) because the treatment and outcomes differ for such patients; because Iowa opted out of submitting the HIV flag, we excluded this registry from the analysis. Finally, we excluded cases with missing values for the Ann Arbor stage (n = 899) or the poverty index (n = 3), which were used in the risk score calculations (discussed later).

COD

Underlying CODs were ascertained by cancer registries from death certificate codes obtained from the National Center for Health Statistics. The *International Classification of Diseases, Tenth Revision*, was used to code CODs. CODs can be misattributed on death certificates. To correct for known errors with COD attribution, the SEER program recently developed a special COD variable that indicates whether the death was due to the primary cancer diagnosis or other causes.[19,20] We used this variable to assign a broad set of CODs to capture deaths due to DLBCL among people with an incident DLBCL diagnosis. Specifically, for DLBCL cases in SEER, we considered a death as due to DLBCL if it was coded to a death from any hematologic malignancy, another cancer (if the person had DLBCL as the only incident cancer, a COD coded to another cancer site was assumed to be a miscoding), or a related neoplastic condition.[20] Separately, additional noncancer CODs were assessed on the basis of clinical judgment as complications of DLBCL or its treatment, and they were adapted from the Know Your Chances risk chart produced by the SEER program.[21,22] Supporting Table 1 (see online supporting information) lists the *International Classification of Diseases, Tenth Revision*, codes used to define the DLBCL and noncancer COD outcomes.

Statistical Analysis

DLBCL cases were followed from diagnosis until death, the development of another malignancy, loss to follow-up, or December 31, 2012 (maximum follow-up of 11 years). Prior studies have examined the risk of second cancers in NHL patients,[23-25] and second cancers can complicate the determination of whether CODs are due to the primary cancer. As a result, we chose to censor cases when they developed a second malignancy; few DLBCL cases (n = 215 [1.2%]) exited the study because of second malignancies. Among these 215 cases, leukemia (n = 42 [20%]), lymphoma (n = 41 [19%]), and digestive system cancers (n = 37 [17%]) were the 3 most common second cancers.

We used multivariate Cox proportional hazards models to identify independent predictors of DLBCL-specific death. The available predictors included the age at diagnosis, sex, race, Hispanic ethnicity, marital status,

TABLE 1. Characteristics of Diffuse Large B-Cell Lymphoma Patients and Predictors of Cancer-Specific Death in the R-CHOP Era (SEER-12 Registries, 2002-2011).

Patient Characteristic (n = 18,047)	No.	%	Cox Model		
			Hazard Ratio	95% CI	*P*
Age at diagnosis					<.0001
20-59 y	6551	36.3	1.0		
60-69 y	3889	21.6	1.5	1.4-1.6	
70-79 y	4176	23.1	2.3	2.2-2.5	
≥80 y	3431	19.0	3.6	3.4-3.9	
Sex					<.0001
Male	9615	53.3	1.0		
Female	8432	46.7	0.9	0.8-0.9	
Race					.0009
White	14,434	80.0	1.0		
Black	1292	7.2	1.2	1.0-1.3	
Other	2321	12.9	1.1	1.0-1.2	
Ethnicity					<.0001
Non-Hispanic	15,562	86.2	1.0		
Hispanic	2485	13.8	1.2	1.1-1.3	
Ann Arbor stage					<.0001
I	5243	29.1	1.0		
II	3811	21.1	1.2	1.1-1.3	
III	2853	15.8	1.6	1.5-1.8	
IV	6140	34.0	2.4	2.2-2.6	
Chemotherapy					<.0001
Yes	14,051	77.9	0.5	0.4-0.5	
No/unknown	3996	22.1	1.0		
Radiation					<.0001
Yes	4149	23.0	0.8	0.7-0.8	
No/unknown	13,898	77.0	1.0		
Marital status[a]					<.0001
Yes	10,072	55.8	0.8	0.8-0.9	
No	7975	44.2	1.0		
County-level poverty					.0621
Low	8741	48.4	1.0		
Medium	8971	49.7	1.1	1.0-1.2	
High	335	1.9	1.1	0.8-1.4	

Abbreviations: CI, confidence interval; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone; SEER, Surveillance, Epidemiology, and End Results.
The SEER-12 registries include the Atlanta, Connecticut, Detroit, Hawaii, New Mexico, San Francisco–Oakland, Seattle–Puget Sound, Utah, Los Angeles, San Jose–Monterey, rural Georgia, and Alaska Native tumor registries. Patients diagnosed between 2002 and 2011 were followed until December 31, 2012.
[a] For marital status, the no category consists of single, divorced, separated, widowed, and unknown groups.

county-level poverty,[26,27] Ann Arbor stage,[28] and initial course of therapy (chemotherapy or radiation). Interactions between stage and radiation were considered in the model but were dropped because they were not significant. Each DLBCL case received a risk score calculated as the sum of the coefficients estimated from the Cox model multiplied by their covariate values. Although chemotherapy and radiation were included as adjustment factors in the multivariate model, we did not include them in the calculation of risk scores because treatments were not randomly assigned and it would be inappropriate to make clinical judgments about treatment on the basis of the associations. In addition, chemotherapy data from SEER registries are incomplete.[29] Thus, the remaining terms in the risk model can be interpreted as the estimated risk of DLBCL-specific mortality after adjustments for any effects of treatment. Patients were classified into tertiles by categorization of the individual risk scores into low-, medium-, and high-risk groups.

For each risk group, DLBCL-specific survival curves were calculated with an actuarial method. We then used a mixture cure model to estimate the cure proportion[30-32] separately for each risk group. The model assumed that the overall DLBCL population was a mixture of 2 groups: a cured group that experienced no excess mortality and an uncured group that continued to experience excess mortality throughout follow-up. The cure proportion was modeled with a logit link. We assumed that the DLBCL-specific survival times of the uncured group followed a log-logistic distribution; for sensitivity analyses, we fitted 2 additional models with Weibull and log-normal distributions. We used the SAS macro PSPMCM for fitting the

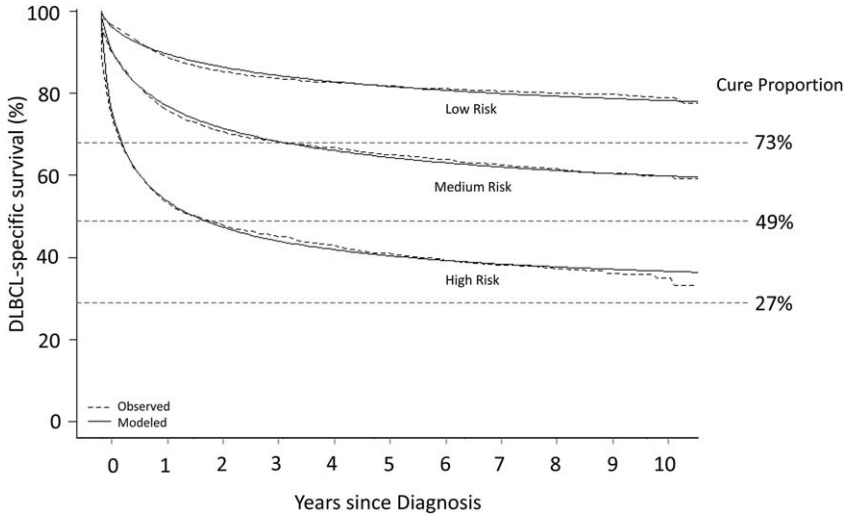

Figure 1. DLBCL-specific survival among DLBCL patients observed and estimated with a cure model. Observed DLBCL-specific survival curves are shown with dashed lines for low-, medium-, and high-risk groups, and the corresponding predicted DLBCL-specific survival curves from a cure model are shown with solid lines. For the cure model, we assumed that the DLBCL-specific survival times of the uncured group followed a log-logistic distribution. The estimated cure proportions are shown by the horizontal lines for the 3 groups. DLBCL indicates diffuse large B-cell lymphoma.

mixture cure model.[32] We compared the observed DLBCL-specific survival curves with the predicted curves to assess the model fit. Prior research suggests that the survival of people alive 2 years after a DLBCL diagnosis approaches the survival of the general population (ie, their DLBCL-specific mortality tends to be zero).[12] Therefore, for a sensitivity analysis checking the reliability of our cure model estimates, we assessed conditional survival 2 years after the diagnosis for DLBCL cases (overall and for patients known to have been treated with chemotherapy). The idea behind plotting these conditional survival curves was to determine whether there was any flattening overall or in the treated group that would suggest a time after which there was no excess mortality from lymphoma (ie, evidence of a cure).

For noncancer CODs, we compared the observed number of deaths with the expected number of deaths in the general population with standardized mortality ratios (SMRs). We divided the follow-up into 0 to 59 and $\geq$60 months after the DLBCL diagnosis to distinguish between early and late events. Ninety-five percent confidence intervals (CIs) for the SMRs and tests for differences in the SMRs across follow-up periods were calculated under the assumption of a Poisson distribution. SEER*Stat and SAS were used to perform the SMR analysis.[33]

RESULTS

Our analysis included 18,047 DLBCL cases diagnosed in SEER areas (Table 1). The majority of the cases were male (53.3%), were white (80.0%), were of non-Hispanic ethnicity (86.2%), were married (55.8%), and lived in counties associated with low or medium poverty levels (48.4% or 49.7%). The median age at diagnosis was 66 years. More than a third of the cases (34.0%) were diagnosed with stage IV disease. Most (77.9%) were treated with chemotherapy, whereas radiotherapy was reported for only 23.0% of cases.

Overall, there were a total of 8274 deaths. Of these deaths, 6288 (76%) were due to DLBCL, and 1986 (24%) were attributed to noncancer causes. In the multivariate Cox model, DLBCL-specific mortality was associated with an older age at diagnosis (hazard ratio [HR] for an age of 60-69 vs 20-59 years, 1.5 [95% CI, 1.4-1.6]; HR for an age of 70-79 vs 20-59 years, 2.3 [95% CI, 2.2-2.5]; HR for an age of $\geq$80 vs 20-59 years, 3.6 [95% CI, 3.4-3.9]), black race (HR for blacks vs whites, 1.2 [95% CI, 1.0-1.3]), Hispanic ethnicity (HR, 1.2 [95% CI, 1.1-1.3]), and an advanced stage at diagnosis (HR for stage IV vs stage I, 2.4 [95% CI, 2.2-2.6]), whereas lower DLBCL-specific mortality was observed in females (HR, 0.9 [95% CI, 0.8-0.9]) and married patients (HR, 0.8 [95% CI, 0.8-0.9]). The receipt of chemotherapy or radiation was also associated with a lower risk of DLBCL-specific death.

In Figure 1, observed and predicted DLBCL-specific survival curves from the cure model (dotted and solid lines, respectively) are shown for low-, medium-, and high-risk DLBCL cases. For the low-risk group, the observed survival curve showed some flattening at the end of the study follow-up period. In contrast, the survival curves for the

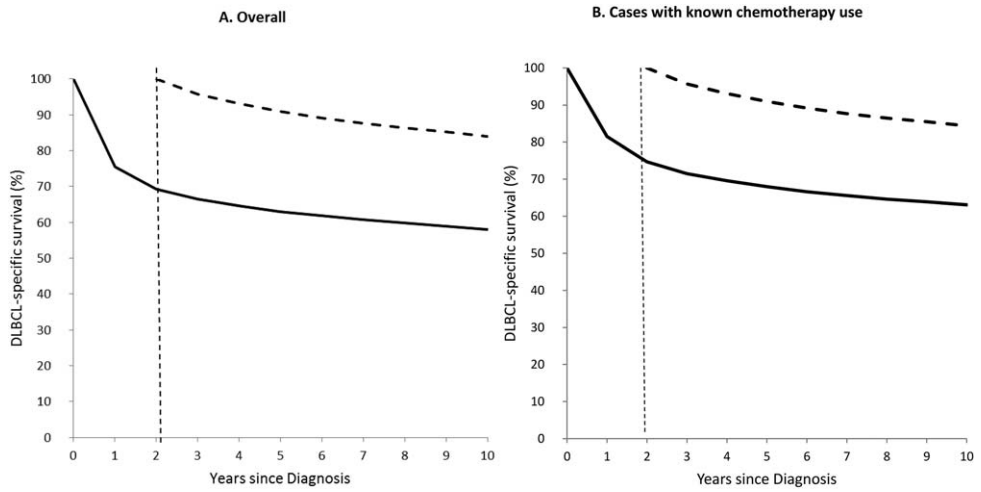

Figure 2. DLBCL-specific survival overall and among patients with known chemotherapy use for patients surviving 2 years after their diagnosis. DLBCL-specific survival curves are shown for (A) all patients and (B) those treated with chemotherapy. The black, solid line in each panel represents unconditional survival, whereas the black, dashed line represents survival after the DLBCL diagnosis conditional on a patient being alive at 2 years, as indicated by the vertical line. DLBCL indicates diffuse large B-cell lymphoma.

medium- and high-risk groups appeared to be still falling, and this indicated that DLBCL cases in these groups continued to die of their lymphoma. The 10-year DLBCL-specific survival rates for the low-, medium-, and high-risk groups were 80%, 60%, and 36%, respectively.

The predicted DLBCL-specific survival from the cure model seems to fit the observed survival curves well (Fig. 1). The predicted cure proportion was 73% (95% CI, 72%-76%) for low-risk patients, 49% (95% CI, 47%-52%) for medium-risk patients, and 27% (95% CI, 25%-30%) for high-risk patients. Importantly, the estimated cure fractions (shown by the horizontal lines in Fig. 1) were far below the end of the survival curves, and this indicated that the extrapolation required to reach the cured proportion was substantial. The median survival times for the uncured patients were 23.1, 18.1, and 6.6 months in the low-, medium-, and high-risk groups, respectively. In sensitivity analyses, we refitted cure models under the assumption of Weibull and log-normal distributions (Supporting Figs. 1 and 2, respectively [see online supporting information]). With these Weibull and log-normal distributions, the predicted cure proportions were 78% and 63% for low-risk patients, 59% and 41% for medium-risk patients, and 37% and 26% for high-risk patients, respectively.

In Figure 2, we present estimates of DLBCL-specific survival conditional on being alive 2 years after the diagnosis. Among all DLBCL cases who survived 2 years after their diagnosis and even among those cases with known chemotherapy use, the curves appear to be still decreasing at the end of the follow-up period.

As shown in Table 2, DLBCL cases had an elevated risk of death due to noncancer causes overall in comparison with the general population (SMR, 1.41 [95% CI, 1.35-1.48]). Mortality risks were highest for a number of specific conditions such as infection (SMR, 3.13 [95% CI, 2.76-3.54]), including pneumonia/influenza (SMR, 1.68 [95% CI, 1.31-2.12]) and septicemia (SMR, 1.88 [95% CI, 1.36-2.53]); gastrointestinal diseases (SMR, 2.50 [95% CI, 2.08-2.97]), including ulcer disease (SMR, 4.92 [95% CI, 2.45-8.88]) and chronic liver disease and cirrhosis (SMR, 2.95 [95% CI, 2.11-4.0]); and blood diseases (SMR, 4.64 [95% CI, 3.06-6.75]). Mortality was also elevated for vascular diseases (SMR 1.35, [95% CI, 1.25-1.44]), including coronary heart disease (SMR 1.47, [95% CI, 1.35-1.60]). Patients had a reduced risk of mortality due to neurological diseases (SMR, 0.65 [95% CI, 0.50-0.82]) and specifically Alzheimer disease (SMR, 0.53 [95% CI, 0.37-0.74]). Mortality was not different than what was expected for stroke, diabetes mellitus, chronic obstructive pulmonary disease, urinary tract diseases, and accidents and injuries. SMRs for some conditions (eg, infections, gastrointestinal diseases, and blood diseases) were dramatically elevated within the initial 5 years after the diagnosis but declined after 5 years ($P < .05$; Table 2).

DISCUSSION

This is the first population-based study assessing cure outcomes and deaths due to noncancer causes for DLBCL patients in the R-CHOP era. Previous research has shown that survival after DLBCL has improved considerably

TABLE 2. SMRs for Specific Noncancer CODs Among Diffuse Large B-Cell Lymphoma Cases Diagnosed in the Modern R-CHOP Era

Noncancer COD	Total			0-59 mo			≥60 mo			*P* for difference between 2 time periods
	Observed Deaths	SMR	95% CI	Observed Deaths	SMR	95% CI	Observed Deaths	SMR	95% CI	
Total	1788	**1.41**	1.35-1.48	1479	**1.56**	1.48-1.64	309	0.99	0.88-1.10	<.0001
Vascular diseases	784	**1.35**	1.25-1.44	639	**1.44**	1.33-1.56	145	1.04	0.88-1.23	.005
Coronary heart disease	533	**1.47**	1.35-1.60	439	**1.58**	1.43-1.73	94	1.11	0.9-1.36	.002
Stroke	100	1.00	0.81-1.21	82	1.07	0.85-1.33	18	0.76	0.45-1.20	.162
Infection	261	**3.13**	2.76-3.54	226	**3.57**	3.12-4.07	35	**1.74**	1.22-2.43	<.0001
Pneumonia/influenza	71	**1.68**	1.31-2.12	56	**1.73**	1.31-2.25	15	1.49	0.84-2.46	.596
Septicemia	43	**1.88**	1.36-2.53	36	**2.07**	1.45-2.87	7	1.26	0.51-2.60	.149
Diabetes mellitus	51	1.08	0.80-1.42	43	1.18	0.86-1.59	8	0.73	0.31-1.44	.197
Lung diseases	185	**1.29**	1.11-1.48	159	**1.47**	1.25-1.71	26	0.73	0.48-1.07	.008
COPD	83	0.84	0.67-1.04	64	0.86	0.66-1.10	19	0.79	0.47-1.23	.735
Gastrointestinal diseases	128	**2.50**	2.08-2.97	108	**2.76**	2.26-3.33	20	**1.64**	1.00-2.54	.037
Ulcer disease	11	**4.92**	2.45-8.80	9	**5.2**	2.38-9.87	2	3.96	0.48-14.3	.299
Chronic liver disease and cirrhosis	41	**2.95**	2.11-4.00	37	**3.45**	2.43-4.76	4	1.25	0.34-3.2	.078
Blood diseases	27	**4.64**	3.06-6.75	26	**5.95**	3.89-8.72	1	0.69	0.02-3.84	.662
Venous thromboembolism	2	1.27	0.15-4.59	2	1.65	0.2-5.95	0			
Urinary tract diseases	54	1.19	0.89-1.55	42	1.22	0.88-1.65	12	1.08	0.56-1.88	.704
Neurological diseases	65	**0.65**	0.5-0.82	50	**0.68**	0.5-0.9	15	**0.56**	0.31-0.92	.506
Alzheimer disease	34	**0.53**	0.37-0.74	24	**0.52**	0.33-0.77	10	0.57	0.27-1.04	.822
Accidents and injuries	69	1.13	0.88-1.43	54	1.16	0.87-1.52	15	1.01	0.57-1.67	.582
All other noncancer CODs combined	179	**1.20**	1.03-1.39	146	**1.37**	1.16-1.61	33	0.77	0.53-1.08	.002

Abbreviations: CI, confidence interval; COD, cause of death; COPD, chronic obstructive pulmonary disease; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone; SMR, standardized mortality ratio.
Bolded SMRs are significantly different from 1.00 ($P < .05$). A blank indicates that because of 0 observed deaths, the SMR, 95% CI, and *P* value were not calculated.

over time. The 5-year DLBCL-specific survival rate went from 37% in 1975 to 66% in 2005.[34] Despite this dramatic improvement, we have found that more than three-quarters of all deaths among DLBCL patients in the R-CHOP era are still due to DLBCL. Although noncancer deaths constitute a smaller fraction, our study noted elevated risks from a number of noncancer CODs in comparison with the US general population.

We applied a cure model to SEER data for newly diagnosed DLBCL cases. Cure models allow survival information on patients with sufficiently long follow-up to be split into 2 components: the proportion cured (those who do not experience any mortality from their disease, even many years after their diagnosis) and the proportion destined to die of their disease. For DLBCL, the estimated cure proportions were 73% for low-risk patients, 49% for medium-risk patients, and 27% for high-risk patients according to a log-logistic distribution. From the sensitivity analyses, in which we refitted additional mixture cure models with Weibull and log-normal distributions, the cure proportions were 63% to 78% for low-risk patients, 41% to 59% for medium-risk patients, and 26% to 37% for high-risk patients. Because of the range of cure estimates, it is difficult to be certain about the proportion of DLBCL patients who are cured. Cure proportions are challenging to estimate because they typically rely on extrapolations beyond the observed survival time. As stressed by others,[30,31,35] fitting a cure model requires a long follow-up period after the diagnosis. We had only 11 years of follow-up, which may not be long enough to provide accurate estimates of cure proportions. The DLBCL-specific survival curves that we present show leveling off, but importantly, there is still some decrease at the end of the follow-up period. The continued gradual decline in DLBCL-specific survival over time was also seen when we estimated survival among patients alive 2 years after their diagnosis. These results indicate that although there is likely a fraction of patients who are cured, it is difficult to be definitive on this point, and at least some long-term survivors of DLBCL may continue to die of their malignancy.

Even though outcomes are often favorable for DLBCL patients, especially among those treated with immunochemotherapy, some patients experience late relapse. For example, Maurer et al[12] reported that 8% of patients relapse within 2 to 7 years after the diagnosis. The relapse rate is lower with increasing time after the diagnosis but is still approximately 4% at 5 years.[11] This pattern of late relapse is seen in patients with early-stage disease,[11,36] a favorable International Prognostic Index,[11] or extranodal disease involvement.[11] The late-relapse

phenomenon in this patient population is manifested in our DLBCL-specific survival curves (Fig. 1) and explains why we could not confidently estimate the cure fractions.

DLBCL patients also have an elevated risk of dying of a number of other conditions, as shown in Table 2. Mortality risks were elevated for vascular disease (SMR, 1.35) and specifically for coronary heart disease (SMR, 1.47), this risk being significantly elevated during the first 5 years after the DLBCL diagnosis. Mortality from infections (SMR, 3.13), including pneumonia/influenza (SMR, 1.68) and septicemia (SMR, 1.88), was also elevated. Given that DLBCL patients are immunocompromised by their disease and subsequent treatment with chemotherapy, we were not surprised to see an elevated risk of death from infection, and the SMRs for infection declined over time. Mortality from blood diseases (eg, anemia, thrombocytopenia, and clotting disorders) was elevated (SMR, 4.64), especially during the first 5 years after the diagnosis (SMR, 5.95), and may likewise be related to complications of DLBCL or its treatment. Previous research has shown that common CODs in this patient population include therapy-related deaths, such as complications from hemolytic anemia, infections, side effects of chemotherapy drugs, and other causes.[4,11,12] Doxorubicin-related cardiotoxicity is a major noncancer COD among DLBCL patients treated with R-CHOP.[12] Venous thromboembolism can also occur as a treatment complication,[12,17] although mortality from this condition was not elevated in our study. The reduced mortality due to neurological diseases (SMR, 0.65) and specifically Alzheimer disease (SMR, 0.53) may partly indicate a bias; that is, patients with severe dementia or another debility may not be evaluated or treated for DLBCL. This hypothesis is supported by the finding of a reduced incidence of DLBCL diagnoses among elderly patients with neurologic diseases.[37]

The accuracy of our analyses depends on the methods used by the National Center for Health Statistics to assign underlying CODs. Assigning an underlying COD for an individual with multiple medical problems, including cancer, is challenging because there is often uncertainty about the chain of events leading to death. For our cure models, we used an algorithm recently developed by SEER to capture cancer-specific deaths.[20] According to this algorithm, any cancer COD is attributed to DLBCL-specific death if DLBCL was the patient's only diagnosed cancer. The assumption here is that if the person had DLBCL as the only incident cancer, then CODs indicating another cancer were miscoded; for example, the COD may incorrectly indicate the site of metastasis. This approach was reasonable in our study because of this issue of miscoding on death certificates and also because we censored people if they actually developed a second cancer. With respect to our SMR analysis, it is possible that undercounting or overcounting of deaths occurred. Diabetes and hypertension deaths, for example, are probably undercounted because they are often reported as contributing factors rather than the underlying COD.[38] We considered these CODs separately from DLBCL-specific deaths, even though some of the conditions are caused by DLBCL or its treatment. It is thus possible that some of these noncancer deaths would have contributed as events had we estimated cure proportions with relative survival, which compares all-cause mortality in a diseased cohort with that in the general population.[39] However, the number of noncancer CODs was small in comparison with the number of DLBCL-specific deaths, and the cancer-specific curves and relative survival curves were similar (not shown).

There are several strengths of our study. Our results are population-based and incorporate high-quality US cancer registry data. SEER registries reliably capture DLBCL cases in their catchment areas, and they have complete follow-up information for more than 95% of cases, so reporting of survival is reliable.[1] Our results are more generalizable than those from single centers, and clinical trials are unlikely to include representative samples of older, sicker, and low-income patients.[40,41] Therefore, our study best reflects outcomes among unselected DLBCL patients experiencing typical patterns of care.

A few limitations should be noted. Because we relied on data collected by cancer registries, the risk model that we used to categorize DLBCL cases lacked some useful clinical variables (eg, performance status and serum lactate dehydrogenase level) included in clinical risk models.[8,42,43] With these other models, it may be possible to identify very low-risk groups that indeed show clear evidence of a cure.[12] Another limitation of our approach is that we could not examine death from second cancers because the algorithm that we used assigned CODs only for first cancers. However, second cancers after a primary NHL have been assessed in other studies, and although they are an important issue, they are rare events.[23] Lastly, we lacked robust data on treatment and especially chemotherapy use.[29]

A final limitation of our analysis is that we could not determine which patients received R-CHOP, although we were able to incorporate SEER data on the receipt of any chemotherapy. Thus, the estimates that we present in our article may be less useful for treating clinicians than for researchers and policymakers interested in the entire population of recently diagnosed DLBCL patients. Survival for patients who received chemotherapy was better than

survival for the cohort overall (Fig. 2). However, even in the treated group, the survival curves were still falling at the end of follow-up. As for the cohort overall, this observation makes it difficult to determine with certainty the proportion of cured patients in the chemotherapy-treated group.

In conclusion, using population-based data, we show that DLBCL patients diagnosed in the modern R-CHOP treatment era still experience substantial mortality due to their cancer and other noncancer causes. Although DLBCL-specific mortality levels off over time, there is no clear plateau, and even patients who achieve 2-year survival are still at risk of dying of their lymphoma. Mortality from vascular diseases, infections, and blood diseases is also particularly elevated. Additional clinical research is needed to develop optimal treatments for DLBCL and strategies to prevent long-term relapse and treatment-related deaths. In the interim, clinicians should be aware of these long-term risks, and the impact of recently published strategies for improving the care of DLBCL survivors should be evaluated.[44]

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The authors made no disclosure.

AUTHOR CONTRIBUTIONS

Nadia Howlader: Conceptualization, methodology, software, formal analysis, investigation, data curation, writing–original draft, writing–review and editing, and visualization. **Angela B. Mariotto:** Software, formal analysis, data curation, and writing–review and editing. **Caroline Besson:** Validation, formal analysis, data curation, and writing–review and editing. **Gita Suneja:** Conceptualization, methodology, validation, formal analysis, data curation, and writing–review and editing. **Kim Robien:** Formal analysis, data curation, and writing–review and editing. **Naji Younes:** Software, formal analysis, data curation, and writing–review and editing. **Eric A Engels:** Conceptualization, methodology, validation, formal analysis, writing–review and editing, and supervision.

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