

LYMPHOID NEOPLASIA

Disparities in survival by insurance status in follicular lymphoma

Jordan S. Goldstein,¹ Loretta J. Nastoupil,² Xuesong Han,³ Ahmedin Jemal,³ Elizabeth Ward,³ and Christopher R. Flowers¹¹Emory University, Winship Cancer Institute, Atlanta, GA; ²The University of Texas MD Anderson Cancer Center, Houston, TX; and ³American Cancer Society, Atlanta, GA

KEY POINTS

- Privately insured patients have improved OS among patients of all ages with FL.
- Expanding access to care through insurance has the potential to improve FL outcomes.

Follicular lymphoma (FL) is the second most common non-Hodgkin lymphoma and most common indolent non-Hodgkin lymphoma. Lower socioeconomic status is associated with poor outcomes in FL, suggesting that access to care is an important prognostic factor; however, the association between insurance status and FL survival has not been sufficiently examined. The National Cancer Database, a nationwide cancer registry, was used to evaluate 43 648 patients with FL diagnosed between 2004 and 2014. All analyses were performed on 2 cohorts segmented at age 65 years to account for changes in insurance status with Medicare eligibility. Cox proportional hazard models calculated hazard ratios (HRs) with confidence intervals (CIs) for the association between insurance status and overall survival (OS) controlling for the available sociodemographic and prognostic factors. Kaplan-Meier curves display outcomes by

insurance status for patients covered by private insurance, no insurance, Medicaid, or Medicare. When compared with patients younger than age 65 years with private insurance, patients younger than age 65 years with no insurance (HR, 1.96; 95% CI, 1.69-2.28), with Medicaid (HR, 1.82; 95% CI, 1.57-2.12), and with Medicare (HR, 1.96; 95% CI, 1.71-2.24) had significantly worse OS after adjusting for sociodemographic and prognostic factors. Compared with patients age 65 years or older with private insurance, those with Medicare only (HR, 1.28; 95% CI, 1.17-1.4) had significantly worse OS. For adults with FL, expanding access to care through insurance has the potential to improve outcomes. (Blood. 2018;132(11):1159-1166)

Introduction

Follicular lymphoma (FL) is the second most common non-Hodgkin lymphoma (NHL) overall and most common indolent NHL, with an estimated 14 000 diagnosed cases per year in the United States.¹ Accounting for up to 20% of NHL cases globally, FL is a slow-growing tumor that often responds well to initial therapy.² However, advanced-stage FL is an incurable disease characterized by frequent relapses, often with increasing aggressiveness, and the ability to transform into more aggressive lymphoid malignancies.³ The variable disease course and lack of cure has resulted in variable treatment strategies, without a standard of care. Overall survival (OS) in FL has improved with the incorporation of rituximab immunotherapy over the past decade.^{4,5} However, heterogeneity in FL outcomes persists. Relapse occurs in up to 20% of patients within the first 24 months of first-line treatment and confers a poor prognosis.⁶⁻⁸ To date, a limited number of prognostic parameters have been identified for predicting outcomes in FL.

The selection of cancer diagnostics and treatments may depend on a patient's insurance status.⁹⁻¹¹ Patients with no insurance or Medicaid, when compared with those with private insurance, are more likely to be diagnosed at an advanced stage for all cancers.⁹ Disparities in treatment and outcomes related to insurance status have been examined for some patients with aggressive NHL,¹² but

are less clear for FL and other indolent NHLs. For instance, NHL patients with Medicaid or no insurance are less likely to receive immunotherapy treatments such as rituximab, a therapy known to improve FL outcomes.^{13,14} In another study, older adolescents and young adults with lymphoma had a wider gap between the onset of cancer symptoms and diagnosis if they had Medicaid or no insurance than if they had private insurance.¹⁵ In other studies, patients without private insurance have been shown to have significantly worse outcomes for 2 aggressive lymphomas: diffuse large B-cell lymphoma and Hodgkin lymphoma.^{12,16}

For patients with FL, lower neighborhood socioeconomic status (SES) is associated with substantially poorer survival, suggesting that access to care plays an important role in outcomes.¹⁷ The social determinants of FL prognosis remain unclear, and literature on the relationship between access to care and FL outcomes is scarce. We examined the relationship between insurance status and OS for FL in a national patient cohort.

Methods

Data source

Data were obtained from the National Cancer Database (NCDB), a nationwide, hospital-based cancer registry sponsored by the American Cancer Society and American College of Surgeons.

The NCDB contains 34 million historical records, captures data for approximately 70% of newly diagnosed cancer cases across the United States, and obtains data from more than 1500 Commission on Cancer (CoC)-accredited facilities, beginning in 1989.¹⁸ Patients' vital status and date of death are reported to the NCDB annually by the CoC facilities.¹⁹

Study population

Patients with FL were identified by using the International Classification of Diseases for Oncology, 3rd edition, histology codes 9690, 9691, 9695, and 9698, following the International Lymphoma Epidemiology Consortium (Interlymph) hierarchy of lymphoid neoplasms and the 2008 World Health Organization classification.²⁰ Patients with FL were included in the study if they were age ≥ 18 years, were diagnosed with FL as their first primary tumor between 2004 and 2014, received all or part of their first course of treatment at the reporting facility, and were HIV-negative. Only HIV-negative patients were included in this study because of the significant confounding by HIV status on the relationship between insurance status and survival. Patients were excluded if insurance status was missing ($n = 759$), or the reporting facility was not CoC-accredited in the follow-up years ($n = 4598$), as were those who had government-sponsored insurance (Veterans Affairs and Indian/Public Health Services) ($n = 497$), because this category combines various heterogeneous populations in a small sample size (Figure 1).

Study variables

Insurance status was defined as primary payer at the time of diagnosis and was grouped into the following categories: private insurance, no insurance, Medicaid, and Medicare. Race/ethnicity was classified as white, Hispanic, black, and other. Because the NCDB does not capture information on individual-level SES, we used ZIP code-level education, measured as proportion of adults without a high school diploma according to patient's ZIP code of residence as a marker of SES.^{21,22} ZIP code-level education level was obtained from the 2012 American Community Survey and categorized into $<7\%$, 7% to 12.9% , 13% to 20.9% , and $>21\%$ of adults without a high school diploma.²³ Disease stage was defined according to the American Joint Committee on Cancer *Cancer Staging Manual* and sorted into early stage (I, II) and advanced stage (III, IV).²⁴ A Charlson-Deyo comorbidity score was calculated on the basis of the patient's preexisting medical conditions and comorbidities.²⁵ Type and date of initial treatment were recorded. OS was calculated (in months) as time to event from the date of diagnosis through 31 December 2014, the date of death, or the date of last contact, whichever occurred first.

Statistical analysis

To compare the sociodemographic and clinical characteristics of the study cohort by insurance status, χ^2 analysis was used. Because of the substantial change in the insurance landscape at age 65 years with Medicare eligibility, all analyses were performed on a cohort of patients age <65 years and separately on a cohort age ≥ 65 years. Because the Medicaid and uninsured patients age ≥ 65 years each consisted of $<1\%$ of the elderly population, they were removed from the analysis. Kaplan-Meier survival curves were drawn by insurance status, and log-rank tests were performed. Multivariable log-binomial models were generated to estimate risk ratios and 95% confidence intervals (CIs) while controlling for sociodemographic factors (sex, race,

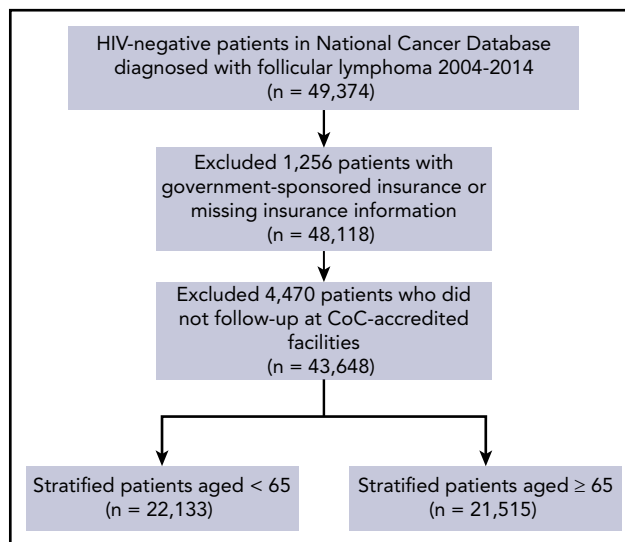


Figure 1. CONSORT diagram depicting FL case selection process. The total number of FL patients who met inclusion and exclusion criteria was 43 648. These patients were then stratified into 2 cohorts of patients age <65 and ≥ 65 years.

and education) to assess the relationship between insurance status and advanced-stage (III/IV vs I/II) disease, presence of B symptoms (yes vs no), comorbidities (yes vs no), initial treatment modality (systemic treatment including chemotherapy and/or immunotherapy vs no systemic treatment), and treatment within 1 month (yes vs no). Univariable and multivariable Cox proportional hazards models were fitted after confirming that the proportional hazards assumption was met for all independent variables. To examine the effect of prognostic factors (stage, B symptoms, comorbidity, time from diagnosis to treatment) on the survival disparity observed as a result of insurance status, models were fitted with variables added using forward selection and included if the significance criterion of 0.10 was met. The covariates considered for inclusion were sex, race, education level, presence of B symptoms, stage, comorbidity score, type of treatment, and time from diagnosis to treatment. Additional analyses were performed to (1) assess the impact of age on the relationship between insurance status and outcomes in the elderly cohort by generating Kaplan-Meier curves by insurance status and univariable and multivariable Cox regression models for subgroups of patients age ≥ 70 years and age ≥ 75 years, and (2) assess the impact of stage by generating Kaplan-Meier curves stratified by insurance status for early-stage and advanced-stage patients. All statistical analyses were performed using R version 3.3.2 software (R Project for Statistical Computing). The threshold for statistical significance was set at $\alpha = 0.05$.

Results

We identified 43 648 patients diagnosed with FL between 2004 and 2014, of whom 47% had private insurance, 3% were uninsured, 4% had Medicaid, and 46% had Medicare (Table 1). Of the 22 133 FL patients age <65 years, 80% had private insurance, 6% had no insurance, 6% had Medicaid, and 8% had Medicare. Of the 21 515 patients age ≥ 65 years, 13% had private insurance and 86% had Medicare. Less than 1% of the patients age ≥ 65 years had Medicaid or had no insurance and were not included in the analyses for this cohort.

Table 1. Descriptive characteristics for patients with FL age <65 and ≥65 years

Characteristic	Patients age <65 years						Patients age ≥65 years					
	Total	Private, %	No insurance, %	Medicaid, %	Medicare, %	P	Total	Private, %	Medicare, %	Medicare, %	P	
Sex												
Male	11 108	50.8	53.1	44.7	46	<.0001	9 727	51.6	45	<.0001		
Female	11 025	49.2	46.9	55.3	54		11 492	48.4	55			
Race/ethnicity												
White	17 325	81	61.7	60.4	78.5	<.0001	18 121	82.3	85.9	<.0001		
Hispanic	1 460	4.8	19.1	18	5.9		594	4	2.6			
Black	1 349	5	11.1	13	7.8		780	4.5	3.6			
Other	1 849	8.5	7.5	8	7.3		1 616	8.6	7.5			
Unknown	150	0.7	0.6	0.6	0.5		108	0.7	0.5			
Percent with no high school diploma												
<7	6 247	31.6	15.8	11	17.8	<.0001	5 784	30.6	26.7	<.0001		
7-12.9	7 420	34.6	26.3	29.9	31.3		7 450	34.6	35.2			
13-20.9	5 137	21.9	27.8	29.1	28.3		5 106	21.7	24.4			
>21	3 080	10.7	29.2	29.2	21.6		2 622	11.8	12.4			
Unknown	249	1.2	0.9	0.8	1		257	1.3	1.2			
B symptoms present												
Yes	4 139	16.6	31.2	28.7	21.6	<.0001	3 206	14.2	15.3	.0688		
No	16 309	75.5	63.1	66	70.4		15 993	77.6	75			
Unknown	1 685	7.9	5.7	5.4	8		2 020	8.3	9.7			
Stage												
I/II	8 574	40	29.5	30.7	40.1	<.0001	9 105	43.8	42.8	.0813		
III/IV	11 675	51.7	61.7	61.1	49.9		9 904	44.6	47			
Unknown	1 884	8.4	8.8	8.2	9.9		2 210	11.6	10.2			
Comorbidities												
0	19 152	88.6	84.9	79.4	73.1	<.0001	16 422	80.1	77	.0002		
1	2 436	9.7	12.3	15.6	19.7		3 605	15.6	17.2			
≥2	545	1.8	2.8	5	7.2		1 192	4.3	5.8			
Initial treatment												
Systemic	13 838	61	71.7	71.6	62.9	<.0001	11 805	54.2	55.9	.0959		
None	7 629	35.7	26.9	25.6	35.5		8 890	43.3	41.7			
Days from diagnosis to treatment												
0-14	8 264	37.9	35.3	36.5	34	.0002	7 439	34.2	35.2	.0412		
15-30	3 342	15.1	14.6	15.2	15.7		3 041	12.8	14.6			
>30	6 437	28.4	34.1	32.1	30.1		5 748	28.1	26.9			
Unknown	4 090	18.7	16	16.2	20.2		4 991	24.9	23.3			

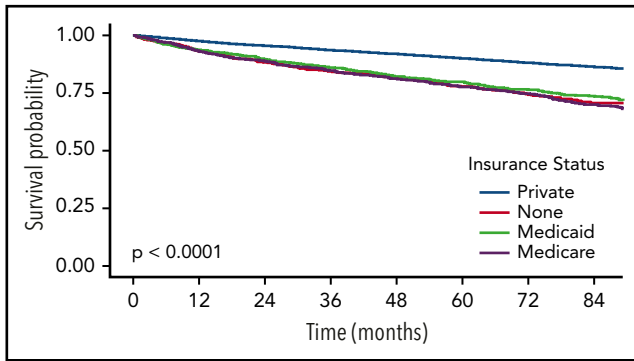


Figure 2. OS by insurance status for FL patients age <65 years. OS for the cohort was 92% at 3 years, 88% at 5 years, and 84% at 7 years.

Through 2014, 11 547 (26%) patients with FL had died. The median follow-up was 57.9 months in the cohort age <65 years and 42.8 months in the cohort age ≥ 65 years. For the cohort age <65 years, the median ages at diagnosis were 54, 52, 52, and 59 years for private insurance, no insurance, Medicaid, and Medicare, respectively, and was 54 years (interquartile range, 47-60 years) across all insurance types. For the cohort age ≥ 65 years, the median ages at diagnosis were 71 and 75 years for private insurance and Medicare, respectively, and 74 years (interquartile range, 69-80 years) across both insurance types. Patients with no insurance or Medicaid were more likely to be black or Hispanic, live in an area with mostly poorly educated people, have B symptoms, and be diagnosed at an advanced stage when compared with those with private insurance or Medicare (Table 1). Patients age <65 years who were uninsured or Medicaid-insured were more likely to present at an advanced stage, present with B symptoms, and have comorbidities after adjusting for sociodemographic factors (supplemental Table 1, available on the *Blood* Web site). Patients with Medicare who were age <65 years were more likely to have B symptoms and comorbidities (supplemental Table 1). Meanwhile, patients with Medicare who were age ≥ 65 years were significantly more likely to have comorbidities and receive treatment with systemic therapy than those privately insured (supplemental Table 2).

For FL patients age <65 years, OS was 92% at 3 years, 88% at 5 years, and 84% at 7 years. The OS rates for privately insured, uninsured, Medicaid-insured, and Medicare-insured patients age <65 years were 90%, 78%, 80%, and 78%, respectively, at 5 years (Kaplan-Meier curves shown in Figure 2). OS was significantly worse for uninsured, Medicaid-insured, and Medicare-insured patients age <65 years compared with those privately insured with hazard ratios (HRs) of 2.34 (95% CI, 2.06-2.65), 2.22 (95% CI, 1.96-2.51), and 2.45 (95% CI, 2.22-2.71), respectively. When adding sociodemographic, prognostic, and treatment factors to the model, the HRs remained significant for uninsured, Medicaid-insured, and Medicare-insured at 1.96 (95% CI, 1.69-2.28), 1.83 (95% CI, 1.57-2.12), and 1.96 (95% CI, 1.71-2.24), respectively (Table 2). Disease stage, presence of B symptoms, and comorbidities were significant predictors of FL survival in patients, which contributed to the survival disparities seen with insurance status.

For FL patients age ≥ 65 years, OS was 73% at 3 years, 63% at 5 years, and 52% at 7 years. The OS rates for privately insured and

Medicare-insured patients age ≥ 65 years were 69% and 62%, respectively, at 5 years (Kaplan-Meier curves shown in Figure 3). Medicare-insured patients age ≥ 65 years had significantly worse OS compared with those with private insurance with an HR of 1.33 (95% CI, 1.24-1.43). After controlling for sociodemographic and clinical factors, Medicare insurance remained significantly associated with worse OS with an HR of 1.28 (95% CI, 1.17-1.4) (Table 3).

Discussion

To the best of our knowledge, this is the first US nationwide investigation into the relationship between insurance status and

Table 2. Multivariable HRs for FL patients age <65 years

	HR (95% CI)	P
Insurance status		
Private insurance	1.00 (ref)	
No insurance	1.96 (1.69-2.28)	<.0001
Medicaid	1.83 (1.57-2.12)	<.0001
Medicare	1.96 (1.71-2.24)	<.0001
Sex		
Male	1.00 (ref)	
Female	0.78 (0.71-0.85)	<.0001
Race/ethnicity		
White	1.00 (ref)	
Black	0.98 (0.83-1.17)	.8462
Hispanic	0.72 (0.59-0.88)	.0014
Other race	0.95 (0.81-1.12)	.5616
Unknown race	1.01 (0.56-1.82)	.9828
Percent with no high school diploma		
<7	1.00 (ref)	
7-12.9	1.19 (1.05-1.34)	.0051
13-20.9	1.4 (1.24-1.59)	<.0001
>21	1.42 (1.22-1.64)	<.0001
B symptoms		
Not present	1.00 (ref)	
Present	1.35 (1.22-1.49)	<.0001
Stage		
I/II	1.00 (ref)	
III/IV	1.69 (1.52-1.87)	<.0001
Comorbidity score		
0	1.00 (ref)	
1	1.71 (1.52-1.93)	<.0001
2+	3.1 (2.61-3.69)	<.0001
Initial treatment		
Systemic	1.00 (ref)	
None	0.81 (0.71-0.92)	<.0001
Days to treatment		
0-14	1.00 (ref)	
15-30	0.82 (0.73-0.93)	.0012
30+	0.69 (0.62-0.76)	<.0001

ref, reference.

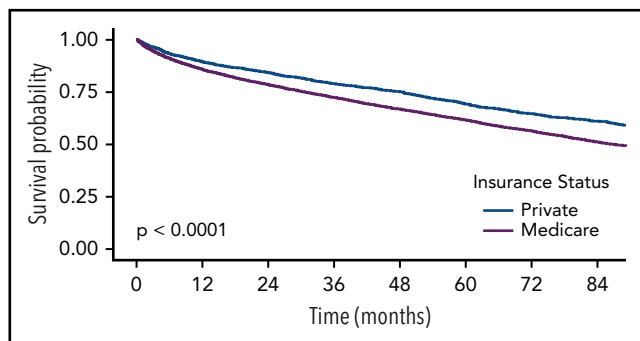


Figure 3. OS by insurance status for FL patients age ≥ 65 years. OS for the cohort was 73% at 3 years, 63% at 5 years, and 52% at 7 years.

OS for patients with FL as well as the first to examine this relationship in an indolent lymphoma. We found that adults age < 65 years who were uninsured, had Medicaid, or had Medicare had inferior survival in comparison with those with private insurance. Similarly, among patients age ≥ 65 years with FL, those with Medicare had significantly worse OS compared with privately insured patients. Patients who were uninsured or had Medicaid more commonly had poorer SES, advanced stage, B symptoms, and multiple comorbidities, likely contributing to the observed survival difference. These associations persisted when controlling for the known and available sociodemographic and prognostic factors. The findings of the study indicate that improving access to affordable quality health care may reduce disparities in survival for those currently lacking coverage.

In our additional analyses, private insurance remained a significant predictor of improved OS relative to no insurance, Medicaid, and Medicare when stratified by early and advanced stage for patients age < 65 years (supplemental Figure 2) and for patients age ≥ 65 years (supplemental Figure 3). These results suggest that although stage is an important factor in how insurance status relates to FL survival, stage does not fully explain the disparate outcomes, and lead-time bias is unlikely to be the sole source for this difference. Meanwhile, insurance status remained a significant predictor of worse OS for Medicare patients in the cohort age ≥ 70 years by log-rank test and univariable and multivariable Cox regression models, and in the elderly cohort age ≥ 75 years by log-rank test and univariable Cox regression model. It is possible that the multivariable Cox regression model did not meet significance criteria in the cohort age ≥ 75 years because of a reduced sample size. These results suggest that although age is an important factor that influences outcomes within the elderly cohort, insurance status is an independent predictor of outcomes for elderly patients.

For FL patients age < 65 years, Medicare survival mirrors that of uninsured and Medicaid-insured patients. Medicare patients age < 65 years, were much more likely to have comorbidities that contribute to the observed worse outcomes. This arises because young patients can receive Medicare if they qualify for Social Security Disability Insurance or have end stage renal disease and are receiving dialysis or had a kidney transplant. Thus, patients insured by Medicare age ≥ 65 years had a less pronounced risk of having comorbidities, although they continued to have poorer prognosis compared with the elderly who are insured privately.

Our results showed that patients with Medicaid, Medicare, or no insurance age < 65 years were more likely to have a delay in treatment and were more likely to receive systemic therapy than their privately insured counterparts; however, these associations were not found in the elderly cohort. For both cohorts, a delay in treatment and treatment other than systemic therapy were associated with improved survival. This observed improved outcome is likely the result of those patients having less severe disease at diagnosis. Unlike many other malignancies, systemic therapy and prompt treatment are not required or recommended for many patients with FL who are asymptomatic at diagnosis and do not have evidence of any of the Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria.²⁶ These factors include any nodal or extranodal tumor mass with a diameter ≥ 7 cm, involvement of ≥ 3 nodal sites each with a diameter ≥ 3 cm, B symptoms, splenomegaly, pleural effusions or

Table 3. Multivariable HRs for FL patients age ≥ 65 years

	HR (95% CI)	P
Insurance status		
Private insurance	1.00 (ref)	
Medicare	1.28 (1.17-1.4)	$< .0001$
Sex		
Male	1.00 (ref)	
Female	0.88 (0.83-0.93)	$< .0001$
Race/ethnicity		
White	1.00 (ref)	
Black	0.96 (0.83-1.11)	.5958
Hispanic	0.67 (0.55-0.82)	$< .0001$
Other race	1.02 (0.92-1.12)	.7651
Unknown race	1.44 (0.98-2.12)	.0627
Percent with no high school diploma		
< 7	1.00 (ref)	
7-12.9	1.03 (0.96-1.11)	.4219
13-20.9	1.09 (1.01-1.18)	.0279
> 21	1.19 (1.09-1.31)	.0002
B symptoms		
Not present	1.00 (ref)	
Present	1.38 (1.29-1.48)	$< .0001$
Stage		
I/II	1.00 (ref)	
III/IV	1.35 (1.27-1.43)	$< .0001$
Comorbidity score		
0	1.00 (ref)	
1	1.44 (1.35-1.55)	$< .0001$
2+	2.33 (2.11-2.57)	$< .0001$
Initial treatment		
Systemic	1.00 (ref)	
None	0.97 (0.9-1.04)	.3489
Days to treatment		
0-14	1.00 (ref)	
15-30	0.96 (0.89,1.04)	.3173
30+	0.84 (0.78-0.89)	$< .0001$

ascites, Eastern Cooperative Oncology Group performance status >1 , or lactate dehydrogenase or $\beta 2$ -microglobulin above normal levels. Unfortunately, complete assessment of GELF criteria for initiation of therapy is not possible in this data set. Large clinical data sets that include these criteria are needed to understand the interactions between clinical and social determinants on cancer outcomes.

Given the heterogeneity of outcomes and treatment options for FL, establishing factors that affect prognosis has been a central research focus. The most widely adopted FL risk stratification model has been FL International Prognostic Index, which includes age, stage, hemoglobin level, number of nodal areas, and serum lactate dehydrogenase levels.²⁷ Lack of biological information in our registry data set prevented us from incorporating some of these data into our study. However, our results confirmed the importance of advanced stage and B symptoms as predictors of worse OS.^{27,28} Our study also contributes new information on prognostic factors with comorbidity score ≥ 1 as a significant, independent predictor of worse OS. In addition to the factors currently used in the FL International Prognostic Index, insurance status and comorbidity score should be evaluated for inclusion in future FL prognostic models.

Significant heterogeneity exists in the first-line management of FL. Commonly used options include watchful waiting, radiotherapy, single-agent chemotherapy, immunotherapy, and chemoimmunotherapy. Initial treatment decisions often rely upon patient age, performance status, stage, and goals of care.²⁹ Several studies have shown improved clinical course for FL in the rituximab era; however, watchful waiting remains a viable option for many.³⁰⁻³⁵ Those who opted for watchful waiting in our analysis showed improved outcomes compared with those who received systemic treatment, which suggests that watchful waiting can be useful for the appropriately selected FL patient. Future randomized trials are essential to better identify the ideal patients for watchful waiting. Meanwhile, prior studies using the NCDB showed that patients without private insurance and those with low SES and black race are less likely to be the recipients of treatment with chemoimmunotherapy.¹³ This could be an important driver of the observed disparities in outcomes relative to insurance status, and one that is likely to grow as expensive therapies such as idelalisib, ibrutinib, and obinutuzumab continue to grow in use.³⁶⁻³⁹

This study has several limitations. First, because the study uses a retrospective database, we were unable to control for all possible confounders. Some potential confounders, such as individual-level SES, health literacy, or adherence to follow-up, were not collected in the NCDB. State of residence was not provided in the NCDB Participant User Files; thus, we were unable to examine how the variability in state-run Medicaid programs had an impact on outcomes in FL. Furthermore, we were unable to assess the impact of immunotherapy treatment over the time period because rituximab, an immunotherapy shown to have significant survival benefit in FL, was collected as chemotherapy rather than immunotherapy until 2013. Second, since insurance status was recorded only as primary payer at the time of diagnosis, it was not possible to account for dual insurance coverage or changes in insurance status over time. For instance, patients older than age 65 years recorded as

having private insurance were likely to have private coverage supplementing insurance with Medicare. Third, it is possible that the facilities available to patients with low SES or no insurance may not provide detailed diagnoses using the World Health Organization classification, which would confound the results. Finally, the results may not be fully generalizable to the US population because all data came from CoC-accredited hospitals, which may underrepresent the most disadvantaged patients.

Despite these limitations, the study has several strengths, including the large sample size, consistent vital status reporting, and inclusion of crucial factors that affect FL survival. Such factors include B symptoms, comorbidities, time to treatment, and HIV status.

Patients without health insurance, or with inadequate health insurance, may experience substantial barriers to quality care in the form of access, cost, or administration, which would contribute to further health inequality.⁴⁰ The Affordable Care Act passed in 2010 has improved patient access to care with more adults connecting to the health care system, obtaining a regular source of care, and being able to afford the care they require.^{41,42} Coverage expansion has been associated with earlier oncologic diagnosis and timelier oncologic care.^{43,44} The expansion of Medicaid has been successful in improving mortality, with the largest improvement in health care–amenable conditions such as cancer.⁴⁵ Although insurance through Medicaid can be associated with improved outcomes compared with no insurance, the benefits of Medicaid may be falsely lowered because of uninsured patients waiting until they qualified for Medicaid to see a physician about their cancer symptoms.⁴⁶ This is suggested by the significantly increased likelihood of Medicaid patients presenting in an advanced stage. It is also worth noting that Medicaid insurance still confers a worse OS for FL than private insurance, although this effect may be somewhat exaggerated. Health care policy should be based on evidence and, for patients with FL, improving access to care for those who are unable to afford private insurance has the potential to substantially improve outcomes.⁴⁷

In conclusion, our study finds that insurance status contributes to survival disparities in FL. Future studies on outcomes in FL should include insurance status as an important predictor. Further research on prognosis for FL should examine the impact of public policy, such as the passage of the Affordable Care Act, on FL outcomes, and should examine other factors that influence access to care, such as individual-level SES, regular primary care visits, access to prescription medications, and care affordability.

Acknowledgments

This work was supported in part by the Winship Research Informatics and Biostatistics and Bioinformatics Shared Resources of Winship Cancer Institute of Emory University; by National Institutes of Health (NIH), National Cancer Institute award no. P30CA138292 and grant no. K24CA208132 (C.R.F.); and by NIH, National Center for Advancing Translational Sciences award no. UL1TR000454.

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Authorship

Contribution: J.S.G. performed data analysis; and J.S.G., L.J.N., X.H., A.J., E.W., and C.R.F. were involved in study conception and design, data interpretation, and manuscript preparation.

Conflict-of-interest disclosure: C.R.F. received consultancy fees from AbbVie, Spectrum, Celgene, Optum Rx, Seattle Genetics, Gilead Sciences, and Bayer; and research funding from AbbVie, Acerta, Celgene, Gilead Sciences, Infinity Pharmaceuticals, Janssen Pharmaceuticals, Millennium Pharmaceuticals/Takeda, Spectrum, Onyx Pharmaceuticals, Pharmacyclics, the Burroughs Wellcome Fund, the V Foundation, and the National Institutes of Health. The remaining authors declare no competing financial interests.

Correspondence: Christopher R. Flowers, Department of Hematology and Oncology, Winship Cancer Institute, Emory University, 1365

Clifton Rd, Building B, Suite 4300, Atlanta, GA 30322; e-mail: crflowe@emory.edu.

Footnotes

Submitted 12 March 2018; accepted 6 July 2018. Prepublished online as *Blood* First Edition paper, 24 July 2018; DOI 10.1182/blood-2018-03-839035.

The online version of this article contains a data supplement.

The publication costs of this article were defrayed in part by page charge payment. Therefore, and solely to indicate this fact, this article is hereby marked "advertisement" in accordance with 18 USC section 1734.

REFERENCES

1. Teras LR, DeSantis CE, Cerhan JR, Morton LM, Jemal A, Flowers CR. 2016 US lymphoid malignancy statistics by World Health Organization subtypes [published online ahead of print 12 September 2016]. *CA Cancer J Clin*. doi:10.3322/caac.21357.
2. [No authors listed]. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. *Blood*. 1997;89(11):3903-3918.
3. Johnson PW, Rohatiner AZ, Whelan JS, et al. Patterns of survival in patients with recurrent follicular lymphoma: a 20-year study from a single center. *J Clin Oncol*. 1995;13(1):140-147.
4. Swenson WT, Wooldridge JE, Lynch CF, Forman-Hoffman VL, Chrischilles E, Link BK. Improved survival of follicular lymphoma patients in the United States. *J Clin Oncol*. 2005;23(22):5019-5026.
5. Tan D, Horning SJ, Hoppe RT, et al. Improvements in observed and relative survival in follicular grade 1-2 lymphoma during 4 decades: the Stanford University experience. *Blood*. 2013;122(6):981-987.
6. Salles G, Seymour JF, Offner F, et al. Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a phase 3, randomised controlled trial. *Lancet*. 2011;377(9759):42-51.
7. Maurer MJ, Ghesquieres H, Ansell SM, et al. Event-free survival at 12 months (EFS12) from diagnosis is a robust endpoint for disease-related survival in patients with follicular lymphoma in the immunochemotherapy era [abstract]. *Blood*. 2014;124(21). Abstract 1664.
8. Casulo C, Byrtek M, Dawson KL, et al. Early relapse of follicular lymphoma after rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone defines patients at high risk for death: An analysis from the National LymphoCare Study. *J Clin Oncol*. 2015;33(23):2516-2522.
9. Ward EM, Fedewa SA, Cokkinides V, Virgo K. The association of insurance and stage at diagnosis among patients aged 55 to 74 years in the national cancer database. *Cancer J*. 2010;16(6):614-621.
10. Halpern MT, Ward EM, Pavluck AL, Schrag NM, Bian J, Chen AY. Association of insurance status and ethnicity with cancer stage at diagnosis for 12 cancer sites: a retrospective analysis. *Lancet Oncol*. 2008;9(3):222-231.
11. Ward E, Halpern M, Schrag N, et al. Association of insurance with cancer care utilization and outcomes. *CA Cancer J Clin*. 2008;58(1):9-31.
12. Han X, Jemal A, Flowers CR, Sineshaw H, Nastoupil LJ, Ward E. Insurance status is related to diffuse large B-cell lymphoma survival. *Cancer*. 2014;120(8):1220-1227.
13. Flowers CR, Fedewa SA, Chen AY, et al. Disparities in the early adoption of chemoimmunotherapy for diffuse large B-cell lymphoma in the United States. *Cancer Epidemiol Biomarkers Prev*. 2012;21(9):1520-1530.
14. Shih YC, Elting LS, Halpern MT. Factors associated with immunotherapy use among newly diagnosed cancer patients. *Med Care*. 2009;47(9):948-958.
15. Martin S, Ulrich C, Munsell M, Taylor S, Lange G, Bleyer A. Delays in cancer diagnosis in underinsured young adults and older adolescents. *Oncologist*. 2007;12(7):816-824.
16. Parikh RR, Grossbard ML, Green BL, Harrison LB, Yahalom J. Disparities in survival by insurance status in patients with Hodgkin lymphoma. *Cancer*. 2015;121(19):3515-3524.
17. Keegan TH, McClure LA, Foran JM, Clarke CA. Improvements in survival after follicular lymphoma by race/ethnicity and socioeconomic status: a population-based study. *J Clin Oncol*. 2009;27(18):3044-3051.
18. Lerro CC, Robbins AS, Phillips JL, Stewart AK. Comparison of cases captured in the national cancer data base with those in population-based central cancer registries. *Ann Surg Oncol*. 2013;20(6):1759-1765.
19. American College of Surgeons. National Cancer Database. <https://www.facs.org/quality-programs/cancer/ncdb>.
20. Turner JJ, Morton LM, Linet MS, et al. InterLymph hierarchical classification of lymphoid neoplasms for epidemiologic research based on the WHO classification (2008): update and future directions. *Blood*. 2010;116(20):e90-e98.
21. Robert SA. Community-level socioeconomic status effects on adult health. *J Health Soc Behav*. 1998;39(1):18-37.
22. Robert SA, Strombom I, Trentham-Dietz A, et al. Socioeconomic risk factors for breast cancer: distinguishing individual- and community-level effects. *Epidemiology*. 2004;15(4):442-450.
23. Newman AM, Bratman SV, To J, et al. An ultrasensitive method for quantitating circulating tumor DNA with broad patient coverage. *Nat Med*. 2014;20(5):548-554.
24. Greene FL, Page DL, Fleming DL, Fritz AG, Balch CM, Haller DG. American Joint Committee on Cancer Staging Manual, 6th ed. New York, NY: Springer-Verlag; 2002.
25. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol*. 1992;45(6):613-619.
26. Brice P, Bastion Y, Lepage E, et al. Comparison in low-tumor-burden follicular lymphomas between an initial no-treatment policy, prednimustine, or interferon alfa: a randomized study from the Groupe d'Etude des Lymphomes Folliculaires. Groupe d'Etude des Lymphomes de l'Adulte. *J Clin Oncol*. 1997;15(3):1110-1117.
27. Solal-Céligny P, Roy P, Colombat P, et al. Follicular lymphoma international prognostic index. *Blood*. 2004;104(5):1258-1265.
28. Federico M, Bellei M, Marcheselli L, et al. Follicular lymphoma international prognostic index 2: a new prognostic index for follicular lymphoma developed by the international follicular lymphoma prognostic factor project. *J Clin Oncol*. 2009;27(27):4555-4562.
29. Gribben JG. How I treat indolent lymphoma. *Blood*. 2007;109(11):4617-4626.
30. Hiddemann W, Kneba M, Dreyling M, et al. Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. *Blood*. 2005;106(12):3725-3732.
31. Herold M, Haas A, Srock S, et al; East German Study Group Hematology and Oncology Study. Rituximab added to first-line mitoxantrone, chlorambucil, and prednisolone chemotherapy followed by interferon maintenance prolongs survival in patients with

- advanced follicular lymphoma: an East German Study Group Hematology and Oncology Study. *J Clin Oncol*. 2007;25(15):1986-1992.
32. Marcus R, Imrie K, Solal-Celigny P, et al. Phase III study of R-CVP compared with cyclophosphamide, vincristine, and prednisone alone in patients with previously untreated advanced follicular lymphoma. *J Clin Oncol*. 2008;26(28):4579-4586.
 33. Salles G, Mounier N, de Guibert S, et al. Rituximab combined with chemotherapy and interferon in follicular lymphoma patients: results of the GELA-GOELAMS FL2000 study. *Blood*. 2008;112(13):4824-4831.
 34. Solal-Céligny P, Bellei M, Marcheselli L, et al. Watchful waiting in low-tumor burden follicular lymphoma in the rituximab era: results of an F2-study database. *J Clin Oncol*. 2012;30(31):3848-3853.
 35. Nastoupil LJ, Sinha R, Byrtek M, et al. Outcomes following watchful waiting for stage II-IV follicular lymphoma patients in the modern era. *Br J Haematol*. 2016;172(5):724-734.
 36. Gopal AK, Kahl BS, Flowers CR, et al. Idelalisib is effective in patients with high-risk follicular lymphoma and early relapse after initial chemoimmunotherapy. *Blood*. 2017;129(22):3037-3039.
 37. Gopal AK, Kahl BS, de Vos S, et al. PI3K δ inhibition by idelalisib in patients with relapsed indolent lymphoma. *N Engl J Med*. 2014;370(11):1008-1018.
 38. Sehn LH, Goy A, Offner FC, et al. Randomized phase II trial comparing obinutuzumab (GA101) with rituximab in patients with relapsed CD20+ indolent B-cell non-Hodgkin lymphoma: final analysis of the GAUSS study. *J Clin Oncol*. 2015;33(30):3467-3474.
 39. Maddocks K, Christian B, Jaglowski S, et al. A phase 1/1b study of rituximab, bendamustine, and ibrutinib in patients with untreated and relapsed/refractory non-Hodgkin lymphoma. *Blood*. 2015;125(2):242-248.
 40. Coverage Matters. Insurance and Health Care. Washington, DC: National Academy Press; 2001.
 41. Shartz A, Long SK, Anderson N. Access to care and affordability have improved following affordable care act implementation; problems remain. *Health Aff (Millwood)*. 2016;35(1):161-168.
 42. Sommers BD, Gawande AA, Baicker K. Health insurance coverage and health - what the recent evidence tells us. *N Engl J Med*. 2017;377(6):586-593.
 43. Robbins AS, Han X, Ward EM, Simard EP, Zheng Z, Jemal A. Association between the affordable care act dependent coverage expansion and cervical cancer stage and treatment in young women. *JAMA*. 2015;314(20):2189-2191.
 44. Loehrer AP, Song Z, Haynes AB, Chang DC, Hutter MM, Mullen JT. Impact of health insurance expansion on the treatment of colorectal cancer. *J Clin Oncol*. 2016;34(34):4110-4115.
 45. Sommers BD, Baicker K, Epstein AM. Mortality and access to care among adults after state Medicaid expansions. *N Engl J Med*. 2012;367(11):1025-1034.
 46. Bradley CJ, Given CW, Roberts C. Late stage cancers in a Medicaid-insured population. *Med Care*. 2003;41(6):722-728.
 47. Sommers BD. Why health insurance matters and why research evidence should too. *Acad Med*. 2017;92(9):1228-1230.