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ORIGINAL REPORT

Survival Disparities in Patients With Lymphoma According to Place of Residence and Treatment Provider: A Population-Based Study

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A B S T R A C T

Purpose

Health disparities exist according to an individual's place of residence. We evaluated the association between primary area of residence (urban *v* rural) according to treatment provider (university based *v* community based) and overall survival in patients with lymphoma and determined whether there are patient groups that could benefit from better coordination of care.

Patients and Methods

Population-based, retrospective cohort study of 2,330 patients with centrally confirmed lymphoma from Nebraska and surrounding states and treated by university-based or community-based oncologists from 1982 to 2006.

Results

Among urban residents, 321 (14%) were treated by university-based providers (UUB) and 816 (35%) were treated by community-based providers (UCB). Among rural residents, 332 (14%) were treated by university-based providers (RUB), and 861 (37%) were treated by community-based providers (RCB). The relative risk (RR) of death among UUB, UCB, and RUB were not statistically different. However, RCB had a higher risk of death (RR, 1.37; 95% CI, 1.14 to 1.65; $P = .01$; and RR, 1.26; 95% CI, 1.06 to 1.49; $P = .01$) when compared with UUB and RUB, respectively. This association was true in both low- and intermediate-risk patients. Among high-risk patients, UCB, RUB, and RCB were all at higher risk of death when compared with UUB.

Conclusion

Survival outcomes of patients with lymphoma may be associated with place of residence and treatment provider. High-risk patients from rural areas may benefit from better coordination of care.

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INTRODUCTION

Health disparities exist according to place of residence.[1-8] Rural patients are less likely to receive optimal treatment, and have less favorable outcomes for different types of illnesses.[1,2,5,8-10] This disparity can be due to many factors including lack of access to quality health care providers.[2,11,12] Rural patients have also been shown to present with more severe disease, have lower socioeconomic status, and have generally poorer health habits.[1,4,6,8,13] Despite the predisposition of rural patients for inferior outcomes, studies in some chronic diseases have shown that outcome disparities according to place of residence can be improved through standardization of care using medical outreach teams, implementing practice guidelines, using nurse navigators, and tracking clinician performance.[1,2,8,14-16]

Outcome disparity also exists according to academic affiliation of health care providers.[17] In stage I and II breast cancer, breast conserving surgeries were more likely to be performed on patients treated by university-based providers.[9] In colorectal cancer, patients treated by university-based providers were less likely to have local recurrence and death when compared with patients treated by community-based providers.[18,19] It is not known whether cancer outcomes differ according to patient's place of residence and treatment provider.

In 1982, the Nebraska Lymphoma Study Group (NLSG) was established as collaboration between community-based and university-based oncologists and pathologists throughout Nebraska and surrounding states. Such collaboration allows for centralized diagnosis and staging, while affording community-based patients therapies according to

physician preference, and the expertise and facilities of university-based oncologists as needed. With the rising incidence of lymphoma in the United States, we used the NLSG collected data to evaluate whether a disparity exists in the outcomes of patients with lymphoma according to place of residence and treatment provider. Findings from this study would allow us to identify patients who may benefit from better coordination of care.

PATIENTS AND METHODS

Data Source

Data were obtained from the University of Nebraska Medical Center (UNMC) Oncology Database; a password protected, web-based database of patients with cancer. Data pertaining to patients with lymphoma was reported to the NLSG. A common consent form approved by the institutional review board at UNMC is used for all patients. Patient-, disease-, and treatment-related data are collected, as well as, fresh, frozen, and fixed tissues for pathologic and immunologic studies. Data are sent to a central office in Omaha, NE, where a rigorous data verification and audit process are implemented by trained data specialists. Audits are verified from various medical, pathology, laboratory, and ancillary reports. Follow-up information is obtained every 6 months. Causes of deaths are ascertained from death certificates or medical records and are confirmed by the attending oncologist. The NLSG invites its members to educational meetings and are also informed of ongoing clinical trials at UNMC. The UNMC institutional review board approved this study.

Patients

Patients included are primarily from the state of Nebraska, with some from the states of CO, WY, SD, KS, MO, and IA. A total of 3,619 consented patients were reported to the NLSG between 1982 and 2006. Three hundred twenty-nine patients (9%) had missing residential ZIP codes, while 960 (26%) had incomplete prognostic clinical data. Thus, a total of 2,330 patients were included in this study. Patients included were similar in age and sex distribution to patients with missing data, with a higher rate of Hodgkin's lymphoma (HL). The 5-year overall survival (OS) between the excluded and included patients were similar, 59% versus 57%, respectively. Follow-up information was obtained for all patients until December, 2007.

Variables Analyzed

The main variable analyzed classified patients into four groups: urban residents treated by university-based provider (UUB, n = 321), urban residents treated by community-based provider (UCB, n = 816), rural residents treated by university-based provider (RUB, n = 332), and rural residents treated by community-based provider (RCB, n = 861). Place of residence was defined according to the rural urban commuting area code assigned to the ZIP code of the patient's primary residence at diagnosis.[20] We dichotomized the rural urban commuting area classification into urban or rural designation. Urban areas consisted of urban commuting and urban core, while rural areas consisted of large rural commuting, large rural core, small rural commuting, and small rural core. Oncologists who treated the patient's lymphoma first were classified according to academic affiliation. University-based consisted of oncologists from UNMC, Creighton University Medical Center, and the Veterans' Administration of Nebraska and Western Iowa and see mainly hematologic malignancies, while community-based consisted of oncologists who do not have any academic affiliations. Community-based oncologists treat a wide range of malignancies, not limited to lymphoma, and can either be in solo or group practice. Figure 1 shows the distribution of the patients according to place of residence and treatment provider.

Table 1 presents all the variables included in the analyses. The residential ZIP code was used to derive the patient's mean household income using the 2000 US Census (categorized into quartile distribution), as well as the distance from place of residence to treatment provider.[21] In addition, the distance from place of residence to UNMC was approximated to provide an index of how far patients need to travel to seek university-based treatment.

Eight clinical risk factors were identified and used to categorize patients according to prognostic risk groups (see bottom of Table 1). Type of lymphoma was categorized into low grade, high grade, and HL as has been used in other observational studies[22-25] by the NLSG principal pathologist with expertise in lymphoma (D.D.W.); details of classification are presented as footnote in Table 1. Because no universally accepted way of classifying the risk for all

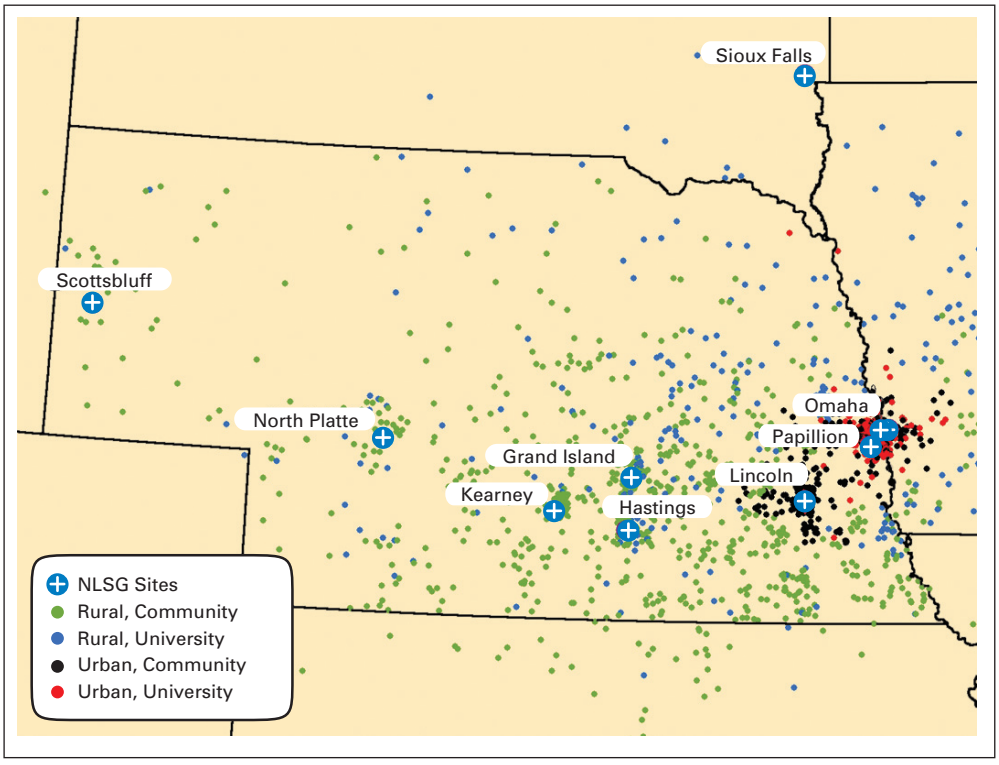

Fig 1. Map showing the distribution of patients included in the study according to place of residence and type of treatment provider NLSG, Nebraska Lymphoma Study Group.

Table 1. Patient Demographic and Disease Characteristics According to Place of Residence and Treatment Provider

Characteristic	Urban University Based		Urban Community Based		Rural University Based		Rural Community Based		*P*
	No.	%	No.	%	No.	%	No.	%	
No. of patients	321	14	816	35	332	14	861	37	
Median age, years	54		62		60		66		**< .01**
Range	19-94		19-93		19-92		19-96		
Age group									**< .01**
< 40	83	25	139	17	65	20	99	12	
40-60	115	36	233	29	98	30	222	26	
> 60	123	38	444	54	169	51	540	63	
Male sex	168	52	432	53	177	53	443	51	.92
Race/ethnicity									**< .01**[*]
White	299	93	787	96	327	98	850	99	
Black	14	4	15	2	0	0	1	< 1	
Asian	3	1	1	< 1	2	< 1	1	< 1	
Hispanic	2	< 1	10	1	0	0	8	1	
Native American	1	< 1	1	< 1	3	1	1	< 1	
Other	2	< 1	2	< 1	0	0	0	0	
Median household income, $	44,101		42,023		35,449		35,240		**< .01**
≤ 30,000	23	7	60	7	38	11	117	14	
30,001-39,999	92	29	263	32	260	78	685	80	
40,000-44,999	64	20	162	20	24	7	49	6	
≥ 45,000	142	44	331	41	10	3	10	1	
Karnofsky performance score at diagnosis									.11
80-100	286	89	703	86	297	89	732	85	
< 80	35	11	113	14	35	11	129	15	
Disease type									**.02**
Low grade non-Hodgkin's lymphoma†	51	16	143	18	59	18	159	18	
High grade non-Hodgkin's lymphoma‡	183	57	506	62	206	62	555	64	
Hodgkin's lymphoma§	87	27	167	20	67	20	147	17	
Ann Arbor stage at diagnosis									**< .01**
I-II	123	38	373	46	119	36	387	45	
III-IV	198	62	443	54	213	64	474	55	
Presence of B symptoms	83	26	217	27	99	30	234	27	.66
Tumor bulk, cm									**.04**
< 5	132	41	384	47	130	39	362	42	
≥ 5	189	59	432	53	202	61	499	58	
Nodal involvement									.09
None	29	9	108	13	41	12	125	15	
At least 1	292	91	708	87	291	88	736	85	
Extranodal involvement									.47
None	137	43	383	47	150	45	376	44	
At least 1	184	57	433	53	182	55	485	56	
Elevated lactate dehydrogenase	125	39	258	32	140	42	299	35	**< .01**
Risk group‖									.08
Low	144	45	394	48	131	39	361	42	
Intermediate	119	37	293	36	139	42	335	39	
High	58	18	129	16	62	19	165	19	
No. of chemotherapy cycles									.07
1-3	94	29	195	24	96	29	200	23	
> 3	191	60	553	68	207	62	583	68	
Missing	36	11	68	8	29	9	78	9	
Radiation as part of treatment	104	32	222	27	79	24	229	27	**< .01**
Transplantation as part of treatment									**< .01**
Yes	61	19	88	11	54	16	85	10	
No	260	81	728	89	278	84	776	90	

(continued on following page)

Table 1. Patient Demographic and Disease Characteristics According to Place of Residence and Treatment Provider (continued)

Characteristic	Urban University Based		Urban Community Based		Rural University Based		Rural Community Based		*P*
	No.	%	No.	%	No.	%	No.	%	
Year of treatment¶									**< .01**
1982-1988	65	20	192	24	133	40	209	24	
1989-1993	50	16	228	28	53	16	256	30	
1994-1998	69	22	234	29	52	16	236	27	
1999-2006	137	43	162	20	94	28	160	18	
Distance to treatment center									
Median	8		5		107		48		**< .01**
Range	< 1-472		< 1-469		25-491		< 1-456		
Distance to UNMC									
Median	8		51		107		138		
Range	< 1-473		< 1-665		25-491		22-602		**< .01**

NOTE. Bold font indicates statistical significance.
Abbreviation: UNMC, University of Nebraska Medical Center.
**P* value applies to comparison between white and non-white.
†Low-grade lymphomas included: diffuse follicular center grade 1, diffuse follicular center grade 2, extranodal marginal zone, lymphoplasmacytic, nodal marginal zone, splenic marginal zone, diffuse small cleaved, extramedullary plasmacytoma, follicular mixed, follicular small cleaved, mucosa-associated lymphoid tissue, monocytoid B, non-Hodgkin's not otherwise specified, natural killer cell granular lymphocytic proliferation, and small lymphocytic.
‡High-grade lymphomas included: precursor T lymphoblastic, lymphoblastic, small noncleaved non-Burkitt's, peripheral gamma delta T cell, anaplastic large T/null cell, peripheral T cell, follicular large, Burkitt's, precursor B lymphoblastic, B-cell unclassifiable, composite, diffuse large B cell, diffuse mixed, and Burkitt-like.
§Types of Hodgkin's disease included: not otherwise specified, interfollicular, lymphocyte depleted, lymphocyte predominate, lymphocyte rich, mixed cellularity, and nodular sclerosis.
‖Risk factors included: age ≥ 60 years, Karnofsky performance score < 80, Ann Arbor stage III or IV, presence of B symptoms, elevated lactate dehydrogenase, tumor bulk ≥ 5.0 cm, at least one nodal involvement, at least one extranodal involvement (low risk: ≤ 3 risk factors present; intermediate risk: 4 to 5 risk factors present; high risk: ≥ 6 risk factors present).
¶Cut points determined by quartile distribution of patients by year of treatment in the entire Nebraska Lymphoma Study Group database.

kinds of lymphoma is available, we identified these risk factors from the data available. Alternatively, the International Prognostic Index (IPI) score was computed for patients with non-Hodgkin's lymphoma (NHL).[26] The distribution of patients according to IPI risk groups were dichotomized into low risk (low and low-intermediate risk IPI) or high risk (high-intermediate and high IPI) categories to have adequate statistical power. The Hasenclever prognostic index for HL was not computed because of missing hemoglobin levels and serum albumin for majority of the patients.

Outcomes Evaluated

The primary outcome of interest was OS defined as death from any cause. Time to event was computed from date of lymphoma diagnosis to time of death or last contact. We also evaluated progression-free survival (PFS) defined as presence of progression or death. Time to event for PFS was from the date of lymphoma diagnosis to time of progression, death, or last contact. We also evaluated whether death was related to lymphoma or due to disease progression.

Statistical Analysis

Univariate comparisons of all characteristics according to the four groups were done using the χ^2 test for categorical data and Kruskal-Wallis test for continuous data. Time-specific probability estimates of PFS and OS were obtained through the Kaplan-Meier estimation method and compared using the log-rank test.[27] The multivariate Cox proportional hazards regression analysis were used: to identify which pretreatment risk factors predict OS, to delineate the number of risk factors that have unique risk level thresholds, and to elucidate the urban-rural and treatment provider effect. All model building tested for the assumption of proportionality using time-dependent covariates.[28] The first set of Cox models were done to identify which clinical risk factors are associated with OS. Pretreatment covariates listed in Table 1 were evaluated using a stepwise approach. Covariates with an α of at least .05 were retained in the models. All Cox models were stratified for type of lymphoma (low grade, high grade, and HL). Eight factors were found to be associated with OS. The sum of risk factors per patient was determined and tested for statistical difference using stratified Cox regression analysis. The best cut point for number of risk factors was selected from the model with the largest partial likelihood.[29] We determined the following categories: low risk (one to three risk factors), intermediate risk (four to five risk factors), and high risk (≥ six risk factors). The final set of stratified Cox regression models were done to evaluate the association of our four level main effects (UUBs as reference group, UCB, RUB, and RCB) with OS and PFS as a whole and then separately according to risk levels. In addition, we tested whether adding income, distance traveled, and year of treatment altered the association between the main variable and outcomes. Because of the exploratory nature of our study, we used an α of .05 to decide on statistical significance despite performing multiple comparisons. All analyses were performed using SAS software, version 9.1 (SAS Institute, Cary NC).

RESULTS

Patient and Disease Characteristics

Table 1 presents the patient characteristics. RCB patients were more likely to be older (median age, 66 years) compared with UUB, UCB and RUB patients (median age, 54 *v* 62 *v* 60, respectively). Both RUB and RCB patients were also more likely to be white, have lower median household income, and travel greater distance to seek lymphoma-related treatment when compared with UUB and UCB. Median distance traveled by UCB patients to obtain treatment was 5 miles, and increases to 51 miles if treatment was sought from a university-based provider. Conversely, among RCB treated patients, the median distance traveled was 48 miles, and increases to 138 miles when treatment was sought from university-based provider. A slightly higher proportion of aggressive lymphomas in the RCB cohort (64%) compared with UUB (57%), UCB (62%), and RUB (62%) were noted, although no differences in the proportion of individual types of NHL were found across the groups. There was no difference in the distribution of patients according to risk level. There was also no difference in the distribution of patients according to risk level over

time. More patients from rural areas and treated by community-based providers was noted in the earlier time period, while there are more patients from urban areas treated by university-based providers in the more recent period.

Treatment-Related Characteristics

A total of 23 community-based treatment sites representing 65 physicians and three university-based treatment sites representing eight physicians were included in the study. Although UUB patients were more likely to receive radiation as part of treatment (32%) compared with UCB (27%), RUB (24%), and RCB (27%), this difference was no longer noted after stratifying for type of lymphoma. The number of chemotherapy cycles patients received was also not different across groups. The use of hematopoietic cell transplantation (HCT), a common treatment for relapsed lymphoma and shown to be curative for diffuse large cell and Hodgkin's lymphoma, was significantly higher in patients treated by university-based providers (UUB = 19%; RUB = 16%) compared with patients treated by community-based providers (UCB = 11%; RCB = 10%, $P < .01$). The use of rituximab in diffuse large cell lymphoma from the year 2000, was significantly higher in UUB (64%) and RUB (73%) compared with patients treated by community-based providers (UCB = 40%; RCB 51%, $P = .04$).

Clinical Outcomes

Figure 2 shows the plot of OS probability according to patient groups. There was no statistically significant difference in the 5-year probability of OS among UUB, UCB, and RUB patients (66% *v* 59% *v* 61%), but patients in the RCB group had a significantly inferior 5-year OS (51%; $P < .001$). Table 2 presents the multivariate analyses evaluating the risk of death. Using all 2,330 patients, the relative risk (RR) of death among UUB, UCB, and RUB were not statistically different. However, RCB had a higher risk of death when compared with UUB (RR, 1.37; 95% CI, 1.14 to 1.65; $P = .01$), as well as when compared with RUB (RR, 1.26; 95% CI, 1.06 to 1.49; $P = .01$). Income and distance traveled were not statistically associated with the outcomes evaluated. The year of treatment was associated with risk of death, with a significant improvement noted over time. The association noted between main variable and outcome remained with year of treatment in the model. We failed to detect any significant differences in the risk of progression or death across groups.

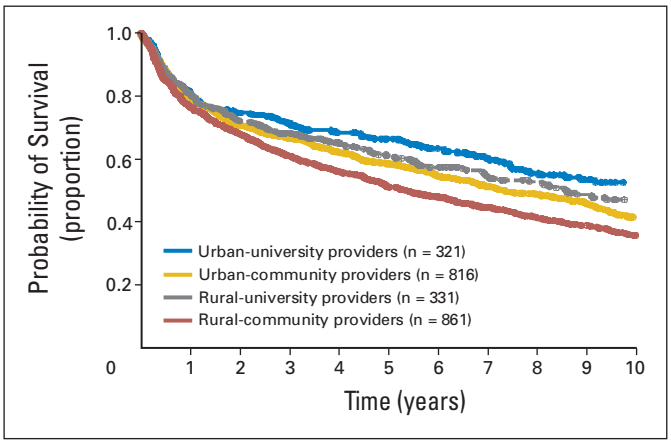

Fig 2. Probability of overall survival according to place of residence and treatment provider (all patients).

Subset analysis of patients according to risk level showed that among low-risk patients (Table 2), RCB was at 56% higher risk of death than UUB (RR, 1.56; 95% CI, 1.12 to 2.18; $P = .01$). Among intermediate-risk patients (Table 2), RCB was at 43% higher risk of death than UUB (RR, 1.43; 95% CI, 1.08 to 1.89; $P = .01$). Using RUB as reference group, RCB had a higher risk of death (RR, 1.58; 95% CI, 1.15 to 2.17; $P < .01$; RR, 1.44; 95% CI, 1.12 to 1.86; $P < .01$) for low- and intermediate-risk groups, respectively. Among high-risk patients (Table 2, Fig 3), the risks of death were all higher in the UCB, RUB, and RCB cohorts compared with the UUB cohort. Subset analysis among patients with NHL and with high risk IPI scores showed RCB patients were 40% more at higher risk of death than UUB (RR, 1.40; 95% CI, 1.08 to 1.82; $P < .01$), while UCB and RUB were not significantly different than UUB. No statistically significant difference in the risk of death among patients with low or low-intermediate IPI scores by patient groups was found. In addition, analyses of risk of progression or death showed no statistically significant differences by place of residence and treatment provider according to the study risk level and IPI scores.

Causes of Death

Patients from rural areas (RUB and RCB) were slightly more likely to die from primary disease (lymphoma) than patients from urban areas (80% *v* 75%; $P = .04$). Sixty percent of the patients in the RCB group died from lymphoma-related causes, while 82%, 72%, and 56% of the patients in the UUB, UCB, and RUB groups, respectively, died from lymphoma-related causes. Deaths due to disease progression was, however, not significantly different according to patient groups.

DISCUSSION

To our knowledge, this is the first study to show that patients with lymphoma from rural areas treated by community-based providers have inferior OS than UUB, UCB and RUB patients. This relationship was seen in different patient risk levels. In addition, our study showed that among high-risk patients, OS was inferior in all other patient groups when compared with UUB patients.

Generally, university-based physicians practice evidenced-based medicine that has superior outcomes. Various phase II and III clinical trials thought to have a positive impact on patients' outcomes are also more likely to be offered to patients.[9,17] The inferior results we found in RCB patients may be explained by the disparity in the type of treatment offered. For instance, our study showed that HCT and rituximab, although shown to have superior outcomes[30-37] in lymphoma, were less likely to be extended to patients treated by community-based providers. Alternatively, this can be explained by the systematic differences in the type of patients treated according to place of residence and treatment provider. However, this was not true in our study sample. Our study was able to consistently show the inferior outcome of RCB patients regardless of risk level, but for rural patients in the high-risk level outcomes are inferior regardless of where treatment is performed. This suggests that patient's area of residence in itself may be an independent risk factor for outcome. Our previous study in patients with lymphoma who underwent autologous HCT have demonstrated this.[7] We think this may be related to a rural patient's logistical support structure that prevents them from acquiring consistent quality care, probably because of longer distance traveled.

Our findings may suggest that regionalization of lymphoma treatment to university-based providers is a reasonable option. But

Table 2. Multivariate Analysis on Risk of Death According to Primary Area of Residence and Treatment Provider

	Risk of Death*															
	All Patients				Low†				Intermediate‡				High§			
Main Effect	No.	RR	95% CI	*P*	No.	RR	95% CI	*P*	No.	RR	95% CI	*P*	No.	RR	95% CI	*P*
Urban/university-based	321	1.0			144	1.0			119	1.0			58	1.0		
Urban/community-based	816	1.16	0.97 to 1.40	.11	394	1.27	0.90 to 1.77	.17	293	1.27	0.95 to 1.69	.10	129	1.51	1.06 to 2.16	**.02**
Rural/university-based	332	1.09	0.88 to 1.36	.44	131	0.99	0.65 to 1.49	.96	139	1.0	0.71 to 1.39	.98	62	1.75	1.16 to 2.64	**.01**
Rural/community-based	861	1.37	1.14 to 1.65	**.01**	361	1.56	1.12 to 2.18	**.01**	335	1.43	1.08 to 1.89	**.01**	165	1.54	1.09 to 2.17	**.01**
Rural/university-based	332	1.0			131	1.0			139	1.0			62	1.0		
Rural/community-based	861	1.26	1.06 to 1.49	**.01**	361	1.58	1.15 to 2.17	**< .01**	335	1.44	1.12 to 1.86	**< .01**	165	0.90	0.65 to 1.24	.52

NOTE. Bold font indicates statistical significance.
*Model stratified by type of lymphoma (low grade, high grade, and Hodgkin's disease).
†Low risk: ≤ 3 risk factors present.
‡Intermediate risk: 4 to 5 risk factors present.
§High risk: ≥ 6 risk factors present.

there are also advantages to acquiring treatment from community-based providers. Care in the community may be less expensive as it precludes having to make strenuous trips to a distant provider in an unfamiliar city.[5,38] These factors are not trivial because cancer treatment in general when delivered closer to home has been shown to maintain or improve the patient's quality of life through the support of family and friends.[39-47] If interventions are to be designed toward improving outcomes, distance must not be a barrier to one's ability to obtain or be provided evidence-based treatments. However, it should be noted that the decision-making process on where to obtain treatment is intrinsically less complex for patients from urban areas than for patients from rural areas. Studies have shown that rural patients would prefer to receive treatment from community-based providers.[48,49] This has profound implications as to what kind of intervention can be designed to improve outcomes among rural patients.

There are several limitations to our study. One third of the patients were excluded due to unknown ZIP codes and incomplete prognostic clinical data. However, the survival outcome was similar between the included and excluded patients. Our study is retrospective and therefore cannot with certainty establish causality. Our study sample consisted of residents within the Midwest, and may have limited generalizability. However, since the central issue behind rural health care is based on dispersion and isolation of its population, we believe our findings can be generalized to other regions in the United States. It may actually be worst in other US regions where there are more racial or ethnic minorities. An analysis performed on specific types of lymphoma that received similar treatments would have been ideal; however, we did not have adequate statistical power to perform these analyses. Our study did not account for physician factors (training, experience, practice type, volume case load) that may have an impact on outcomes. This analysis requires physician level information and need to account for correlated data. Finally, we classified the treatment provider at the time of initial treatment of lymphoma. The complex patterns of shifting care, referrals, and level of interactions between the university- and community-based providers are not captured in this retrospective study. Despite all of these limitations, our study is still the largest population-based study conducted in this area of research and may serve as basis for further studies.

Our study highlights that despite the increase in new and innovative treatments for lymphoma, the issue of how these treatments are extended to patients in rural areas remain unmet. Outreach programs designed to improve availability of effective treatments especially to those in the rural areas should be implemented especially in high-risk patients with lymphoma.

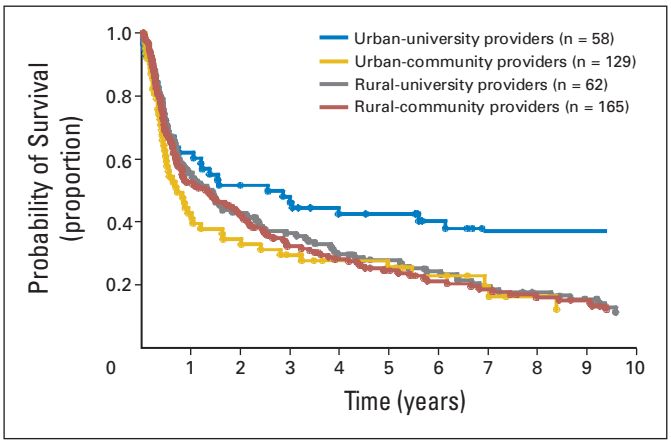

Fig 3. Probability of overall survival according to place of residence and treatment provider (high-risk patients).

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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