Statewide Geographic Variation in Outcomes for Adults With Acute Myeloid Leukemia in North Carolina

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BACKGROUND: Population-based studies have demonstrated survival disparities related to socioeconomic factors for patients with acute myeloid leukemia (AML). The objective of the current study was to determine whether the local health care infrastructure, represented by Area Health Education Centers (AHEC) region, or treating center experience, represented by National Cancer Institute Comprehensive Cancer Center (NCICCC) designation, were associated with outcomes among patients with AML in North Carolina. **METHODS:** Patients who were diagnosed with AML from 2003 to 2009 were identified using the University of North Carolina Lineberger Integrated Cancer Information and Surveillance System, a database linking insurance claims to the North Carolina Cancer Registry. A Cox proportional-hazards model was used to explore survival based on AHEC region. A subset of patients who received inpatient chemotherapy was examined to evaluate the impact of treatment at an NCICCC. **RESULTS:** Nine hundred patients were identified in the study period, 553 of whom received inpatient chemotherapy therapy within 30 days of diagnosis. Almost one-half of these patients (n = 294) received chemotherapy at a non-NCICCC. Among the patients who received intensive inpatient therapy, residence in 3 of 9 AHEC regions was associated with a higher risk of mortality (hazard ratio: range, 1.97-4.03; $P < .01$) at 1 year in multivariate analysis. Treatment at a non-NCICCC was not associated with an increased risk of mortality at 1 year (hazard ratio, 1.25; 95% confidence interval, 0.95-1.65). **CONCLUSIONS:** Survival among patients with AML in North Carolina varies according to geographic region. Further examination of local practice and referral patterns may inform strategies to improve AML outcomes across the state. *Cancer* 2016;122:3041-50.

KEYWORDS: acute myeloid leukemia, Area Health Education Centers, disparities, North Carolina, survival.

INTRODUCTION

Background

Acute myeloid leukemia (AML) is the most common leukemia in adults, with approximately 20,830 new cases in the United States[1] and 671 new cases projected in North Carolina in 2015.[2] Overall survival for patients with AML has increased because of hematopoietic stem cell transplantation, improved supportive care, and intensified chemotherapy regimens.[3] Unfortunately, this increased survival is not distributed evenly across patients. Recent population-based studies have reported decreased overall survival associated with African American race,[4-7] Hispanic ethnicity,[8] and enrollment in Medicaid.[5,8] Furthermore, the differences in survival between African Americans and whites have increased over the last 20 years.[3]

The underlying reasons for the poorer outcomes among certain populations are not well understood. It has been reported that AML tumor biology does not contribute to racial disparities. In fact, studies have demonstrated that African Americans experience worse outcomes despite presenting at a younger age and with a more favorable cytogenetic profile.[4,5,9,10] Recently published findings suggest that racial survival disparities may be caused in part by differences in treatment or access to care. Patel et al reported that, when controlling for other factors, such as age, cytogenetics, and patient comorbidities, African Americans were less likely to receive chemotherapy for any type of AML. Controlling for the intensity of chemotherapy attenuated this racial disparity in survival.[11] Furthermore, even greater differences in survival between African Americans and whites have been observed among those with acute promyelocytic leukemia—an AML subtype that is usually associated with favorable outcomes.[10] These findings raise the concern that African Americans may not be receiving timely administration of appropriate, targeted therapy. The degree to which individual demographic

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factors affect survival varies from 1 study to another, and some smaller, single-institution studies have not reported an association between race or income and worse outcomes.[9,12] This suggests that demographic features like race actually may be surrogate markers for other factors affecting outcome, such as decreased access to quality care.

One such potential variable that is not well understood is the impact of receiving treatment at a National Cancer Institute Comprehensive Cancer Center (NCICCC) as opposed to other health care facilities. The NCICCC designation has been proposed as an indicator of quality of care. Population-based studies have demonstrated improved outcomes for patients with a variety of solid tumors who are treated at NCICCCs[13-15] and indicated that certain minorities are less likely to receive treatment at an NCICCC.[16] However, the impact of treatment at an NCICCC for patients with hematologic malignancies is less clear. By using the California cancer registry, Wolfson and colleagues demonstrated that receiving treatment at an NCICCC improved survival outcomes among patients who were treated for various solid tumors[13] and among adolescents and young adults with any type of hematologic malignancy. It is noteworthy that those studies also demonstrated that African American race, Hispanic ethnicity, and increased distance to an NCICCC decreased the odds of receiving care at an NCICCC.[17] The state of North Carolina offers a unique opportunity to examine the impact of regional variation and treatment center expertise on survival from AML, because it contains 3 NCICCCs and a robust Area Health Education Centers (AHEC) program. The mission of the AHEC program in each state is to improve access to quality health care by increasing the distribution of health care professionals through community/academic educational partnerships.[18] North Carolina is divided into 9 AHEC regions in which the resources of academic centers are directed to underserved areas. All parts of the state are included within a designated AHEC region. In the field of oncology, this takes the form of education for community providers, including nurses, nurse practitioners, and primary care physicians. Survival disparities by AHEC region have not been described for any malignancy.

Objectives

The primary objective of this study was to examine the impact of AHEC region on survival among adults with AML in North Carolina, a state with a large rural population. We hypothesized that variation in regional health care delivery would contribute to survival differences using AHEC region as the geographic unit of analysis. The secondary objective of this study was to examine the impact of treating facility expertise, as represented by NCICCC designation, on overall survival for patients with AML in North Carolina. We hypothesized that treatment at an NCICCC would be associated with superior overall survival.

MATERIALS AND METHODS

Study Population

A retrospective cohort of adult patients with AML was identified using the University of North Carolina Integrated Cancer Information and Surveillance System (ICISS). The ICISS data comprise a nationally unique, state-based data set representing linkage of the North Carolina Central Cancer Registry (NC CCR) (>400,000 patients) to over 6 million unique beneficiaries in Medicare, Medicaid, and private insurance plans across the state.

We included all patients aged >18 years in the NC CCR who had a diagnosis of AML between 2003 and 2009 (N = 2508). Patients were excluded if they were initially diagnosed on death certificate or at autopsy (N = 83) or if they had nonspecified/ineligible *International Classification of Diseases for Oncology, 3rd edition* histology codes: leukemia, not otherwise specified (NOS); myeloid leukemia, NOS; acute leukemia, NOS; and acute promyelocytic leukemia (N = 278). Patients who had multiple primary AML diagnoses were excluded (N = 2). Patients who died within 1 week of diagnosis date also were excluded to retain those who were clearly eligible to initiate intensive therapy (N = 158). To ensure that we could observe complete health care use, patients were required to have continuous insurance enrollment from 1 month before their AML diagnosis to 3 months postdiagnosis or until death (N = 1198). We also excluded patients who appeared simultaneously under multiple payers within the study period (N = 17). We excluded patients who were missing a claim for bone marrow biopsy within 30 days before and 14 days after diagnosis (N = 201). Finally, we excluded patients who did not have complete geolocation information (census tract or complete address/zip code), which was required for the categorization of sociodemographic variables described below. There were 900 individuals who met all study inclusion criteria.

Exposure and Outcome Measurement

Patients were assigned to AHEC regions based on cancer registry geocoding of the patient's address at diagnosis.

Straight-line (Euclidean) distance to the nearest possible NCICCC was calculated for all patients using the geocoded addresses of the 3 NCICCCs and the patient's address at diagnosis. Patients who received inpatient chemotherapy were divided into those who received therapy at an NCICCC versus a non-NCICCC. All institutions within North Carolina were included.

For the inpatient chemotherapy cohort, data on the distance to both NCICCCs and non-NCICCCs were required. Unfortunately, complete addresses and geocoding for certain non-NCICCCs were not available. Therefore, these analyses used the distance from the patient's home to the zip code centroid of the treating facility. Others have demonstrated that differences in distance measurements are very small between a patient's home and the treating facility when using either physical addresses or zip code centroids.[19]

Inpatient chemotherapy within 30 days of diagnosis was identified through insurance claims for chemotherapy during the first or second hospitalization and/or a specific regimen and administration date captured by the registry. The time to death was measured from the date of diagnosis until date of death reported in the cancer registry. Patients were censored if they were missing a death date (ie, still alive) or if they died >12 months after diagnosis.

Covariates

Information from the cancer registry was used to identify patient's age, sex, race, year of diagnosis, and sequence of cancer occurrence. The registry also provided information on the specific tumor sequence and histology. Insurance enrollment data were used to categorize patients according to the type of insurance coverage. Claims were then used to calculate the Charlson comorbidity index (CCI) and to identify receipt of allogeneic hematopoietic stem cell transplantation.

Sociodemographic covariates, which were defined using census tract information from the American Community Survey (2005-2009), included quartile of median income, percentage of population unemployed, percentage of population living in poverty, and percentage of population with less than a high school diploma. Rural versus urban residence also was included (defined from Rural-Urban Commuting Area codes [RUCA])[20] using the zip code approximation RUCA. The zip code RUCA was selected to provide a second level of geographic detail. The Rural Health Research Center indicates that the agreement between zip code and census tract RUCA is 99%.[21]

Statistical Analysis

We used generalized estimating equations to control the regional clustering effect, to estimate the odds of receiving inpatient chemotherapy in the entire cohort (N = 900), and to estimate the odds of receiving therapy at an NCICCC for the inpatient chemotherapy cohort (N = 553) while adjusting for other measured covariates. The covariates included age, sex, race, insurance type, CCI, distance to hospital, resident AHEC region, and the sociodemographic variables discussed above.

For both the full cohort and the cohort that received inpatient chemotherapy within 30 days (N = 553), we applied Cox proportional-hazards modeling to estimate predictors associated with survival. Model assumptions regarding proportional hazards were met. Covariates for all models included age, sex, race, insurance type, CCI, rural versus urban zip code, AHEC region, and the sociodemographic variables discussed above. For the inpatient chemotherapy cohort, treatment at an NCICCC versus a non-NCICCC was also included. Multicollinearity between the main exposure variables was tested by examining a variance inflation factor (<10). In addition, a generalized estimating equation was used to identify the factors associated with an increased odds of receiving therapy at an NCICCC. Sensitivity analyses were performed to check the regression estimates with or without the exclusion of patients who died within 1 week after diagnosis. All analyses were conducted using the SAS statistical software package (version 9.4; SAS Institute, Inc, Cary, NC).

RESULTS

Cohort Demographics

Nine hundred patients with newly diagnosed AML were included in our cohort. The majority of patients were aged >60 years (74%; age range, 19-97 years; mean age, 65.3 years) and were non-Hispanic whites (85%). The cohort had a slightly higher proportion of males (54%). Consistent with the age distribution of the study sample, most were enrolled in Medicare only (57%), 24% had some form of private insurance, and 19% had Medicaid coverage. Patients were evenly distributed among the 4 median household income quartiles. One-third of patients had a primary residence in a rural area, and two-thirds had a primary residence located >40 miles from the nearest NCICCC.

Most patients had de novo AML (78%) and limited comorbidities, with a Charlson score of 0 (83%). Inpatient chemotherapy was received by 61% of patients in the cohort within 30 days of diagnosis. Only 5% of

TABLE 1. Cohort Summary

	No. of Patients (%)			
	All Patients	Outpatient or No Chemotherapy	Inpatient Chemotherapy at an NCICCC	Inpatient Chemotherapy at a non-NCICCC
Variable	900 (100)	347 (39)	294 (33)	259 (29)
Age group, y				
19-40	87 (10)	—[a]	44 (15)	33 (12)
40-59	147 (16)	24 (7)	65 (22)	58 (22)
60-69	220 (24)	63 (18)	87 (30)	70 (27)
70-79	275 (31)	127 (37)	76 (26)	72 (28)
≥80	171 (19)	122 (35)	22 (7)	27 (10)
Sex				
Female	410 (46)	159 (46)	138 (47)	113 (44)
Male	490 (54)	188 (54)	156 (53)	146 (56)
Race				
Non-Hispanic white	764 (85)	309 (89)	246 (84)	209 (81)
Other	136 (15)	38 (11)	48 (16)	50 (19)
Household income quartile				
First	226 (25)	91 (26)	75 (26)	60 (23)
Second	225 (25)	94 (27)	69 (23)	62 (24)
Third	224 (25)	76 (22)	81 (28)	67 (26)
Fourth	225 (25)	86 (25)	69 (23)	70 (27)
% Population with less than a high school diploma				
Mean ± SD	16.9 ± 9.3	16.4 ± 9.1	18.1 ± 9.2	16 ± 9.4
Range	0-50	0-41	1-47	0-50
% Unemployment				
Mean ± SD	7.7 ± 4.1	7.7 ± 4.1	7.9 ± 3.8	7.3 ± 4.4
Range	0-34	0-32	0-24	0- 34
% Population living in poverty				
Mean ± SD	13.4 ± 8.4	13.4 ± 8.1	14 ± 8.7	12.8 ± 8.5
Range	0-63	1-63	2-55	0-59
Health care plan				
Medicare only	510 (57)	244 (70)	128 (44)	138 (53)
Private or private + Medicare	218 (24)	56 (16)	98 (33)	64 (25)
Any Medicaid	172 (19)	47 (14)	68 (23)	57 (22)
NC AHEC region				
Greensboro	99 (11)	37 (11)	45 (15)	17 (7)
Southern Regional	64 (7)	19 (5)	37 (13)	—[a]
Mountain	89 (10)	42 (12)	—[a]	39 (15)
Northwest	175 (19)	61 (18)	41 (16)	41 (16)
Charlotte	160 (18)	72 (21)	22 (7)	66 (25)
Wake	115 (13)	41 (12)	45 (15)	29 (11)
Area L	39 (4)	16 (5)	—[a]	13 (5)
Eastern	109 (12)	41 (12)	26 (9)	42 (16)
South East	50 (6)	18 (5)	28 (10)	—[a]
First or only cancer				
Yes	701 (78)	258 (74)	232 (79)	211 (81)
No	199 (22)	89 (26)	62 (21)	48 (19)
Charlson score[b]				
0	745 (83)	274 (79)	246 (84)	225 (87)
≥1	155 (17)	73 (21)	48 (16)	34 (13)
HSCT by 1 y				
No	852 (95)	342 (99)	262 (89)	248 (96)
Yes	48 (5)	—[a]	32 (11)	—[a]
Distance to NCICCC, miles				
<40	287 (32)	106 (31)	116 (39)	65 (25)
40-70	252 (28)	98 (28)	79 (27)	75 (29)
>70	361 (40)	143 (41)	99 (34)	119 (46)

Abbreviations: HSCT, hematopoietic stem cell transplantation; NC AHEC, North Carolina Area Health Education Center; NCICCC, National Cancer Institute Comprehensive Cancer Center; SD, standard deviation.

[a] Values for cell sizes <11 were suppressed to protect patient confidentiality. Patients with missing data were not included.

[b] These scores include patients who could not to be assessed.

TABLE 2. Survival Models: Risk of Mortality at 1 Year Postdiagnosis for the Full Cohort and the Inpatient Chemotherapy Cohort

	HR (95%CI)	
Variable	Full Cohort	Inpatient Chemotherapy Cohort
Age group, y		
19-40	Referent	Referent
40-59	1.52 (0.96-2.41)	1.4 (0.84-2.34)
60-69	2.96 (1.89-4.64)[a]	2.98 (1.77-5.03)[a]
70-79	3.69 (2.34-5.84)[a]	3.68 (2.13-6.39)[a]
≥80	7.59 (4.71-12.22)[a]	8.34 (4.53-15.32)[a]
Sex		
Male	Referent	Referent
Female	0.89 (0.75-1.05)	0.88 (0.69-1.12)
Race		
Non-Hispanic white	Referent	Referent
Other	1.06 (0.81-1.37)	1.1 (0.8-1.53)
Household income quartile[b]		
First	1.22 (0.81-1.86)	1.26 (0.7-2.26)
Second	1.18 (0.86-1.62)	1.25 (0.81-1.93)
Third	1.02 (0.77-1.33)	1.01 (0.69-1.46)
Fourth	Referent	Referent
Rural zip code		
No	Referent	Referent
Yes	0.99 (0.81-1.22)	1.04 (0.77-1.40)
% Population with less than high school diploma[c]	1.00 (0.99-1.02)	1.00 (0.98-1.03)
% Unemployment[c]	0.99 (0.97-1.02)	0.99 (0.96-1.03
% Population living in poverty[c]	0.99 (0.98-1.01)	0.99 (0.97-1.01)
Health care plan		
Medicare only	0.91 (0.71-1.17)	0.87 (0.63-1.21)
Private or private + Medicare	Referent	Referent
Any Medicaid	1.36 (1.00-1.85)[a]	1.24 (0.83-1.85)
NC AHEC region		
Greensboro	Referent	Referent
Southern Regional	1.57 (0.93-2.63)	1.65 (0.95-2.86)
Mountain	1.62 (0.94-2.81)	1.03 (0.56-1.88)
Northwest	1.22 (0.85-1.76)	1.12 (0.68-1.84)
Charlotte	2.00 (1.25-3.19)[a]	1.54 (0.94-2.54)
Wake	1.47 (1.02-2.10)[a]	1.97 (1.19-3.25)[a]
Area L	2.76 (1.59-4.80)[a]	4.03 (2.15-7.53)[a]
Eastern	2.63 (1.56-4.45)[a]	2.21 (1.3-3.74)[a]
South East	1.53 (0.82-2.88)	1.07 (0.53-2.14)
First or only cancer		
Yes	Referent	Referent
No	1.12 (0.92-1.36)	1.37 (1.03-1.83)[a]
Charlson score		
0[d]	Referent	Referent
≥1	1.68 (1.36-2.07)[a]	1.34 (0.98-1.83)
Inpatient chemotherapy		
Yes	Referent	—
No	1.28 (1.07-1.54)[a]	—
HSC by 1 y		
Yes	Referent	Referent
No	2.09 (1.15-3.83)[a]	2.86 (1.41-5.81)[a]
Distance to NCICCC, miles		
<40	Referent	—
40-70	0.87 (0.62-1.22)	—
>70	0.66 (0.44-1.00)[a]	—
Distance to treating facility, miles		
<20	—	Referent
≥20	—	1.14 (0.85-1.52)
Treatment at NCICCC		
Yes	—	Referent
No	—	1.25 (0.95-1.65)

Abbreviations: CI, confidence interval; HR, hazard ratio; HSCT, hematopoietic stem cell transplantation; NC AHEC, North Carolina Area Health Education Center; NCICCC, National Cancer Institute Comprehensive Cancer Center.

[a] $P < .05$.

[b] Missing data were not included.

[c] This was considered as a continuous variable.

[d] These scores include patients who could not be assessed.

TABLE 3. Factors Associated With Treatment at a National Cancer Institute Comprehensive Cancer Center

Variable	OR (95% CI)
Age group, y	
19-40	Referent
40-59	0.68 (0.33-1.41)
60-69	1.27 (0.57-2.85)
70-79	1.34 (0.54-3.35)
≥80	0.99 (0.36-2.70)
Sex	
Male	Referent
Female	1.05 (0.68-1.63)
Race	
Non-Hispanic white	Referent
Other	0.85 (0.44-1.66)
Household income quartile	
First	0.26 (0.08-0.82)[a]
Second	0.48 (0.19-1.22)
Third	0.75 (0.38-1.48)
Fourth	Referent
% Population with less than high school diploma[b]	1.03 (0.99-1.07)
% Unemployment[b]	1.03 (0.96-1.11)
% Population living in poverty[b]	1.01 (0.98-1.05)
Rural zip code	
No	Referent
Yes	1.14 (0.64-2.01)
Health care plan	
Medicare only	0.54 (0.29-0.99)[a]
Private or private + Medicare	Referent
Any Medicaid	1.04 (0.51-2.09)
NC AHEC region	
Greensboro	Referent
Southern Regional	1.74 (0.45-6.69)
Mountain	0.06 (0.01-0.25)[a]
Northwest	0.46 (0.19-1.10)
Charlotte	0.12 (0.04-0.36)[a]
Wake	0.42 (0.19-0.90)[a]
Area L	0.12 (0.03-0.49)[a]
Eastern	0.14 (0.04-0.51)[a]
South East	1.62 (0.34-7.67)
Charlson score	
0	Referent
≥1	2.14(1.09-4.22)[a]
HSCT by 1 y	
Yes	Referent
No	0.34 (0.14-0.83)[a]
Distance to NCICCC, miles	
<40	Referent
40-70	0.74 (0.31-1.76)
>70	0.69 (0.25-1.92)
Distance to treating facility, miles	
<20	Referent
≥20	5.28 (3.13-8.93)[a]

Abbreviations: CI, confidence interval; HSCT, hematopoietic stem cell transplantation; NC AHEC, North Carolina Area Health Education Center; NCICCC, National Cancer Institute Comprehensive Cancer Center; OR, odds ratio.

[a] $P < .05$.

[b] This was considered as a continuous variable.

patients proceeded to undergo allogeneic stem cell transplantation within 1 year of diagnosis. However, when analyzed by age, we observed that 16% of patients aged < 60 years underwent stem cell transplantation (Table 1).

Survival Analysis for Full Cohort

Home residence in 4 of 9 NC AHEC regions was associated with an increased risk of mortality (hazard ratio [HR], 1.47-2.63; $P < .05$) at 1 year in multivariate analysis. As expected, a higher burden of comorbid illness (CCI, ≥ 1; HR, 1.68; 95% confidence interval [CI], 1.36-2.07; $P < .001$) and receipt of only outpatient or no chemotherapy (HR, 1.28; 95% CI, 1.07-1.54; $P < .01$) were associated with an increased risk of mortality. Similarly, the patients who did not undergo allogeneic hematopoietic stem cell transplantation within 1 year of diagnosis had an increased risk of mortality (HR, 2.09; 95% CI, 1.15-3.83; $P < .05$). Enrollment in Medicaid was also associated with increased mortality compared with individuals who were enrolled in private insurance (HR, 1.36; 95% CI, 1.00-1.85; $P < .05$). Race, rural residence, and the income, education, and poverty level of the patient's zip code were not associated with increased mortality at 1 year in multivariate analysis (Table 2).

Survival Analysis for the Inpatient Chemotherapy Cohort

Patients aged > 60 years were less likely to receive inpatient chemotherapy (ages 18-40 years vs 60-69 years: odds ratio [OR], 0.38; 95% CI, 0.18-0.79; $P < .01$; ages 70-79 years: OR, 0.17; 95% CI, 0.08-0.37; $P < .001$; aged ≥ 80 years: OR, 0.06; 95% CI, 0.03-0.12; $P < .001$). The remaining covariates were not associated with the receipt of inpatient chemotherapy, including distance to the nearest NCICCC.

Among the patients who received inpatient chemotherapy, nearly one-half were treated at a non-NCICCC (N = 294). Factors that were associated with a decreased likelihood of receiving treatment at an NCICCC included residence in 5 of 9 AHEC regions (OR, 0.06-0.42; $P < .05$). Increased distance from home to the treating facility was associated with an increased likelihood of treatment at an NCICCC (>20 vs < 20 miles: OR, 5.28; 95% CI, 3.13-8.93; $P < .001$) and a higher comorbidity index score (OR, 2.14; 95% CI, 1.09-4.22; $P < .05$) (Table 3). However, distance from home to the nearest NCICCC was not associated with treatment at an NCICCC.

Multivariate analysis did not demonstrate a higher risk of mortality at 1 year associated with treatment at a non-NCICCC compared with an NCICCC (HR, 1.25; 95% CI, 0.95-1.65) when controlling for AHEC region. For the inpatient chemotherapy cohort, residence in 3 of 9 AHEC regions was associated with increased mortality while controlling for all other covariates (HR range, 1.97-4.03, $P < .01$ for each) (Fig. 1). The distance from the

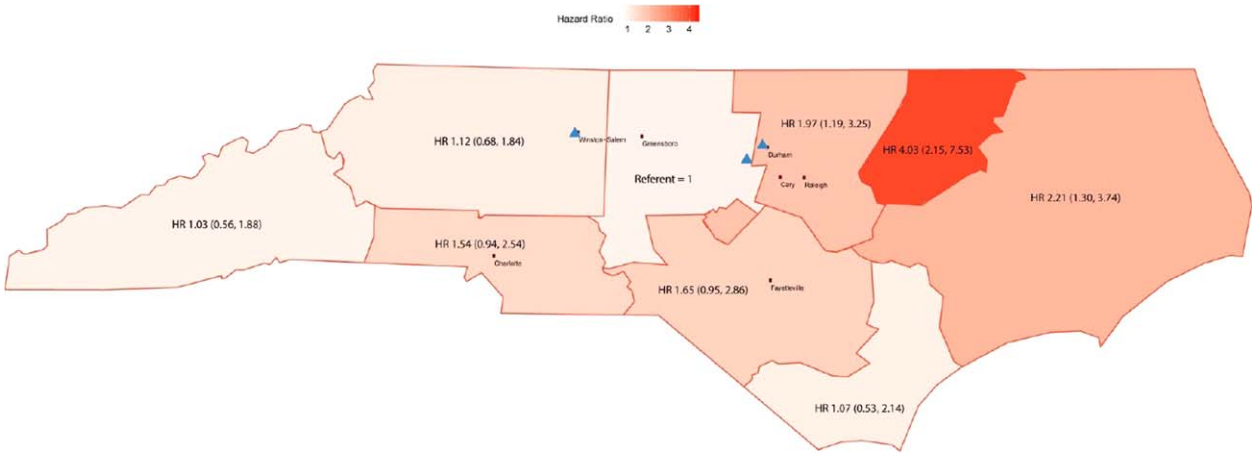

Figure 1. Hazard ratios (HRs) with 95% confidence intervals are illustrated from a survival analyses according to Area Health Education Centers region for adults with acute myeloid leukemia in North Carolina who received inpatient chemotherapy from 2003 to 2009 (n = 553). Cities with populations > 100,000 are noted.

patient's residence to the treating facility or nearest NCICCC was not associated with mortality. Similar to the model including the full study cohort, increasing age (eg, ages 60-69 years: HR, 2.98; 95% CI, 1.77-5.03; $P < .001$). However, CCI ≥ 1 was not significantly associated with mortality (HR, 1.34; 95% CI, 0.98-1.83). Again, sociodemographic variables based on census level data (income, unemployment, poverty level, education) were not associated with survival in multivariate analysis (Table 2).

DISCUSSION

By using the North Carolina ICISS, a statewide tumor registry linked to a multipayer insurance claims database, we observed that survival among patients with AML in North Carolina varied according to geographic region. These regional survival disparities persisted despite controlling for regional demographic variables (education, poverty level, unemployment rate, income) and patient variables (sex, race, health care plan, distance to treating facility, comorbidities). In analyses of the full patient cohort, worse outcomes were associated with residence in 4 of 9 AHEC regions. Three of those regions retained a significant association with worse outcomes in an analysis of the subset of patients who received intensive inpatient therapy. Observing survival differences according to region of residence in both the full and subgroup cohorts suggests that the intensity of therapy alone is insufficient to account for these regional disparities.

The causative factors for these geographic survival disparities are not clear from our data and will require further investigation. Through discussion with the AHEC program office, we have learned that there are statistically significant differences in health care resources among AHEC regions, with Area L reporting some of the lowest resources and highest burden of disease (Table 4). For example, compared with the referent AHEC region, Area L has fewer general practitioners and radiation oncologists per 100,000 population (19.1 vs 30.5 and 0.6 vs 1.9, respectively). Information regarding specific financial resources or the availability of other subspecialty providers was not available. The higher proportion of radiation oncologists in the referent region may suggest greater availability of all subspecialists involved in the care of patients with cancer, and this may contribute to improved outcomes. Data from the American Community Survey also highlight important sociodemographic differences among the AHEC regions (Table 4), although these differences do explain the survival differences observed in our study. For example, compared with the referent AHEC region, Area L is characterized by a lower percentage of non-Hispanic whites (45.5% vs 69%), a lower per-capita income ($19,000 vs $ 23,000), a higher percentage of residents without a high school education (16.8% vs 13.9%), and a higher percentage of the population living in poverty (21% vs 16.3%). However, another AHEC region associated with increased mortality (Wake) has a more favorable sociodemographic profile. Compared with the referent region, Wake has a similar percentage of non-Hispanic whites (61.3% vs 66.6%), a higher per capita income ($28,326 vs $25,010), and a lower percentage of the population living in poverty (11.8% vs 15.3%).

TABLE 4. The Average of County-Level Measurements by Area Health Education Center Region in North Carolina

	American Community Survey 2005-2009[a]						Health Resources and Services Administration Resource File[b]		
AHEC Region	Total Population in Thousands	Per Capita Income in Thousands of Dollars	% Non-Hispanic White Population	% Population Aged ≥ 25 Years With Less Than a High School Diploma	% Population Living in Poverty	Total Hospital Beds per 100,000 Population in 2005	Total General Practitioners per 100,000 Population in 2005	Total Radiation Oncologists per 100,000 Population in 2005
Area L	297.9	19	45.5	16.8	21	259	19.1	0.6
Charlotte	1662.1	23	71.6	12.7	13.7	264.8	26	0.9
Eastern	970.7	21	62.6	13.3	16.5	258	22	0.8
Greensboro	1076.9	23	69	13.9	16.3	201.5	30.5	1.9
Mountain	719.4	21	89.2	13.8	16	265.6	43.3	0.8
Northwest	1511.8	22	84.6	15.3	15.2	297	35.2	0.7
South East	444	22	69.8	13.6	17.3	218.9	22.2	0.6
Southern Regional	850.3	19	54.1	13.9	21	280.3	23.8	0.9
Wake	1512.6	23	57.4	13.2	16.3	325.2	25.6	0.9

Abbreviations: AHEC, Area Health Education Center (North Carolina); NCICCC, National Cancer Institute Comprehensive Cancer Center.

[a] Source: The United States Census Bureau. American Community Survey (available at: https://www.census.gov/programs-surveys/acs/data.html); Accessed April 1, 2016.

[b] Source: Health Resources and Services Administration (available at: www.ahrf.hrsa.gov); Accessed April 1, 2016.

We hypothesized that treatment at an NCICCC would be associated with better outcomes for patients with AML in North Carolina. Among those who received intensive inpatient therapy, we did not observe a significant association between treatment at an NCICCC and mortality at 1 year when controlling for AHEC region (HR, 1.25; 95% CI, 0.95-1.65). Treatment at an NCICCC, as discussed above, has been associated with superior outcomes for patients with solid tumors[13-15] but attenuates the survival disparities among adolescents and young adult patients who have hematologic malignancies.[17] The finding that treatment at an NCICCC was not significant in our study may suggest that NCICCC designation is not an appropriate indicator for quality care in this patient population. We do not have validated quality measures for the care of patients with hematologic malignancies that can be abstracted from population-level data, as is the case for solid tumors, for which surgical management often provides this opportunity. It is unclear whether the superior outcomes among patients with hematologic malignancies noted by Wolfson et al at NCICCCs reflect inherent quality and resource availability (blood banks, clinical pathology, interventional radiology, etc) or simply greater experience because of increased patient volumes. High-volume facilities have been associated with improved outcomes for patients with solid tumors, particularly when surgery features prominently in the management of those tumors.[22] However, the impact of treatment center volume on outcomes for hematologic malignancies is largely unreported.

Alternatively, our data may reflect that finding that sicker patients are treated at NCICCCs. We did observe that patients with higher Charlson morbidity scores were more likely to be treated at an NCICCC. By using claims data, we were limited in fully exploring patient-level disease and morbidity information, so we may not have been able to fully account for variations in medical comorbidity.

In contrast to several previous studies, we did not observe an effect of patient demographic variables on survival. Both in the full cohort and in the intensive inpatient therapy subgroup analyses, neither race, sex, income, nor rural primary residence was associated with changes in survival. We may not have observed racial disparities, because our study cohort included a smaller proportion of nonwhite patients compared with prior population-based studies. Within the full cohort, patients who were enrolled in Medicaid had poorer outcomes; however, this difference did not persist among the subgroup that ho received intensive inpatient therapy. This suggests that the

disparity is associated in some way with publicly insured individuals gaining access to intensive therapy, because the survival difference is no longer evident once intensive therapy is obtained. In their examination of the relation between treatment at an NCICCC and cancer outcomes, Wolfson and colleagues also reported a decreased odds of receiving treatment at an NCICCC with a lack of private insurance. Insurance coverage affects care in multiple ways, beginning with initial access to the health care system and continuing with the way in which provider referrals are made. In our study, we did observe that patients in the lowest income quartile were less likely to be treated at an NCICCC (OR, 0.26; 95% CI, 0.08-0.82; $P < .05$). Additional studies are needed to better understand the correlation between insurance type and treatment at, or referral to, an NCICCC in North Carolina. Conceivably, certain combinations of payer type and region of primary residence (AHEC region) could be associated with lower rates of referral to NCICCCs and, ultimately, poorer survival outcomes.

Identifying differences in survival among various geographic regions in North Carolina could lead to improvements in the delivery of care for patients with AML. Like in any claims-based analysis, we had limited patient-level clinical information. However, we believe our data demonstrating regional survival disparities that cannot be explained by variation in individual sociodemographic variables suggest that other features of the local health care infrastructure are affecting outcomes for patients with AML. Complex local factors, possibly related to subspecialty provider density, diagnosis, and referral and treatment patterns, may be influencing survival. The finding that treatment at an NCICCC varies significantly by AHEC region points to differences in geographic referral patterns and care delivery as a major focus for future investigation. Our hope is that further examination of local practice and referral patterns will inform strategies to improve AML outcomes across North Carolina.

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The authors made no disclosures.

AUTHOR CONTRIBUTIONS

Ashley T. Freeman: Conceptualization, investigation, and writing–original draft. Anne-Marie Meyer: Conceptualization, methodology, and formal analysis. Andrew B. Smitherman: Conceptualization, investigation, and writing–review and editing. Lei Zhou: Methodology and formal analysis. William A. Wood: Conceptualization, supervision, and writing–review and editing. Ethan Basch: Writing–review and editing, and supervision. Thomas C. Shea: Writing–review and editing and supervision.

REFERENCES

1. Siegel R, Miller K, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin*. 2015;65:5-29.
2. North Carolina Cancer Registry. Projected New Cancer Cases and Deaths for All Sites, 2014. Available at: http://www.schs.state.nc.us/schs/CCR/proj14site.pdf. Accessed September 10, 2015.
3. Pulte D, Redaniel MT, Jansen L, et al. Recent trends in survival of adult patients with acute leukemia: overall improvements, but persistent and partly increasing disparity in survival of patients from minority groups. *Haematologica*. 2013;98:222-229.
4. Sekeres MA, Peterson B, Dodge RK, et al. Differences in prognostic factors and outcomes in African Americans and whites with acute myeloid leukemia. *Blood*. 2004;103:4036-4042.
5. Byrne MM, Halman LJ, Koniaris LG, et al. Effects of poverty and race on outcomes in acute myeloid leukemia. *Am J Clin Oncol*. 2011;34:297-304.
6. Bradley CJ, Dahman B, Jin Y, et al. Acute myeloid leukemia: how the uninsured fare. *Cancer*. 2011;117:4772-4778.
7. Patel MI, Ma Y, Mitchell BS, Rhoads KF. Understanding disparities in leukemia: a national study. *Cancer Causes Control*. 2012;23:1831-1837.
8. Kristinsson SY, Derolf AR, Edgren G, et al. Socioeconomic differences in patient survival are increasing for acute myeloid leukemia and multiple myeloma in Sweden. *J Clin Oncol*. 2009;27:2073-2080.
9. Bierenbaum J, Davidoff AJ, Ning Y, Tidwell ML, Gojo I, Baer MR. Racial differences in presentation, referral and treatment patterns and survival in adult patients with acute myeloid leukemia: a single-institution experience. *Leuk Res*. 2012;36:140-145.
10. Patel MI, Ma Y, Mitchell BS, Rhoads KF. Age and genetics: how do prognostic factors at diagnosis explain disparities in acute myeloid leukemia. *Am J Clin Oncol*. 2015;38:159-164.
11. Patel MI, Ma Y, Mitchell BS, Rhoads KF. How do differences in treatment impact racial and ethnic disparities in acute myeloid leukemia. *Cancer Epidemiol Biomarkers Prev*. 2015;24:344-349.
12. Rodriguez CP, Baz R, Jawde RA, et al. Impact of socioeconomic status and distance from treatment center on survival in patients receiving remission induction therapy for newly diagnosed acute myeloid leukemia. *Leuk Res*. 2008;32:413-420.
13. Wolfson JA, Sun CL, Wyatt LP, Hurria A, Bhatia S. Impact of comprehensive cancer centers on outcome: results from a population-based study. *Cancer*. 2015;121:3885-3893.
14. Paulson EC, Mitra N, Sonnad S, et al. National Cancer Institute designation predicts improved outcomes in colorectal cancer surgery. *Ann Surg*. 2008;126:318-329.
15. Birkmeyer NJ, Goodney PP, Stukel TA, Hillner BE, Birkmeyer JD. Do cancer centers designated by the National Cancer Institute have better surgical outcomes? *Cancer*. 2005;103:435-441.
16. Huang LC, Ma Y, Ngo J, et al. What factors influence minority use of National Cancer Institute-designated cancer centers? *Cancer*. 2014;120:399-407.
17. Wolfson J, Can-Lan S, Wyatt L, et al. Impact of care at NCI comprehensive care centers on outcomes in children, adolescents and young adults with hematologic malignancies. *Blood*. 2014;124:556-556.
18. Health Resources and Services Administration. Area Health Education Centers. Available at: http://bhpr.hrsa.gov/grants/areahealtheducationcenters/. Accessed October 1, 2015.

19. Jones SG, Ashby AJ, Momin SR, et al. Spatial implications associated with using Euclidean distance measurements and geographic centroid imputation in health care research. *Health Serv Res*. 2010; 45:316-327.
20. Morrill R, Cromartie J, Hart G. Metropolitan, urban, and rural commuting areas: toward a better depiction of the United States settlement system. *Urban Geography*. 1999;20:727-748.
21. Rural Health Research Center (RUCA). RUCA data: ZIP code RUCA approximation. Available at: http://depts.washington.edu/uwruca/ruca-approx.php. Accessed April 1, 2016.
22. Liu CJ, Chou YJ, Teng CJ, et al. Association of surgeon volume and hospital volume with the outcome of patients receiving definitive surgery for colorectal cancer: a nationwide population-based study. *Cancer*. 2015;121:2782-2790.