Research Article

Cancer Epidemiology, Biomarkers & Prevention

Adolescents and Young Adults with Acute Lymphoblastic Leukemia and Acute Myeloid Leukemia: Impact of Care at Specialized Cancer Centers on Survival Outcome

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Abstract

Background: Adolescents and young adults (AYA; 15–39 years) with acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) experience inferior survival when compared with children. Impact of care at NCI-designated Comprehensive Cancer Centers (CCC) or Children's Oncology Group sites (COG) on survival disparities remains unstudied.

Methods: Using the Los Angeles cancer registry, we identified 1,870 ALL or AML patients between 1 and 39 years at diagnosis. Cox regression analyses assessed risk of mortality; younger age + CCC/COG served as the referent group. Logistic regression was used to determine odds of care at CCC/COG, adjusting for variables above.

Results: ALL outcome: AYAs at non-CCC/COG experienced inferior survival (15–21 years: HR = 1.9, $P = 0.005$; 22–29 years: HR = 2.6, $P < 0.001$; 30–39 years: HR = 3.0, $P < 0.001$). Outcome at CCC/COG was comparable between children and young AYAs (15–21 years: HR = 1.3, $P = 0.3$; 22–29 years: HR = 1.2, $P = 0.2$) but was inferior for 30- to 39-year-olds (HR = 3.4, $P < 0.001$). AML outcome: AYAs at non-CCC/COG experienced inferior outcome (15–21 years: HR = 1.8, $P = 0.02$; 22–39 years: HR = 1.4, $P = 0.06$). Outcome at CCC/COG was comparable between children and 15- to 21-year-olds (HR = 1.3, $P = 0.4$) but was inferior for 22- to 39-year-olds (HR = 1.7, $P = 0.05$). Access: 15- to 21-year-olds were less likely to use CCC/COG than children ($P < 0.001$). In 22- to 39-year-olds, public/uninsured (ALL: $P = 0.004$; AML<0.001), African American/Hispanics (ALL: $P = 0.03$), and 30- to 39-year-olds (ALL: $P = 0.03$) were less likely to use CCC/COG.

Conclusions: Poor survival in AYAs with ALL and AML is mitigated by care at CCC/COG. Barriers to CCC/COG care include public/uninsured, and African American/Hispanic race/ethnicity.

Impact: Care at CCC/COG explains, in part, inferior outcomes in AYAs with ALL and AML. Key sociodemographic factors serve as barriers to care at specialized centers. *Cancer Epidemiol Biomarkers Prev; 26(3); 312–20. ©2017 AACR.*

Introduction

Adolescents and young adults (AYA; 15–39 years) are designated a vulnerable population by the National Cancer Institute (NCI) due to the lack of improvement in survival in this group as compared with children and adults (1, 2). Furthermore, AYAs with acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) have inferior survival when compared with patients diagnosed during childhood (≤14 years). Although several possible causes of the inferior outcomes observed among AYAs [such as race/ethnicity, socioeconomic status (SES), and insurance] have been examined (3), site of care for their cancer could play an important role but remains unexplored.

The U.S. system of cancer care was deemed to be in crisis by the Institute of Medicine in 2013, with recommendations to develop a system of national quality measurement and reduce disparities in access to care for underserved populations. Although measurement of quality is key to realizing these goals, the current systems lack precision and breadth in quality metrics (4, 5). We used the NCI designation of comprehensiveness to a cancer center as a population-level surrogate that encompasses aspects of health care delivery that are currently unmeasurable at the national level. This study addresses knowledge gaps by evaluating the contribution of treatment site to outcome disparities experienced by AYAs, and also examines the barriers to accessing specialized care.

Materials and Methods

Using the Los Angeles County Cancer Surveillance Program (CSP), we assembled a population-based cohort of 1,956 patients with newly diagnosed ALL or AML between the ages of 1 and 39 years. Diagnoses were between 1998 and 2008, ensuring near-complete follow-up for 5 or more years. CSP collects data on all new cancer diagnoses among county residents, and is a member of the California Cancer Registry and the NCI-funded Surveillance, Epidemiology and End Results (SEER) program (6). Eligible patients were diagnosed and treated within the county. ICDO-3 histology codes were employed to identify cases (ALL: 982.0,

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982.6–982.8, 983.5–983.7; AML: 980.3–980.5, 984.0–986.1, 986.6–987.4, 989.1–993.1). Only first primary malignancies were included. Human T-cell lymphotrophic virus–related leukemias were excluded (ICDO-3 982.7). This project was approved by the State of California's Committee for the Protection of Human Subjects and the institutional review boards of City of Hope and the University of Alabama at Birmingham.

Treatment site

To evaluate treatment sites uniquely designated by the NCI for care of children and/or adults with cancer, we considered those which had received designation either as a Comprehensive Cancer Center (CCC) or a Children's Oncology Group (COG) site; the NCI employs rigorous criteria for both of these designations, including standards for breadth and depth in research along with performance requirements. We examined the impact of receiving care at a CCC/COG on survival outcomes, as well as predictors of care at these sites. We examined both admission-level and tumor-level registry data, systematically examining the treatment facility associated with each episode of care in the registry. For analyses, patients were assigned to the treatment facility where they received all or part of the first course of treatment. We considered patients treated at CCC/COG if: (i) at any age they were cared for at one of three CCCs in LAC (UCLA/Jonsson, USC/Norris/CHLA, or City of Hope) or (ii) at $\leq$21 years they were cared for at one of three COG sites without CCC designation (Kaiser Permanente, Harbor-UCLA, or Cedars-Sinai). All other patients were considered to have received care at one of 89 non-CCC/COG sites (Supplementary Fig. S1).

Dependent variables

Overall survival. Both overall survival (OS) and leukemia-specific survival served as dependent variables in evaluating the impact of treatment site on outcome difference by age.

Treatment site. Treatment site served as the dependent variable in determining predictors of care at CCC/COG.

Independent variables

Age at diagnosis. Both OS and age-dependent insurance access provided the rationale for creating data-driven age categories for multivariable analyses for each diagnosis (Supplementary Table S1). First, OS was examined within both ALL and AML (Table 1 and Supplementary Table S1). Because of substantial survival differences between 1- to 9-year-olds and 10- to 14-year-olds with ALL (89.1% vs. 72.3%, $P < 0.0001$), likely due to disease biology (7), we excluded 1- to 9-year-olds and retained patients ages 10 and older in the regression analysis; thus, 10- to 14-year-olds served as the referent group of "children" for ALL. In AML, given the absence of a substantial survival differences between 1- to 9-year-olds and 10- to 14-year-olds (66.2% vs. 59.1%, $P = 0.07$), we retained patients >1 year of age at diagnosis in the regression analysis; to this end, 1- to 14-year-olds served as the referent group for "children."

In addition, there was a difference in access to public insurance in the state of California for patients $\leq$21 years old and those >21 years old during the study period. Similarly, access to a pediatric service differs more substantially after the age of 21 years. Thus, we considered one break point to be 21 years (15–21 years vs. 22–39 years), but next considered survival in AYA subgroups. In ALL, due to survival differences between 22- to 29-year-olds (41.5%) and 30- to 39-year-olds (35.4%; $P < 0.0001$), we split older AYAs into one group encompassing 22- to 29-year-olds and another with 30- to 39-year-olds. In AML, with no substantial survival differences between 22- to 29-year-olds (51.1%) and 30- to 39-year-olds (47.5%; $P = 0.07$), "older AYAs" were grouped together as 22- to 39-year-olds. For the purposes of evaluating access (odds of receiving care at CCC/COG), the groups were considered more homogeneously due to equal insurance access in California for patients $\leq$21 years and comparable access at >21 years; thus, 1- to 21-year-old patients were considered together where patients 22 to 39 years old were considered separately.

Race/ethnicity. The CSP variables for race and ethnicity are abstracted from medical records according to cancer registry protocol (8). We evaluated race/ethnicity using the categories: non Hispanic white (NHW), Hispanic, African American, and Asian/Pacific Islander (API). Because of small numbers, Alaskan Native/Other patients and those with unknown/missing ethnicity were excluded ($n = 23$; 0.5%).

Payor. Insurance was collapsed into three categories (public, private, none) using the following criteria: (i) private insurance: HMO, PPO, managed care, fee-for-service (FFS) and insurance NOS; (ii) public insurance: Medicaid, Medicaid managed care, County-funded NOS, Medicare/Medicaid NOS, Medicare with supplement, Medicare with Medicaid eligibility, TriCare, Military, Veterans Affairs, and Indian Health Service; (iii) uninsured: self-pay or no insurance. Those with unknown/missing payor were excluded ($n = 179$; 4%).

Table 1. Survival by age at diagnosis: AYAs versus children

	5-year OS[a]		Hazard of death[b]	
Primary diagnosis	**OS[a] (95% CI)**	***P***	**HR[b] (95% CI)**	***P***
Acute lymphoblastic leukemia				
1–9 years	89.1% (86.7–91.5)	<0.001	1.0	—
10–14 years	72.3% (65.6–79.0)		2.5 (1.8–3.4)	<0.001
15–21 years	55.7% (47.7–63.7)		4.4 (3.2–6.0)	<0.001
22–29 years	41.5% (30.7–52.3)		7.0 (5.0–9.9)	<0.001
30–39 years	35.4% (25.8–45.0)		8.6 (6.3–11.7)	<0.001
Acute myeloid leukemia				
1–14 years	62.8% (54.1–71.5)	0.03	1.0	—
15–21 years	48.9% (37.9–59.9)		1.6 (1.1–2.5)	0.02
22–39 years	48.9% (42.5–55.3)		1.5 (1.1–2.1)	0.02

[a]OS: Kaplan–Meier survival analysis.
[b]HR: univariable Cox regression.

SES. CSP's variable for SES employs 2000 census block data (education and median household income). Quintiles were collapsed into three categories; the lowest and highest neighborhood quintiles remained in the low- and high-SES groups, respectively. The second, third, and fourth quintiles were collapsed into a mid-SES group. We excluded patients if SES was missing/unknown ($n = 21$; 0.5%). All analyses were repeated with inclusion of patients missing sociodemographic data with identical results (data not shown).

Distance. CSP provided residential addresses at diagnosis. We geocoded hospital addresses and measured straight line distance between patient residence and the nearest CCC/COG using Geographic Information Systems [(GIS); ArcMap 10.2, esri]. We chose this approach, because Euclidean distance is correlated with drive time (9).

Statistical analysis

Impact of treatment site on difference in overall survival by age at diagnosis. Using an evaluable cohort of 1,870 patients, overall survival was calculated using Kaplan–Meier survival analysis, (log-rank tests detected differences between groups). The assumption of proportionality was verified through visualization of the Kaplan–Meier curves and inclusion of time-dependent variables; no violation was observed. Cox regression analysis provided hazard ratios (HR) of death associated with 95% confidence intervals (CI); univariable and multivariable results are presented. Cox regression analyses modeled overall survival and proportional subdistribution hazards model examined death from primary disease (considering death from other causes as a competing risk). Unless otherwise specified, multivariable models were adjusted for treatment site, age at diagnosis, gender, race/ethnicity, SES, and payor; covariate results are presented in Supplementary Table S2. Interaction between treatment site and age ($P \leq 0.05$) led us to create a composite variable, with patients diagnosed at a younger age and treated at CCC/COG serving as a referent group.

Predictors of care at CCC/COG sites. Logistic regression techniques were used to identify predictors of receiving care at a CCC/COG; the magnitudes of association are presented as ORs with 95% CI. In California, insurance-based access to healthcare is available to all patients 21 years and younger, with federally mandated Title V coverage for children with special health care needs terminating at 21 years. Further, patients diagnosed at age 21 or younger are often treated by the pediatric team. Because of these reasons, analyses examining predictors of care at CCC/COG were stratified by age group (1–21 and 22–39 years).

All findings were comparable when adjusted for year of diagnosis (data not shown). Two-sided tests with $P < 0.05$ were considered statistically significant. SAS 9.3 (SAS Institute, Cary, NC) was used for all analyses.

Results

Clinical and sociodemographic characteristics of the cohort are summarized in Table 2 and Supplementary Fig. S2. The majority of patients (71%) with ALL were children (1–14 years), whereas the majority with AML (56%) were older AYAs (22–39 years). A smaller proportion of AYAs (21%) were treated at CCC/COG sites as compared to children (80%, $P < 0.0001$). Similarly, a smaller proportion of AYAs were publicly insured (35%) as compared with children (65%, $P < 0.0001$). Across diagnoses and payors, a higher proportion of children were treated at CCC/COG as compared to AYAs (Fig. 1). There was a trend toward a higher representation of AYAs versus children in the lowest SES group (62.5% vs. 37.5%; $P = 0.09$). Differences in racial/ethnic representation were not statistically significant (children: NHW 21.1%, Hispanic 67.5%, African American 3.7%, API 7.7%; AYAs: NHW 20.5%, Hispanic 65.3%, African American 5.5%, API 8.7%; $P = 0.2$).

Acute lymphoblastic leukemia

Survival. Overall, 5-year survival rates were highest among the 10- to 14-year-olds and declined with age (10–14 years: 72.3%; 15–21 years: 55.7%; 22–29 years: 41.5%; 30–39 years: 35.4%; $P < 0.001$; Table 1). AYAs treated at non-CCC/COG facilities had poorer 5-year survival (40.6%) as compared to those treated at CCC/COG facilities (59.8%, $P = 0.004$; Fig. 2 and Supplementary Table S3). In multivariable modeling, a composite variable representing age and treatment site (referent group: 10- to 14-year-olds treated at CCC/COG) revealed that both 15- to 21-year-olds (HR = 1.9; 95% CI, 1.2–2.8; $P = 0.005$) and 22- to 29-year-olds (HR = 2.6; 95% CI, 1.8–3.9; $P < 0.001$) not treated at CCC/COG had an increased hazard of death, whereas CCC/COG patients did not (15- to 21-year-olds: HR = 1.3; 95% CI, 0.8–2.1; $P = 0.3$; 22- to 29-year-olds: HR = 1.2; 95% CI; 0.2–5.0; $P = 0.8$). These findings were comparable in terms of leukemia-specific mortality in which patients not treated at CCC/COG had an increased hazard of death (15- to 21-year-olds: HR = 1.7; 95% CI; 1.1–2.7; $P = 0.02$; 22- to 29-year-olds: HR = 2.1; 95% CI; 1.4–3.1, $P < 0.001$) whereas CCC/COG patients did not (15- to 21-year-olds: HR = 1.2; 95% CI, 0.7–1.9; $P = 0.5$; 22- to 29-year-olds: HR = 1.1, 95% CI; 0.3–4.6; $P = 0.9$). The hazard of death among AYAs ≥30 years was increased, regardless of treatment site both overall (CCC/COG: HR = 3.4; 95% CI; 1.8–6.4; $P < 0.001$; non-CCC/COG: HR = 3.0; 95% CI; 2.1–4.5; $P < 0.001$) and in terms of leukemia-specific mortality (CCC/COG: HR = 2.1; 95% CI, 1.4–3.1; $P < 0.001$; non-CCC/COG: HR = 2.6; 95% CI, 0.3–4.6; $P < 0.001$; Table 3).

Treatment site. A higher proportion of children were treated at CCC/COG (10–14 years: 70.6%) as compared with 15–21 (50.5%) or 22- to 39-year-olds (12.3%, $P < 0.001$; Fig. 1). Among 10- to 21-year-olds, older age was associated with a lower odds of CCC/COG treatment (15–21 years vs. 10–14 years: OR = 0.4; 95% CI, 0.3–0.7; $P < 0.001$), whereas sociodemographic factors were not associated with treatment site (race/ethnicity [African American/Hispanic: OR = 0.5; 95% CI, 0.3–1.0; $P = 0.06$; API: OR = 0.8; 95% CI, 0.3–2.2; $P = 0.6$)]; SES (mid: OR = 1.1; 95% CI, 0.5–2.4; $P = 0.9$; low: OR = 1.3; 95% CI, 0.5–3.4; $P = 0.6$); payor [public/none: OR = 1.0 (95% CI, 0.6–1.6; $P = 1.0$)]; distance (>10 miles: OR = 1.2; 95% CI, 0.7–2.1; $P = 0.4$). In patients ≥22 years, both race/ethnicity [African American/Hispanic vs. NHW (referent group): OR = 0.3; 95% CI, 0.1–0.9; $P = 0.03$] and insurance [public/uninsured vs. private (referent group): OR = 0.1; 95% CI, 0.03–0.5; $P = 0.004$] predicted a lower odds of CCC/COG treatment whereas distance did not (>10 miles: OR = 1.2; 95% CI, 0.7–2.1; $P = 0.4$). In addition, 30- to 39-year-olds were more

Table 2. Patient characteristics overall and by treatment site

	Acute lymphoblastic leukemia			
	Total (n = 1,380)	**CCC/COG (n = 809)**	**Non-CCC (n = 571)**	***P***
Age				
1–14 years	978 (70.9%)	687 (84.9%)	291 (51.0%)	<0.001
15–21 years	190 (13.8%)	96 (11.9%)	94 (16.5%)	
22–39 years	212 (15.4%)	26 (3.2%)	186 (32.6%)	
Gender				
Female	573 (41.5%)	335 (41.4%)	238 (41.7%)	0.9
Male	807 (58.5%)	474 (58.6%)	333 (58.3%)	
Race/ethnicity				
NHW	275 (19.9%)	182 (22.5%)	93 (16.3%)	0.02
African American	49 (3.6%)	26 (3.2%)	23 (4.0%)	
Hispanic	962 (69.7%)	541 (66.9%)	421 (73.7%)	
Asian/Pacific Islander	94 (6.8%)	60 (7.4%)	34 (6.0%)	
Insurance				
Private	712 (51.6%)	423 (52.3%)	289 (50.6%)	0.2
Public	605 (43.8%)	356 (58.8%)	249 (43.6%)	
Uninsured	63 (4.6%)	30 (3.7%)	33 (5.8%)	
SES				
High	170 (12.3%)	105 (13.0%)	65 (11.4%)	0.6
Middle	758 (54.9%)	444 (54.9%)	314 (55.0%)	
Low	452 (32.8%)	260 (32.1%)	192 (33.6%)	
Distance to nearest CCC/COG (miles)				
Median (IQR)	7.0 (6.0)	6.8 (6.4)	7.3 (5.1)	0.5
Mean (SD)	8.5 (6.7)	8.7 (7.5)	8.3 (5.2)	
	Acute myeloid leukemia			
	Total (n = 490)	**CCC/COG (n = 177)**	**Non-CCC (n = 313)**	***P***
Age				
1–14 years	131 (26.7%)	97 (54.8%)	34 (10.9%)	<0.001
15–21 years	85 (17.4%)	36 (20.3%)	49 (15.7%)	
22–39 years	274 (55.9%)	44 (24.9%)	230 (73.5%)	
Gender				
Female	228 (46.5%)	80 (45.2%)	148 (47.2%)	0.7
Male	262 (53.5%)	97 (54.8%)	165 (52.7%)	
Race/ethnicity				
NHW	115 (23.5%)	40 (22.6%)	75 (24.0%)	0.98
African American	34 (6.9%)	13 (7.3%)	21 (6.7%)	
Hispanic	284 (58.0%)	103 (58.2%)	181 (57.8%)	
Asian/Pacific Islander	57 (11.6%)	21 (11.9%)	36 (11.5%)	
Insurance				
Private	267 (54.5%)	100 (56.5%)	167 (53.4%)	0.09
Public	180 (36.7%)	68 (38.4%)	112 (35.8%)	
Uninsured	43 (8.8%)	9 (5.1%)	34 (10.9%)	
SES				
High	54 (11.0%)	22 (12.4%)	32 (10.2%)	0.7
Middle	298 (60.8%)	107 (60.5%)	191 (61.0%)	
Low	138 (29.2%)	48 (27.1%)	90 (28.8%)	
Distance to nearest CCC/COG (miles)				
Median (IQR)	7.9 (7.3)	7.5 (7.2)	8.0 (7.2)	0.8
Mean (SD)	10.0 (7.8)	9.7 (8.2)	10.2 (7.6)	

Abbreviations: CCC/COG: NCI-Designated Comprehensive Cancer Center or Children's Oncology Group site; IQR, interquartile range.

likely to receive care at CCC/COG when compared with 22- to 29-year-olds (OR = 3.1; 95% CI, 1.1–8.4; $P = 0.03$; Table 4). These age-related findings were comparable when stratified by SES and payor (data not shown), and age remained an independent predictor despite adjustment for these variables.

Acute myeloid leukemia

Survival. Overall survival was superior in children and declined with age (1–14 years: 62.8%; 15–21 years: 48.9%; 22–39 years: 48.9%; $P = 0.03$; Table 1). AYAs had comparable outcome at CCC/COG and non-CCC/COG in univariable analysis (48.1% vs. 49.1%, $P = 0.9$; Fig. 2 and Supplementary Table S3). However, in multivariable regression including a composite age/treatment site variable (reference group: 1- to 14-year-olds at CCC/COG), 15- to 21-year-olds not treated at CCC/COG saw an increased hazard of death (HR = 1.7; 95% CI, 1.1–3.0; $P = 0.02$), whereas CCC/COG patients did not (HR = 1.3; 95% CI, 0.7–2.3; $P = 0.4$). Findings regarding leukemia-specific mortality were comparable, as patients not treated at CCC/COG had an increased hazard of death (HR = 1.9; 95% CI, 1.1–3.4; $P = 0.02$), whereas CCC/COG patients did not (HR = 1.4; 95% CI, 0.8–2.7; $P = 0.3$). All 22- to 39-year-olds, irrespective of site of care, had an increased hazard of death overall as compared to children (CCC/COG: HR = 3.4; 95% CI, 1.8–6.4; $P < 0.001$; non-CCC/COG: HR = 3.0; 95% CI, 2.1–4.5; $P < 0.001$). Findings were comparable regarding leukemia-specific mortality (CCC/COG: HR = 1.5; 95% CI, 0.99–2.3; $P = 0.06$; non-CCC/COG: HR = 1.6; 95% CI, 0.9–2.8; $P = 0.1$; Table 3).

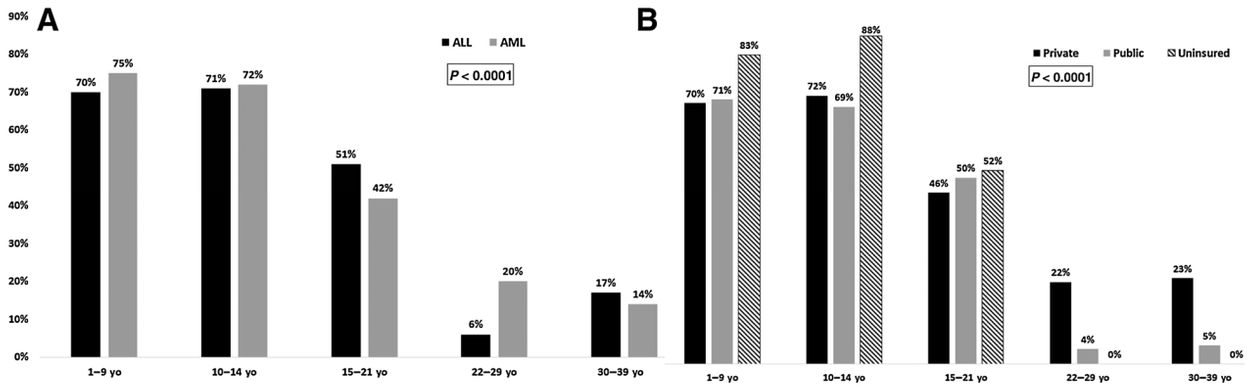

Figure 1.

Proportion of children, adolescents, and young adults with hematologic malignancies treated at CCCs or COG sites. Proportions are presented by age (**A**) and diagnosis and by age and payor (**B**).

Treatment site. A higher proportion of children with AML were treated at CCC/COG sites (1–9 years: 75.3%; 10–14 years: 72.2%) as compared with 15- to 21-year-olds (42.4%) or 22- to 39-year-olds (16.1%, $P < 0.0001$). In older AYAs, a higher proportion of privately insured (22–29 years: 22%; 30–39 years: 23%) as compared to publicly insured (22–29 years: 4%, 30–39 years, 5%, $P < 0.0001$) patients were treated at CCC/COG sites (Fig. 1). In a multivariable model restricted to patients $\leq$21 years, older age (15–21 years) alone was associated with a lower odds of treatment at a CCC/COG (OR = 0.3; 95% CI, 0.1–0.5; $P < 0.001$) whereas sociodemographic factors were not associated with treatment site. This included race/ethnicity (African American/Hispanic: OR = 1.1; 95% CI, 0.5–2.6; $P = 0.8$; API: OR = 1.7; 95% CI, 0.4–6.6; $P = 0.5$), SES (mid: OR = 0.6; 95% CI, 0.2–1.8; $P = 0.4$; low: OR = 0.6; 95% CI, 0.2–2.2; $P = 0.4$), payor (public/none: OR = 1.7; 95% CI, 0.9–3.2; $P = 0.1$), and distance (>10 miles: OR = 0.8; 95% CI, 0.4–1.6; $P = 0.6$). In 22- to 39-year-olds, payor predicted lower odds of treatment at a CCC/COG (public/uninsured: OR = 0.1; 95% CI, 0.03–0.5; $P = 0.004$; Table 4).

Discussion

These population-level findings reveal that AYAs diagnosed with ALL at <30 years or with AML at <22 years have poor outcomes when not treated at CCC/COG sites when compared with CCC/COG sites, and treatment at CCC/COG sites can mitigate the outcome difference between AYAs and children in these patients. We identify age, lack of private insurance, and nonwhite race/ethnicity as potential barriers to receiving treatment at a CCC/COG in ALL and AML, while living further from the nearest CCC/COG did not serve as a potential barrier.

In the setting of AYA disparities and the IOM call to action (5, 10), both the potential effect of quality of care on survival and barriers to access to quality care, deserve examination. System-level effects on outcomes in cancer have been evaluated in terms of payor, surgical volume, safety net status, technology, and academic status and size (bed number); the influence of decision-making and care delivery has been examined with respect to

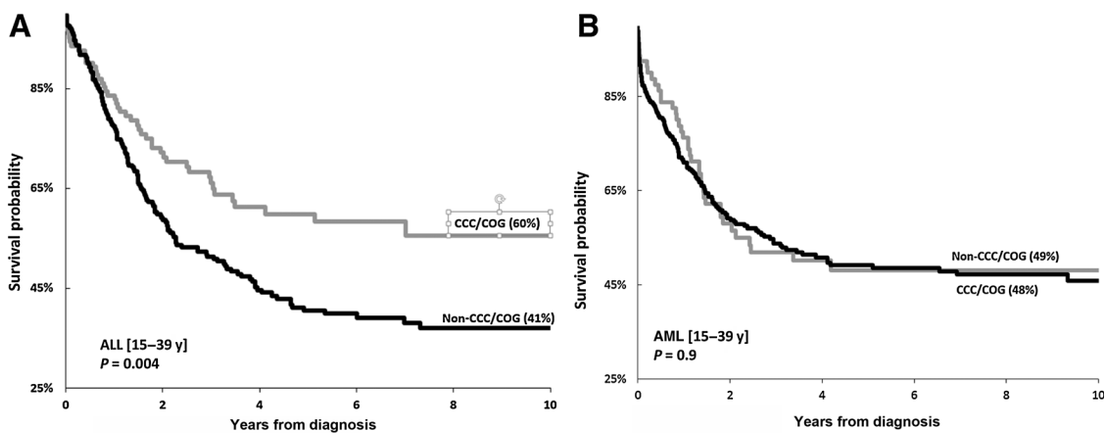

Figure 2.

OS by treatment site AYAs with ALL and AML. Overall survival is presented by treatment site. **A,** OS in AYAs with ALL by treatment site (CCC/COG vs. other); **B,** OS in AYAs with AML by treatment site (CCC/COG vs. other).

Table 3. Impact of age and treatment site on OS

			Hazard of death[a]			
			Overall survival[b]		Leukemia-specific survival[c]	
Primary diagnosis	Age[c]	Treatment site[d]	HR (95% CI)	*P*	HR (95% CI)	*P*
Acute lymphoblastic leukemia						
	10–14 years	CCC/COG	1.0	—	1.0	—
		Non-CCC/COG	0.6 (0.3–1.2)	0.1	0.6 (0.3–1.1)	0.1
	15–21 years	CCC/COG	1.3 (0.8–2.1)	0.3	1.2 (0.7–1.9)	0.5
		Non-CCC/COG	**1.9 (1.2–2.8)**	**0.005**	**1.7 (1.1–2.7)**	**0.02**
	22–29 years	CCC/COG	1.2 (0.2–5.0)	0.8	1.1 (0.3–4.6)	0.9
		Non-CCC/COG	**2.6 (1.8–3.9)**	**<0.001**	**2.1 (1.4–3.1)**	**<0.001**
	30–39 years	CCC/COG	**3.4 (1.8–6.4)**	**<0.001**	**2.6 (1.2–5.4)**	**0.01**
		Non-CCC/COG	**3.0 (2.1–4.5)**	**<0.001**	**2.2 (1.5–3.4)**	**<0.001**
Acute myeloid leukemia						
	1–14 years	CCC/COG	1.0	—	1.0	—
		Non-CCC/COG	0.8 (0.4–1.6)	0.5	0.9 (0.5–1.9)	0.9
	15–21 years	CCC/COG	1.3 (0.7–2.3)	0.4	1.4 (0.8–2.7)	0.3
		Non-CCC/COG	**1.8 (1.1–3.0)**	**0.02**	**1.9 (1.1–3.4)**	**0.03**
	22–39 years	CCC/COG	**1.7 (1.0–2.9)**	**0.05**	1.6 (0.9–2.8)	0.1
		Non-CCC/COG	1.4 (1.0–2.1)	0.06	1.5 (0.99–2.3)	0.06

[a]Bolded values represent statistically significant findings, $P < 0.05$.
[b]Cox regression multivariable analysis adjusted for race/ethnicity, socioeconomic status, payor.
[c]Cox regression multivariable analysis, death by other causes considered as competing risk, adjusted for race/ethnicity, socioeconomic status, payor.
[d]Derived variable in model combined age group and treatment site (CCC/COG).

guideline adherence, clinical trial enrollment, and cooperative group affiliation (2, 11–13). However, previous studies explored these factors in older patients, or in patients with specific non-hematologic malignancies and/or in specific surgical settings (14). Facility factors have been explored in common adult-onset malignancies (12, 15, 16). Many aspects of health care delivery remain unmeasured, with neither AYAs nor patients with hematologic malignancies examined in detail. Relevant unmeasured items include supportive care, multidisciplinary decision-making, and therapy delivery mechanisms, all components of the NCI comprehensiveness designation (17); the absence of a granular, validated measure delving into cancer care delivery (10) necessitates evaluation of surrogate measures such as care at an NCI designated comprehensive cancer center or a COG member site.

Multiple domains potentially contribute to the AYA Gap: host and cancer biology, therapeutic exposures, health behaviors, and health care delivery [sociocultural factors, access, clinical trial enrollment, and unmeasurable aspects of treatment site (supportive care, therapy decisions)]. We find that care at CCC/COG sites mitigates poor survival in 15- to 21- and 22- to -29-year-olds when compared with 10- to 14-year-old children in ALL, with no apparent impact in 30- to 39-year-olds. Similarly in AML, care at CCC/COG sites mitigates poor survival in 15- to 21-year-olds while in 22- to 39-year-olds there is no apparent impact on survival. In older patients (30- to 39-year-olds with ALL, 22- to 39-year-olds with AML), other aspects of disease or care are likely too dominant to be overcome by treatment site alone. These findings are comparable across both overall and leukemia-specific survival.

In ALL, groundbreaking genome-wide work in the last decade has revealed unique AYA susceptibility profiles (18), and the predominance of the novel Philadelphia-like phenotype, which likely requires an additional component to therapy (19). Comparable AML studies have been less conclusive; however, age-based biologic differences exist (20) and hypotheses regarding novel risk stratification are being tested (1). ALL and AML have traditionally been treated with different approaches dependent upon the service/clinic to which the AYA presents (adult vs. pediatric; ref. 21, 22). Although the field now recognizes that multiagent, pediatric-inspired chemotherapy regimens have superior outcome to other regimens in AYA patients with ALL (21, 23–25), these regimens have not been uniformly adopted, and their adoption could possibly differ by site of treatment. Guidelines for treatment of AYA patients with ALL were instituted in 2012 by the National Comprehensive Cancer Network; ALL is the only diagnosis to have distinct AYA therapeutic recommendations which have included treatment either with pediatric-inspired multiagent chemotherapy or enrollment on clinical trial (26, 27). During the time period covered by our study (1998–2008), there is evidence for support for these ALL regimens in younger AYAs and minimally in older AYAs, with the approach still evolving both within and outside of NCICCCs (28). Previous studies indicate that the key difference in the AML therapeutic approach is dose intensity which is higher in pediatric protocols. In these AML trials, patients on pediatric protocols had superior outcome to those on adult protocols; however, interpretation of the specific predictors of outcome is challenging as age played a significant role in the outcome (22). On pediatric AML protocols, AYAs saw higher risk of treatment-related mortality (29). Our study finds that treatment at CCC/COG facilities mitigates the difference in outcome between younger AYAs and children. We speculate that aspects of the NCI designation of comprehensiveness or designation as a COG member site, which impact outcome in AYAs likely include: supportive care, multidisciplinary care coordination, therapy choice, and delivery.

Understanding access to specialized care becomes crucial with the demonstrated impact of CCC/COG care on AYA outcomes. Adolescents (15- to 21-year-olds) with ALL and AML were less likely to receive treatment at CCC/COG when compared with those <15 years of age, despite adjustment for sociodemographic factors. In fact, sociodemographic factors did not impact access to care at CCC/COG facilities in this age group. However, among 22- to 39-year-old leukemia patients, lacking private insurance was associated with lower odds of utilizing CCC/COG; this is consistent with Californians "aging out" of federally mandated coverage at 21 years of age.

Table 4. Likelihood of receiving care at CCC/COG versus non-CCC/COG facility[a,b]

	≤21-year-olds[c]		22- to 39-year-olds		
	OR[d] (95% CI)	***P***		**OR (95% CI)**	***P***
Acute lymphoblastic leukemia					
Age group					
10–14 years[d]	1.0	—	22–29 years	1.0	—
15–21 years	**0.4 (0.3–0.7)**	**<0.001**	30–39 years	**3.1 (1.1–8.7)**	**0.03**
Race/ethnicity					
NHW	1.0	—		1.0	—
African American/Hispanic	0.5 (0.3–1.0)	0.06		**0.3 (0.1–0.9)**	**0.03**
Asian/Pacific Islander	0.8 (0.3–2.2)	0.6		0.6 (0.1–4.0)	0.6
SES					
High	1.0	—		1.0	—
Middle	1.1 (0.5–2.4)	0.9		1.5 (0.4–5.2)	0.6
Low	1.3 (0.5–3.4)	0.6		0.7 (0.1–4.4)	0.7
Insurance					
Private	1.0	—		1.0	—
Public/none	1.0 (0.6–1.6)	1.0		**0.1 (0.03–0.5)**	**0.004**
Distance from nearest age-appropriate CCC/COG site					
≤10 miles	1.0	—		1.0	—
>10 miles	1.2 (0.7–2.1)	0.4		0.7 (0.3–1.8)	0.4
Acute myeloid leukemia					
Age group					
1–14 years	1.0	—	22–29 years	1.0	—
15–21 years	**0.3 (0.1–0.5)**	**<0.001**	30–39 years	0.6 (0.3–1.2)	0.1
Race/ethnicity					
NHW	1.0	—		1.0	—
African American/Hispanic	1.2 (0.5–2.8)	0.8		0.6 (0.3–1.4)	0.3
Asian/Pacific Islander	1.7 (0.4–6.7)	0.5		1.2 (0.5–3.0)	0.8
SES					
High	1.0	—		1.0	—
Middle	0.6 (0.2–1.9)	0.4		0.9 (0.4–2.5)	0.9
Low	0.6 (0.2–2.3)	0.5		0.6 (0.2–2.3)	0.4
Insurance					
Private	1.0	—		1.0	—
Public/none	1.4 (0.8–2.6)	0.3		**0.3 (0.1–0.8)**	**0.02**
Distance from nearest age-appropriate CCC/COG site					
≤10 miles	1.0	—		1.0	—
>10 miles	0.8 (0.4–1.6)	0.5		1.2 (0.6–2.4)	0.7

[a]Logistic regression, adjusted for all variables including gender.
[b]Bolded values: statistically significant, $P < 0.05$.
[c]OR with 95% CI.
[d]Includes 10- to 14-year-olds with ALL and 1- to 14-year-olds with AML.

Distance did not impact CCC/COG utilization in ALL or AML. Distance has been associated with care at CCC/COG sites in older AYAs in Los Angeles County with central nervous system tumors (30) and adult-onset tumors (31); thus these findings in ALL and AML could reflect a lower level of comfort among non-CCC/COG facilities to treat acute leukemia, including a need for higher intensity supportive care; these aspects were examined using NCI designation as a surrogate. It is conceivable that distance is less of a factor in this study due to examination of a single county, which would limit the generalizability of these findings across the United States; however, Los Angeles County spans 4,751 square miles and was home to 9.8 million people in 2008. The strong presence of health maintenance organizations in California could possibly confound a distance effect, as distance may behave differently in an alternate health care landscape. Nevertheless, potential limitations to the generalizability of these findings are minimized by the size and population of the county, which alone would rank as the eighth most populous state with robust multiracial, multiethnic representation.

Payor predicts CCC/COG utilization for older AYA patients with ALL and AML, whereas SES does not; race/ethnicity remains an independent predictor of treatment site in older AYAs with ALL. This pattern is consistent with the notion that payor serves as a significant driver of the location of care after adjusting for race/ethnicity and neighborhood-level SES. An association between payor contracts and referral patterns is implicated by the different behavior among age groups of publicly insured patients; whereas publicly insured older AYAs are less likely to be treated at CCC/COG sites, there is a trend toward younger publicly insured AML patients being more likely to receive such care. This conflicting pattern between patients ≤21 years and those >21 years is in line with the concept that the patients <21 years may be receiving pediatric services at the specialized site; this also echoes studies (32) that have reported that pediatric centers accept 15- to 21-year-olds regardless of insurance status.

In addition, race/ethnicity and age emerge as independent predictors of treatment site among older AYAs with ALL, with patients from African American and Hispanic backgrounds and 22- to 29-year-olds less likely to receive treatment at CCC/COG than their NHW and 30- to 39-year-old counterparts. AYAs are a unique population, and may be at one of many different phases of young adulthood, whether at school or work full- or part-time,

with a living situation that ranges from living alone or with friends to living with spouses, partners or parents; these aspects likely impact the source of insurance for an AYA as well (employer-based, parent-based, public, none). Each of these findings warrants investigation to understand these barriers at a granular level.

Registries provide unique population-level data, but with inherent limitations; these include a lack of detailed clinical, health behavior and care delivery data including adherence to prescribed therapy. For example, these data lack white blood cell count at diagnosis, chromosome copy number, or cytogenetic details, thus limiting our inclusion of these in analyses. The neighborhood-level sociodemographic factors (income and education) used to create the SES variable may vary from individual-level measurements; in addition, race/ethnicity is abstracted from the medical record and may differ from the gold standard of self-report. Nevertheless, these variables serve as the best available measures in population-level analyses which are able to uncover novel findings outside of the idealistic clinical trial setting. Decisions regarding physician assignment (pediatric or adult service) by age at diagnosis vary by treatment facility, and the registry does not document which specialty/service treated a patient at any particular site, nor the therapy given. We have previously published our observations for other cancer diagnoses, and found that health coverage predicts treatment site (30). Thus, in this study, we have grouped patients with comparable access to public coverage; 15- to 21-year-olds at a site designated as COG for pediatrics (but not as CCC) were assigned to COG. Repeating analyses without inclusion of the 3 COG sites that were not affiliated with an NCI-designated CCC yielded comparable findings (Supplementary Table S4). Our *a priori* assignment conservatively assigns 15- to 21-year-olds to pediatric services. Any misclassification bias would mute our results rather than changing their direction or enhancing them; in fact, our treatment site effect would be more pronounced if we considered this age cutoff to be younger.

These population-level findings indicate that poor survival among the younger AYA with ALL (<30 years) and AML (<22 years) as compared to children can be mitigated by treatment at CCC/COG facilities. We present a novel, systems-level approach to a pervasive challenge. This study highlights the need for ongoing investigations into health care delivery in cancer, specifically in AYAs and patients facing barriers to access (lacking private insurance; underrepresented minorities). No individual element of healthcare delivery is mutually exclusive, and generalizing outcomes from one component overlooks the quintessential integrative model (33) in which each element contributes to the overall end point of high-quality care. Our recognition of barriers to care at specialized centers highlights a gap in provision of high-quality cancer care in vulnerable populations. It becomes imperative to respond to IOM recommendations to both develop quality measurement and simultaneously improve access, as it is crucial that attention to these items moves beyond typical adult-onset cancers and older populations and includes AYAs who remain stranded between the pediatric and adult healthcare systems.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

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