Title

Treatment Complications and Survival Among Children and Young Adults With Acute Lymphoblastic Leukemia.

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Treatment Complications and Survival Among Children and Young Adults With Acute Lymphoblastic Leukemia

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QUESTION ASKED: Does location of inpatient treatment throughout therapy in children and young adults with acute lymphoblastic leukemia impact long-term survival, complications, and costs?

SUMMARY ANSWER: We found that inpatient treatment received at a specialized cancer center throughout therapy is associated with superior survival in both children and young adults. While the incidence of complications was similar by location of care, hospitalization costs were significantly higher for patients receiving all treatment at a specialized cancer center.

WHAT WE DID: Using population-based data from the California Cancer Registry that are linked to statewide hospitalizations, we examined the impact of the location of inpatient care throughout the full course of therapy on potential treatment-related complications and survival in children (0-18 years) and young adults (19-39 years) with acute lymphoblastic leukemia. Furthermore, given that specialized cancer centers may be more expensive than community hospitals, we evaluated the cost of inpatient treatment by location of care.

WHAT WE FOUND: Our study demonstrates that receiving all inpatient treatment at a specialized cancer center is associated with superior leukemia-specific and overall survival in children and young adults. However, access to care at a specialized cancer center does not appear uniform insofar as young adults and those of African American and Hispanic race/ethnicity are less likely to receive all care at a specialized cancer center. Given the considerable impact that care at a specialized cancer center may have on leukemia survival, further research should explore how to improve access for these groups of patients.

BIAS, CONFOUNDING FACTORS: Our study lacked details on specific treatment and biological factors (such as minimal residual disease, etc) to consider in our propensity scores and survival analyses. As a result, there may be residual confounding factors from the imbalance in baseline characteristics among patients treated at specialized cancer centers versus those treated at nonspecialized cancer centers. The use of propensity score–weighted models mitigated this bias; therefore, it is less likely that the differences in measured baseline characteristics could account for the difference noted in survival outcomes. However, this database allows for population-level analysis of sociodemographic and clinical factors impacting survival that have not been previously described.

REAL-LIFE IMPLICATIONS: Given the associated improvement in survival seen with patients treated at a specialized cancer center, our findings support the clinical recommendation that children and young adult patients with this complex and relatively rare diagnosis be referred to and treated at specialized cancer centers.

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ASSOCIATED CONTENT

Appendix

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CARE DELIVERY

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abstract

PURPOSE We previously demonstrated lower early mortality for young adults (YAs) with acute lymphoblastic leukemia (ALL) who received induction treatment at specialized cancer centers (SCCs) versus community hospitals. The aim of this study is to determine the impact of inpatient location of treatment throughout therapy on long-term survival, complications, and cost—associations that have not yet been evaluated at the population level.

METHODS Using the California Cancer Registry linked to a hospitalization database, we identified patients, 0-39 years of age, diagnosed with first primary ALL who received inpatient treatment between 1991 and 2014. Patients were classified as receiving all or part or none of their inpatient treatment at an SCC within 3 years of diagnosis. Inverse probability–weighted, multivariable Cox regression models estimated the associations between location of treatment and sociodemographic and clinical factors with survival. We compared 3-year inpatient costs overall and per day by age group and location of care.

RESULTS Eighty-four percent (0-18 years; n = 4,549) of children and 36% of YAs (19-39 years; n = 683) received all treatment at SCCs. Receiving all treatment at an SCC was associated with superior leukemia-specific (hazard ratio [HR], 0.76; 95% CI, 0.67 to 0.88) and overall survival (HR, 0.87; 95% CI, 0.77 to 0.97) in children and in YAs (HR, 0.71; 95% CI, 0.61 to 0.83; HR, 0.70; 95% CI, 0.62 to 0.80) even after controlling for complications. The cost of inpatient care during the full course of therapy was higher in patients receiving all of their care at SCCs.

CONCLUSION Our results demonstrate that inpatient treatment at an SCC throughout therapy is associated with superior survival; therefore, strong consideration should be given to referring these patients to SCCs.

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INTRODUCTION

Cancer continues to be a leading cause of nonaccidental death in children and adolescents and young adults (AYAs).[1] For acute lymphoblastic leukemia (ALL), the most common cancer diagnosis in children, there has been substantial progress in treatment over time.[2-4] Despite improvements in outcomes, there continues to be a significant disparity in survival by age.[5-7] Differences in time to diagnosis, biology, treatment adherence, complications, and access to specialized cancer care have been implicated in these survival differences.[8-11]

Access to and use of specialized cancer care is of particular importance as a potential contributor to survival disparities in the AYA patient population, because AYAs may receive treatment by either pediatric or adult oncologists at a variety of settings.[7] Previous work by our group and others demonstrated that young adult (YA) patients with leukemia who received induction treatment at a specialized cancer center (SCC) had lower 60-day mortality, highlighting the importance of appropriate specialized care for this age group.[12,13] In addition, treatment complications can affect ALL outcomes, resulting in higher early mortality, intensive care unit admissions, and prolonged hospitalizations.[9,11,14] However, it remains unclear whether location of care affects treatment complications and long-term survival.

Therefore, using the California Cancer Registry (CCR) and hospitalization data, our objective was to examine the impact of location of inpatient care throughout the full course of therapy on potential treatment-related

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complications and survival in children and AYAs with ALL. Furthermore, given that SCCs may be more expensive than community hospitals, we evaluated the cost of inpatient treatment by location of care. We hypothesized that older patients would be more likely to receive treatment at non-SCCs and that treatment at non-SCCs would result in higher complication rates, resulting in longer inpatient stays and inferior survival.

METHODS

Study Population

Patients 0-39 years old who were hospitalized in California between 1991 and 2014 with a first primary diagnosis of ALL were eligible for this study. A diagnosis of ALL was defined using morphology codes from the International Classification of Diseases for Oncology (ICD-O-3): B cell (9728, 9812-9818, 9836), T cell (9729, 9837), or not otherwise specified (9727, 9811, 9835). We excluded patients from the CCR who were diagnosed on death certificate only or with 0/invalid survival time (n = 25), patients without a hospital admission within 3 years of diagnosis (n = 445), and those with a simultaneous cancer diagnosis within 60 days of ALL diagnosis (n = 16); this resulted in a final study population of 7,275 patients. We divided the cohort into children (0-18 years; n = 5,398) and YAs (19-39 years; n = 1,877) separately on the basis of previously described differences in ALL outcomes and location of care in the pediatric versus YA population.[13-15]

Study Database

This study used the CCR linked with the Office of Statewide Health Planning and Development (OSHPD) Patient Discharge Database (PDD). The CCR contains information on > 99% of all patients diagnosed with cancer in California. The PDD contains longitudinal information for each patient on all admissions at acute care hospitals in California (except 14 federal hospitals). This linked database includes date of diagnosis, age at diagnosis, sex, marital status, neighborhood socioeconomic status (SES), health insurance at diagnosis treatment (eg, chemotherapy, radiation, transplantation), principal hospital diagnosis, and up to 24 secondary hospital diagnoses based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), hospital admission date, length of stay, hospital name, and location.

Location of Care

SCCs were defined as Children's Oncology Group (COG) member and/or National Cancer Institute Comprehensive Cancer Center (NCI-CCC)–designated centers.[16] COG hospitals are considered centers of excellence for the treatment of pediatric cancer. However, there is not a corresponding designation for YAs; therefore, we used the NCI-CCC designation as a surrogate.[13] There are 28 SCCs in California, and they were defined as a COG-member institution or NCI-CCC for children ≤ 18 years at diagnosis and an NCI-CCC for older adolescents and YAs > 18 years at diagnosis.[14,15] We previously found that 87% of patients with ALL 15-18 years of age are treated in the pediatric setting, and 94% of 19- to 39-year-olds are treated in the adult settings,[15] supporting the classification of SCCs in the 2 age groups. Patients were classified as receiving all or part/none of their care at an SCC on the basis of chemotherapy administration within first 3 years from diagnosis to capture length of standard treatment. The groups of patients who received part and none of their inpatient treatment at SCCs were analyzed together, because only a small percentage of children (3.6%) received part of their care at an SCC, and the larger percentage of YAs (18.2%) who received part of their care at an SCC had similar survival to those who received none of their care at an SCC. Patients may have had their initial diagnosis at a non-SCC and still be considered as having received all care at an SCC if their other treatment-related admissions were at an SCC or if they only had non–treatment-related admissions to a non-SCC, such as febrile neutropenia. Case listings of patient admissions and related ICD-9 codes were independently reviewed by 2 hematologist/oncologists (E.M.A., M.M.).

Study Covariates

For health insurance (available from 1996 forward), we considered publicly insured (Medicaid and other government-assisted programs) and uninsured together in the analysis, because public insurance may be indicative of retroactive enrollment at diagnosis.[17] Private health insurance included health maintenance organizations, preferred provider organizations, and military care. Neighborhood SES is based on a widely used index created using US Census and American Community Survey data, as described previously.[18] The presence of comorbidities in the 2 years before diagnosis or at ALL diagnosis were determined using the Elixhauser index (developed in OSHPD and previously described),[19-21] on the basis of ICD-9 codes linked to an individual patient. Complications within 3 years from diagnosis were categorized as: bleeding, sepsis, thrombosis, liver failure, renal failure, respiratory failure, and cardiac arrest and determined based on the presence of a corresponding ICD-9 code.[19,20]

Statistical Analysis

Descriptive statistics (χ^2 tests) were used to examine the relationship between patient characteristics, complications, and location of care for children (0-18 years) and YAs (19-39 years). Kaplan-Meier analysis was used to determine leukemia-specific and overall survival by age and location of care. Propensity score methodology was used to mitigate potential confounding of baseline characteristics by location of care.[21] Multivariable logistic regression was used to estimate propensity scores for all versus part/none of care at SCC, predicted from age, sex, race/ethnicity, year of diagnosis, neighborhood SES, health insurance type,

TABLE 1. Selected Sociodemographic and Clinical Characteristics of Children and Young Adults With Acute Lymphoblastic Leukemia Hospitalized Within 3 Years of Diagnosis, by Age at Diagnosis, California, 1991-2014

	0-18 Years Old			19-39 Years Old		
Characteristic	**All Care (n = 4,549)**	**Part/None (n = 849)**	***P***	**All Care (n = 683)**	**Part/None (n = 1,194)**	***P***
Sex						
Male	2,660 (58.5)	504 (59.4)		445 (65.2)	761 (63.7)	
Female	1,889 (41.5)	345 (40.6)	.629	238 (34.9)	433 (36.3)	.537
Race/ethnicity						
NH White	1,314 (28.9)	320 (37.7)		271 (39.7)	394 (33.0)	
NH African American	211 (4.6)	50 (5.9)		19 (2.8)	65 (5.4)	
Hispanic	2,668 (58.7)	373 (43.9)		310 (45.4)	625 (52.4)	
Asian/PI	356 (7.8)	106 (12.5)	< .001	83 (12.2)	110 (9.2)	< .001
Health insurance[a]						
Private	1,865 (49.6)	414 (72.1)		283 (50.9)	587 (59.4)	
Public/no insurance	1,865 (49.6)	153 (26.7)		267 (48.0)	396 (40.1)	
Unknown	33 (0.9)	7 (1.2)	< .001	6 (1.1)	5 (0.5)	.003
Neighborhood SES						
Low SES	3,376 (74.2)	568 (66.9)		454 (66.5)	789 (66.1)	
High SES	1,140 (25.1)	276 (32.5)	< .001	218 (31.9)	382 (32.0)	
Unknown	33 (0.7)	5 (0.6)		11 (1.6)	23 (1.9)	.883
Year of diagnosis						
1991-1996	1,007 (22.1)	329 (38.8)		151 (22.1)	251 (21.0)	
1997-2002	1,431 (31.5)	234 (27.6)		148 (21.7)	295 (24.7)	
2003-2008	1,342 (29.5)	161 (19.0)		184 (26.9)	308 (25.8)	
2009-2014	769 (16.9)	125 (14.7)	< .001	200 (29.3)	340 (28.5)	.521
Chemotherapy						
Yes	4,489 (98.7)	836 (98.5)		670 (98.1)	1,148 (96.2)	
No	57 (1.3)	13 (1.5)		10 (1.5)	44 (3.7)	
Unknown	< 5	< 5	.61	< 5	< 5	.012
Radiation						
Yes	677 (14.9)	177 (20.9)		266 (39.0)	414 (34.7)	
No	3,872 (85.1)	672 (79.2)	< .001	417 (61.1)	780 (65.3)	.064
Transplantation						
Yes	324 (7.1)	65 (7.7)		242 (35.4)	296 (24.8)	
No	4,225 (92.9)	784 (92.3)	.581	441 (64.6)	898 (75.2)	< .001
Subtype						
T cell	549 (12.1)	121 (14.3)		174 (25.5)	300 (25.1)	
B cell	2,945 (64.7)	523 (61.6)		432 (63.3)	720 (60.3)	
NOS	1,055 (23.2)	205 (24.2)	.127	77 (11.3)	174 (14.6)	.124
Comorbidity						
No	2,588 (56.9)	491 (57.8)		274 (40.1)	444 (37.2)	
Yes	1,961 (43.1)	358 (42.2)	.611	409 (59.9)	750 (62.8)	.209
Bleeding						
Yes	388 (8.5)	80 (9.4)		137 (20.1)	240 (20.1)	
No	4,161 (91.5)	769 (90.6)	.396	546 (79.9)	954 (79.9)	.983

(continued on following page)

TABLE 1. Selected Sociodemographic and Clinical Characteristics of Children and Young Adults With Acute Lymphoblastic Leukemia Hospitalized Within 3 Years of Diagnosis, by Age at Diagnosis, California, 1991-2014 (continued)

	0-18 Years Old			19-39 Years Old		
Characteristic	**All Care (n = 4,549)**	**Part/None (n = 849)**	***P***	**All Care (n = 683)**	**Part/None (n = 1,194)**	***P***
Sepsis						
Yes	2,115 (46.5)	410 (48.3)		412 (60.3)	772 (64.7)	
No	2,434 (53.5)	439 (51.7)	.335	271 (39.7)	422 (35.3)	.061
Thrombosis						
Yes	40 (0.9)	14 (1.7)		31 (4.5)	63 (5.3)	
No	4,509 (99.1)	835 (98.4)	.039	652 (95.5)	1,131 (94.7)	.481
Liver failure						
Yes	50 (1.1)	11 (1.3)		33 (4.8)	39 (3.3)	
No	4,499 (98.9)	838 (98.7)	.619	650 (95.2)	1,155 (96.7)	.089
Renal failure						
Yes	414 (9.1)	68 (8.0)		203 (29.7)	321 (26.9)	
No	4,135 (90.9)	781 (92.0)	.306	480 (70.3)	873 (73.1)	.187
Respiratory failure						
Yes	271 (6.0)	54 (6.4)		124 (18.2)	253 (21.2)	
No	4,278 (94.0)	795 (93.6)	.65	559 (81.8)	941 (78.8)	.114
Cardiac arrest						
Yes	59 (1.3)	10 (1.2)		22 (3.2)	58 (4.9)	
No	4,490 (98.7)	839 (98.8)	.777	661 (96.8)	1,136 (95.1)	.091
Vital status (alive)						
Yes	3,614 (79.5)	608 (71.6)		338 (49.5)	468 (39.2)	
No	935 (20.6)	241 (28.4)	< .001	345 (50.5)	726 (60.8)	< .001

NOTE. Data are presented as No. (%).

Abbreviations: NH, non-Hispanic; NOS, not otherwise specified; PI, Pacific Islander; SES, socioeconomic status.

[a]Limited to patients diagnosed from 1996-2014 (n = 5,881).

subtype, and comorbidities.[21] We then used inverse probability weighting in the multivariable Cox regression models to estimate the associations between location of care with overall and leukemia-specific survival.

Patients ages 0-18 and 19-39 years were evaluated in separate models. For deceased patients, survival time was measured in days from the date of diagnosis to the date of death from any cause for overall survival and to the date of death from leukemia for leukemia-specific survival. Patients who died of other causes were censored at the time of death in analyses of leukemia-specific survival. Patients alive at the study end date (December 31, 2014) were censored at this time or at the date of last known follow-up. Multivariable regression models included variables significantly associated with the outcome in univariate models (eg, age, race/ethnicity, neighborhood SES, comorbidity, year of diagnosis, and health insurance) or with a priori hypotheses for inclusion (eg, transplantation, second cancer, complication, and location of care). In all survival models, the proportional hazards assumption was assessed numerically on the basis of cumulative sums of Martingale residuals and visually on the basis of inspection of the survival curves (log [−log] of the survival distribution function by log [months]); variables that violated this assumption were included as stratifying variables to allow for differing baseline hazards associated with these variables (age in the children and leukemia subtype in the YAs). Complications, second cancer, and transplantation were included as time-dependent covariates. Sensitivity analyses were performed removing both patients with second malignancy and those who underwent transplantation separately. Results are presented as hazard ratios (HRs) and 95% CIs. In addition, multivariable logistic regression models were used to determine factors associated with having any complication. Results are presented as odds ratio (OR) and corresponding CI. Statistical analyses were performed using SAS statistical software (version 9.4; SAS Institute, Cary, NC), and a 2-sided P value $< .05$ was considered statistically significant.

TABLE 2. Multivariable Logistic Regression Model of Factors Associated With Having Any Complication Within 3 Years From Diagnosis Among Hospitalized Children and Young Adults With Acute Lymphoblastic Leukemia

Variable	0-18 Years	19-39 Years
Age, years		
0-4	Reference	
5-9	0.80 (0.70 to 0.92)	
10-14	**1.45 (1.23 to 1.70)**	
15-18	**1.71 (1.42 to 2.04)**	
19-24		Reference
25-29		1.11 (0.84 to 1.46)
30-34		**1.44 (1.07 to 1.93)**
35-39		**1.55 (1.14 to 2.09)**
Sex		
Male	Reference	Reference
Female	1.10 (0.98 to 1.23)	1.01 (0.81 to 1.27)
Race/ethnicity		
NH White	Reference	Reference
Asian/PI	1.12 (0.91 to 1.39)	1.25 (0.86 to 1.80)
Hispanic	**1.22 (1.07 to 1.39)**	**1.42 (1.11 to 1.82)**
NH AA	1.15 (0.88 to 1.51)	1.75 (0.99 to 3.10)
Neighborhood SES		
Low SES	Reference	Reference
High SES	**0.81 (0.71 to 0.93)**	0.92 (0.73 to 1.17)
Year of diagnosis		
1991-1996	Reference	Reference
1997-2002	0.99 (0.85 to 1.15)	1.04 (0.76 to 1.41)
2003-2008	0.99 (0.85 to 1.16)	**1.54 (1.10 to 2.15)**
2009-2014	**0.76 (0.63 to 0.92)**	0.90 (0.65 to 1.25)
Subtype		
B cell	Reference	Reference
T cell	**1.32 (1.10 to 1.57)**	0.85 (0.66 to 1.09)
NOS	1.07 (0.93 to 1.23)	0.91 (0.65 to 1.28)
Comorbidity		
Yes	**1.52 (1.36 to 1.70)**	**1.56 (1.26 to 1.95)**
No	Reference	Reference
Care at SCC		
All	Reference	Reference
Part/none	1.05 (0.90 to 1.23)	1.06 (0.85 to 1.32)
Health insurance[a]		
Private/military	Reference	Reference
Public/none	1.07 (0.94 to 1.22)	**1.38 (1.07 to 1.78)**

NOTE. Data are presented as odds ratio (95% CI).

Abbreviations: AA, African American; NH, non-Hispanic; NOS, not otherwise specified; PI, Pacific Islander; SCC, specialized cancer center; SES, socioeconomic status.

[a]Health insurance variable available from 1996-2014.

Cost Analysis

OSHPD includes total charges for each admission and hospital-level financial information from 1995 forward; these were used to calculate the cost (adjusted for inflation to 2016 dollars) for each admission,[22] excluding peripartum and traumatic accident related. One health maintenance organization system in California (that includes both SCCs and non-SCCs) does not report charges to OSHPD and was excluded from the cost analysis (13% of patients). In addition, patients were required to have at least 3 years of follow-up from diagnosis and at least 80% of charge data available to be included in the main analysis (n = 5,167). We compared mean and median costs of admissions overall and per day and number of inpatient days by age group and location of care using *t* tests and Kruskal-Wallis tests. We conducted sensitivity analyses (1) limiting our analyses to only patients with all charge data available (n = 5,118), and (2) excluding patients with transplantation (n = 693) to determine the impact of these factors on the results.

RESULTS

Patient Characteristics and Location of Care

There were 7,275 patients with newly diagnosed ALL included in our study (Table 1). Eighty-four percent of children and 36.4% of YAs received all care at an SCC. The only significant difference observed in complications by location of care was incidence of thrombosis among children (all care at SCC, 0.9% *v* part/none, 1.7%; $P = .039$); this difference was not seen in YAs.

Factors Associated With Location of Care

In children, those of Hispanic race/ethnicity (*v* non-Hispanic white), diagnosed more recently, and with public/no insurance (*v* private insurance) were more likely to receive all inpatient care at an SCC (Appendix Table A1, online only). YAs with public/no insurance also were more likely to receive all inpatient care at an SCC. Older pediatric patients (15-18 *v* 0-4 years) and YAs of Hispanic and African American race/ethnicity were less likely to receive all care at an SCC. This analysis was used to construct a propensity score for receiving care at an SCC. The median and spread of propensity scores in each group were nearly identical, indicating that the covariates used to estimate propensity have a similar distribution.

Factors Associated With Complications

In children and YA patients, the odds of having a complication did not differ by location of inpatient care. However, we observed that the odds of having a complication were higher among those who were older and of Hispanic race/ethnicity (*v* non-Hispanic white; Table 2). The OR of a complication was also higher among YAs with public/no insurance (OR, 1.38; 95% CI, 1.07 to 1.78).

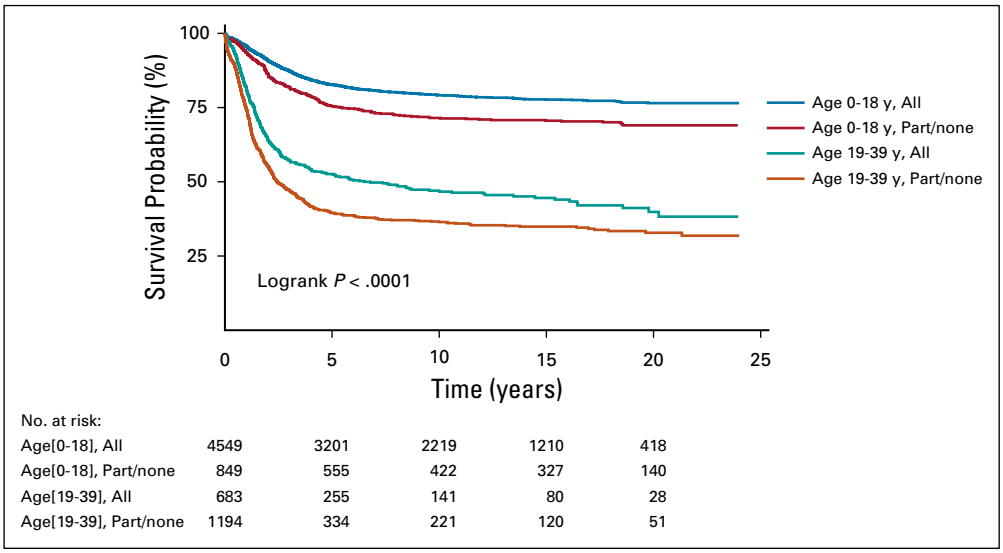

FIG 1. Kaplan-Meier analysis of overall survival in children and young adults with acute lymphoblastic leukemia hospitalized within 3 years of diagnosis by age at diagnosis and location of inpatient treatment, California 1991-2014.

Factors Associated With Long-Term Survival

Over a median follow-up time of 7.5 years (interquartile range, 2.2-14.7 years), overall survival was 78.9% for children and 45.7% for YAs. Survival differed by location of inpatient care (children: all treatment at SCCs, 80% *v* part/none, 72.3%; *P* value < .001; YAs: all treatment at SCCs, 51.4% *v* part/none, 41.6%; *P* value < .001; Fig 1).

In children, receiving all care from an SCC was associated with significantly better leukemia-specific (HR, 0.79; 95% CI, 0.69 to 0.90 *v* part/none) and overall survival (HR, 0.87; 95% CI, 0.78 to 0.98; Table 3, Model 1). This association was similar after the addition of complications (any *v* none) to the model (Table 3, Model 2). Children of Asian/Pacific Islander (HR, 1.35; 95% CI, 1.04 to 1.77 *v* non-Hispanic white) or Hispanic race/ethnicity (HR, 1.58; 95% CI, 1.32 to 1.88) experienced worse leukemia-specific survival, as did patients who had public or no health insurance (HR, 1.30; 95% CI, 1.11 to 1.53 *v* private insurance). Associations were similar for overall survival, except that African American patients also had worse overall survival (HR, 1.50; 95% CI, 1.14 to 1.98).

In YAs, receiving all inpatient care at an SCC was associated with improved leukemia-specific (HR, 0.71; 95% CI, 0.61 to 0.83) and overall survival (HR, 0.72; 95% CI, 0.63 to 0.81; Table 4, Model 1). Results were similar with the addition of complications in the model (Table 4, Model 2). In addition, YAs of Hispanic race/ethnicity (HR, 1.38; 95% CI, 1.14 to 1.65) and had public/no health insurance (HR, 1.34; 95% CI, 1.12 to 1.61) experienced worse leukemia-specific survival (Table 4, Model 1). Similar associations were observed for overall survival (Table 4). There was no significant difference in outcomes in the sensitivity analyses removing patient with second malignancies and transplantations separately (data not shown).

Cost by Age and Location of Care

Average hospitalization costs ($360,921 *v* $214,119) and number of inpatient days (100 *v* 70 days) were higher among YAs than children with ALL, respectively (data not shown). In addition, overall and per-day costs varied by location of care, with substantially higher costs for both children and YA patients receiving all their care at SCCs (Table 5). The number of inpatient days was similar for children and YA patients treated at SCCs and non-SCCs. In the sensitivity analyses excluding patients receiving transplantation, the mean cost was lower at both SCCs and non-SCCs, but the differences in costs in children and YAs by location of care remained (data not shown). In addition, results were similar when analyses were limited to patients with complete charge data (data not shown).

DISCUSSION

In this large California population-based cohort of children and YA patients with ALL, we found superior leukemia-specific and overall survival for children and YA patients who received all inpatient ALL care at an SCC. Complication incidence was similar by location of care, and hospitalization costs were statistically significantly higher for patients receiving all treatment at an SCC. These data suggest that SCCs may be better at management of complications and continuing potentially curative therapy. If so, either treating all children and YA patients with ALL at SCCs or dissemination of knowledge and skills to manage treatment of ALL and complications more broadly might improve overall outcomes.

Our findings add to the growing body of literature supporting the conclusion that treatment at SCCs is important for improving ALL outcomes in YAs. This study demonstrated improved survival throughout the typical duration of therapy for patients treated at SCCs with primary ALL.

TABLE 3. Inverse Probability–Weighted Models of Characteristics Associated With Leukemia-Specific and Overall Survival Among Hospitalized Children (0-18 years) With Acute Lymphoblastic Leukemia

	Leukemia Specific		Overall	
Variable	**Model 1**	**Model 2**	**Model 1**	**Model 2**
Sex				
Male	Reference	Reference	Reference	Reference
Female	0.69 (0.59 to 0.80)	0.65 (0.56 to 0.76)	0.69 (0.61 to 0.78)	0.67 (0.59 to 0.75)
Race/ethnicity				
NH White	Reference	Reference	Reference	Reference
Asian/PI	1.35 (1.04 to 1.77)	1.33 (1.01 to 1.73)	1.29 (1.03 to 1.60)	1.27 (1.02 to 1.58)
Hispanic	1.58 (1.32 to 1.88)	1.47 (1.23 to 1.75)	1.45 (1.25 to 1.68)	1.35 (1.16 to 1.56)
NH AA	1.36 (0.95 to 1.95)	1.28 (0.89 to 1.84)	1.50 (1.14 to 1.98)	1.43 (1.08 to 1.88)
Neighborhood SES				
Low SES	Reference	Reference	Reference	Reference
High SES	0.95 (0.80 to 1.12)	1.06 (0.89 to 1.26)	0.93 (0.81 to 1.07)	1.03 (0.89 to 1.19)
Year of diagnosis				
1991-1996	Reference	Reference	Reference	Reference
1997-2002	0.90 (0.76 to 1.07)	0.84 (0.71 to 1.00)	0.83 (0.72 to 0.96)	0.79 (0.68 to 0.91)
2003-2008	0.54 (0.44 to 0.65)	0.51 (0.42 to 0.62)	0.50 (0.43 to 0.59)	0.48 (0.40 to 0.56)
2009-2014	0.49 (0.37 to 0.64)	0.46 (0.35 to 0.61)	0.39 (0.30 to 0.49)	0.37 (0.29 to 0.48)
Transplantation[a]				
Yes	6.91 (5.77 to 8.28)	6.16 (5.15 to 7.38)	6.05 (5.16 to 7.10)	5.47 (4.67 to 6.40)
No	Reference	Reference	Reference	Reference
Comorbidity[a]				
Yes	1.35 (1.17 to 1.55)	1.19 (1.03 to 1.37)	1.29 (1.15 to 1.45)	1.14 (1.01 to 1.29)
No	Reference	Reference	Reference	Reference
Second cancer[a]				
Yes	1.89 (0.83 to 4.31)	1.72 (0.75 to 3.93)	8.50 (5.77 to 12.53)	7.72 (5.23 to 11.40)
No	Reference	Reference	Reference	Reference
Complications[a]				
Yes		5.14 (4.32 to 6.12)		4.65 (4.03 to 5.37)
No		Reference		Reference
Care at SCC				
Partial/none	Reference	Reference	Reference	Reference
Always	0.79 (0.69 to 0.90)	0.77 (0.67 to 0.89)	0.87 (0.78 to 0.98)	0.87 (0.77 to 0.97)
Health insurance[b]				
Private/military	Reference	Reference	Reference	Reference
Public/none	1.30 (1.11 to 1.53)	1.28 (1.09 to 1.51)	1.22 (1.06 to 1.40)	1.18 (1.02 to 1.36)

NOTE. Data are presented as hazard ratio (95% CI). Models are stratified by 5-year age group. Model 1: Without complication in the model. Model 2: With complication in the model.

Abbreviations: AA, African American; NH, non-Hispanic; NOS, not otherwise specified; PI, Pacific Islander; SCC, specialized cancer center; SES, socioeconomic status.

[a]Transplantation, second cancer, and complications are time-dependent variables.

[b]Limited to patients diagnosed from 1996-2014 (n = 5,881).

These findings are supported by previous work demonstrating reductions in early mortality in children and AYAs with leukemia on the basis of initial location of care.[12,23] In addition, the results are similar to a prior study in Los Angeles County that found improved survival for AYA patients receiving all initial care at NCI-CCCs.[13] However, our study also identified that there are disparities in receiving care at SCCs in California, with older patients and those of

TABLE 4. Inverse Probability–Weighted Models of Characteristics Associated With Leukemia-Specific and Overall Survival Among Hospitalized Young Adult Patients With Acute Lymphoblastic Leukemia

	Leukemia Specific		Overall	
Variable	**Model 1**	**Model 2**	**Model 1**	**Model 2**
Age, years				
19-24	Reference	Reference	Reference	Reference
25-29	1.02 (0.82 to 1.27)	1.04 (0.84 to 1.30)	1.18 (1.00 to 1.41)	1.22 (1.03 to 1.45)
30-34	1.28 (1.04 to 1.58)	1.17 (0.95 to 1.44)	1.32 (1.11 to 1.57)	1.20 (1.01 to 1.42)
35-39	1.52 (1.24 to 1.86)	1.36 (1.11 to 1.67)	1.50 (1.27 to 1.78)	1.34 (1.13 to 1.59)
Sex				
Male	Reference	Reference	Reference	Reference
Female	0.85 (0.73 to 1.00)	0.89 (0.76 to 1.05)	0.82 (0.72 to 0.94)	0.84 (0.74 to 0.96)
Race/ethnicity				
NH White	Reference	Reference	Reference	Reference
Asian/PI	1.08 (0.81 to 1.45)	1.05 (0.79 to 1.41)	1.03 (0.81 to 1.30)	1.01 (0.80 to 1.29)
Hispanic	1.38 (1.14 to 1.65)	1.38 (1.14 to 1.66)	1.32 (1.13 to 1.53)	1.33 (1.14 to 1.54)
NH AA	0.84 (0.52 to 1.34)	0.77 (0.48 to 1.24)	1.24 (0.91 to 1.70)	1.20 (0.88 to 1.65)
Neighborhood SES				
Low SES	Reference	Reference	Reference	Reference
High SES	0.80 (0.67 to 0.96)	0.78 (0.65 to 0.93)	0.77 (0.66 to 0.89)	0.75 (0.65 to 0.86)
Transplantation[a]				
Yes	1.88 (1.57 to 2.24)	1.68 (1.40 to 2.01)	1.78 (1.54 to 2.07)	1.62 (1.39 to 1.88)
No	Reference	Reference	Reference	Reference
Comorbidity[a]				
Yes	1.41 (1.19 to 1.66)	1.26 (1.07 to 1.49)	1.23 (1.08 to 1.40)	1.08 (0.95 to 1.24)
No	Reference	Reference	Reference	Reference
Second cancer[a]				
Yes	2.45 (1.27 to 4.72)	2.26 (1.17 to 4.39)	3.08 (1.94 to 4.90)	3.09 (1.94 to 4.91)
No	Reference	Reference	Reference	Reference
Complication[a]				
Yes		6.30 (4.95 to 8.01)		6.37 (5.24 to 7.74)
No		Reference		Reference
Care at SCC				
Partial/none	Reference	Reference	Reference	Reference
Always	0.71 (0.61 to 0.83)	0.71 (0.61 to 0.83)	0.72 (0.63 to 0.81)	0.70 (0.62 to 0.80)
Health insurance[b]				
Private/military	Reference	Reference	Reference	Reference
Public/none	1.34 (1.12 to 1.61)	1.24 (1.03 to 1.49)	1.35 (1.16 to 1.57)	1.23 (1.06 to 1.44)

NOTE. Data are presented as hazard ratio (95% CI). Models are stratified by year and subtype. Model 1: Without complication in the model. Model 2: With complication in the model.

Abbreviations: AA, African American; NH, non-Hispanic; NOS, not otherwise specified; PI, Pacific Islander; SCC, specialized cancer center; SES, socioeconomic status.

[a]Transplantation, Second Cancer, and Complication are time-dependent variables.

[b]Limited to patients diagnosed from 1996-2014 (n = 5,881).

African American and Hispanic race/ethnicity less likely to receive all care at an SCC. In addition, even after adjusting for location of care, we found that children of Asian/Pacific Islander, Hispanic, and African American race/ethnicity and YAs of Hispanic race/ethnicity continued to have poor survival compared with non-Hispanic white patients, in keeping with previous reports.[5,24,25] Disparities in outcomes were also identified for patients with public/no health

TABLE 5. Hospitalization Cost and Days by Age and Location of Care in Children and Young Adults Diagnosed With Acute Lymphoblastic Leukemia

Age	Care at SCC	Mean Cost	STD	Median Cost	IQR	Mean Cost per Day	STD	Median Cost per Day	IQR	Mean Hospitalization Days	STD	Median Hospitalization Days	IQR
Children (0-18 years)	All	216,439	282,175	121,039	65,949-249,703	2,840	1,317	2,529	2,011-3,386	70	63	50	29-90
	Part/none	191,082	302,072	84,529	37,520-217,339	2,283	1,342	1,865	1,408-2,947	72	73	47	22-98
	P	.008		< .001		< .001		< .001		.703		.135	
Young adults (19-39 years)	All	380,556	294,759	308,864	166,592-508,116	3,730	1,361	3,537	2,707-4,586	99	62	87	52-131
	Part/none	346,706	356,451	241,847	100,933-454,311	3,224	1,523	2,917	2,209-3,946	101	79	87	41-138
	P	.016		< .001		< .001		< .001		.968		.128	

Abbreviations: IQR, interquartile range (25%–75%); SCC, specialized cancer center; STD, standard deviation.

insurance, indicating that lack of insurance access and coverage can negatively affect outcomes for patients. Our previous study found that African American and Hispanic young adults with cancer were less likely to have private insurance, which may potentially affect the poor outcomes noted in these patients in these populations.[26] Given the impact that care at an SCC may have on leukemia survival, additional research should explore how to improve access for these groups of patients.

Superior outcomes at SCCs are believed to relate to the expertise of delivering complex care, differences in treatment regimens, or increased access to clinical trials at these institutions.[12,15] Although we were not able to investigate these factors, we were able to consider whether differences in survival outcomes by location of care were due to complications. Despite complications being associated with worse survival, we found similar rates of complications by location of care. Although we hypothesized that complications would differ by location of care, our findings suggest that other factors are contributing to the survival differences and need to be the focus of future research. However, we did observe that the likelihood of complications increased with age, which may be due to the more intense therapy they receive compared with younger patients. There are data to suggest that adolescent patients have worse symptoms when compared with younger patients.[27,28] In addition, the likelihood of complications was also higher among Hispanics and YAs with public/no insurance, the etiology of which is unclear; identifying ways to prevent and mitigate the negative impact of complications in these patients is an important area of future research.

Although location of care may influence survival outcomes, there are potential cost implications associated with care at SCCs. Adult medicine and hematology/oncology have incorporated the financial cost of health care into treatment delivery models and recommendations, but pediatric hematology/oncology has been slower to adopt this. Literature demonstrating differences in cost by location of inpatient treatment is lacking in young patients.[29,30] This study demonstrates that hospitalization costs and number of inpatient days were higher among YAs than children, and hospitalization costs were higher in those receiving all care at SCCs. The reason for the cost difference is not clear but may be related to patients at SCCs having more complicated treatment courses requiring further interventions or the known increased cost structure associated with academic health centers, factors we could not directly assess in this study. Because inpatient costs do not reflect the total burden associated with cancer care, future studies should consider how location of care affects outpatient, emergency department, and out-of-pocket costs to have a more comprehensive overall cost picture.

Our study was limited by the lack of information on treatment regimens. In addition, we did not have details on important laboratory prognostic factors to consider in our propensity scores and survival analyses. As a result, there is likely to be some residual confounding factors resulting from unmeasured covariates (selection bias) among patients treated at SCCs versus non-SCCs. However, it is unlikely that the differences in measured baseline characteristics after using propensity score–weighted models solely account for the differences in outcomes. The use of the propensity score reduced the standardized mean differences to $< 10\%$ for most variables, and the survival benefit associated with receiving care at SCCs persisted. In addition, although hospitalizations account for a large share of health care spending in the United States,[31] we were unable to include other costs incurred by individuals and the health care system (eg, outpatient costs) to more fully capture cost differences by location of care. Despite these limitations, this linked database allows for population-level analysis of sociodemographic and clinical factors affecting survival that have not been previously described.

Overall, our findings add to existing knowledge regarding the optimal location of treatment of children and AYAs with ALL, which can help inform referral patterns and insurance policy coverage. Our study demonstrates that treatment at an SCC throughout therapy is associated with better survival in children and YA patients with ALL. However, access to care at an SCC does not appear uniform, with YAs and those of African American and Hispanic race/ethnicity less likely to receive all care at an SCC. Given the associated improvement in survival seen with patients treated at an SCC, our findings support the clinical recommendation that children and YA patients with this complex and relatively rare diagnosis be referred to and treated at SCCs. Policy recommendations would need to consider more fully the potential additional costs and health care access issues associated with this recommendation that could affect health disparities. Because treatment at an SCC may not be feasible for all patients, future research and interventions should also identify ways to improve care for these patients through knowledge dissemination, telemedicine, or outreach clinics.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Treatment Complications and Survival Among Children and Young Adults With Acute Lymphoblastic Leukemia

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APPENDIX

TABLE A1. Adjusted Logistic Regression Model of Factors Associated With Receiving All Care at a Specialized Cancer Center (*v* partial or no care) Within 3 Years From Diagnosis Among Hospitalized Pediatric, Adolescent, and Young Adult Patients With Acute Lymphoblastic Leukemia

Variable	0-18 Years Old	19-39 Years Old
Age, years		
0-4	Reference	
5-9	0.99 (0.81 to 1.21)	
10-14	0.86 (0.69 to 1.07)	
15-18	0.37 (0.30 to 0.46)	
19-24		Reference
25-29		0.85 (0.65 to 1.09)
30-34		0.77 (0.59 to 1.00)
35-39		0.82 (0.63 to 1.07)
Sex		
Male	Reference	Reference
Female	0.99 (0.85 to 1.15)	0.95 (0.78 to 1.16)
Race/ethnicity		
NH White	Reference	Reference
Asian/PI	0.76 (0.59 to 0.99)	1.09 (0.79 to 1.51)
Hispanic	1.53 (1.28 to 1.84)	0.65 (0.52 to 0.81)
NH AA	0.97 (0.69 to 1.37)	0.41 (0.24 to 0.71)
Neighborhood SES		
Low SES	Reference	Reference
High SES	0.85 (0.71 to 1.02)	0.85 (0.68 to 1.06)
Year of diagnosis		
1991-1996	Reference	Reference
1997-2002	2.07 (1.71 to 2.51)	0.80 (0.60 to 1.08)
2003-2008	2.91 (2.35 to 3.61)	0.94 (0.70 to 1.26)
2009-2014	2.16 (1.69 to 2.77)	0.92 (0.68 to 1.24)
Subtype		
B cell	Reference	Reference
T cell	1.07 (0.85 to 1.35)	0.88 (0.69 to 1.11)
NOS	1.16 (0.96 to 1.40)	0.68 (0.49 to 0.93)
Comorbidity		
Yes	1.00 (0.85 to 1.17)	0.90 (0.73 to 1.10)
No	Reference	Reference
Health Insurance[a]		
Private	Reference	Reference
Public/none	2.44 (1.98 to 3.02)	1.59 (1.27 to 2.00)

NOTE. Data are presented as odds ratio (95% CI).

[a]Health insurance variable available from 1996-2014.

Abbreviations: AA, African American; NH, non-Hispanic; NOS, not otherwise specified; PI, Pacific Islander; SES, socioeconomic status.