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Risk of hospitalization among survivors of childhood and adolescent acute lymphoblastic leukemia compared to siblings and a general population sample

Judy Y. Ou^{a,b,*}, Rochelle R. Smits-Seemann^c, Sapna Kaul^d, Mark N. Fluchel^{a,e}, Carol Sweeney^{a,f}, Anne C. Kirchhoff^{a,b}

^aCancer Control and Population Sciences, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT 84112, United States

^bDepartment of Pediatrics, Division of Pediatric Hematology/Oncology, University of Utah School of Medicine, Salt Lake City, UT 84113, United States

^cDepartment of Institutional Research and Reporting, Salt Lake Community College, Salt Lake City, UT 84123, United States

^dDepartment of Preventive Medicine and Community Health, University of Texas Medical Branch, Galveston, TX 77555, United States

^eDepartment of Pediatric Hematology/Oncology, Salt Lake City Primary Children's Hospital, UT 84132, United States

^fDivision of Epidemiology, Department of Medicine, University of Utah School of Medicine, Salt Lake City, UT 84132, United States

Abstract

Background: Acute Lymphoblastic Leukemia (ALL) has a high survival rate, but cancer-related late effects in the early post-treatment years need documentation. Hospitalizations are an indicator of the burden of late effects. We identify rates and risk factors for hospitalization from five to ten years after diagnosis for childhood and adolescent ALL survivors compared to siblings and a matched population sample.

Methods: 176 ALL survivors were diagnosed at 22 years between 1998 and 2008 and treated at an Intermountain Healthcare facility. The Utah Population Database identified siblings, an age- and sex-matched sample of the Utah population, and statewide inpatient hospital discharges. Sex-

*Corresponding author at: 2000 Circle of Hope Dr. 4126W, Salt Lake City, UT 84112, United States. Judy.ou@hci.utah.edu (J.Y. Ou).
Authorship contribution statement

Judy Y. Ou is the first author, conceptualized the aims of the paper and the analysis plan, completed the majority of the analyses, and writing of the manuscript.

Rochelle R. Smits-Seemann and Sapna Kaul organized the dataset, created the variables used in the analysis, contributed to the writing of the methods section, and helped edit the manuscript.

Mark N. Fluchel provided clinical guidance with the writing of the manuscript, and contributed to the discussion section of the paper. Carol Sweeney played a key role in the design of the study and assembly of the dataset.

Anne C. Kirchhoff is the principal investigator on the project, helped to direct the analyses, and contributed heavily to the text and editing of the manuscript.

Conflict of interest

The authors report no conflicts of interest.

and birth year-adjusted Poisson models with Generalized Estimating Equations and robust standard errors calculated rates and rate ratios. Cox proportional hazards models identified demographic and clinical risk factors for hospitalizations among survivors.

Results: Hospitalization rates for survivors (Rate:3.76, 95% CI = 2.22–6.36) were higher than siblings (Rate:2.69, 95% CI = 1.01–7.18) and the population sample (Rate:1.87, 95% CI = 1.13–3.09). Compared to siblings and population comparisons, rate ratios (RR) were significantly higher for survivors diagnosed between age 6 and 22 years (RR:2.87, 95% CI = 1.03–7.97 vs siblings; RR:2.66, 95% CI = 1.17–6.04 vs population comparisons). Rate ratios for diagnosis between 2004 and 2008 were significantly higher compared to the population sample (RR:4.29, 95% CI = 1.49, 12.32), but not siblings (RR:2.73, 95% CI = 0.54, 13.68). Survivors originally diagnosed with high-risk ALL did not have a significantly higher risk than siblings or population comparators. However, high-risk ALL survivors (Hazard ratio [HR]:3.36, 95% CI = 1.33–8.45) and survivors diagnosed from 2004 to 2008 (HR:9.48, 95% CI = 1.93–46.59) had the highest risk compared to their survivor counterparts.

Conclusions: Five to ten years after diagnosis is a sensitive time period for hospitalizations in the ALL population. Survivors of childhood ALL require better long-term surveillance.

Keywords

Survivors; Health services research; Epidemiologic research designs; Siblings

1. Introduction

Although 95% of acute lymphoblastic leukemia (ALL) patients diagnosed in childhood attain remission [1,2], long-term survivors are at risk for chronic conditions, called late effects, due to chemotherapy and radiation used during cancer treatment [3-5]. Hospitalizations are an indicator of the potential severity and type of late effects among cancer survivors. Although risk for hospitalization among survivors increases with age [6], the initial years after therapy may be a critical window as a report on childhood cancer survivors found high hospital utilization and costs among survivors during the first 10 years after diagnosis [7]. Investigations of hospitalizations during the initial years after therapy ends can help patients, families, and clinicians have appropriate expectations about health risks for survivors and manage health-related problems while survivors are still children.

Previous studies reporting the risk for morbidity and mortality, including hospitalizations, among survivors of childhood cancer use different methodologies, which yield varying results. Some studies use hospital records and a sample of the general population [3,8], while others rely on the use of self-reported events and siblings as a comparison group [9-11]. Using siblings as a comparison group is an acknowledged method of reducing confounding from unmeasured genetic and socioeconomic differences [12], but the benefits of using siblings as a comparison group is debated because the reduction of bias is limited by the shared confounders among siblings [13]. Studies comparing ALL survivors to a matched population sample using hospital data are consistent in showing that risk for morbidity and mortality is significantly higher among survivors [3,6,8,14,15]. The different comparison groups and methodologies used to report events (self-report vs hospital records)

and confounders could be the source of the varying results. We are unaware of any papers examining how risk estimates for hospitalizations among ALL survivors differ when siblings and a population comparison group are used in the same study, and using a statewide hospital discharge database.

We quantify the rate of hospitalizations among a sample of childhood ALL survivors from five to ten years after diagnosis and compare the risk of hospitalization among survivors to two groups: siblings and a matched population sample. We also identify demographic and clinical risk factors among survivors that increase their vulnerability to hospitalization. We hypothesize that characteristics such as diagnosis at younger age and high risk disease group at diagnosis would confer higher risk for hospitalizations in the first five to ten years after diagnosis [16].

2. Materials and methods

2.1. Data collection

This project reflects a partnership between the University of Utah and Intermountain Healthcare (IH). The Institutional Review Boards of IH and the University of Utah approved this study. IH is a Utah-based health system that includes Primary Children's Hospital (PCH) in Salt Lake City. Because PCH is the only pediatric oncology center in a five-state region that includes Utah, the vast majority of childhood cancer patients diagnosed under the age of 15 in Utah are treated at PCH [17]. Cancer patients ages 15 and older at diagnosis tend to receive care at other cancer centers. However, as many older adolescent leukemia patients (ages 15–22) are seen at PCH, we included this age range for the analysis. IH maintains an enterprise data warehouse (EDW) that integrates data from electronic medical records across IH facilities, and contains a hospital tumor registry that meets American College of Surgeons accreditation standards. We obtained gender, birthdate, diagnosis date, age at diagnosis, white blood cell count at diagnosis, ALL immunophenotype at diagnosis, treatment (e.g. chemotherapy, radiation), and relapses from the EDW.

IH clinical data were linked with the Utah Population Database (UPDB). The UPDB contains linkages between birth and death certificates, drivers' licenses, voter registration records, and family pedigrees for all people during their residence in Utah [7,18]. This linkage allows UPDB to identify siblings with high reliability, generate a population sample, and enables linkages between inpatient hospitalization discharge records maintained by the Utah Department of Health and UPDB-based demographic, vital statistics, and health records [19]. Siblings were identified by linking birth records from subjects with the same mother.

2.2. Subject sampling and eligibility

This study is subset of a larger cohort of childhood cancer patients and survivors [7,18]. We identified 315 ALL patients diagnosed at age 22 years or younger between January 1, 1998 and December 31, 2008, who received any cancer treatment at PCH and had a Utah birth certificate. Cancer patients were matched at diagnosis date in a 1:3 ratio by sex and year of birth to a population sample. This matching was incorporated in all analyses. The population

sample needed a Utah birth certificate, lived in Utah up until their index case's diagnosis date, and could not have a cancer history. All patient siblings with Utah birth certificates were identified by UPDB.

2.3. Exclusion criteria

We defined survivors as patients who were living five years after the first diagnosis date as identified by vital records from the UPDB, a proxy for the end of the ALL treatment [6,18]. We excluded 43 cancer patients who were deceased within five years of diagnosis, and 49 relapsed patients. Survivors who were not identified by UPDB records ($n = 33$) and whose UPDB records indicated that they did not live in Utah five years after diagnosis were excluded ($n = 14$).

Matched population subjects and siblings whose index case did not meet these birth certificate, survivorship, and residency criteria were removed. The remaining population sample to survivor ratio retained a value of 2.9:1.

2.4. Participant follow-up

Follow-up for survivors began five years after the original diagnosis date [10]. Follow-up for the Utah-based population sample began five years after their matched survivor's cancer diagnosis date; follow-up for siblings began when siblings turned the same age as the survivor was five years after diagnosis. Siblings and the population sample were the same age as their index case at enrollment. Subjects were followed until 10 years post-diagnosis, death, emigration out of Utah, or the end of our cohort on December 31, 2013.

2.5. Hospitalization outcomes

Acute-care inpatient hospitalization discharge records were obtained from the Utah Department of Health. Records were dated January 1, 1998 to December 31, 2013, and included the primary ICD-9 diagnosis code and admission date. We omitted hospitalizations that occurred before the start of follow-up and pregnancy-related admissions [7]. Hospitalizations were categorized by their primary ICD-9 chapter: musculoskeletal, digestive, circulatory, mental health, injuries, congenital, secondary neoplasms, nervous system, skin, perinatal, infection, genitourinary, endocrine/metabolic conditions, and respiratory. We also included admissions that were labeled "Supplemental factors," which is an ICD-9 chapter that includes chemotherapy for a second cancer that is not related to ALL or relapses, bacteremia separate from general infections, and fever.

2.6. Demographic and clinical factors

UPDB provided birth year, age, sex, and rural or urban area of residence at birth, which were identified by classifying ZIP codes based on 2010 Rural Urban Commuting Area Codes [20]. ZIP codes that were not included in the 2010 codes were categorized as urban using manual map analysis. Missing values were either invalid or an international zip code. Hispanic ethnicity was determined using a two-step surname matching process [21].

We obtained clinical characteristics from IH's EDW. ALL risk groups included standard risk ALL patients aged 1 and 10 years at diagnosis with a white blood cell (WBC) count of

<50,000/ μ L. High risk ALL patients were assigned if their diagnosis fulfilled one of the following National Cancer Institute criteria: diagnosis at age <1 or >10 years, WBC count 50,000 cells/ μ L, or T-cell phenotype [16,22]. We grouped survivors based on their year of diagnosis: 1998 to 2003, and 2004 to 2008 as a proxy for changes in ALL treatment protocol over time [23]. We identified survivors who received chemotherapy only, and survivors who received chemotherapy in addition to bone marrow transplant and/or radiation treatment.

2.7. Statistical analyses

We compared means and frequencies of hospitalizations and demographic characteristics using Kruskal Wallis, Chi-square tests, and their respective two-sided P-values of 0.05 or less. Hospitalization rates per 100-person years, rate ratios, and confidence intervals adjusted for sex and birth year were calculated with Poisson regression models offset by the log of person-years. We also calculated the rate for each year of follow-up by group. Clustering between matched population subjects and survivors, and between siblings and survivors was accounted for using Generalized Estimating Equations with robust standard errors in the same Poisson model. Rates and ratios compared survivors to siblings, and survivors to the population sample separately. Survivors without siblings were removed for the rate ratio analyses ($n = 52$).

Repeated events survival analysis using Cox proportional hazards models identified risk factors for all documented hospitalizations among survivors. Prior to this, Kaplan-Meier curves were used to check model assumptions. Since survivors had multiple hospitalizations, we tested a model assuming that events were independent from each other, and a model that assumed that hospitalizations were correlated with each other (conditional). Although the models yielded similar results, the conditional model was used because the Akaike information criterion indicated it was the best fit [24]. We used Sandwich variance estimator to account for multiple hospitalizations per participant. Individual and multivariable models were adjusted for birth year and sex. The analysis among survivors was intended to identify explanatory factors, and accordingly variables were included in the multivariable model if the effect estimates were non-null. We indicated significant rate ratios (RR) if the corresponding 95% confidence intervals (CI) excluded the null, and indicated significant two-sided P-values at 0.05 or less.

3. Results

Our cohort included 176 survivors, 232 siblings, and 503 subjects in the population sample at the start of the study. Participants were an average age of 11 years at the start of follow-up and average follow-up time was 4 years (Table 1). The proportion of Non-Hispanic to Hispanic survivors and the population sample were similar. There were significantly more Non-Hispanics in the sibling group than survivors (94.4% vs. 88.1%, $P = 0.02$), although the difference no longer remained significant when survivors without siblings were removed from the analysis.

Most survivors were standard risk patients at diagnosis (66.5%) and received chemotherapy alone (90.9%). Approximately half of survivors were diagnosed under five years of age (53%), and between 1998 and 2003 (43.2%).

Nineteen survivors were hospitalized during follow-up, with a total of 25 hospitalizations, compared to 30 for siblings and 35 for the population sample. More survivors had at least one hospitalization during the five years of follow-up, compared with siblings (13.6% vs 10.3%, $P = 0.34$) and the population sample (6.4%, $P < 0.01$).

We calculated the counts of hospitalizations, person-years, and adjusted rates and their confidence intervals (Table 2). The adjusted hospitalization rate for survivors (3.76 per 100 person years) was higher than either comparison sample (siblings: 2.69, population sample: 1.87).

Average follow-up for survivors diagnosed between 1998 and 2003 was 4.7 person-years; the average for survivors diagnosed between 2004 and 2008 was 2.78 person-years. Hospitalization rates for female survivors, Non-Hispanic survivors, and survivors diagnosed between 2004 and 2008 were higher than their comparison samples (Table 2). The time-stratified analysis identified the highest rate of hospitalizations among survivors in the first year of follow-up, which declined every year after initial follow-up (Table 3). This pattern was consistent for all survivors, irrespective of their year of diagnosis.

Adjusted rate ratios were higher among survivors for several factors of interest (Table 4). Overall, risk for hospitalization among survivors was higher than either comparison group, but was not significant when compared to siblings (siblings: RR = 1.53, 95% CI = 0.54, 4.38; population sample: RR = 2.01, 95% CI = 1.00, 4.03). Compared to the population sample, survivors who were Non-Hispanic (RR = 2.39, 95% CI = 1.11, 5.15), diagnosed between 2004 and 2008 (RR = 4.29, 95% CI = 1.49, 12.32), and treated with chemotherapy only (RR = 2.11, 95% CI = 1.01, 4.41) had a significantly higher risk for hospitalization. These associations maintained similar trends when siblings were the comparison group, but the estimates for Non-Hispanics, diagnoses between 2004 and 2008, and treatment were not significant.

The survival analysis identified characteristics among survivors that increased risk for hospitalization (Table 5). In the multivariable model, survivors diagnosed between 2004 and 2008 were 9.48 (95% CI = 1.93, 46.59) times more likely to be hospitalized than survivors diagnosed between 1998 and 2003. For high risk survivors, the risk for hospitalization was more than 3-fold (3.36) higher than that of standard risk patients (95% CI = 1.33, 8.45). Female survivors were twice as likely as male survivors to be hospitalized (HR = 2.11, 95% CI = 0.88–5.02), but the estimate was not significant.

The distribution of hospitalization diagnosis differed by group (Fig. 1). The most common primary diagnosis was the ICD-9 code for “Supplemental factors”, which includes chemotherapy for second cancer (20%), bacteremia, and fever; musculoskeletal (16%), and digestive (16%). For siblings, digestive (27%), musculoskeletal (17%), and circulatory (10%) were the most common primary diagnosis codes. For the population sample, mental health (20%), injury (20%) and respiratory (14%) were the most common primary ICD-9 diagnosis codes. A Fisher’s exact test for the overall distribution of the ICD-9 codes showed significant differences between survivors and the population sample ($P < 0.001$), and between survivors and siblings ($P < 0.001$).

4. Discussion and conclusions

We find elevated rates and risk for hospitalization during the first five to ten years after diagnosis among a cohort of pediatric and adolescent ALL cancer survivors compared to siblings and a population sample. Survivors who are Non-Hispanic, diagnosed between 2004 and 2008, treated with chemotherapy only, and who were born in urban areas are at higher risk for hospitalization. High risk ALL diagnosis classification is significantly associated with a greater risk of hospitalization even after accounting for other clinical factors, which is consistent with a previous study from this cohort [23]. As the highest rates of hospitalizations occurred in the first year of follow-up five years after diagnosis, and the average age of the survivors at the start of follow-up in our study is 11 years, our results show the need for risk-based care to identify and manage emerging health problems for ALL survivors early in the survivorship period while they are still children.

A previous study of ALL cancer survivors reports that the risk for chronic health disorders among survivors compared to siblings is moderate for certain health conditions [11]. Here we report a significantly higher risk for hospitalization among survivors diagnosed between ages 6 to 22 years when compared to siblings. The risk for hospitalization is higher when we compare survivors to the population sample, a trend that is also found in other studies utilizing a population comparison group [3,6,14,15].

Using our study as an example, we can see that in general, the risk estimate for the full sample comparing survivors and the population group is higher than the risk estimate for the full sample that uses the sibling comparison group. The risk estimate for the full sample that uses the population comparison group is statistically significant, while the estimate using the sibling comparisons does not attain statistical significance. These differences may be attributed to several reasons. Risk estimates from paired sibling analyses are less likely to be confounded by shared factors like genetics and family background than a population sample [12]. However, the risk estimates using siblings as a comparison group are more likely to be attenuated due to error in measuring exposure and non-shared confounders than the population comparison [13]. In this study, the attenuation we see in the risk estimates when using the sibling comparison group is not likely to be a result of error in measuring cancer survivorship because we use cancer registry data to identify cancer survivors. Since siblings may be several years older than their index case, one possible explanation for the attenuation in the sibling comparisons is the lack of measurement for non-shared confounders like health insurance or household income, as well as unmeasured physical or mental conditions in the sibling group that could lead to hospitalizations. Although the sibling-pair estimates may be biased by non-shared confounders that we are unable to measure, the risk estimates for the population sample are similar in direction and magnitude to those obtained from the sibling analyses. Thus, the sibling estimates are not likely to be highly biased, but also they do not show significant differences.

Considering these caveats, the attenuation of the estimates in our sibling analysis could imply that the health risks among survivors may be underestimated in sibling studies. Siblings may be more appropriate when confounding factors are shared equally among siblings, and if generalizability of the results is not a concern. For policy purposes related to

evaluating healthcare utilization or other related concerns, using the general population as a comparison group may be more appropriate. We suggest researchers carefully consider their study questions when designing their comparison groups in cancer survivorship studies.

This study defines survivorship starting five years from their first diagnosis date, which is a proxy for the time most ALL patients finished therapy [6] as treatment lasts approximately two years for girls and three years for boys [25]. The high rates and rate ratios we report indicate early survivorship as a sensitive time window for hospitalizations. In our data, the fifth year after diagnosis has the highest hospitalization rate among cancer survivors. This finding is similar to our earlier assessment that reports increased hospital utilization and charges from diagnosis to four to six years postdiagnosis, which then plateaued after six years-post diagnosis [7].

In the multivariable survival analysis, cancer survivors diagnosed between 2004 and 2008 have a 9-fold increased risk for hospitalization than survivors diagnosed between 1998 and 2003 [23]. The increased risk in survivors diagnosed between 2004 and 2008 could reflect changes in provider behaviors regarding hospitalizations for cancer survivors, or other access patterns we are not able to investigate [23]. Although the average length of follow-up in 2004 and 2008 is shorter than 1998 and 2003, this difference in the average length follow-up is unlikely to bias our results as we ran analyses examining rates by year, and did not find evidence of bias by length of follow-up.

In addition, we find that survivors diagnosed with ALL at age 6 and older have a higher rate of hospitalizations than siblings and population comparisons, but this was not the case for survivors diagnosed at age 5 and younger. This may imply that patients diagnosed with ALL at older ages face additional risks and may warrant closer monitoring at the end of therapy.

Hospitalization rates among Hispanic survivors are lower than Hispanics in the population sample and siblings. Since morbidity among Hispanic survivors is comparable with Non-Hispanic White survivors when health conditions are measured by self-report [26], our results may reflect differences in health insurance access and familiarity with the health care system, rather than a lowered risk for hospital-related late effects among Hispanic survivors [27]. While there is literature demonstrating that adult Hispanic patients who are immigrants may return to their home country when diagnosed with a severe illness due to access to care issues [28], we are not aware of studies on whether this pattern could affect children with cancer. Using UPDB for our study gives us the advantage of knowing the last date known in Utah for each study subject and therefore we do not believe our results to be biased by missing hospitalizations for subjects who left the state. Additional follow-up or studies with larger numbers of Hispanic survivors would be of interest to confirm these findings.

Types of hospitalizations among ALL survivors differ from siblings and the population sample. Many observed person-years in this study fall in early adolescence. In this time frame, mental health concerns are the most frequent reason for hospitalization among the population sample. "Supplemental factors" (e.g. secondary cancers and infections), musculoskeletal, and digestive concerns are the reasons for hospitalization most frequently found among survivors. Musculoskeletal morbidity is a concern during ALL treatment, and

our analyses suggest these issues may cause morbidity post-treatment [29]. Finally, existing studies report differences in long-term health outcomes among ALL survivors by sex [6], and we find that female survivors have a higher, non-significant, risk for hospitalization than males. Female survivors more frequently report poorer health status, higher morbidity, and obesity than male survivors [30,31], which may contribute to the elevated risk and warrants future investigation.

We are limited by data from one state, although statewide explorations can provide meaningful clinical insights [7,18]. We also lack information about household income and health insurance status, which could influence their ability to seek care. Ethnicity may be misclassified, but not likely as our estimates reflect the Census distribution of ethnicity in Utah [32], and using Hispanic surname and other health care records has good specificity [33]. We focused our sample on survivors who were at least five years from diagnosis and had not experienced a relapse. These relapsed cases may have more complications posttreatment due to their increased exposure to cancer treatment, but we are unable to determine whether their risk for hospitalization due to late effects is higher or lower than survivors who did not relapse. Finally, PCH is the only pediatric oncology clinic in the state. An earlier report found that 97% of children with cancer aged 0 to 9 years and 82% of children aged 10 and 14 years attend PCH [17]. However, adolescents aged 15 to 19 years were less likely to attend PCH for their care; rather they attended adult cancer centers or community clinics for their care [17]. Physicians may not refer older adolescents to pediatric oncology care, meaning that our study population may not include these older adolescents with ALL.

Despite these limitations, our study has several strengths. Using discharge records to measure hospitalizations ensures that the outcome is not influenced by participant recall [6,10]. Our estimates demonstrate that there are substantial health risks for survivors who are closer to their diagnosis period, which is a key time to ensure health issues are managed in outpatient settings. Studies in the United Kingdom and Canada using hospitalization records report higher rates than our study, but these countries have universal insurance and differ with respect to inclusion criteria and demographic composition [3,14]. An additional strength is the incorporation of every recorded hospitalization in the survival analysis. Analyses examining time to first event are more common but may yield different results than longitudinal studies that use all of the recorded outcomes [34]. The modeling strategy used in this paper incorporates all available hospitalizations to utilize all of the available data.. Our study of shorter term survivors also complements results from the Childhood Cancer Survivor Study, which is comprised of longer-term survivors diagnosed from 1973 to 1999. We also are able to track participant residence in and out of Utah over time frame of the cohort, and find that movement out of Utah is minimal during follow-up (<1%).

As of 2010, a total of 379,112 survivors of childhood cancer of all ages live in United States, 30,171 of whom were ALL survivors aged 20 or younger [35]. As these survivors age into adolescence and young adulthood, both survivors and their clinicians need to be aware of their risk for late effects. Services for cancer survivors should center on prevention of survivor-specific health conditions. Clinicians and health care systems can use this

information to ensure that appropriate patient care and management strategies are provided for this growing population of cancer survivors.

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Abbreviations:

ALL	acute lymphoblastic leukemia
EDW	enterprise data warehouse
IH	Intermountain Healthcare
PCH	Primary Children's Hospital
UPDB	Utah Population Database

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Fig. 1. Distribution of Primary Hospitalization Diagnoses among Survivors of Childhood and Adolescent Acute Lymphoblastic Leukemia, Siblings, and a Matched Population Sample from 5 to 10 Years Post-Diagnosis.

Characteristics of Survivors of Childhood and Adolescent Acute Lymphoblastic Leukemia from 5 to 10 Years Post-Diagnosis, Siblings, and a Population Sample.

Table 1

	Survivors		Siblings		Population Sample	
	n = 176		n = 232		n = 503	
	N	Column%	N	Column%	N	Column%
Demographics						
Age at cohort entry, years (mean, range)	11.4	5.1, 26.6	11.3	5.1, 24.3	11.4	5.1, 26.6
Sex						
Male	99	56.3	112	48.3	283	56.3
Female	77	43.8	120	51.7	220	43.7
Ethnicity						
Non-Hispanic	155	88.1	219	94.4	454	90.3
Hispanic	21	11.9	13	5.6	49	9.7
Residential area at diagnosis						
Rural	60	34.1	75	32.3	154	30.6
Urban	116	65.9	157	67.7	349	69.4
Clinical Factors						
Diagnosis year						
1998 to 2003	76	43.2	NA		NA	
2004 to 2008	100	56.8	.		.	
Treatment						
BMT and chemotherapy	5	2.8	NA		NA	
Radiation and chemotherapy	11	6.3	.		.	
Chemotherapy only	160	90.9	.		.	
Risk group at diagnosis						
Standard Risk	117	66.5	NA		NA	
High Risk	54	30.7	.		.	
Infants	5	2.8	.		.	
Age at diagnosis						
0 to 5 years	94	53.4	NA		NA	

	Survivors		Siblings		Population Sample		<i>P</i> ^c
	N	Column%	N	Column%	N	Column%	
	n = 176		n = 232		n = 503		
6 to 22 years	82	46.6	.	.	.	.	

BMT: Bone marrow transplant.

^a Comparison for the N = 124 survivors with siblings.

^b *P*-value for survivors vs siblings;

^c *P*-value for survivors vs Utah population (matched on sex and birth year).

* Significant at *P* 0.05.

Hospitalization Counts and Sex and Birth Year Adjusted Hospitalization Rates per 100 Person-Years for Survivors of Childhood and Adolescent Acute Lymphoblastic Leukemia from 5 to 10 Years Post-Diagnosis, Siblings, and a Population Sample.

Table 2

	Survivors				Siblings				Population Sample			
	N = 176				N = 232				N = 503			
	Ct	PY	Rate	95% CI	Ct	PY	Rate	95% CI	Ct	PY	Rate	95% CI
Full Sample	25	650.87	3.76	2.22, 6.36	30	1009.29	2.69	1.01, 7.18	35	1803.46	1.87	1.13, 3.09
Demographic Characteristics												
Sex												
Male	9	348.12	2.61	1.10, 6.19	15	511.75	3.66	1.19, 11.32	10	965.97	1.02	0.42, 2.46
Female	16	302.76	4.92	2.50, 9.70	15	497.54	2.54	1.11, 5.80	25	837.5	2.73	1.49, 5.01
Ethnicity												
Not Hispanic	23	570.04	3.97	2.28, 6.91	28	952.23	2.71	0.94, 7.84	28	1627.62	1.66	0.93, 2.97
Hispanic	2	80.83	1.79	0.27, 11.79	2	57.06	2.62	1.01, 6.78	7	175.84	3.5	1.52, 8.04
Residential area												
Rural	5	199.51	2.38	0.94, 6.02	16	352.75	4.72	0.93, 23.90	9	532.27	1.58	0.77, 3.27
Urban	20	451.36	4.32	2.34, 7.99	14	656.54	1.74	0.82, 3.71	26	1271.19	1.96	1.05, 3.66
Clinical Factors												
Diagnosis year												
1998 to 2003	8	393.38	1.87	0.67, 5.27	14	538.33	2.09	0.84, 5.18	24	1107.96	1.98	1.16, 3.36
2004 to 2008	17	257.49	6.69	3.95, 11.33	16	470.96	3.04	0.60, 15.32	11	695.5	1.55	0.58, 4.18
Treatment												
BMT and/or radiation with chemotherapy	1	63.85	1.54	0.18, 13.29	6	92.67	7.55	2.75, 20.75	3	190.01	1.56	0.28, 8.50
Chemotherapy only	24	587.03	3.9	2.23, 6.85	24	916.62	2.19	0.66, 7.25	32	1614.46	1.85	1.07, 3.21
Risk group at diagnosis												
High risk and infants	14	225.74	5.79	3.06, 10.95	15	336.21	4.18	1.93, 9.04	21	630.67	3.1	1.97, 4.90
Standard risk	11	425.13	2.77	1.16, 6.58	15	673.08	2.53	0.53, 12.00	14	1172.79	1.26	0.49, 3.25
Age at diagnosis												
0 to 5 years	7	337.03	2.07	0.91, 4.73	17	566.61	4.16	1.21, 14.23	16	970.29	1.7	0.71, 4.07
6 to 22 years	18	313.85	4.6	2.26, 9.37	13	442.68	1.97	0.91, 4.28	19	833.18	1.73	1.00, 3.01

Ct.: Total number of hospitalizations, more than 1 per person possible; PY: Person years; CI: Confidence Interval.

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Table 3

Yearly Rates per 100 Person-Years by Diagnosis Year and Comparison Group from 5 to 10 Years Post-Diagnosis.

	5 years post-diagnosis			6 years post-diagnosis			7 years post-diagnosis			8 years post-diagnosis			9 years post-diagnosis		
	Rate	95% CI		Rate	95% CI		Rate	95% CI		Rate	95% CI		Rate	95% CI	
All participants															
Survivors	7.12	3.63, 13.94		2.48	0.96, 6.35		1.79	0.57, 5.67		2.65	1.06, 6.59		0.62	0.09, 4.40	
Siblings	3.02	0.83, 10.96		0.74	0.15, 3.76		2.11	0.82, 5.44		1.73	0.72, 4.16		2.29	0.96, 5.42	
Population Sample	1.42	0.60, 3.35		1.83	0.82, 4.05		<i>a</i>			1.64	0.83, 3.24		1.78	0.9, 3.50	
Diagnosis year: 1998 to 2003															
Survivors	5.42	2.06, 14.26		2.51	0.61, 10.36		<i>a</i>			1.01	0.13, 7.68		<i>a</i>		
Siblings	1.69	0.47, 6.11		1.35	0.3, 6.08		<i>a</i>			<i>a</i>			4.19	1.71, 10.26	
Population Sample	1.19	0.36, 3.95		1.78	0.64, 4.95		<i>a</i>			2.82	1.17, 6.82		3.65	1.79, 7.43	
Diagnosis year: 2004 to 2008															
Survivors	7.91	3.76, 16.65		2.35	0.58, 9.48		2.81	0.80, 9.80		3.93	1.4, 10.99		<i>a</i>		
Siblings	4.19	1.64, 10.7		<i>a</i>	<i>a</i>		1.52	0.36, 6.45		3.13	1.14, 8.61		<i>a</i>		
Population Sample	1.47	0.55, 3.91		1.82	0.75, 4.4		<i>a</i>			0.29	0.04, 2.11		<i>a</i>		

CI: Confidence Interval.

^aCells with no data indicate no hospitalizations occurred during that time period, or that there were not enough events to allow for meaningful rates and 95% CI to be estimated.

Table 4

Sex and Birth Year Adjusted Rate Ratios for Hospitalizations among Survivors of Childhood and Adolescent Acute Lymphoblastic Leukemia from 5 to 10 Years Post-Diagnosis Compared to Siblings and a Population Sample

	<u>Model 1: Survivors (n = 124) vs Siblings (n = 232) (ref)</u>		<u>Model 2: Survivors (n = 176) vs Population Sample (n = 503) (ref)</u>	
	Rate Ratio	95% CI	Rate Ratio	95% CI
Full Sample	1.53	0.54, 4.38	2.01*	1.00, 4.03
Demographic Category				
Sex				
Male	0.81	0.15, 4.44	2.54	0.73, 8.83
Female	2.09	0.73, 6.00	1.80	0.78, 4.16
Ethnicity				
Not Hispanic	1.67	0.94, 2.99	2.39*	1.11, 5.15
Hispanic	NA	.	0.55	0.09, 3.48
Area of residence				
Rural	0.69	0.17, 2.81	1.53	0.52, 4.53
Urban	2.58	0.86, 7.73	2.21	0.95, 5.09
Clinical Factors				
Diagnosis year				
1998 to 2003	0.97	0.22, 4.39	0.95	0.29, 3.14
2004 to 2008	2.73	0.54, 13.68	4.29*	1.49, 12.32
Treatment				
BMT and/or radiation with chemotherapy	0.24	0.02, 2.64	0.94	0.37, 2.42
Chemotherapy only	1.97	0.57, 6.81	2.11*	1.01, 4.41
Risk group at diagnosis				
High risk and infants	1.63	0.58, 4.59	1.86	0.89, 3.89
Standard risk	1.14	0.18, 7.21	2.19	0.59, 8.16
Age at diagnosis				
0 to 5 years	0.46	0.13, 1.60	1.21	0.37, 3.95
6 to 22 years	2.87*	1.03, 7.97	2.66*	1.17, 6.04

CI: Confidence Interval.

Model 1 excludes survivors without siblings; Model 2 includes all survivors.
* Significant at $P = 0.05$.

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Table 5

Risk Factors for Hospitalization among Survivors of Childhood and Adolescent Acute Lymphoblastic Leukemia from 5 to 10 Years Post-Diagnosis

	Individual models ^a N = 176		Multivariable model ^a N = 176	
	Hazard Ratio	95% CI	Hazard Ratio	95% CI
Demographic Category				
Sex				
Female	1.88	0.74, 4.77	2.11	0.88, 5.02
Male	1		1	
Ethnicity				
Hispanic	0.93	0.22, 3.93		
Not Hispanic	1			
Area of residence				
Rural	0.63	0.24, 1.62		
Urban	1			
Clinical Factors				
Treatment				
BMT &/or Radiation	0.45	0.06, 3.38		
Chemotherapy only	1			
Risk group at diagnosis				
High risk	3.08 *	1.19, 7.93	3.36 *	1.33, 8.45
Standard risk	1		1	
Diagnosis year				
2004 to 2008	14.45 *	3.41, 61.16	9.48 *	1.93, 46.59
1998 to 2003	1		1	
Age at diagnosis				
0 to 5 years	1.21	0.46, 3.18	1.33	0.53, 3.33
6 to 22 years	1		1	

CI: Confidence Interval, BMT: Bone marrow transplant.

^aAdjusted for birth year and sex.

* Significant at $p = 0.05$.