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Original Research Article

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

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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- 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.
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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

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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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.

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