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Survival among children diagnosed with acute lymphoblastic leukemia in the United States by race and age, 2001-2009: findings from the CONCORD-2 Study

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<td>Ward, Kevin; Emory University</td>
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<td>Bonaventure, Audrey; London School of Hygiene and Tropical Medicine, NCDEU</td>
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<td>Keywords:</td>
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Running title: Acute lymphoblastic leukemia survival among children in the U.S.

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Precis: This study describes the survival of children with acute lymphoblastic leukemia in the US utilizing the most comprehensive and up-to-date cancer registry data. We found overall survival from childhood ALL in the US to be high, but disparities by race exist.

Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention or the National Cancer Institute.

Key words: Acute lymphoblastic leukemia, childhood cancer, childhood leukemia, population-based cancer survival, leukemia
Abstract

Introduction

Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy in the United States (US). This study describes the survival of children with ALL in the US utilizing the most comprehensive and up-to-date cancer registry data.

Methods

We utilized data from 37 state cancer registries that cover approximately 80% of the US population. We estimated age-standardized survival up to 5 years for children aged 0-14 years diagnosed with ALL during two time periods: 2001-2003 and 2004-2009.

Results

We included 17,500 children with ALL. The pooled age-standardized net survival estimates for all US registries combined were 95% at 1 year, 90% at 3 years and 86% at 5 years for children diagnosed during 2001-2003, and 96%, 91%, and 88%, respectively, for those diagnosed during 2004-2009. Black children diagnosed during 2001-2003 had lower 5-year survival (84%) than white children (87%) and less improvement in survival by 2004-2009. For 2004-2009, 1-year and 5-year survival was 95.7% and 88.6% for white children and 95.5% and 83.6% for black children. For 2004-2009, Survival was highest among children aged 1-4 years (95%) and lowest among children less than one year of age (60%).

Discussion

We found overall net survival from childhood ALL in the US to be high, but disparities by race still exist, especially beyond the first year after diagnosis. Clinical and public health strategies are needed to improve healthcare access, clinical trial enrollment, treatment, and survivorship care for children with ALL.
Introduction

One of the great successes in medicine in the United States (US) has been the increasing survival of children with cancer. In the past 50 years, 5-year survival from all cancers combined among children in the US has increased from under 60% to nearly 80%. Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy worldwide, accounting for 20-30% of overall childhood cancer incidence. Before 1950, childhood ALL was uniformly fatal. In the 1960s, five-year survival for children with ALL in the US was less than 10%. Since then, five-year survival has dramatically improved, from 57% between 1975 and 1979 to 90% between 2003 and 2009. This increase in survival is consistent with stable incidence rates and decreasing mortality rates.

Progress made in childhood ALL survival in developed countries over the past four decades largely stems from clinical and public health-related cancer control efforts. These include increasing clinical trial enrollment, improved supportive care, and risk-directed therapy that optimizes the efficacy of existing antileukemic agents. Pediatric cancer collaborative treatment groups, which have reported enrollment of over two-thirds of childhood ALL cases over the past two decades, designed randomized clinical trials that used risk-adaptive algorithms to adjust the intensity of treatment based upon factors such as ALL subtype and chromosomal changes, age and white blood count on diagnosis, presence of disease in the central nervous system, and persistence of residual disease during treatment. In addition to improving relapse-free and overall survival, a risk-based approach has allowed clinicians to reduce toxicities that contribute to late complications and mortality.

Clinical trials and ensuing advances in risk-based therapy have contributed to the remarkable progress in improving clinical outcomes in the US and other countries. This success lies in contrast to five-year survival of less than 40% in many developing countries, which largely results from abandonment of therapy and high treatment-related mortality. Five-year net survival for children diagnosed with ALL has been previously estimated above 85% in the US, while it was still below 50% in several less wealthy countries participating in the worldwide cancer survival comparison of the CONCORD-2 study. The CONCORD-2 study established worldwide surveillance of cancer survival in 67 countries using data from over 25 million persons diagnosed with cancer from 279 cancer registries. This study builds upon the CONCORD-2 study and describes the survival of children with ALL in the US utilizing the most comprehensive and up-to-date cancer registry data available by race and age.

Methods

We used data from 37 state-wide cancer registries that participated in the CONCORD-2 study, covering approximately 80% of the US population, and consented to inclusion of their data in the more detailed analyses reported here. We analysed individual records for 17,500 children (0-14 years) diagnosed with precursor-cell acute lymphoblastic leukemia (ICD-O-3 morphology codes 9727-9729; 9835-9837) during 2001-2009 and followed up to December 31, 2009. We included all children with ALL in the
analyses, even if the child had had a previous malignancy. In the extremely rare instance that a child was diagnosed with ALL on two or more occasions during 2001-2009, only the first occurrence was considered in the survival analyses.

We estimated net survival up to 5 years, with 95% confidence intervals (CI), for children diagnosed during 2001-2003 and 2004-2009, by race and state. We used the Pohar Perme estimator\(^{25}\) of net survival. Net survival can be interpreted as the probability of survival up to a given time since diagnosis, after controlling for other causes of death (background mortality). To control for differences in background mortality between participating states, by race and over time, we constructed life tables of all-cause mortality in the general population of each state from the number of deaths and the population, by single year of age, sex, calendar year and, where possible, by race (black, white), using a flexible Poisson model.\(^{26}\) The life tables have been published.\(^{27}\)

Children were grouped by diagnosis year into two calendar periods (2001-2003 and 2004-2009) to reflect changes in the methods used by US cancer registries to collect data on stage at diagnosis. From 2001-2003, most registries coded stage directly from medical records to Surveillance, Epidemiology, and End Results Summary Stage 2000.\(^{10}\) Since 2004, all registries have derived Summary Stage 2000 using the Collaborative Staging System.\(^{11}\)

We estimated net survival using the cohort approach for patients diagnosed in 2001-2003, since all patients had been followed up for at least five years by December 31, 2009. We used the complete approach to estimate five-year net survival for patients diagnosed during 2004-09, because five years of follow-up data were not available for all patients. Net survival was estimated for three age groups (0–4, 5–9 and 10–14 years). We obtained age-standardized estimates by assigning equal weights to the three age-specific estimates.\(^{28}\) If two of the three age-specific estimates could not be obtained, we present only the pooled, unstandardized survival estimate for all age groups 0-14 years combined. Unstandardized estimates are italicized in Supplemental Table. To better explore the trend by age, the first age group was split into two subgroups. (Table 3) Trends, geographic variations and differences in survival by race are presented graphically in bar-charts and funnel plots.\(^{29}\) More details on data and methods are provided in the accompanying article [Allemani et al., 2017].

**Results**

Data meeting the eligibility criteria for analyses came from 37 states comprising 80% of the total US population (Table 1). Of the 17,500 children with ALL, 83.7% were white, 8.9% were black and 7.4% were of other/unknown races. Almost all (98.5%) cases were morphologically verified (Table 1). There were no differences in morphological verification by race.

Figure 1 presents a visual snapshot of the absolute change in 5-year age-standardized net survival between 2001-2003 and 2004-2009, by geographic region. For the US overall, there was an absolute increase in survival of 1.7% between those periods.
One-, 3- and 5-year age-standardized net survival for all races in the pooled US population represented in this study were 95.3% (CI: 94.6-95.9), 89.7% (CI: 88.8-90.7), and 86.4% (CI: 85.3-87.4) respectively, in 2001-2003 and 95.7% (CI: 95.3-96.1), 90.7% (CI: 90.0-91.4), and 88.1% (CI: 87.2-88.9) in 2004-2009 (Table 2). Despite these increases in survival, disparities still exist between racial groups. In 2001-2003, 5-year net survival was 86.6% (CI: 85.5-87.7) for whites but 83.8% (CI: 80.3-87.3) for blacks. During 2004-2009, survival increased marginally for whites (88.6% (CI: 87.6-89.5) but remained the same for blacks 83.6% (CI: 80.6-86.6) resulting in a slight widening of the racial divergence in survival during the period 2001-2009. Five-year age-standardized estimates for children diagnosed during 2004-2009 ranged from 85.2% to 98.6% in the Northeast, 81.7% to 92.2% in the South, 87.8% to 90.3% in the Midwest and 86.0% to 95.9% in the West (Supplementary Table 2).

Five-year net survival for children aged <1 year, 1-4, 5-9, and 10-14 years were 60.5% (CI: 53.4-67.6), 92.5% (CI: 91.5-93.5), 89.2% (CI: 87.7-90.8), and 79.4% (CI: 76.9-81.9), respectively, in 2001-2003, and 60.1% (CI: 54.5-65.7), 94.5% (CI: 93.7-95.3), 90.4% (CI: 89.0-91.8), and 81.5% (CI: 79.4-83.6) respectively, in 2004-2009 (Table 3). Survival was highest among children aged 1 to 4 years and lowest among those less than one year of age, with a 30 percentage point difference between these two age groups in both time periods. Survival was consistently slightly higher in girls than boys, with the largest differences observed in infants under 1 year of age throughout 2001-2009.

Funnel plots (Figure 2) display graphically the variation in survival between states and by race. 5-year age-standardized net survival was generally lower among black children (solid circles) than among white children (open circles), although net survival estimates for black children were only available for three states: this is due to the difficulty of constructing life tables for blacks in some states and in producing age-standardized estimates of net survival (see methods section). Similar patterns were observed during 2004-2009.

Discussion

In this manuscript, we report the most comprehensive analysis of cancer survival to date among children with ALL in the US, with data from 37 cancer registries covering approximately 80% of the national population. We found short-term survival from childhood ALL in the US to be high. For all participating US states combined, the pooled estimate of 1-year net survival for children diagnosed during 2004-2009 was 95.7% [95% CI 95.3-96.1%], while 5-year survival was 88.1% [95% CI 87.2-88.9%]. These 5-year survival estimates from a population-based US cohort are slightly lower but still closely aligned with the 5-year survival estimates of 91.4% from the Children’s Oncology Group ALL randomized trials for a similar period (2000-2005) and the same age group. Our results were also within the same range as most countries in Northern and Central Europe, and close to those in Canada (90.6% [88.6-92.7%] for 2005-2009). Our results are consistent with stable incidence rates and decreasing mortality rates for childhood ALL in the US.
Despite the high overall survival, there were geographic and racial disparities. One-year survival for children diagnosed during 2004-2009 ranged from 91.4% to 98.9% in the Northeast. Differences in five-year survival were even larger, ranging from 81.7% to 98.6% (Supplemental Table). Racial disparities were larger for longer-term survival than for shorter-term survival.

Five-year survival for black children was typically 3 to 5 percentage points lower than for white children. Geographic differences in survival may be explained, in part, by survival differences between white and black children. Survival is generally lower for black children, and the proportion of black children varies by state. However, we found that survival for black children was similar, if not higher, to that of white children in some states (Supplemental Table). This suggests that the distribution of black and white children does not explain all of the geographic differences in survival. Although genetic polymorphisms may partially explain racial differences in ALL outcomes\textsuperscript{30}, these differences are more likely to be the reflection of differences in socioeconomic status and access to care.\textsuperscript{31,32} The survival patterns by race we found are consistent with higher incidence rates among white children and higher mortality rates among black children.\textsuperscript{10-12}

Survival by age at diagnosis is consistent with previous data.\textsuperscript{33} Survival of infants diagnosed with ALL is markedly lower than that for any other age group, which reflects the high prevalence and mortality of infant ALL cases with mixed lineage leukemia gene rearrangements\textsuperscript{1}. This population-based study confirms previous findings that the highest survival is found in children aged 1-4 years, with decreasing survival as age increases toward adolescence\textsuperscript{33}. We also found, as previously reported,\textsuperscript{34} that boys have lower survival from ALL than girls. This gender difference was more marked in infants, for whom survival was the lowest, and remained in the most recent period (2004-2009).

Five-year survival for ALL in the United States is amongst the highest in the world and it improved from 83.1% to 87.7% between 1995 and 2009 as reported from the CONCORD–2 Study\textsuperscript{9}. The high survival may reflect, in part, the intensity of clinical investigation performed to establish the diagnosis, which would be expected to improve the definition of morphological type and thus the selection of the most appropriate treatment. One indicator of the intensity of diagnosis is the percentage of cases for which microscopic confirmation of the diagnosis was available. For children diagnosed with ALL during the period 1995-2009 covered by the CONCORD-2 study, morphologic verification was available for 98.4% of patients among all US registries combined and ranged between 85.6% and 100% among participating states\textsuperscript{9}. As reported here, morphological verification was similar among both black and white children diagnosed during 2001-2009. The low percentage of cases for which the diagnosis was based on clinical rather than pathological evidence is not likely to be the result of selective case ascertainment among participating cancer registries, since all the registries were certified by the North American Association of Central Cancer Registries as having met data quality and completeness standards.

**Clinical perspective**
Important advances in childhood ALL survival have been achieved through both clinical and public health efforts. Clinical advances include improved supportive care and recognition of avenues to reduce the toxicity of therapy without compromising overall outcome. These advances in childhood ALL survival have spanned all age groups, races, and both genders. Clinicians have had increased success with managing frequent complications of ALL including tumor lysis syndrome, infection during neutropenia, thrombosis, hemorrhage, anaphylaxis, and suppression of the hypothalamic-pituitary-adrenal axis. Additionally, intrathecal therapy has been increasingly used instead of cranial irradiation for patients with central nervous system disease, thereby reducing radiation-associated morbidity and mortality. There has been an increasing use of immunophenotyping and cytogenetic characterization to predict outcome and relapse, and thus to guide risk-based adjustments in therapy. Advanced genetic characterization of ALL can contribute to improved diagnostic evaluation and enhance clinicians’ ability to monitor the response to therapy. Additionally, recent genotyping techniques have allowed clinicians to detect germ-line differences that may predict response to therapy, as well as chemotherapy-related side-effects.

Cancer control perspective

Many of these clinical advances have been achieved in conjunction with public health-related cancer control efforts, including increasing clinical trial enrollment and improving survivorship care. Much of the substantial improvement in survival among children with cancer is attributable to increasing clinical trial enrollment. Clinical trials identify the most effective treatments and allow those treatments to be brought to patients. Sustained efforts by comprehensive cancer control programs to support clinical trial enrollment for children with cancer are needed to improve survival even further for children with ALL. Comprehensive cancer control programs can support efforts to increase referral to and enrollment in existing clinical trials, increase the number of clinical trials available, and reduce regulatory barriers to enrollment in clinical trials.

With survival increasing, cancer control efforts must also focus on the long-term health of childhood ALL survivors. Of the 14 million cancer survivors in the US, over 50,000 are survivors of childhood ALL. Treatment of ALL may result in long-term health effects that may adversely affect the long-term health of childhood cancer survivors. Survivors of childhood ALL are at increased risk for poor overall health, osteoporosis, growth hormone deficiency, impaired exercise capacity, cardiomyopathy, infertility, cataracts, short stature, neurocognitive deficits, and poor functional status. Comprehensive cancer control programs could encourage the adoption of survivorship care plans, which the Institute of Medicine recommends for all cancer survivors. Survivorship care plans provide summaries of clinical treatments and help cancer survivors understand potential late effects, anticipatory guidance, and long-term follow-up care. Comprehensive cancer control programs could also support efforts to improve providers’ knowledge of established follow-up guidelines, such as the Children’s Oncology Group Long-Term Follow-Up Guidelines. More widespread implementation of
these guidelines could help improve and harmonize providers’ knowledge on potential late effects, screening, evaluation, anticipatory guidance, counseling, and other interventions.\textsuperscript{49}

Additionally, comprehensive cancer control programs could encourage innovative uses of cancer registry data to improve cancer survivorship. Examples of effective activities include Centers for Disease Control and Prevention (CDC)-supported efforts to utilize existing cancer registry data to populate survivorship care plans.\textsuperscript{50} Improved surveillance of late effects among cancer survivors, using population-based cancer registries, will become an essential approach to improve understanding of variations in long-term morbidity and mortality, and potentially to improve outcomes.

Comprehensive cancer control programs can also support efforts to decrease disparities among children with ALL. While there were negligible differences in 1-year survival by race, we found black children had lower 5-year survival compared to white children. This may reflect differences in treatment over time and be related to socioeconomic status.\textsuperscript{51-53} Cancer control efforts that increase access to care among lower socioeconomic status families may help to reduce racial discrepancies in treatment and outcomes.

Limitations

One limitation of this study is that it does not include patients aged 15 or older. Many previous reports have included patients aged 15-19 in an evaluation of childhood. Therefore, comparing this study to other studies must account for differences in study population age.\textsuperscript{2,3,10}

Records of children diagnosed with leukemia were selected for analysis if their ICD-O-3 morphological code was in the 6 codes proposed by the HAEMACARE group for ALL.\textsuperscript{54,55} Despite the fact that ALL is the most common childhood malignancy worldwide, absolute case numbers are generally small and caution is needed in interpreting the data. Survival was estimated separately for each state, and estimates covering approximately 80% of the US population were also obtained by pooling the data from all participating states. Survival estimates could not be age-standardized for the less populous states, because the data were sparse. This limitation applies particularly to comparison of survival between blacks and whites, because in most states, black children represent fewer than 20% of ALL cases.

Conclusions

Survival from childhood ALL has been improving overall in 37 US states between 2001-2003 and 2004-2009. Because of the relative rarity of childhood ALL, national and international collaboration groups that pool patient numbers and coordinate multi-center research efforts are essential.\textsuperscript{13} Continued collaboration will be critical in reducing health inequalities in survival from childhood ALL, as well as in advancing childhood ALL treatment. Similar research efforts will continue to play a central role in improving outcomes in other childhood cancers where survival is still well below 90%. Comprehensive cancer control programs can support efforts to increase clinical trial enrollment, provider’s knowledge
of established follow-up guidelines and encourage the use of survivorship care plans. Close monitoring
of survivors of childhood ALL using population-based cancer registry data is essential to monitor the
effect of the implementation of new medical and public health strategies aimed at improving survival.
Table 1: Acute lymphoblastic leukemia: number of children (0-14 years) diagnosed 2001-2009 and included in survival analysis, with quality data indicators, by US state and race

Table 2: Leukemia in children: age-standardized net survival (%) at 1-, 3- and 5-years for females diagnosed 2001-2009, by race and calendar period of diagnosis.

NS= Net Survival

Table 3: Acute lymphoblastic leukemia: net survival (NS,%) at 1,3, and 5 years after diagnosis for children (0-14 years) diagnosed 2001-2009, by age, race, sex and calendar period of diagnosis: United States

A: population coverage represents 80.6% of the US population in 2009 (data from the UN Population Division). B: Age-standardized. NS= Net Survival

Figure 1: Acute lymphoblastic leukemia; five year age-standardized net survival(%) for children (0-14 years) diagnosed during 2001-2003 and 2004-2009, and absolute change (%): US states grouped by geographic region

US states: 37 participating states (80.6% population coverage). States are ranked within each geographic region by the survival estimate for 2004-2009. Dark Color- NPCR registries; pale colors-SEER registries. * Registries affiliated with both programs. Only age-standardized survival estimates were plotted. †Change (%) not plotted because at least one estimate was not age-standardized

Figure 2: Acute lymphoblastic leukemia- 5 year age-standardized net survival (%) for children (0-14 years), by calendar period of diagnosis

Note: Each data point represents the survival estimate for a US state, either for blacks (3 states) or whites (27 states)

Supplemental Table: Acute lymphoblastic leukemia: age-standardized net survival (%) at 1,3, and 5 years for children (0-14 years) diagnosed 2001-2009, by US state, race, and calendar period of diagnosis: geographic region and Census division

Survival estimates that are not age-standardized are italicized. Dashes (-) indicate where a survival estimate could not be produced. NS= net survival. CI= confidence interval
Table 2. Leukemia in children: age-standardized net survival (%) at 1-, 3- and 5-years for children diagnosed 2001-2009, by race and calendar period of diagnosis.

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NS = Net Survival
Table 3. Acute lymphoblastic leukemia: net survival (NS, %) at 1.3 and 5 years after diagnosis for children (0-14 years) diagnosed 2001-2009, by age, race, sex, and calendar period of diagnosis: United States

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2004-2009

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Figure 1

440x319mm (72 x 72 DPI)
Figure 2

254x190mm (150 x 150 DPI)
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**UNITED STATES**

- **All races**
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    - **NS**
    - **95% CI**
    - **NS**
    - **95% CI**
  - **White**
    - **NS**
    - **95% CI**
    - **NS**
    - **95% CI**

**NORTHEAST**

- **New England**
  - **Connecticut**
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    - **95% CI**
    - **NSE**
    - **95% CI**
    - **NSE**
    - **95% CI**
    - **NSE**
    - **95% CI**
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    - **95% CI**
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    - **NSE**
    - **95% CI**
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    - **95% CI**
    - **NSE**
    - **95% CI**
    - **NSE**
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  - **Rhode Island**
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    - **NSE**
    - **95% CI**
    - **NSE**
    - **95% CI**

**Mid Atlantic**

- **New Jersey**
  - **NPCR**
    - **NSE**
    - **95% CI**
    - **NPCR**
    - **95% CI**
    - **NPCR**
    - **95% CI**
    - **NPCR**
    - **95% CI**
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**SOUTH**

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    - **NSE**
    - **95% CI**
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**Table 2 - Net survival by race formatted noHiddenColumns_noTitles_xlsx - ALL in children**

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<tr>
<td></td>
<td>3</td>
<td>92.9</td>
<td>88.4</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>88.7</td>
<td>83.0</td>
</tr>
</tbody>
</table>

Table 2 - Net survival by race formatted_noHiddenColumns_noTitles.xls - ALL in children