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Association of Age with Acuity and Severity of Illness at Initial Presentation and with Overall Survival in Children, Adolescents, and Young Adults with Leukemia

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B.S., Indiana University, 2013
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Abstract

Association of Age with Acuity and Severity of Illness at Initial Presentation and with Overall Survival in Children, Adolescents, and Young Adults with Leukemia

By Tarun Jain, M.D.

Background: Adolescent and Young Adult (AYA) patients (ages 15-39 years) with leukemia are at a higher risk for mortality than younger patients. The acuity of illness and its impact on mortality in AYA versus younger patients has been understudied.

Objectives: To determine the association of age at diagnosis with acuity or severity of illness and with overall survival in patients presenting with new diagnoses of leukemia.

Methods: We performed a retrospective analysis of a cohort of patients aged 1-21 years who presented with leukemia to Children's Healthcare of Atlanta between 2010-2018. High acuity of illness was defined as any intensive care unit resource use in the first 72 hours following presentation (yes/no). High severity of illness was defined as having either an initial white blood cell count ≥ 50,000 cells/microliter or central nervous system disease (yes/no). Multivariable logistic regression was used to estimate the association of age with acuity or severity of illness, controlling for sex, race/ethnicity, insurance, and leukemia type. Survival analysis was performed using Kaplan-Meier curves and Cox proportional hazards regression models to estimate the association between age and survival. We also conducted a mediation analysis to test the extent to which acuity and severity can explain the age differences in survival.

Results: The median age of the cohort (N=688) was 6 years (interquartile range 3-12 years; 65.7% aged 1-9 years, 34.3% aged 10-21 years), 53.8% were male, 48.1% were non-Hispanic White, and 41.9% had private insurance. In considering the National Cancer Institute (NCI) age parameters for AYA, 15.1% of patients were 15-21 years. Diagnoses included B-cell acute lymphoblastic leukemia (ALL) (68.3%), AML (16.7%), T-cell ALL (10.8%), and other leukemias (4.2%).

High acuity of illness at initial presentation was seen in 24.7% of patients, and high severity of illness at initial presentation was seen in 38.1% of patients. Patients aged 10 and older were more likely than those younger to have high acuity of illness at initial presentation (adjusted odds ratio [OR]) for 10-21 years versus 1-9 years: 1.94, 95% confidence interval [CI]): 1.32-2.85). Age at diagnosis was not significantly associated with high severity of illness (adjusted OR for 10-21 years versus 1-9 years: 1.25, 95% CI: 0.88-1.78). High acuity at initial presentation, but not high severity, was associated with a higher risk of death (hazard ratio of death for high acuity versus low acuity at 6 months post-diagnosis: 3.44, 95% CI: 1.51-7.85). High acuity explained 23% (95% CI: 2–44%) of the survival differences by age group at 6 months.

Conclusion: Patients ≥ 10 years of age were more likely than younger patients to present with high acuity of illness, and high acuity was significantly associated with increased mortality. While the causality between age, biology of leukemia, and acuity of illness is not clear, this research is a step toward informing potential for strategies in child health toward narrowing age disparities in leukemia outcomes.

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TABLE OF CONTENTS

LIST OF TABLES AND FIGURES

INTRODUCTION

Background

Age at initial presentation is known to be associated with overall survival in patients with leukemia in the pediatric and adolescent and young adult (AYA) years. For example, patients greater than or equal to 10 years of age with B-cell acute lymphoblastic leukemia (B-ALL) have been identified by the National Cancer Institute (NCI) as having a higher risk for treatment failure and decreased event-free survival compared to younger patients. This age threshold continues to be a criterion for classifying a patient as having high-risk B-ALL, and these patients therefore receive more intensive therapy.[1,2] Surveillance, Epidemiology, and End Results (SEER) data from 2016-2020 also demonstrate age-related differences in overall survival with leukemia, with 24.1% of those aged 10-14 and 30.9% of those aged 15-19 dying from leukemia, compared to 22.5% aged 1-4 and 18.1% aged 5-9.[3] Decreased overall survival by age has been targeted in initiatives to improve outcomes in the AYA population, defined by the NCI as those between ages 15 to 39 with cancer.[3-5]

Knowledge Gap

Multiple reasons have been proposed for these age-related disparities in disease-free and overall survival. These reasons include a higher likelihood of aggressive disease biology in children with B-ALL who are ages ≥ 10 years, differences in access to care for a variety of societal reasons, inferior treatment tolerance, and unique psychosocial challenges associated with the adolescent developmental station **(Figure 1)**.[4,5] One proximal reason that has not been explored as a driver of survival differences by age is acuity and severity of illness at initial presentation.

We define acuity of illness as the degree of morbidity at initial presentation of cancer diagnosis estimated by the level of care required for a patient. While acuity of illness has been described as mediating the relationship between race and induction mortality in acute myeloid leukemia (AML), as well as induction mortality in infant ALL and AML, little is known about whether acuity mediates the association between age at leukemia diagnosis and mortality, specifically in the AYA population.[6-9] In addition, the relationship between acuity of illness and overall survival has not been explored.

Leukemia has a heterogeneity of biologic subtypes and does not have a classic cancer staging system; hence, the extent of disease burden at presentation is difficult to quantitate. In patients with lymphomas and solid tumors, severity of illness has been historically described by cancer staging lexicon; yet, these systems do not apply to leukemia, where initial risk has historically been assigned based on rates of treatment failure with conventional therapy. In patients with B-ALL, this risk is based on disease characteristics at presentation, including white blood count (WBC), central nervous system (CNS) involvement, cytogenetic findings, and age ($\geq$ or < 10 years) at presentation.[10,11] No similar system exists for T-ALL, AML, or CML, which are less common in younger children, but more common in adolescent patients.[12,13] The association of age with severity of illness and with overall survival has not been explored across all pediatric leukemias.

Research Questions

The current study aims to address the gaps in the literature regarding the potential association of age with acuity, or age with severity, of illness at initial presentation of leukemia. We constructed a cohort of patients with leukemia treated at a single large pediatric institution

and conducted a retrospective cohort study, where the association of age with acuity or severity of illness and with overall survival was analyzed.

LITERATURE REVIEW

Age-Related Disparities in Overall Survival

Recent improvements in overall survival in patients with all types of cancer are not as pronounced in AYA patients as they are in younger and older patients with similar diseases. The NCI has defined AYAs as a subgroup of patients diagnosed with cancer aged 15-39 years. In an analysis of SEER data from 2015-2019 considering all cancer types, AYAs had a higher mortality rate, at 8.8 deaths/100,000 patients, compared to younger children, who had 2.0 deaths/100,000 patients. Furthermore, from 2001 to 2018, the decrease in death rate was smaller in AYAs at 0.9% per year compared to younger children at 1.5% per year.[14] However, while age 15-39 represents a point of biologic and developmental transition, this age range does not necessarily apply in terms of disease biology and treatment outcomes across all diseases. For example, one of the NCI criteria for high-risk B-ALL is age 10 years or greater. Meanwhile, in review of data from Children's Oncology Group (COG) clinical trials for Hodgkin lymphoma, patients ages 12 years or older had lower event free survival than younger patients.[15] Initiatives to address outcome disparities have focused on various drivers of illness that affect all AYAs, including medical insurance, access to healthcare, delays in diagnosis, and psychosocial challenges associated with adolescent development and life transitions from childhood to adulthood.[5,16,17]

Disparities in access to healthcare among AYAs compared to younger children include differences in insurance coverage, time to diagnosis, treatment with differing chemotherapy regimens, and treatment at pediatric versus adult institutions by pediatric or medical oncologists. AYAs are more likely to be uninsured compared to younger children.[18] In an analysis of patients in the National Cancer Database (NCDB) between 2004-2010, uninsured or publicly insured

AYAs were more likely to present with advanced stage disease (among non-leukemia diagnoses) than AYAs with private insurance.[19] In an analysis of pediatric AML patients in the Pediatric Health Information Systems (PHIS) database, individuals with public insurance were more likely to require ICU-level resources than those with private insurance.[7] Insurance type is also associated with differences in overall survival. In a large single-institution study of AYAs with all types of cancer, patients with private insurance had higher 5-year conditional survival compared to those with public insurance.[20] Furthermore, in an analysis of SEER data from 2007-2014, AYAs who were uninsured or who had public insurance were noted to have an increased risk of death compared to those with private insurance, even after adjusting for cancer stage at diagnosis.[21] Interestingly, in an NCDB analysis, Medicaid expansion under the Affordable Care Act (ACA) was found to be associated with an increase in stage I diagnoses and a reduction in stage IV diagnoses among all cancers, suggesting that increased public policy solutions toward access to care led to earlier symptom-based detection of cancers.[22] In turn, Medicaid expansion was also associated with improved 2-year overall survival.[23] Notably, some of these analyses including cancer stage as the outcome have excluded patients with leukemia, where the staging systems do not apply.

Cancers affecting children and most cancers affecting the AYA population, including leukemia, do not have any reliable screening for disease prior to presentation. As a result, diagnosis of cancer requires primary and community healthcare providers to have an index of suspicion for recognizing symptoms, especially in AYAs. Increased lag times to diagnosis of leukemia often occur. In younger children, caregivers often notice alarming signs or symptoms and can advocate for medical attention and workup. However, as AYAs often separate from caregiver involvement, they may not raise the same concerns due to lack of awareness, a

developmentally appropriate sense of immortality, or embarrassment about a medical condition.[16,24] Lack of engagement with a regular healthcare team may further isolate them from letting anyone know of initial symptoms. At the physician level, non-specific signs and symptoms may lead to incorrect diagnoses and lag in referral to a specialist, especially given the lower incidence of pediatric and AYA cancers in the general population compared to adult cancers.

Treating institutions and facility type can vary between age groups and have been found to be associated with differences in overall survival. Kahn and colleagues noted that among patients in the New York State Medicaid Program with Hodgkin Lymphoma, AYAs were less likely to receive treatment at an NCI-designated Cancer Center or COG facility than younger children, which in turn was associated with lower overall survival.[25] Similarly, among AYA patients with ALL in California and Texas, treatment at non-specialized cancer centers was associated with lower overall and leukemia-specific survival and was more likely in AYAs older than 18 years of age.[26] These facilities are more likely to have and offer clinical trials, which have been associated with improved outcomes in part due to strict protocols that allow for minimal variability and gaps in treatment. In addition, these facilities may be more likely to recognize and provide the important ancillary and supportive care services needed to maintain treatment intensity and adherence and to mediate treatment toxicity in AYAs. Treatment of pediatric-type cancers like leukemia at pediatric cancer centers has also been associated with improved outcomes compared to treatment at adult cancer centers. This difference is attributed in part to more tailored, paternalistic models of care in pediatric centers, which may benefit younger AYAs who have not yet achieved independence from their caregivers.[18] Howell and colleagues note that from 1998 to 2002, only 36% of patients aged 15-19 were treated at

pediatric centers, and patients aged 15-19 with leukemia treated at non-COG sites had lower 5-year overall survival than those treated at COG sites.[27]

AYAs face unique psychosocial challenges. As described by Erikson's Stages of Psychosocial Development, adolescents aged 15-19 years are focused on developing an identity reconciling individual desires with societal expectations, separating from parental involvement, and determining long-term goals. Cancer diagnosis and treatment can interrupt and delay important milestones during this time. Older AYAs build on this developmental stage and start to form long-term relationships with others, and social support can be eroded with treatment as AYAs miss school or work, experience body image changes, and become isolated.[28] The resulting unmet needs can lead to increased complications. For example, AYAs may exert control over their situation by choosing not to adhere to therapy, in turn leading to worse overall survival.[29]

Hematologic Malignancies in AYA

While these challenges affect all AYA patients with cancer, hematologic malignancies – leukemias and lymphomas – are particularly prone to age-associated disparate outcomes. In a review of SEER data between 2000-2016, hematologic malignancies were associated with the highest risk of death within 2 months of initial presentation in AYA patients, with AML being the second leading cause of death and ALL being the fifth leading cause of death among all cancer types in AYAs.[30] Lymphomas are common, with Hodgkin lymphoma accounting for 18% of new cancers among AYAs.[15] Furthermore, while not among the leading types of new cancers among AYAs, leukemia accounts for 10% of deaths among AYAs with cancer.[3] As such, hematologic malignancies provide an important area for intervention in improving outcomes among AYAs.

In addition to access to healthcare and psychosocial challenges, additional factors leading to poor outcomes in AYA leukemia include differences in disease biology, as well as challenges with the delivery of pediatric-based protocols in adult cancer centers and of supportive care for AYA tolerance of toxicities associated with intensive myelosuppressive chemotherapy.

Disease Biology in AYA Leukemia

The incidence of high-risk genetic mutations leading to leukemia varies with age. In ALL, older children are more likely to present with unfavorable genetic mutations, such as *BCR-ABL* fusion or other Philadelphia-like disease. These mutations are associated with biologically more aggressive leukemias at risk of failing current conventional chemotherapy regimens. In contrast, younger children are more likely to present with molecular features associated with improved event-free survival, such as *ETV6-RUNX1* fusion or hyperdiploidy.[5] AYA patients are also more likely to present with T-cell ALL, which was historically associated with higher rates of relapse and lower overall survival compared to younger children.[12] Similarly, in AML, patients 12-17 years of age are more likely to have high-risk mutations like t(6;9) translocation or *FLT3/ITD* activating mutations that contribute to disease that is less responsive to conventional chemotherapy.[13]

In addition to associations with poor overall survival, unfavorable molecular features are associated with hyperleukocytosis, defined as WBC count ≥100,000 cells/microliter on presentation.[31] High numbers of leukemic cells can lead to disseminated intravascular coagulation (DIC) due to increased release of tissue factor and activation of the coagulation cascade, which in turn can lead to severe bleeding symptoms and microthrombi, causing multisystem organ dysfunction. Patients with acute promyelocytic leukemia (APML), the most common subtype of AML in AYAs, commonly present with DIC.[13] Hyperleukocytosis may lead

to tumor lysis syndrome, which can lead to acute kidney injury and renal failure. Associated leukostasis can also lead to CNS bleeding, pulmonary complications, or ischemic strokes.[31]

Leukemia Treatment Toxicities, Comorbidities, and Survivorship

Patients who require increased medical care utilization with leukemia are at risk for poor outcomes. In an analysis of critically ill patients in the Virtual Pediatric Systems dataset, hematologic dysfunction – defined as platelet count <80,000 /mm^3, decrease in platelet count of 50%, or internationalized normalized ratio >2 – was associated with increased mortality and greater numbers of additional dysfunctional organ systems.[32] Multiple Organ Dysfunction Syndrome (MODS), defined as ≥2 organ systems with dysfunction, on Day 1 was also associated with higher Pediatric Overall Performance Category (POPC) and Pediatric Cerebral Performance Category (PCPC) scores, indicating increased overall or cognitive disability at discharge from the ICU.[32,33]

Patients with pediatric ALL currently receive more aggressive cancer treatment compared to younger children based on initial age (used as a surrogate for biological risk) at presentation. For example, per the most recent COG protocols, patients ≥ 10 years fall into the high-risk category of B-cell ALL and receive daunorubicin in addition to the three-drug induction regimen of vincristine, prednisone, and asparaginase given to standard-risk B-cell ALL patients.[34] In contrast, in some diseases, higher risk therapy is defined solely by biologic features. For example, patients with high-risk mutations in AML like the *FLT3/ITD* mutations may be recommended for allogeneic bone marrow transplant as part of their frontline treatment regimen, regardless of age at diagnosis.[35]

In addition to more aggressive treatment, AYAs with leukemia are at risk for treatment-related toxicity and lower treatment tolerance compared to younger children. They have higher rates of avascular necrosis, peripheral neuropathy, hepatotoxicity, and mucositis throughout treatment.[36] These side effects may contribute to dose reductions or omissions as a de-escalation of intensity of cancer treatment, decreased adherence to treatment, and lower health-related quality of life, all contributing to poor overall survival. AYAs also have higher infection-related mortality in ALL and AML.[29] AYA survivors of leukemia have increased risks for secondary malignant neoplasms from treatments like etoposide or radiation, as well as increased incidence of chronic cardiovascular, pulmonary, musculoskeletal, and psychiatric conditions, which ultimately contribute to decreased overall survival.[37]

Acuity and Severity of Illness

Decreased access to care seen in the AYA population may lead to a presentation with increased acuity or severity of illness by the point of diagnosis. In a PHIS analysis of patients with pediatric AML, acuity of illness – defined by ICU-level of care via International Classification of Diseases, Ninth Revision (ICD-9) codes – was evaluated. Black patients were found to have increased acuity of illness within the first 72 hours of initial presentation to the hospital and higher mortality in the first 50 days from the start of chemotherapy (early induction) compared to White patients. Acuity of illness was noted in mediation analysis to mediate 61% of this racial disparity in induction mortality.[7]

While acuity of illness has been described to mediate early induction mortality in black patients with AML, information about longer-term outcomes in patients admitted to the ICU is limited.[33,38] Acuity of illness has been described in pediatric oncology patients with respect to mortality following the first phases of chemotherapy or with respect to in-hospital mortality.[6,7,9]

In a PHIS-based study of acuity of illness and hospital mortality in AML patients, patients aged ≥10 years were significantly more likely than patients <10 years old to require ICU-level resource use in the first 9 months of treatment. In addition, patients aged 15-18 had higher odds of in-hospital mortality during an ICU admission compared to patients aged 3-9.[6]

In a cohort study of pediatric patients with sepsis admitted to the ICU in the state of Washington during 1990 to 2004, 6.5% of initial survivors had late death, defined as 28 days after discharge, with a median time to death of 1 year (interquartile range 1 month to 12.5 years). An oncologic diagnosis was associated with a higher hazard ratio of late death, with a higher risk of death in the first 2 years after discharge and a cumulative hazard of death of 30% at 5 years.[38,39] However, this study does not account for oncology patients who did not have severe sepsis.

Significance of Study

AYA patients with leukemia are more likely to be uninsured or underinsured; insurance status is known to be associated with advanced-stage disease at the point of a cancer diagnosis.[22] AYA patients are also more likely to have more aggressive disease biology, which may contribute to increased disease burden. Acuity and severity of illness are surrogates for disease-related organ injury and disease burden, respectively; they have not been evaluated in pediatric leukemia and may explain age-related differences in overall survival. Understanding their roles in leukemia outcomes is an essential step toward identifying areas for intervention to improve access to and quality of care for AYA patients.

METHODS

Specific Aims and Hypotheses

The hypotheses in this study are directed to understanding whether AYAs with a new diagnosis of leukemia presenting to a large pediatric cancer center are more likely than younger children to present with increased acuity or severity of illness, and whether increased acuity or severity of illness explain previously described age-related differences in overall survival. **Acuity of illness** is defined by the need for intensive medical care required for a patient at initial presentation with a leukemia diagnosis. **Severity of illness** is defined as the extent of leukemia burden in the body. Given the NCI definition of high-risk B-ALL, age ≥10 years was used as a threshold for primary analysis, rather than the NCI threshold of age ≥15 years for AYA. We have the following specific aims:

- **Aim 1 (A1):** Describe demographic and disease characteristics of pediatric and AYA patients at initial presentation with a new diagnosis of leukemia.
- **Aim 2 (A2):**
    - **A2.1:** Determine the association between age and acuity of illness at initial presentation among pediatric and AYA patients presenting with a new diagnosis of leukemia.
        - We hypothesize that patients ages ≥10 years at diagnosis are more likely to have high acuity of illness at initial presentation compared to patients ages 1-9 years.
    - **A2.2:** Determine the association between age and severity of illness at initial presentation among pediatric and AYA patients presenting with a leukemia diagnosis.

        - We hypothesize that patients ages ≥10 years at diagnosis are more likely to have high severity of illness compared to patients ages 1-9 years.

- **Aim 3 (A3):**
    - **A3.1:** Determine the association between acuity of illness at initial presentation and overall survival at 6 months, 1 year, 2 years, and 5 years among pediatric and AYA patients with leukemia.
        - We hypothesize that high (versus low) acuity of illness is associated with decreased overall survival across all time points.
    - **A3.2:** Determine the association between severity of illness at initial presentation and overall survival at 6 months, 1 year, 2 years, and 5 years among pediatric and AYA patients with leukemia.
        - We hypothesize that high (versus low) severity of illness is associated with decreased overall survival across all time points.
    - **A3.3:** Determine whether differences in overall survival between age groups are mediated by acuity or severity of illness at initial presentation.
        - We hypothesize that high acuity or severity of illness mediate age-related differences in overall survival across all time points.

Study Design and Population Selection

This study was a retrospective analysis of a cohort of patients newly diagnosed with leukemia at Children's Healthcare of Atlanta (CHOA) between 2010-2018. Eligible subjects were identified from the CHOA Cancer Registry and linked to electronic medical record (EMR) data via a corporate identification number (the unique patient identifier). The study cohort included patients aged 1-21 years who initially presented to CHOA during 2010-2018 with a new

diagnosis of leukemia. We excluded patients who were initially diagnosed outside of CHOA and subsequently transferred to CHOA. Patients younger than 1 year of age at diagnosis were also excluded, as infant leukemia represents a very high-risk age group for poor outcomes, and these patients receive substantially different treatment compared to children older than one year old.[9] Patients with B- cell lymphoma and T-cell lymphoma were also excluded.

The study protocol was approved by the CHOA Institutional Review Board.

Data Collection and Definitions

Patients eligible for inclusion in the study were identified through the CHOA cancer registry. Demographic characteristics obtained from the cancer registry included sex assigned at birth, race and ethnicity, health insurance status at diagnosis, and type of leukemia. Data on patient disease characteristics were manually abstracted from the EMR by three study team members (TJ, AH, and CC) into a secure REDCap database, guided by a standard operating procedure manual. Variables abstracted about a patient's clinical course included: medications, procedures, clinical services rendered, and hematologic laboratory values for the 30 days before and the first 72 hours following initial presentation to the hospital.

A total of 815 patients were identified who were treated for leukemia at CHOA between 2010-2018. Of these, 45 patients were excluded because they were less than 1 year of age, and 82 patients were excluded because they did not initially present to CHOA when they were diagnosed with leukemia. The final cohort for analysis consisted of 688 patients with leukemia meeting inclusion criteria (**Figure 2**).

Primary Exposure - Age Group

The age of a patient at presentation was considered the primary exposure. For the main analysis, age was dichotomized into two groups (1-9 years of age and 10-21 years of age), based on age 10 years being the previously defined risk criteria for poor event-free survival in ALL by the National Cancer Institute (NCI).[2] In sensitivity analyses, we used an alternative age cutoff point of 15 years based on the NCI definition of AYA (15-39 years).

Covariates

Based on prior literature and our conceptual model (Figure 1), the following demographic and disease-related covariates were included: sex assigned at birth, race and ethnicity, insurance type at the time of diagnosis, and specific leukemia diagnosis:

- **Sex assigned at birth:** Male or female[40]
- **Race and ethnicity:** Non-Hispanic White, Non-Hispanic Black, Hispanic, and non-Hispanic others (including Asian, American Indian/Alaska Native, and Native Hawaiian/Pacific Islander)
- **Insurance status at diagnosis:** Private insurance, Medicaid (including 3 patients with self-pay), or both private insurance and Medicaid
- **Types of leukemia:** B-cell acute lymphoblastic leukemia (B-ALL), acute myeloid leukemia (AML), T-cell acute lymphoblastic leukemia (T-ALL), and other leukemias [including juvenile myelomonocytic leukemia (JMML), chronic myeloid leukemia (CML), and Burkitt's leukemia]

Primary Outcomes: Acuity or Severity of Illness at Initial Presentation

The primary outcomes of interest were: 1) acuity of illness in the first 72 hours following patient presentation and 2) severity of illness in the first 72 hours following patient presentation.

Acuity of illness was defined by the need for ICU admission or any ICU-level resource use. We manually abstracted data on the history of ICU admission and the type of ICU care needed: cardiovascular (vasopressor support to maintain blood pressure, cardiovascular procedures), respiratory (respiratory support, including non-invasive positive pressure and mechanical ventilation), renal (continuous veno-venous hemofiltration or hemodialysis), hematologic (leukapheresis, plasmapheresis), and neurologic (intracranial pressure monitoring, external ventricular drain placement, ventriculoperitoneal shunt placement, emergent laminectomy) organ involvement. The acuity of illness was dichotomized into any ICU-level resource utilization (high acuity) versus no ICU-level resource utilization (low acuity), regardless of physical admission to the ICU.

To assess severity of illness, we manually abstracted information on white blood count (WBC) and central nervous system (CNS) disease status at initial presentation. The severity of illness was dichotomized to high severity (WBC greater than or equal to 50,000 cells/microliter or any CNS disease) versus low severity.

Overall Survival

Patient vital status (i.e., date of death) was ascertained as of December 31, 2020, from the Geogia Cancer Registry, which captures data from the National Death Index. Overall survival was assessed at 6 months, 1 year, 2 years, and 5 years.

Statistical Analysis

In our main analysis, age was dichotomized into two groups (1-9 years of age and 10-21 years of age) based on the NCI criteria for high-risk B-ALL. Statistical analyses were performed

in SAS v.9.4 (Cary, NC) and R v.4.2.3. Statistical significance was pre-specified at p=0.05; all statistical tests were 2-sided.

Aim 1

Distributions of all study variables were examined, and descriptive statistics were reported. Categorical variables were summarized using counts and percentages, and continuous variables were described using means (standard deviation) or medians (interquartile range [IQR]). Bivariate comparisons were conducted to identify differences in patient characteristics and study outcomes between age groups, using Chi-Square tests or Fisher's exact tests, as appropriate.

Aim 2

Logistic regression was used to examine the association between age group and the likelihood of high acuity of illness, as well as the association between age group and the likelihood of high severity of illness. Odds ratios (OR) and 95% confidence intervals (CI) were calculated. Both unadjusted and multivariable models were applied. Multivariable models were adjusted for sex assigned at birth, race and ethnicity, insurance status at diagnosis, and type of leukemia, and were specified as follows:

$$log\frac{p(High\ acuity=1)}{1-p(High\ acuity=1)} = \beta_0 + \beta_1(\text{Age Group}) + \beta_2(\text{Sex Assigned at Birth}) + \beta_3(\text{Race/Ethnicity}) + \beta_4(\text{Insurance Status at Diagnosis}) + \beta_5(\text{Type of Leukemia})$$

$$log\frac{p(High\ severity=1)}{1-p(High\ severity=1)} = \beta_0 + \beta_1(\text{Age Group}) + \beta_2(\text{Sex Assigned at Birth}) + \beta_3(\text{Race/Ethnicity}) + \beta_4(\text{Insurance Status at Diagnosis}) + \beta_5(\text{Type of Leukemia})$$

Aims 3.1 and 3.2

Kaplan-Meier survival curves and Cox proportional hazards models were used to model time from initial cancer diagnosis to death. Patients known to be alive were censored on December 31, 2020, or at different time points (6 months, 1 year, 2 years, and 5 years) post-diagnosis. Survival distributions were plotted using Kaplan-Meier survival curves and compared using log-rank tests. Multivariable Cox proportional hazards models were conducted to examine the association between high acuity (or high severity) of disease at presentation and overall survival, at 6 months and 1, 2, and 5 years post-diagnosis, controlling for covariates described above. The proportional hazards assumption was verified based on Schoenfeld residuals and further examined graphically using log-log survival curves (**Supplemental Figure 1**). The model specification is as follows, where *h(t)* is the hazard rate and $h_0(t)$ is the background hazard of death when all covariates are 0.

$$h(t) = h_0(t) \times e^{\beta_1(High\ Acuity)+\beta_2(Sex\ Assigned\ at\ Birth)+\beta_3(Race\ and\ Ethnicity)+\beta_4(Insurance\ Status\ at\ Diagnosis)+\beta_5(Type\ of\ Leukemia)}$$

$$h(t) = h_0(t) \times e^{\beta_1(High\ Severity)+\beta_2(Sex\ Assigned\ at\ Birth)+\beta_3(Race\ and\ Ethnicity)+\beta_4(Insurance\ Status\ at\ Diagnosis)+\beta_5(Type\ of\ Leukemia)}$$

Aim 3.3

Mediation analysis was performed to quantify the degree to which the association between age and overall survival was explained by the acuity of illness at initial presentation (or by the severity of illness at initial presentation). The *regmedint* package in R was used for this calculation, which allows for non-parametric models like Cox proportional hazards regression.[41] The mediation analysis included the following steps:[7]

1. Verify overall survival differences by age group using Cox proportional hazards regression, controlling for the aforementioned covariates (but not acuity or severity).

2. Examine and verify a statistically significant association between age group and acuity (or severity) of illness at presentation using logistic regression (Aim 2), controlling for the aforementioned covariates.
3. Examine and verify a statistically significant association between acuity (or severity) of illness at presentation and overall survival using Cox proportional hazards regression, controlling for the aforementioned covariates, including age group.[41]
4. Estimate the total effect, direct effect, and indirect effect. The association between age and overall survival, or total effect, can be divided into direct and indirect effects (**Figure 3**). The total effect was the sum of the direct and indirect effects, representing the total influence that age group had on overall survival. The direct effect was defined as the effect of age group on overall survival that is not mediated through acuity (or severity) of illness; it is the influence that age group has directly on overall survival without going through the mediator (acuity [or severity]). The indirect effect was defined as the effect of age group on overall survival that occurs through the mediator (acuity [or severity]); it quantified the extent to which the association between age group and overall survival was explained by the acuity's (or severity's) influence. The proportion of this association that was mediated by acuity (or severity) of illness was calculated by using the R *regmedint* package, with the following equation:[7,41]

$$Proportion\ Mediatiated\ by\ Acuity\ or\ Severity\ of\ Illness$$

$$= \frac{e^{Direct\ Effect}(e^{Indirect\ Effect} - 1)}{(e^{Direct\ Effect}e^{Indirect\ Effect}) - 1}$$

Sensitivity Analyses

Age was dichotomized into two groups (1-14 years of age and 15-21 years of age) based on the NCI age threshold definition of AYA. In addition, age was analyzed as a continuous variable.[4,16] The associations of these alternative measures of age with acuity (or severity) of illness, and with overall survival, were estimated.

Moreover, a composite score of high acuity and high severity of illness was created, with a score of 0 for both low acuity and severity, 1 for either high acuity or high severity, and 2 for both high acuity and high severity. The composite score was then dichotomized into 0-1 versus 2. Logistic regression was used to evaluate the association between age group and composite score of 2 (versus 0-1), with and without controlling for covariates. Furthermore, the Cox proportional hazards regression was used to determine the association between a composite score of 2 and overall survival. Finally, mediation analysis was performed using the *regmedint* package as described above.

RESULTS

Aim 1: Cohort Characteristics

Patient demographic and disease characteristics are reported in **Table 1**. Age had a right-tailed distribution (**Supplemental Figure 2**). The median age was 6 years (interquartile range: 3-12 years). Overall, 53.8% were male, 48.1% were non-Hispanic White, 25.0% were non-Hispanic Black, and 41.9% had private insurance at the point of diagnosis. Diagnoses included B-cell acute lymphoblastic leukemia (ALL) (68.3%), AML (16.7%), T-cell ALL (10.8%), and other leukemias (4.2%).

Comparing patients ages 10-21 with those ages 1-9, nonsignificant differences were seen in the distribution of sex assigned at birth, but significant differences were seen in race/ethnicity ($p=0.04$), insurance status at diagnosis ($p=0.04$), and type of leukemia ($p<0.01$) (**Table 1**). Specifically, a higher proportion of patients 10-21 years of age were non-Hispanic Black compared to those aged 1-9 years (30.9% versus 21.9%). Patients aged 10-21 years were more likely than those ages 1-9 years to have private insurance at diagnosis (46.6% versus 39.4%), and to have AML (24.2% versus 12.8%), T-ALL (16.5% versus 7.7%), and other leukemias (7.2% versus 2.6%).

Aim 2.1: Association Between Age Group and Acuity of Illness

Of the 688 patients in our analytic sample, 170 (24.7%) presented with a high acuity of illness. A higher proportion of patients aged 10-21 years than those of younger age needed ICU admission (30.1% versus 17.3%, $P<0.01$), any cardiovascular (6.4% versus 2.0%, $P<0.01$), respiratory (19.1% versus 7.3%, $P<0.01$), and renal resource utilization (4.2% versus 1.1%, $P<0.01$) in the 72 hours following presentation (**Figure 4)**.

Patients aged 10-21 years had an increased likelihood of presenting with a high acuity of illness compared to those aged 1-9, in both the unadjusted model (OR: 2.35, 95% CI: 1.65-3.36) and multivariable model (OR: 1.94, 95% CI: 1.32-2.85; **Table 2**).

There was a statistically nonsignificant association between sex and the odds of presenting with a high acuity of illness (**Table 2**). Non-Hispanic Black patients had an increased odds of presenting with a high acuity of illness than non-Hispanic White patients in the unadjusted model (OR: 2.01, 95% CI: 1.34-2.95), but not in the multivariable model (OR: 1.32, 95% CI: 0.84-2.07). Patients with Medicaid or uninsured/self-pay had an increased odds of presenting with high acuity of illness in the multivariable model (OR: 1.66, 95% CI: 1.08-2.53).

High acuity of illness was seen in 22.4% of ALL and 33.0% of AML patients. Compared to patients with B-ALL, patients with AML (OR: 2.37, 95% CI: 1.50-3.74), T-ALL (OR: 5.97, 95% CI: 3.56-10.01), and other types of leukemia (OR: 2.53, 95% CI: 1.13-5.64) were more likely to present with a high acuity of illness in the unadjusted model (**Table 2**). A diagnosis of AML (OR: 1.91, 95% CI: 1.18-3.08) and T-ALL (OR: 4.94, 95% CI: 2.84-8.60) remained independent associations for acuity of illness in the multivariable model.

Aim 2.2: Association Between Age Group and Severity of Illness

Of the 688 patients, 262 (38.1%) presented with high severity of disease. The proportion of patients with WBC $\geq$ 50,000 cells/microliter (35.2% versus 21.3%, P<0.01) or with any CNS disease (29.2% versus 22.2%, P=0.04) was higher among patients aged 10-21 than those younger (**Figure 5**).

In the unadjusted model, patients aged 10-21 years had an increased odds of presenting with high severity of illness compared to those aged 1-9 (OR: 1.63, 95% CI: 1.18-2.25), but this

association became nonsignificant in the multivariable model (OR: 1.25, 95% CI: 0.88-1.78) that adjusted for demographics and leukemia type (**Table 3**).

Non-Hispanic Black patients had an increased odds of presenting with high severity of illness in both unadjusted (OR: 2.37, 95% CI: 1.62-3.45) and multivariable (OR: 1.80, 95% CI: 1.18-2.74) models (**Table 3**). Compared to patients with B-ALL, a diagnosis of AML or T-ALL was an independent risk factor for disease severity. Specifically, patients with AML (OR: 2.25, 95% CI: 1.48-3.41), T-ALL (OR: 5.44, 95% CI: 3.20-9.26), and other types of leukemia (OR: 5.46, 95% CI: 2.42-12.28) had higher odds of presenting with a high severity of illness in the unadjusted model. This association persisted in the multivariable model for AML (OR: 1.94, 95% CI: 1.25-2.99), T-ALL (OR: 4.67, 95% CI: 2.67-8.16), and other types of leukemia (OR: 4.99, 95% CI: 2.17-11.50).

Aim 3.1: **Association between acuity of illness and overall survival**

Overall survival at a median follow-up of 3.2 years was lower among patients with a high acuity of illness at initial presentation than those with a low acuity of illness (log-rank test: P = 0.02) (**Figure 6**). The greatest separation between Kaplan-Meier curves occurred at one year from diagnosis. Notably, the median time to death was not identified, as 50% of patients had not died by 5 years post-diagnosis.

In the Cox proportional hazards model without controlling for covariates, high (versus low) acuity of illness was significantly associated with a higher risk of death at 6 months (hazard ratio [HR]: 3.70, 95% CI: 1.72-7.99), 1 year (HR: 2.40, 95% CI: 1.30-4.42) and 5 years (HR 1.72, 95% CI 1.09-2.71) post-diagnosis **(Table 4a)**. In Cox models controlling for covariates, this association remained statistically significant when estimating the risk of death at 6 months

(HR: 3.82, 95% CI: 1.77-8.24) and 1-year post-diagnosis (HR: 2.10, 95% CI 1.14-3.92) **(Table 4b).**

Aim 3.2: **Association between severity of illness and overall survival**

Overall survival was not statistically significantly lower for patients with a high severity of illness at initial presentation compared to those with a low acuity of illness (log-rank test: P = 0.3) (**Figure 7**).

In Cox regression models, high severity of illness was not statistically significantly associated with the risk of death at 6 months or 1, 2, or 5 years post-diagnosis **(Table 5a, Table 5b).**

Aim 3.3: Mediation analysis of acuity of illness on the association between age and overall survival

Patients aged 10-21 years with a diagnosis of leukemia had lower overall survival compared to those aged 1-9 years (P<0.01) (**Figure 8**). In Cox models without controlling for covariates, compared to patients aged 1-9 years, those aged 10-21 years had an increased risk of death at 6 months (HR: 3.12, 95% CI: 1.42-6.87), 1 year (HR: 2.64, 95% CI 1.43-4.85), 2 years (HR: 3.00, 95% CI 1.84-4.88), and 5 years post-diagnosis (HR: 2.98, 95% CI 1.92-4.60) **(Table 6a)**. In multivariable models, the association of older age with mortality persisted with adjustment for sex, race/ethnicity, insurance status at diagnosis, and type of leukemia (without adjusting for acuity or severity) at 6 months (HR 3.08, 95% CI 1.27-7.45), 1 year (HR: 2.43, 95% CI 1.25-4.74), 2 years (HR: 2.46, 95% CI 1.44-4.18), and 5 years (HR 2.47, 95% CI: 1.53-3.99) post-diagnosis **(Table 6b)**; these estimates reflect the “total effect.”

As detailed above, a statistically significant association was found between older age and high acuity of illness in unadjusted and multivariable models (**Table 2**). In addition, high acuity was associated with overall survival (**Table 4, Table 5**). Given the lack of association of severity of illness and age, mediation analysis was only performed to evaluate the acuity of illness as a mediator of the association between age group and overall survival.

Table 7 demonstrates the results of the mediation analysis. After adjusting for covariates, at 6 months post-diagnosis, the "direct effect" of age on overall survival – including the adjustment of high acuity in the model – was statistically significant and reduced from the total effect (HR: 2.71, 95% CI: 1.17-6.27), the "indirect effect" of age on overall survival through acuity was statistically significant (HR: 1.18, 95% CI: 1.01-1.40), and the high acuity of illness explained a significant proportion of the association between age group of 10-21 (versus 1-9) and overall survival (23%, 95% CI: 2-44%). At 1, 2, and 5 years post-diagnosis, the "direct effect" of age on overall survival – including the adjustment of high acuity in the model – remained statistically significant; yet, the mediation effect of acuity of illness on the association between age group and overall survival at later time points was statistically nonsignificant.

Sensitivity Analyses

There were 104 patients aged 15-21 years at initial diagnosis **(Supplemental Table 1)**. Compared to patients aged 1-14 years, patients aged 15-21 years had increased odds of high acuity of illness in the unadjusted model (OR: 1.87, 95% CI: 1.19-2.92), but this association was not statistically significant in the multivariable model (OR: 1.60, 95% CI: 0.99-2.60) **(Supplemental Table 2)**. Patients aged 15-21 years did not have increased odds of high severity of illness compared to patients aged 1-14 **(Supplemental Table 3)**.

When treating age as a continuous measure, every 1-year increase in age was associated with increased odds of high acuity of illness in both unadjusted (OR: 1.06, 95% CI 1.03-1.10) and multivariable (OR: 1.05, 95% CI: 1.01-1.09) models **(Supplemental Table 3)**. Additionally, every 1-year increase in age was associated with increased odds of high severity of illness in the unadjusted model (OR: 1.04, 95% CI: 1.01-1.07), but not in the multivariable model. (**Supplemental Table 3**).

When estimating the composite score, patients ages 10-21 years were more likely than those ages 1-9 years to have both high acuity and high severity (score of 2) at presentation in the unadjusted model (OR: 2.56, 95% CI: 1.69-3.88) and the multivariable model (OR: 1.96, 95% CI: 1.24-3.10) (**Supplemental Table 4)**.

A composite score of 2 (versus score of 0 or 1) was associated with decreased overall survival in the unadjusted Cox model at 6 months (HR: 2.92, 95% CI: 1.30-6.56), 1 year (HR: 2.22, 95% CI: 1.13-4.35), and 5 years (HR: 1.87, 95% CI: 1.09-3.22) post-diagnosis **(Supplemental Table 5)**. Consistent patterns were visualized in the Kaplan-Meier curves **(Supplemental Figure 4)**. The composite score did not explain a statistically significant proportion of the association between age and overall survival at 6 months or 1-, 2-, and 5-year post-diagnosis **(Supplemental Table 6)**.

DISCUSSION

While overall survival has improved across all age groups, these improvements are not as pronounced in patients with AYA leukemia.[14] Decreased access to healthcare and an increased rate of high-risk disease biology by age may lead to differences in acuity or severity of illness at initial presentation with leukemia. In turn, acuity or severity of illness may in part drive previously noted age-related survival differences and represent areas for potential intervention to improve outcomes, but their associations with age and overall survival have not previously been explored. We aimed to 1) describe demographic and disease characteristics of pediatric and AYA patients with new leukemia, 2) determine the association of age group with acuity or severity of illness, and 3) determine the association of acuity or severity of illness and overall survival and whether acuity or severity of illness mediate the relationship between age and overall survival.

In this single institution cohort of patients with leukemia, we found that age was associated with acuity of illness at presentation, which in turn was associated with overall survival. Acuity of illness accounted for 23% of the association between age and overall survival at 6 months. In contrast, severity of illness, as a reflection of disease extent/burden as measured in this analysis, was not associated with age at presentation or overall survival.

Prior studies have assessed the role of acuity of illness in overall survival among patients with pediatric leukemia, as determined by ICU-level resource use based on ICD-9 diagnoses, within the PHIS database **(Supplemental Table 7)**. However, compared to our study, these prior studies differ in approach and population (PHIS database ICD codes; PHIS data containing patients from multiple sites, demographics), primary exposure (e.g. race or age <1 year), disease type (e.g. restricted to AML patients in two studies), and outcomes (e.g. induction or in-hospital mortality). Thus far, this is the first study describing acuity of illness across all types of leukemia

with respect to age group and the AYA population and assessing their role in long-term overall survival past induction or in-hospital mortality.

In keeping with our hypothesis for specific aim 2, we demonstrated the association between older age and acuity of illness. Age was independently associated with acuity at initial presentation when evaluated as a continuous variable (OR: 1.05, 95% CI: 1.01-1.09) or with a cutoff of 10 years (OR: 1.94, 95% CI: 1.32-2.85). When examining the age threshold of 15 years, set by the NCI as the lower bound for AYA, the OR was in the same direction, although not statistically significant in this smaller single institution experience, which is likely underpowered for the analysis.

Insurance status at diagnosis and type of leukemia were also noted to be independently associated with acuity of illness at presentation. While unadjusted models indicated Non-Hispanic Black patients were two times as likely to present with high acuity of illness than Non-Hispanic White patients (OR: 2.37, 95% CI 1.62-3.45), this association was not noted in multivariable models inclusive of insurance status and disease type, which did differ by race/ethnicity **(Table 1**, **Supplemental Table 8)**. Given that Medicaid insurance, AML, and T-ALL were independent associations with high acuity of illness, differences in insurance status or type of leukemia by race/ethnicity may account for differences in acuity of illness and represent important future areas for exploration. Interestingly, patients aged 1-9 were more likely to have Medicaid or be self-pay than patients 10-21, suggesting that differences in insurance status were not driving age-related differences in acuity of illness in this cohort.

Acuity of illness may be related to disease biology. In this analysis, AML and T-ALL were found to have an increased likelihood of high acuity of illness than B-ALL, which may explain previously noted lower overall survival compared to B-ALL with these diseases.

However, whether this relationship is maintained when AML and T-ALL are compared to patients with molecular markers of high-risk B-ALL (e.g. Ph-like disease, intrachromosomal amplification of chromosome 21) is unknown. AML also has alterations associated with poor prognosis (e.g. FLT3/ITD activating mutations) that may contribute to increased acuity. In one study of patients aged 15 years or older in the Danish national registry, neither AML cytogenetic risk group nor the presence of Philadelphia chromosome in ALL patients were associated with increased risk of ICU admission. However, this study accounted for any admission to the ICU within 3 years following diagnosis – rather than at initial presentation – did not include patients less than 15 years of age, and did not address other markers of acuity of illness outside of ICU admission.[42]

A novel finding in our single institution cohort is that acuity of illness at initial presentation was noted to be associated with overall survival. This differs from previous studies looking at any ICU admissions. Separation of Kaplan-Meier curves for high versus low acuity of illness occurs early after initial presentation. These early changes in outcomes may reflect increased mortality associated with MODS.[33,38] While high acuity of illness is not statistically associated with overall survival at 2 years (OR: 1.57, 95% CI 0.94-2.63), a significant association is observed at 5 years (OR: 1.72, 95% CI 1.09-2.71). This pattern is also seen in Kaplan-Meier curves, with an increased gap in overall survival between low and high acuity of illness after the 2-year mark. These results indicate differing patterns and drivers of mortality in early versus later time periods following initial diagnosis. Early mortality may be due to increased morbidity, and therefore toxic death in remission, from requiring ICU admission or ICU level care at initial diagnosis.[33,38] The pattern of later mortality by initial acuity level may represent a downstream effect of high acuity at presentation; patients are at risk for relapse due to

delays in leukemia treatment or inability to deliver full intensity of leukemia therapy because of end-organ morbidity following a tenuous clinical status at presentation. Future directions could assess minimal residual disease by acuity of illness to study whether high acuity of illness impacted chemotherapy delivery; the presence of minimal residual disease after the first phases of chemotherapy portends a poorer prognosis and increased risk for relapse and death.

We note an association between age group and overall survival across all time points. These results are consistent with previous findings by the NCI that patients ≥10 years of age with B-ALL have lower event-free survival compared to younger patients.[2,10] Notably, our cohort also contains patients with T-ALL, AML, and other leukemias that are considered to have higher risk of treatment failure than standard-risk B-ALL, for which age has not previously been considered a prognostic factor, and older patients were found to be more likely to have these diseases. However, the independent association between age and overall survival persists even after adjusting for type of leukemia.[10,11] These results raise a question regarding the NCI definition of "AYA" risk and whether the age threshold for poor outcomes should be lowered from 15 to 10 for not only B-ALL, but other types of leukemia as well.

In mediation analysis, acuity of illness did not account for a statistically significant proportion of the association between age and overall survival at 1, 2, or 5 years. However, at 6 months, acuity of illness explained 23% of age-related differences in overall survival. As time since initial presentation increases, other outcomes and causes of death are important to consider, which are not included in this analysis. For example, relapse or toxic death may account for a higher proportion of differences in overall survival, with longer follow-up time in older children who are known to have more biologically aggressive molecular factors driving disease resistance and the associated increase in toxicity with the needed therapy intensity.

In contrast to other diseases, since leukemia does not have a staging system, we used WBC counts and CNS status as an indicator of disease burden labeled as disease severity. Increased odds of high severity of illness in those aged 10-21 on unadjusted, but not multivariable, analysis may be reflective of the heterogeneity of types of leukemia included in this cohort. For example, AML and T-ALL are more common in patients aged 10-21 in this cohort and are also more commonly associated with higher WBC on presentation, consistent with previous literature.[12,13,31] However, Non-Hispanic Black patients were almost two times as likely to present with high severity of illness than Non-Hispanic White patients in the multivariable model (OR: 1.80, 95% CI 1.18-2.74). Given that type of leukemia was accounted for in multivariable models, increased severity of illness may reflect delays due to decreased access to healthcare and additional social determinants of health not explored in this study, including area deprivation, systemic racism, and insurance discontinuity.

Severity of illness was not noted to be associated with overall survival. Furthermore, on combining high acuity and severity of illness, mediation analyses of the composite score on the association between age and overall survival did not meaningfully change, although the score does not account for a statistically significant proportion of this association at 6 months. This finding may be due to a lack of power, which would be increased by increasing sample size. Nevertheless, other causes of ICU-resource use and high acuity other than the contribution of high severity may play a larger role in overall survival. While our study used WBC and CNS status in the definition of severity of illness, additional granular data from the EMR may be employed to further characterize the extent of leukemia burden in the body. For example, in a study of patients exploring the association of race and acuity of illness at Children's Hospital of Philadelphia and Texas Children's Hospital, Non-Hispanic Black patients with AML were noted

to have higher rates of WBC > 50,000 cells/microliter and uric acid > 10 mg/dL, and Non-Hispanic Black patients with ALL had higher rates of coagulopathy and more than one lab abnormality.[8] Alternative WBC thresholds, such as the hyperleukocytosis definition of ≥100,000 cells/microliter, may also be important to consider.

Study Limitations and Future Directions

While acuity and severity of illness were dichotomized into high versus low with the presence of any contributory factor, each factor may not contribute equally to overall survival differences. For example, early respiratory, hematologic, and neurologic requirements have been associated with higher odds of death than cardiovascular morbidity or transient renal support requirements in younger patients.[33] In addition, the requirement of ICU-level resources for more than one organ system, or MODS, has also been described to be associated with decreased overall survival.[33,38,43] MODS has been described by a number of different criteria, such as the more recent Pediatric Sequential Organ Failure Assessment (pSOFA) score, which accounts for the SpO_2:FiO_2 (peripheral oxygen saturation : fraction of inspired oxygen) ratio, platelet count, bilirubin, mean arterial pressure or vasopressor rate, Glasgow Coma Scale, and creatinine.[43] The requirement for different types of interventions, such as degree of respiratory support, was not accounted for in this study. MODS can also vary by time, and progressive MODS is associated with decreased overall survival.[38]

While CHOA treats 90% of pediatric oncology cases in Georgia and parts of surrounding states, generalizability is limited by this study being conducted at a single institution. Next steps to address this issue include expanding the cohort to patients presenting to and treated by adult oncology at Emory University Winship Cancer Institute, which would also increase power by increasing the number of AYA patients > 21 years in the cohort.

This study also evaluated only overall survival and did not account for other outcomes, such as progression-free survival. Progression-free survival, which examines relapse, has also previously been described to differ by age and may also differ by acuity and severity of illness through the same causal pathway described in **Figure 1.** Accounting for relapse in overall survival and analysis of event-free survival would refine mediation analysis, especially for later mortality.

Evaluating measures of health-related quality of life are also important considerations, as problems such as cognitive impairment and financial toxicity due to ICU-level interventions contribute to decreased event-free and overall survival.[33,38] Use of intensive care unit (ICU)-level resources account for one-third of hospital costs in the United States, and multi-organ dysfunction may lead to increased long-term morbidity that exacerbates cost of care.[38] Patients may face health-related debt and out-of-pocket costs not covered by insurance, as well as interrupted education and work as a consequence of treatment. Compared to those in the same age range without a history of cancer, AYA cancer survivors were noted to have higher annual medical expenditures, regardless of insurance type. They also had higher annual per capita lost productivity compared to those without a history of cancer, as a result of missed work days due to illness or injury.[44] These issues can contribute to difficulties affording treatment and psychological distress, which in turn can lead to worse overall survival.[17]

Future interventions may be focused on modifiable risk factors of high acuity of illness, such as social determinants of health and access to equitable healthcare **(Figure 1)**. A mixed methods approach can be used to build on the results from this study and identify challenges AYA patients at CHOA face. Interventions to raise awareness among community care providers who see AYA patients may also be beneficial.

Conclusions

We found that among children aged 1-21, older age is independently associated with acuity of illness, which explains age-related differences in overall survival at 6 months. In the short term, these findings may be related to death from acute illness, complications from ICU admission, and recurrent hospitalization.[39] While acuity of illness did not explain a statistically significant proportion of the relationship between age and overall survival at 1, 2, and 5 years, the findings are still clinically relevant, especially since interventions to reduce acuity of illness would improve outcomes at all time points.

Decreased access to care due to social determinants of health, area deprivation, insurance discontinuity and systemic racism is one reason why patients may have increased acuity of illness at presentation, and this problem is particularly pervasive in the AYA population. By identifying high-risk groups for increased acuity, one can create interventions to improve outcomes for patients with leukemia before they ever present to the hospital.

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TABLES AND FIGURES

Figure 1: Conceptual Model of Association Between Age and Overall Survival, Mediated by Acuity or Severity of Illness at Presentation

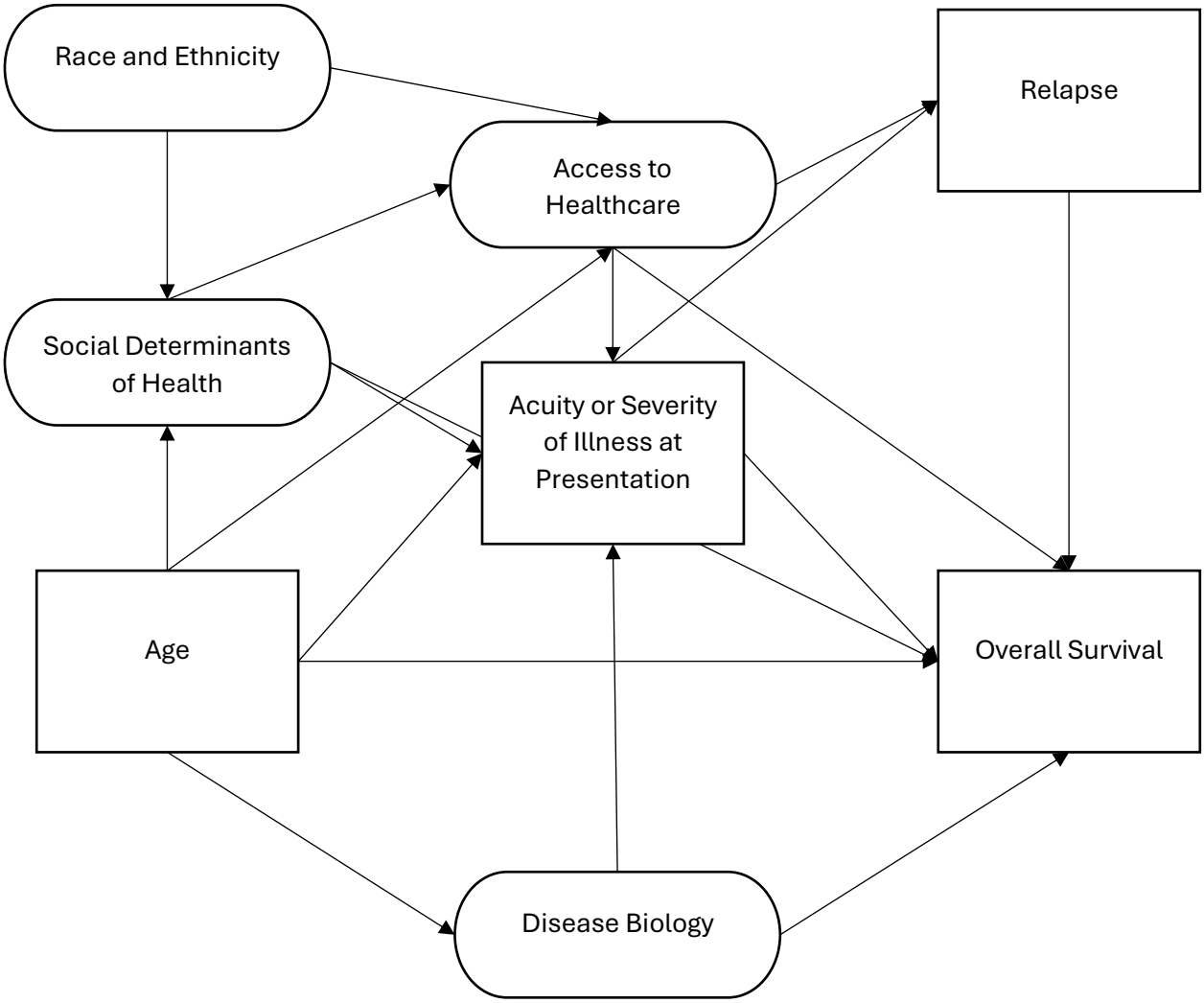
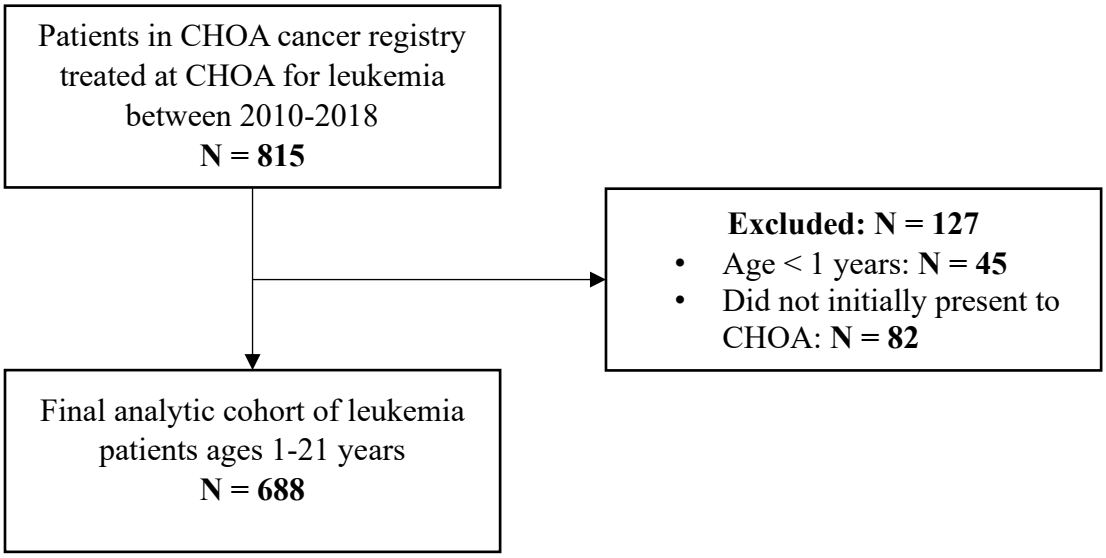


Figure 2: Consort Diagram of Study Population



Abbreviations: CHOA = Children's Healthcare of Atlanta

Figure 3: Variables Considered in Mediation Analysis of the Association of Age Group with Overall Survival: Estimates of the direct (blue) and indirect (green) effects of age group on overall survival

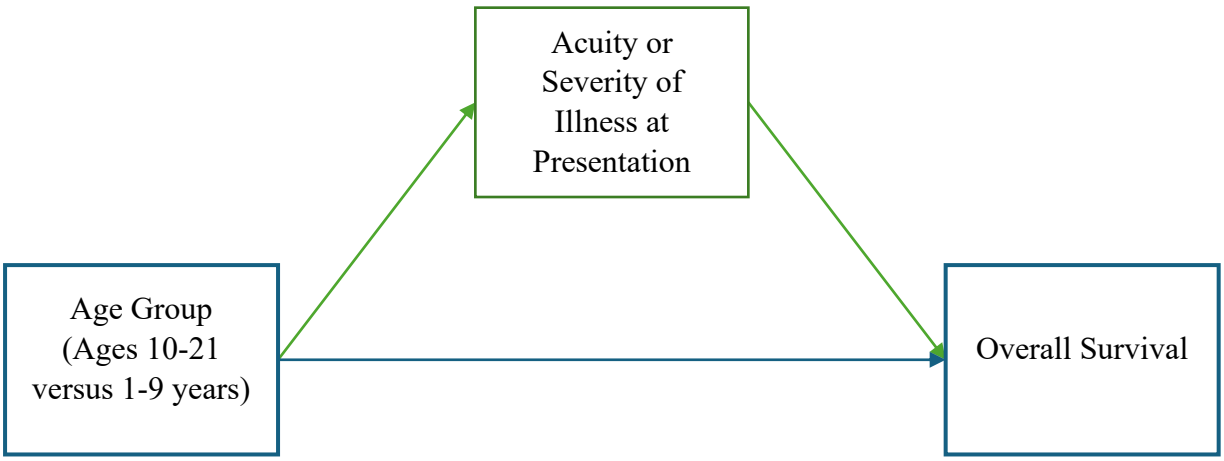


Table 1: Patient and disease characteristics of patients with newly diagnosed leukemia who presented to CHOA between 2010-2018

Participant Characteristics	Age 1-9 N = 452 (65.7%) n (column %)	Age 10-21 N=236 (34.3%) n (column %)	Overall N = 688 n (column %)	P***
Sex				0.19
Male	235 (52.0)	135 (57.2)	370 (53.8)	
Female	217 (48.0)	101 (42.8)	318 (46.2)	
Race/Ethnicity				0.04
Non-Hispanic White	222 (49.1)	109 (46.2)	331 (48.1)	
Non-Hispanic Black	99 (21.9)	73 (30.9)	172 (25.0)	
Hispanic	103 (22.8)	45 (19.1)	148 (21.5)	
Other*	28 (6.2)	9 (3.8)	37 (5.4)	
Insurance Status at Diagnosis				0.04
Medicaid Only or Self-Pay**	250 (55.3)	121 (51.3)	371 (53.9)	
Private Only	178 (39.4)	110 (46.6)	288 (41.9)	
Medicaid and Private	24 (5.3)	5 (2.1)	29 (4.2)	
Type of Leukemia				<0.01
B-ALL	347 (76.8)	123 (52.1)	470 (68.3)	
AML	58 (12.8)	57 (24.2)	115 (16.7)	
T-ALL	35 (7.7)	39 (16.5)	74 (10.8)	
Other (JMML, CML, Burkitt's)	12 (2.6)	17 (7.2)	29 (4.2)	

Abbreviations: B-ALL = B-cell acute lymphoblastic leukemia; AML = acute myeloid leukemia; T-ALL = T-cell acute lymphoblastic leukemia; JMML = juvenile myelomonocytic leukemia; CML = chronic myeloid leukemia

*Other race/ethnicity: Asian (n = 36), American Indian/Alaska Native (n = 1)
**Including 3 patients with Self-Pay
***Chi-Square test of independence

Figure 4: Distribution of acuity of illness by age and by ICU resource utilization overall and by organ system

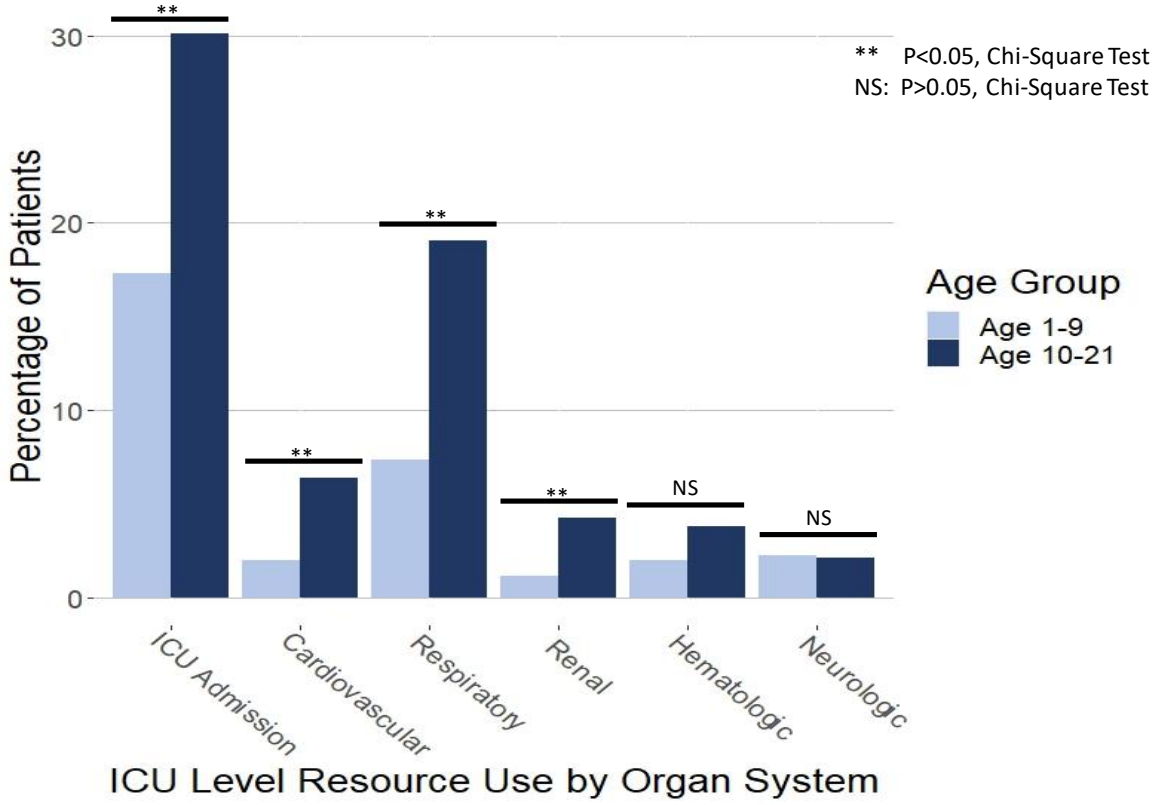


Table 2: Unadjusted and multivariable logistic regression models of high acuity of illness

	High Acuity of Illness	Unadjusted Model of High Acuity		Multivariable Model of High Acuity*	
	N = 170 (24.7%) n (row %)	OR (95% CI)	P***	OR (95% CI)	P***
Age, years					
Age 1-9	86 (19.0)	REF	-	REF	-
Age 10-21	84 (35.6)	2.35 (1.65-3.36)	<0.01	1.94 (1.32-2.85)	<0.01
Sex					
Male	89 (24.1)	REF	-	REF	-
Female	81 (25.5)	1.08 (0.76-1.53)	0.67	1.29 (0.88-1.90)	0.19
Race/Ethnicity					
Non-Hispanic White	74 (22.4)	REF	-	REF	-
Non-Hispanic Black	63 (36.6)	2.01 (1.34-2.95)	<0.01	1.32 (0.84-2.07)	0.23
Hispanic	25 (16.9)	0.71 (0.43-1.17)	0.17	0.62 (0.35-1.08)	0.09
Other**	8 (21.6)	0.96 (0.42-2.19)	0.92	0.81 (0.33-1.99)	0.64
Insurance Status at Presentation					
Private Only	60 (20.8)	REF	-	REF	-
Medicaid Only or Self-Pay	102 (27.5)	1.44 (1.00-2.07)	0.05	1.66 (1.08-2.53)	0.02
Medicaid and Private	8 (27.6)	1.45 (0.61-3.43)	0.40	1.41 (0.56-3.58)	0.46
Type of Leukemia					
B-ALL	81 (17.2)	REF	-	REF	-
AML	38 (33.0)	2.37 (1.50-3.74)	<0.01	1.91 (1.18-3.08)	<0.01
T-ALL	41 (55.4)	5.97 (3.56-10.01)	<0.01	4.94 (2.84-8.60)	<0.01
Other (JMML, CML, Burkitt's)	10 (34.5)	2.53 (1.13-5.64)	0.02	2.09 (0.92-4.78)	0.08

Abbreviations: B-ALL = B-cell acute lymphoblastic leukemia; AML = acute myeloid leukemia; T-ALL = T-cell acute lymphoblastic leukemia; JMML = juvenile myelomonocytic leukemia; CML = chronic myeloid leukemia; OR = odds ratio; CI = confidence interval; REF = reference
*Multivariable model including all variables in table
**Other race/ethnicity: Asian, American Indian/Alaska Native, and Native Hawaiian/Pacific Islander
***Wald test

(See Supplemental Table 2 for sensitivity analyses using age threshold of $<$ or $\geq$ 15 years)

Figure 5: Severity of illness in patients with leukemia by age category

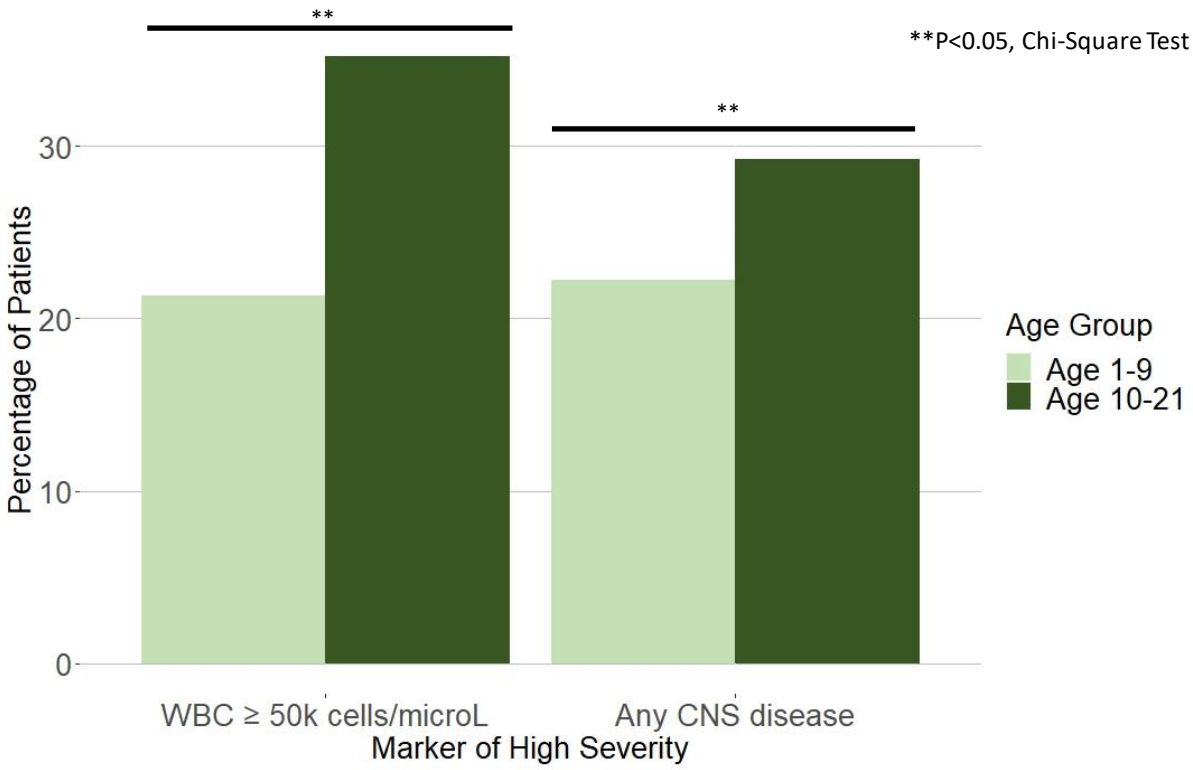


Table 3: Unadjusted and multivariable logistic regression models of high severity of illness

	High Severity of Illness	Unadjusted Model of High Severity		Multivariable Model of High Severity*	
	N = 262 (38.1%) n (row %)	OR (95% CI)	P***	OR (95% CI)	P***
Age, years					
Age 1-9	154 (34.0)	REF	-	REF	-
Age 10-21	108 (45.8)	1.63 (1.18-2.25)	<0.01	1.25 (0.88-1.78)	0.22
Sex					
Male	138 (37.3)	REF	-	REF	-
Female	124 (39.0)	1.08 (0.79-1.46)	0.65	1.26 (0.90-1.77)	0.18
Race/Ethnicity					
Non-Hispanic White	110 (33.2)	REF	-	REF	-
Non-Hispanic Black	93 (54.1)	2.37 (1.62-3.45)	<0.01	1.80 (1.18-2.74)	<0.01
Hispanic	44 (29.7)	0.85 (0.56-1.29)	0.45	0.87 (0.54-1.40)	0.57
Other	15 (40.5)	1.37 (0.68-2.74)	0.37	1.25 (0.60-2.62)	0.56
Insurance Status					
Private Only	100 (34.7)	REF	-	REF	-
Medicaid Only or Self-Pay	148 (39.9)	1.25 (0.90-1.71)	0.17	1.25 (0.86-1.81)	0.25
Medicaid and Private	14 (48.3)	1.76 (0.81-3.78)	0.15	1.65 (0.72-3.81)	0.23
Type of Leukemia					
B-ALL	136 (28.9)	REF	-	REF	-
AML	55 (47.8)	2.25 (1.48-3.41)	<0.01	1.94 (1.25-2.99)	<0.01
T-ALL	51 (68.9)	5.44 (3.20-9.26)	<0.01	4.67 (2.67-8.16)	<0.01
Other (JMML, CML, Burkitt's)	20 (69.0)	5.46 (2.42-12.28)	<0.01	4.99 (2.17-11.50)	<0.01

Abbreviations: B-ALL = B-cell acute lymphoblastic leukemia; AML = acute myeloid leukemia; T-ALL = T-cell acute lymphoblastic leukemia; JMML = juvenile myelomonocytic leukemia; CML = chronic myeloid leukemia; OR = odds ratio; CI = confidence interval

*Multivariable model including all variables in table

**Other race/ethnicity: Asian, American Indian/Alaska Native, and Native Hawaiian/Pacific Islander

***Wald test

(See Supplemental Table 3 for sensitivity analyses using age threshold of < or ≥ 15 years and age as a continuous variable)

Figure 6: Overall survival in patients with leukemia by low (light blue) versus high (dark blue) acuity of illness at initial diagnosis

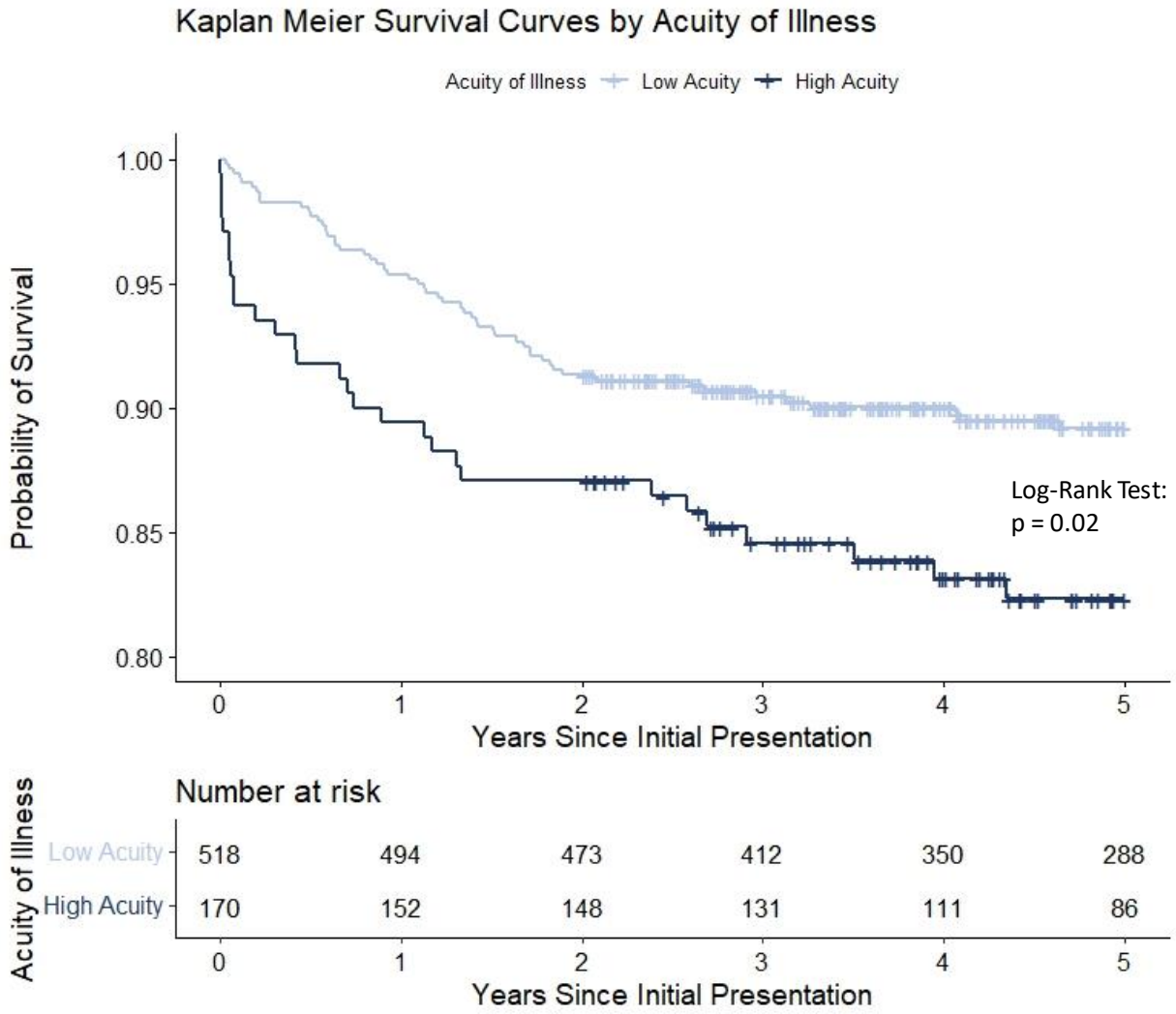


Table 4: Cox proportional hazard regression for a) crude and b) adjusted overall survival by acuity of illness at initial diagnosis of leukemia

A:

	Crude HR of death (95% CI)			
	6 months	**1 year**	**2 years**	**5 years**
High Acuity of Illness (REF Low Acuity)	3.70 (1.72-7.99)	2.40 (1.30-4.42)	1.57 (0.94-2.63)	1.72 (1.09-2.71)

B:

	Adjusted HR of death* (95% CI)			
	6 months	**1 year**	**2 years**	**5 years**
High Acuity of Illness (REF Low Acuity)	3.82 (1.77-8.24)	2.10 (1.14-3.92)	1.34 (0.78-2.32)	1.41 (0.86-2.31)

Abbreviations: HR = hazard ratio; CI = confidence interval; REF = reference

*Covariates = biologic sex, race/ethnicity, insurance status at presentation, type of leukemia

Figure 7: Overall survival by low (light green) versus high (dark green) severity of illness

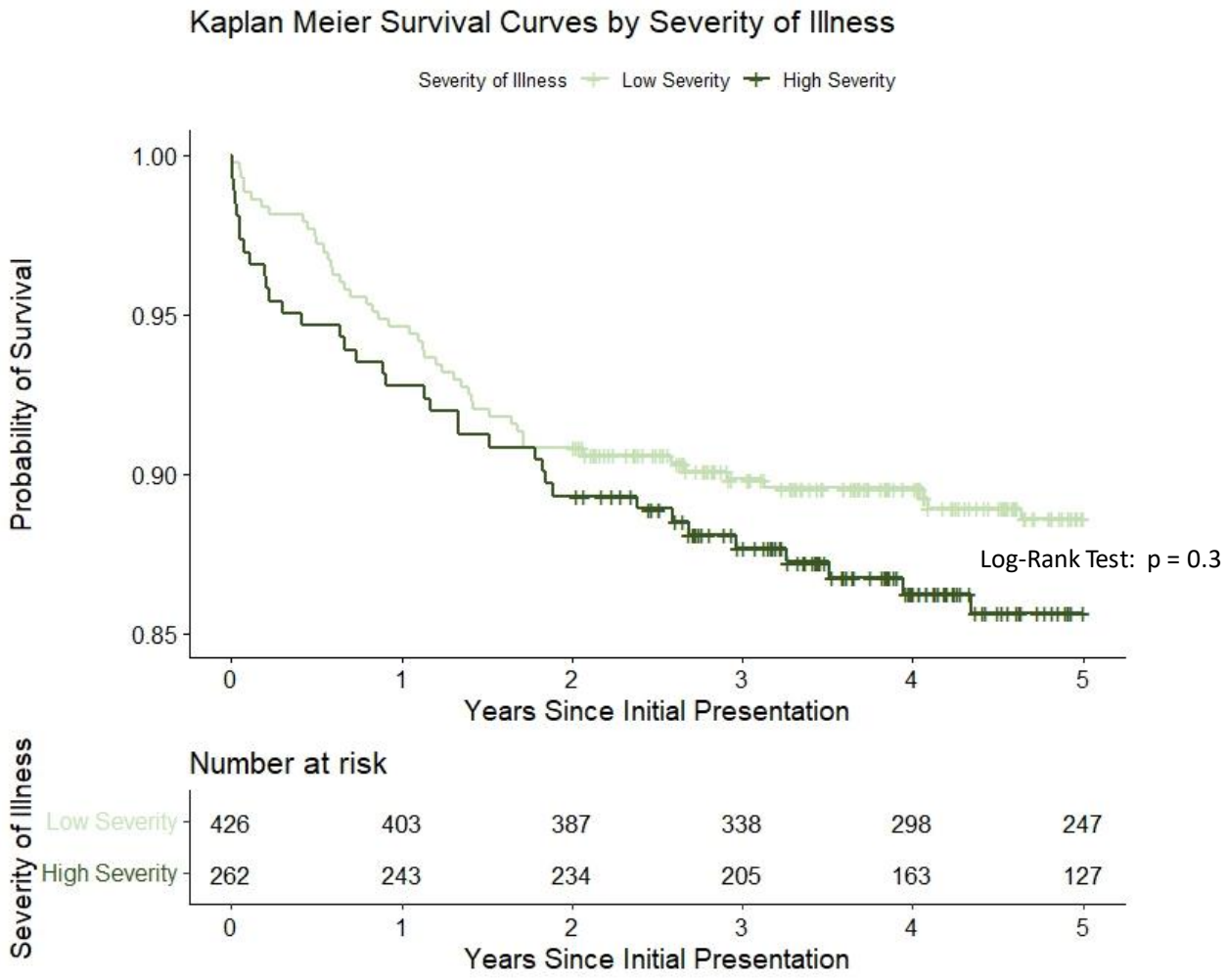


Table 5: Cox proportional hazard regression for a) crude and b) adjusted models for overall survival by severity of illness at initial presentation of leukemia

A)

	Crude HR of death (95% CI)			
	6 months	**1 year**	**2 years**	**5 years**
High Severity of Illness (REF Low Severity)	1.94 (0.90-4.18)	1.37 (0.75-1.93)	1.19 (0.73-1.93)	1.27 (0.83-1.97)

B)

	Adjusted HR of death* (95% CI)			
	6 months	**1 year**	**2 years**	**5 years**
High Severity of Illness (REF Low Severity)	1.89 (0.82-4.34)	1.19 (0.63-2.25)	0.94 (0.57-1.57)	1.01 (0.63-1.62)

Abbreviations: HR = hazard ratio; CI = confidence interval; REF = reference

*Covariates = biologic sex, race/ethnicity, insurance status at presentation, type of leukemia

Figure 8: Overall survival by age 1-9 (light blue) versus age 10-21 (dark blue)

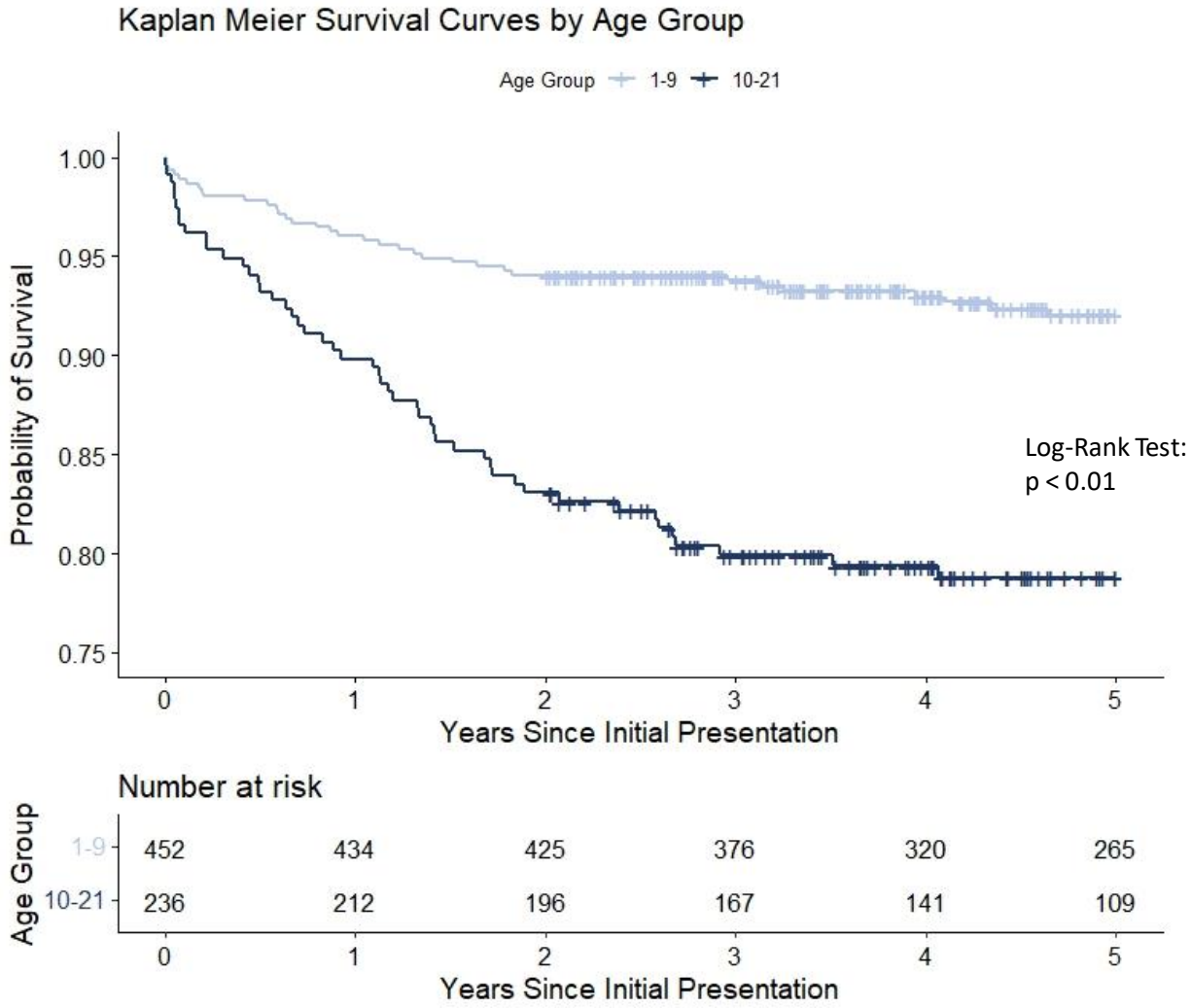


Table 6: Cox proportional hazard regression for a) crude and b) adjusted overall survival by age group at initial diagnosis of leukemia

A)

	Crude HR of death (95% CI)			
	6 months	**1 year**	**2 years**	**5 years**
Age 10-21 (REF 1-9 years)	3.12 (1.42-6.87)	2.64 (1.43-4.85)	3.00 (1.84-4.88)	2.98 (1.92-4.60)

B)

	Adjusted HR of death* (95% CI)			
	6 months	**1 year**	**2 year**	**5 year**
Age 10-21 (REF 1-9 years)	3.82 (1.77-8.24)	2.10 (1.14-3.92)	1.34 (0.78-2.32)	1.41 (0.86-2.31)

Abbreviations: HR = hazard ratio; CI = confidence interval; REF = reference

*Covariates = biologic sex, race/ethnicity, insurance status at presentation, type of leukemia

Table 7: Mediation Analysis for Acuity of Illness on the Association between Age and Overall Survival

	Adjusted HR of death* (95% CI)			
	6 months	**1 year**	**2 years**	**5 years**
Total Effect of Age Group (10-21 versus 1-9 years)	3.22 (1.39-7.46)	2.43 (1.25-4.74)	2.46 (1.44-4.18)	2.47 (1.53-3.99)
Direct Effect of Age Group	2.71 (1.17-6.27)	2.21 (1.15-4.25)	2.42 (1.44-4.06)	2.41 (1.51-3.82)
Indirect Effect of Age Group (Through Acuity)	1.18 (1.01-1.40)	1.10 (0.97-1.24)	1.01 (0.93-1.10)	1.03 (0.95-1.11)
Proportion Mediated	23% (2 - 44%)	15% (-4 - 35%)	3% (-11 - 16%)	5% (-8 - 17%)

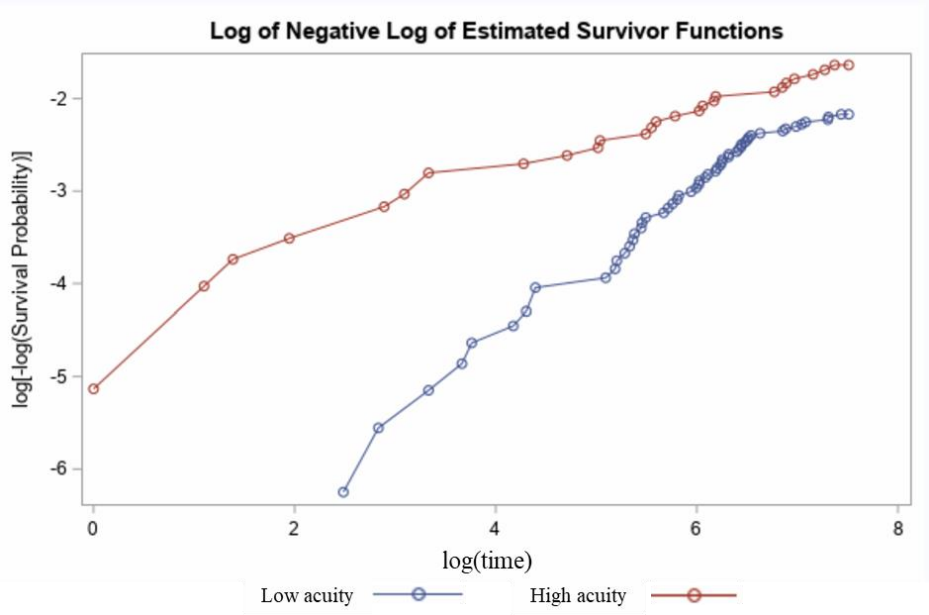
Abbreviations: HR = hazard ratio; CI = confidence interval

*Covariates = biologic sex, race/ethnicity, insurance status at presentation, type of leukemia

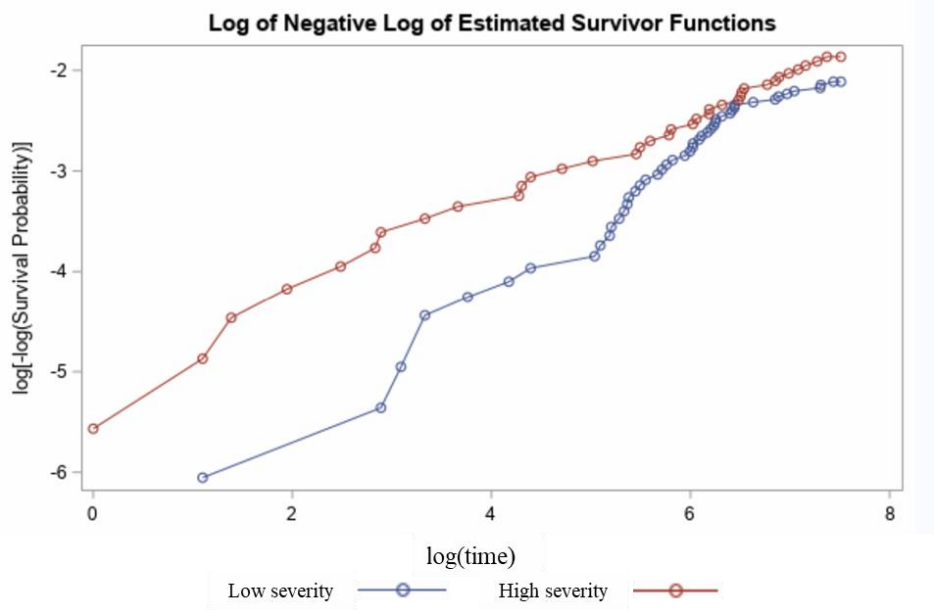
APPENDIX

Supplemental Figure 1: Verification of proportional hazards assumptions with log-log survival curves for A) acuity of illness, b) severity of illness, c) age group, and d) composite score

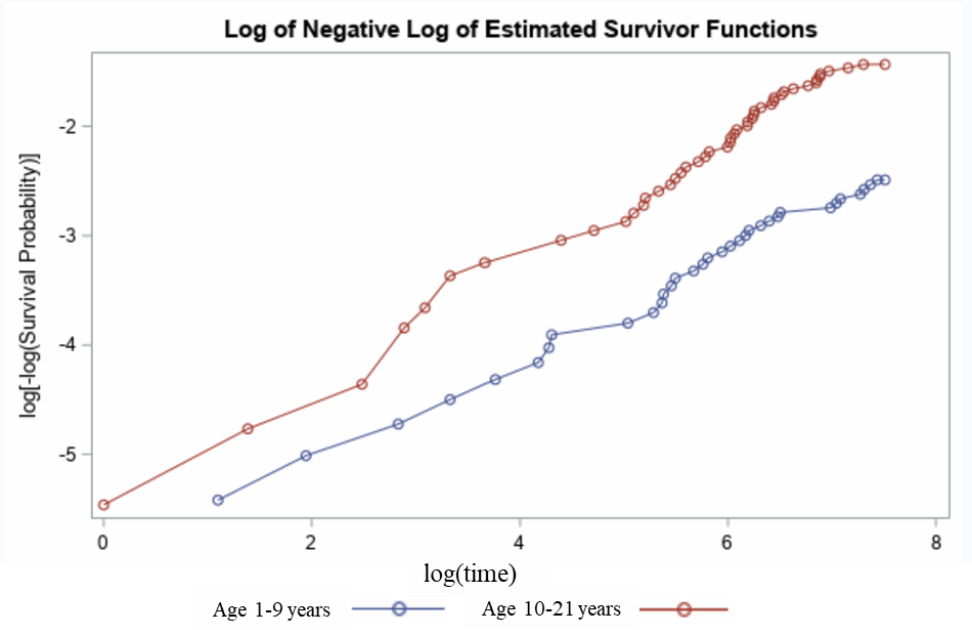
A)



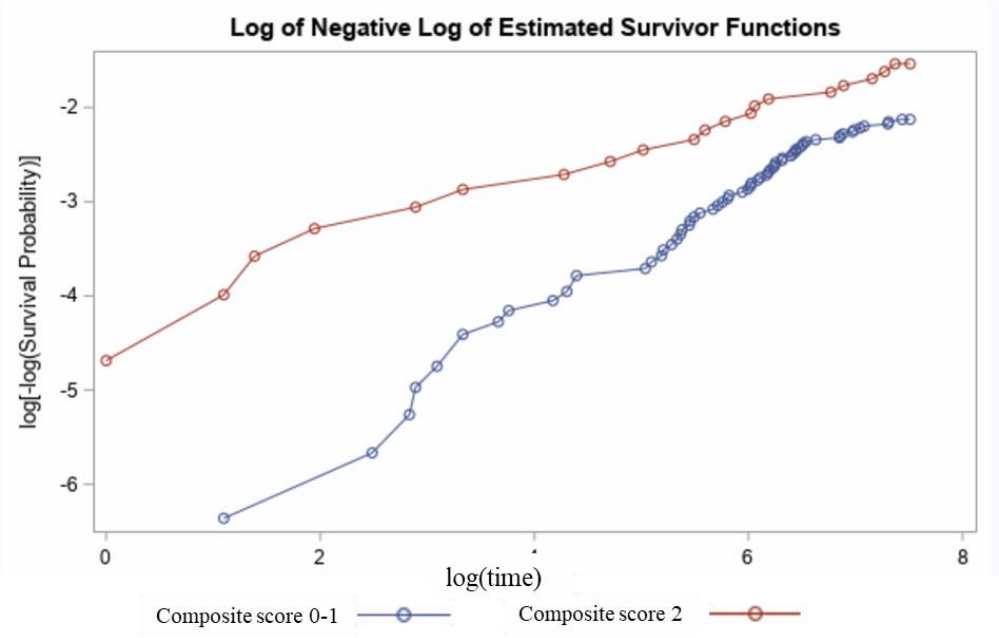
B)



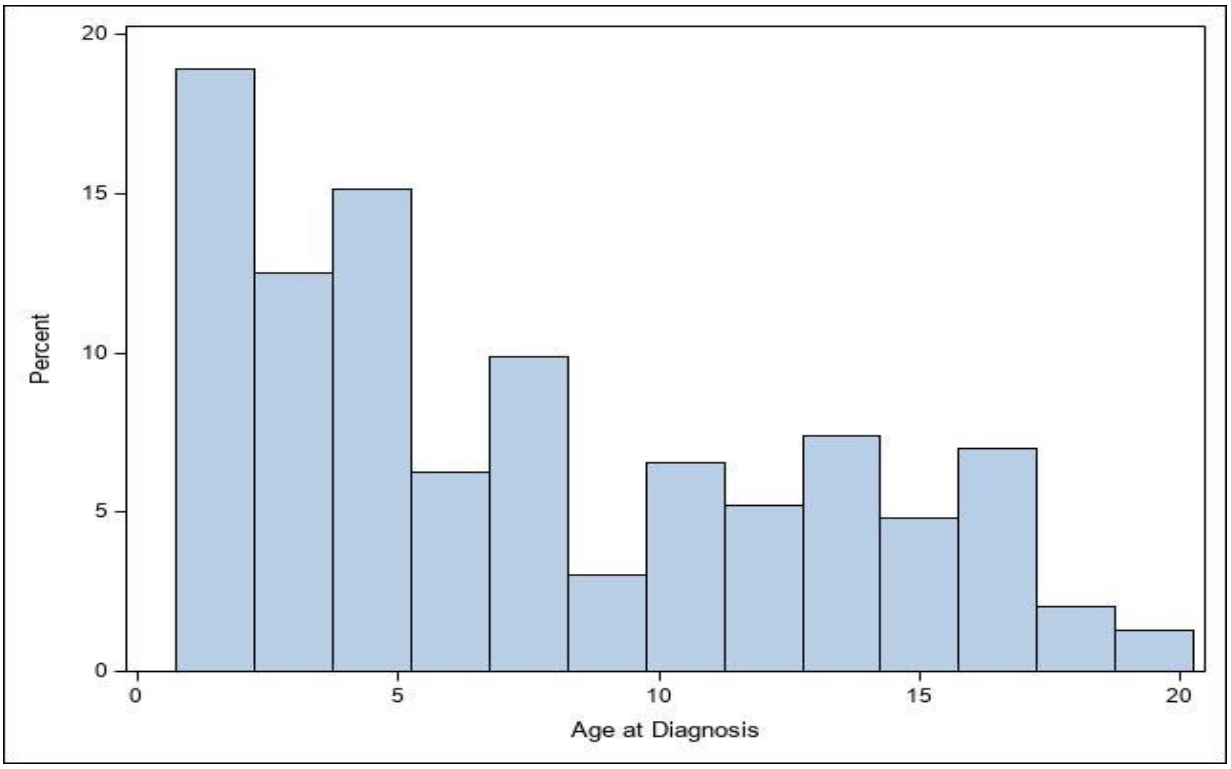
C)


Log of Negative Log of Estimated Survivor Functions
log[-log(Survival Probability)]
-2
-3
-4
-5
0
2
4
6
8
log(time)
Age 1-9 years
Age 10-21 years

D)


Log of Negative Log of Estimated Survivor Functions
log[-log(Survival Probability)]
-2
-3
-4
-5
-6
0
2
6
8
log(time)
Composite score 0-1
Composite score 2

Supplemental Figure 2: Distribution of age in the cohort of leukemia patients presenting to CHOA between 2010-2018



Supplemental Table 1: Patient and disease characteristics of patients with newly diagnosed leukemia who presented to CHOA between 2010-2018, by alternative age categories

	Age 1-14	**Age 15-21**	**Overall**	**P*** **
Participant Characteristics	**N = 584 (84.9%)**	**N=104 (15.1%)**	**N = 688**	
	n (column %)	**n (column %)**	**n (column %)**	
Sex				0.39
Male	310 (53.1)	60 (57.7)	370 (53.8)	
Female	274 (46.9)	44 (42.3)	318 (46.2)	
Race/Ethnicity				0.94
Non-Hispanic White	280 (48.0)	51 (49.0)	331 (48.1)	
Non-Hispanic Black	145 (24.8)	27 (26.0)	172 (25.0)	
Hispanic	128 (21.9)	20 (19.2)	148 (21.5)	
Other*	31 (5.3)	6 (5.8)	37 (5.4)	
Insurance Status at Diagnosis				0.06
Medicaid Only or Self-Pay**	318 (54.5)	53 (51.0)	371 (53.9)	
Private Only	238 (40.8)	50 (48.0)	288 (41.9)	
Medicaid and Private	28 (4.8)	1 (1.0)	29 (4.2)	
Type of Leukemia				<0.01
B-ALL	422 (72.3)	48 (46.2)	470 (68.3)	
AML	84 (14.4)	31 (29.8)	115 (16.7)	
T-ALL	59 (10.1)	15 (14.4)	74 (10.8)	
Other (JMML, CML, Burkitt's)	19 (3.3)	10 (9.6)	29 (4.2)	

Abbreviations: B-ALL = B-cell acute lymphoblastic leukemia; AML = acute myeloid leukemia; T-ALL = T-cell acute lymphoblastic leukemia; JMML = juvenile myelomonocytic leukemia; CML = chronic myeloid leukemia

*Other race/ethnicity: Asian (n = 36), American Indian/Alaska Native (n = 1)
**Including 3 patients with Self-Pay
***Chi-square test of independence

Supplemental Table 2: Unadjusted and multivariable logistic regression models of high acuity of illness by alternative age categories

	High Acuity of Illness	**Unadjusted Model of High Acuity**		**Multivariable Model of High Acuity***	
	N = 170 (24.7%) n (row %)	**OR (95% CI)**	**P****	**OR (95% CI)**	**P****
Age - continuous	-	1.06 (1.03-1.10)	<0.01	1.05 (1.01-1.09)	<0.01
Age 1- 14 years	133 (22.8)	REF	-	REF	-
Age 15-21 years	37 (35.6)	1.87 (1.19-2.92)	<0.01	1.60 (0.99-2.60)	0.06

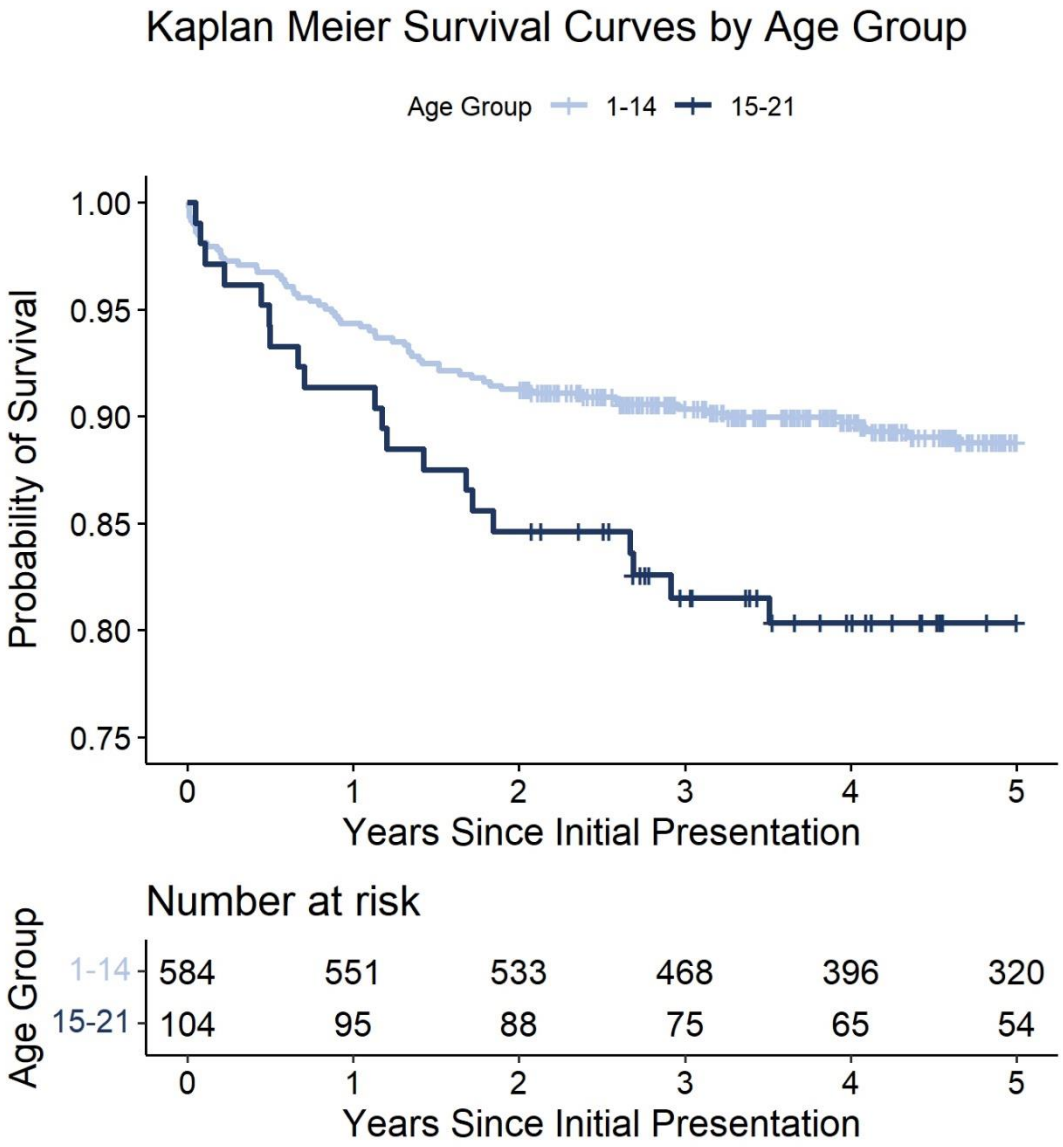
Abbreviations: B-ALL = B-cell acute lymphoblastic leukemia; AML = acute myeloid leukemia; T-ALL = T-cell acute lymphoblastic leukemia; JMML = juvenile myelomonocytic leukemia; CML = chronic myeloid leukemia; OR = odds ratio; CI = confidence interval; REF = reference
*Covariates = biologic sex, race/ethnicity, insurance status at presentation, type of leukemia
**Wald test

Supplemental Table 3: Unadjusted and multivariable logistic regression models of high severity of illness by alternative age categories

	High Severity of Illness	**Unadjusted Model of High Severity**		**Multivariable Model of High Severity***	
	N = 262 (38.1%) n (row%)	**OR (95% CI)**	**P****	**OR (95% CI)**	**P****
Age - continuous	-	1.04 (1.01-1.07)	0.01	1.02 (0.98-1.05)	0.33
Age 1-14 years	58 (13.6)	REF		REF	
Age 15-21 years	46 (17.6)	1.35 (0.89-2.06)	0.16	1.05 (0.66-1.67)	0.83

Abbreviations: B-ALL = B-cell acute lymphoblastic leukemia; AML = acute myeloid leukemia; T-ALL = T-cell acute lymphoblastic leukemia; JMML = juvenile myelomonocytic leukemia; CML = chronic myeloid leukemia; OR = odds ratio; CI = confidence interval; REF = reference
*Covariates = biologic sex, race/ethnicity, insurance status at presentation, type of leukemia
**Wald test

Supplemental Figure 3: Overall survival by age 1-14 (light blue) versus age 15-21 (dark blue)



Log-Rank Test: p = 0.01

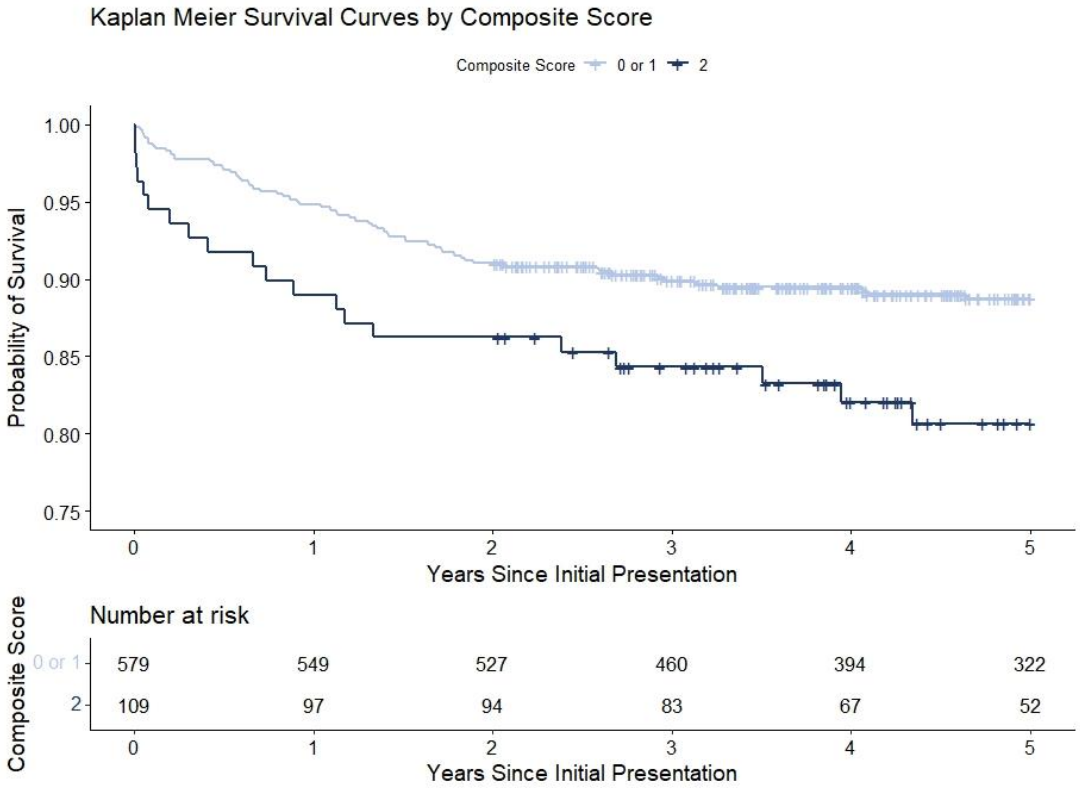
Supplemental Table 4: Unadjusted and multivariable logistic regression models of composite score of high acuity and severity of illness by age

	Composite Score of 2	**Unadjusted Model of Composite Score 2**		**Multivariable Model of Composite Score 2***	
	N = 109 (15.8%) n (row %)	**OR (95% CI)**	**P****	**OR (95% CI)**	**P****
Age 1-9 years	51 (11.3)	REF	-	REF	-
Age 10-14 years	58 (24.6)	2.56 (1.69-3.88)	<0.01	1.96 (1.24-3.10)	0.01

Abbreviations: OR = odds ratio; CI = confidence interval

*Covariates = biologic sex, race/ethnicity, insurance status at presentation, type of leukemia
**Wald test

Supplemental Figure 4: Kaplan-Meier curves comparing overall survival by the composite score of 0 or 1 (light blue) versus the composite score of 2



Log-Rank Test: P = 0.02

Supplemental Table 5: Cox proportional hazard regression for a) crude and b) adjusted overall survival by composite score of acuity and severity of illness at initial diagnosis of leukemia

A)

	Crude HR of death (95% CI)			
	6 months	**1 year**	**2 years**	**5 years**
Composite Score 2 (Reference: Score 0 or 1)	2.92 (1.30-6.56)	2.22 (1.13-4.35)	1.62 (0.90-2.89)	1.78 (1.07-2.95)

B)

	Adjusted HR of death* (95% CI)			
	6 months	**1 year**	**2 years**	**5 years**
Composite Score 2 (Reference: Score 0 or 1)	2.44 (1.00-5.93)	1.84 (0.91-3.73)	1.26 (0.68-2.32)	1.35 (0.76-2.38)

Abbreviations: HR = hazard ratio; CI = confidence interval

*Covariates = biologic sex, race/ethnicity, insurance status at presentation, type of leukemia

Supplemental Table 6: Mediation Analysis for Composite Score on the Association of Age and Overall Survival

	Adjusted HR of death* (95% CI)			
	6 months	**1 year**	**2 years**	**5 years**
Total Effect of Age Group (10-21 versus 1-9 years)	3.39 (1.46-7.84)	2.43 (1.25-4.74)	2.46 (1.44-4.18)	2.47 (1.53-3.99)
Direct Effect of Age Group	2.97 (1.30-6.82)	2.35 (1.23-4.46)	2.43 (1.45-4.06)	2.43 (1.54-3.86)
Indirect Effect of Age Group (Through the Composite Score)	1.12 (0.96-1.34)	1.08 (0.95-1.22)	1.02 (0.93-1.11)	1.03 (0.95-1.12)
Proportion Mediated	0.13 (-0.07-0.34)	0.12 (-0.07-0.31)	0.03 (-0.11-0.17)	0.05 (-0.08-0.17)

Abbreviations: HR = hazard ratio; CI = confidence interval

*Covariates = biologic sex, race/ethnicity, insurance status at presentation, type of leukemia

Supplemental Table 7: Summary of studies evaluating acuity of illness in leukemia patients

Study	Population	Study Design	Exposure	Primary Outcome	Secondary Outcomes	Methods	Primary Findings	Secondary Findings
Current study	Patients aged 1-21 who presented to CHOA between January 2010 and December 2018	Retrospective cohort study	Age group (10-21 years versus 1-9 years)	Acuity or severity of illness and overall survival	-	EMR evaluation of ICU-level of care or markers of severity of illness	Patients aged 10-21 more likely to have high acuity of illness, which mediates the relationship between age and overall survival at 6 months	
Maude et al 2014	Patients aged 28 days old-18 years old in PHIS database between January 1999 and March 2010	Retrospective cohort study	AML versus non-oncologic diagnosis	Hospital mortality within 9 months of initial diagnosis	Prevalence of ICU care, organ failure, sepsis	PHIS database evaluation using ICD-9 codes to define ICU-level of care	Higher mortality rate in ICU for AML patients than for non-oncology patients	AML patients with higher rate of two or more organ failures and cardiovascular failure. Higher odds of death with ICU admission in AML patients who were infants or ≥ 15 years of age.
Winestone et al 2016	AML patients in PHIS database between January 2004-June 2014	Retrospective cohort study	Race: Black versus White patients	Inpatient mortality during induction I (first 50 days of treatment)	Inpatient mortality during induction II, ICU-level resource usage	PHIS database evaluation to define ICU-level of care, defined as acuity of illness. Mediation analysis to assess degree of association between race and induction mortality explained by acuity of illness	Higher mortality among Black patients than White patients in induction I	Higher risk for any ICU-level resource use, ICU-level of care involving two or more systems in first 72 hours in Black patients than in White patients. Acuity of illness mediated 61% of effect of Black race on mortality during induction I.

Ibrahimova et al 2021	ALL and AML patients aged 0-10 years in PHIS database between January 1999-December 2015	Retrospective cohort study	Infants (age <1 year) versus noninfants (age 1-10 years)	Acuity of illness at presentation	Inpatient mortality in the first 34 days following chemotherapy, cumulative number of inpatient days, resource use	PHIS database evaluation to define ICU-level of care, defined as acuity of illness	Infants with ALL and AML more likely to present with high acuity of illness than noninfants	Higher risk for multiorgan dysfunction in infants with ALL and AML compared to noninfants. Infants with ALL with higher induction mortality compared to noninfants aged 1-10 years. Higher cumulative number of inpatient days, antimicrobial, antiemetic, TPN, blood product, GCSF, vasopressor, respiratory use for infants with ALL compared to noninfants.

Abbreviations: ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; PHIS = Pediatric Health Information Systems; ICD = International Classification of Diseases; TPN = total parenteral nutrition; GCSF = granulocyte colony stimulating factor

Supplemental Table 8: Patient and disease characteristics of patients with newly diagnosed leukemia who presented to CHOA between 2010-2018, by race/ethnicity

Participant Characteristics	Non-Hispanic White	Non-Hispanic Black	Hispanic	Other*	Overall	P***
	N = 331 (48.1%)	N=172 (25.0%)	N=148 (21.5%)	N=37 (5.4%)	N = 688	
	n (column %)	n (column %)	n (column %)	n (column %)	n (column %)	
Sex						<0.01
Male	169 (51.1)	94 (54.7)	94 (63.5)	13 (35.1)	370 (53.8)	
Female	162 (48.9)	78 (43.4)	54 (36.5)	24 (64.9)	318 (46.2)	
Insurance Status at Diagnosis						<0.01
Medicaid Only or Self-Pay**	114 (34.4)	120 (69.8)	126 (85.1)	11 (29.7)	371 (53.9)	
Private Only	198 (59.8)	45 (26.2)	20 (13.5)	25 (67.6)	288 (41.9)	
Medicaid and Private	19 (5.7)	7 (4.1)	2 (1.4)	1 (2.7)	29 (4.2)	
Type of Leukemia						<0.01
B-ALL	239 (72.2)	89 (51.7)	120 (81.1)	22 (59.5)	470 (68.3)	
AML	53 (16.0)	39 (22.7)	14 (9.5)	9 (24.3)	115 (16.7)	
T-ALL	26 (7.9)	33 (19.2)	10 (6.8)	5 (13.5)	74 (10.8)	
Other (JMML, CML, Burkitt's)	13 (3.9)	11 (6.4)	4 (2.7)	1 (2.7)	29 (4.2)	

Abbreviations: B-ALL = B-cell acute lymphoblastic leukemia; AML = acute myeloid leukemia; T-ALL = T-cell acute lymphoblastic leukemia; JMML = juvenile myelomonocytic leukemia; CML = chronic myeloid leukemia

*Other race/ethnicity: Asian (n = 36), American Indian/Alaska Native (n = 1)
**Including 3 patients with Self-Pay
***Chi-square test of independence