Drivers of Differential Time to Diagnosis in Pediatric ALL tied to Race and Ethnicity

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Abstract

BACKGROUND: Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy, with diagnosis preceded by symptoms that may include fever, weight loss, fatigue, bleeding and bruising. Timely diagnosis and treatment of ALL may lead to improved outcomes and reduced morbidity from associated complications including tumor lysis syndrome, hyperviscosity, and stroke. PROCEDURE: We performed a retrospective cohort analysis of 274 pediatric pre-B cell ALL and lymphoma patients within Montefiore Health System to determine whether there were factors associated with time from symptom onset to diagnosis. RESULTS: Median time to diagnosis for all patients was 11.5 days (IQR 7.8, 14.3) and was similar between Hispanic, Non-Hispanic Black, and Non-Hispanic White racial/ethnic groups (10.5 vs 14.0 vs 8.0 days; p=0.70), and by male and female patients (14 vs 10 days; p=0.08). Those with Medicaid insurance (n=189) were diagnosed sooner than those with private or self-pay insurance (n=85) (median of 10 vs 16 days; p=0.05). Similar findings were demonstrated when evaluating by Medicaid, Private, and Self-Pay insurance types. English and Other language speakers experienced fewer median days from symptom onset to diagnosis date compared to Spanish speakers (11 vs 7 vs 14; p=0.05). Exploratory analyses suggest that insurance status may impact the time to diagnosis to a greater degree in Non-Hispanics, while English language and female sex may represent a greater advantage to Hispanics. CONCLUSIONS: This study demonstrates that insurance status and language preference may impact the time to diagnosis of pediatric ALL. There is further need to confirm our findings and to study possible causes driving these disparities.
As Corresponding Author, I confirm that all named authors have contributed significantly and approved the submission of this manuscript. We believe the following individuals would be excellent choices as potential reviewers of this manuscript: Dr. Peter Cole, Dr. Lisa Wray, and Dr. Leslie Kersun, all of whom represent experts in the field of pediatric leukemia and have no conflicts of interest.

Dr. Newburger, thank you for your consideration of this manuscript. We look forward to hearing from you.

Sincerely,

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Abbreviation table:

<table>
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<tr>
<th>Abbreviation</th>
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<tr>
<td>ALL</td>
<td>Acute Lymphoblastic Leukemia</td>
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<td>ALLy</td>
<td>Acute Lymphoblastic Lymphoma</td>
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<tr>
<td>PHMC</td>
<td>Pediatric Hematologic Malignancy Cohort</td>
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<td>MHS</td>
<td>Montefiore Health System</td>
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<tr>
<td>EDW</td>
<td>Electronic Data Warehouse</td>
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<td>ED</td>
<td>Emergency Department</td>
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Abstract:

BACKGROUND: Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy, with diagnosis preceded by symptoms that may include fever, weight loss, fatigue, bleeding and bruising. Timely diagnosis and treatment of ALL may lead to improved outcomes and reduced morbidity from associated complications including tumor lysis syndrome, hyperviscosity, and stroke.

PROCEDURE: We performed a retrospective cohort analysis of 274 pediatric pre-B cell ALL and lymphoma patients within Montefiore Health System to determine whether there were factors associated with time from symptom onset to diagnosis.

RESULTS: Median time to diagnosis for all patients was 11.5 days (IQR7.8, 14.3) and was similar between Hispanic, Non-Hispanic Black, and Non-Hispanic White racial/ethnic groups (10.5 vs 14.0 vs 8.0 days; p=0.70), and by male and female patients (14 vs 10 days; p=0.08). Those with Medicaid insurance (n=189) were diagnosed sooner than those with private or self-pay insurance (n=85) (median of 10 vs 16 days; p=0.05). Similar findings were demonstrated when evaluating by Medicaid, Private, and Self-Pay insurance types. English and Other language speakers experienced fewer median days from symptom onset to diagnosis date compared to Spanish speakers (11 vs 7 vs 14; p=0.05). Exploratory analyses suggest that insurance status may impact the time to diagnosis to a greater degree in Non-Hispanics, while English language and female sex may represent a greater advantage to Hispanics.

CONCLUSIONS: This study demonstrates that insurance status and language preference may impact the time to diagnosis of pediatric ALL. There is further need to confirm our findings and to study possible causes driving these disparities.

Introduction:

Pediatric acute lymphoblastic leukemia (ALL) is the most common pediatric malignancy, affecting approximately 30 cases per million children and young adults. Leukemia and lymphoma arise from clonal proliferations of abnormal hematopoietic cells or lymphoid tissue leading to abnormal bone marrow function and malignant infiltration of tissues, ultimately causing multi-organ failure. Outcomes for patients with childhood leukemia and lymphoma have drastically improved over the past 30 years, with exceptional 5-year survival rates of >90% in children and adolescents with newly-diagnosed disease. It has been reported that children with public health insurance who develop a malignancy have inferior long term survival compared with children who have private health insurance, but there has been no analysis of the causes for this disparity. One possible etiology may be the time required for diagnosis of this malignancy. Time from symptom onset to diagnosis can be a critical period for children with malignancies, with diagnosis typically preceded by days to weeks of symptoms that may include fever, night sweats, weight loss, fatigue, bleeding and bruising. Prompt diagnosis and treatment may lead to an overall decrease in morbidity from associated complications and in mortality. However, there is a paucity of data evaluating the extrinsic factors that lead to possibly significant delays in pediatric ALL and acute lymphoblastic lymphoma (ALLy) diagnosis. This study sought to elucidate if time to diagnosis is associated with demographic factors or ALL/ALLy outcomes in a racially diverse patient population.

Methods:

Patients aged 0-25 years old with pre-B cell ALL and acute lymphoblastic lymphoma were identified (n=274) within the Pediatric Hematologic Malignancy Cohort (PHMC), a cohort of 444 patients diagnosed with ALL.
and ALLy within Montefiore Health System (MHS) from 2004-2017. The PHMC comprises a combined retrospective cohort of 180 pediatric patients cared for at the Children’s Hospital at Montefiore and 413 adult and pediatric aged patients from the Hematological Malignancies Cohort at MMC (HMCMMC) 6, which includes all lymphoma and leukemia patients diagnosed within MHS from 2004-2017. Duplicate patient information was removed based on Medical Record Number (MRN) and date of birth (DOB) with demographics, diagnosis date, self reported race and ethnicity, preferred language, vital status, biologic sex, DOB, and diagnosis and time of hypertension extracted using Montefiore’s Electronic Data Warehouse (EDW).

Information regarding time from symptom onset was gathered both through retrospective chart review when available or data extraction within the EDW based on first contact date within Montefiore Cancer Registry and diagnosis date when retrospective chart review was unavailable. Presence or absence of high-risk cytogenetics was determined through retrospective chart review and evaluation of historical logbooks within the Molecular Cytogenetics Laboratory at Albert Einstein College of Medicine, with high-risk cytogenetics being defined as hypodiploid status, IKZF1 mutation, MLL rearrangement, and intrachromosomal amplification of chromosome 21. Data on cytogenetic mutations were available on 158 patients in the PHMC.

Time from symptom onset to diagnosis was compared by insurance type, preferred language, biologic sex, vital status, socioeconomic status11SES was based upon the patient’s census block group and is reported as a summary Z-score relative to the New York State mean using 6 variables (additional details in following reference: 7. Roux AVD, Merkin SS, Arnett D, et al. Neighborhood of Residence and Incidence of Coronary Heart Disease. New England Journal of Medicine. 2001;345(2):99-106. doi:10.1056/nejm200107123450205) (SES), presence of high-risk cytogenetics, and race and ethnicity using Kaplan Meier curves with log rank testing and Wilcoxon testing7,8. Pearson’s Chi-square tests and t-tests were used to evaluate variables normally distributed after visual inspection with non-parametric testing used for variables not normally distributed. Exploratory analyses were performed stratifying the above analyses by race and ethnicity and presence or absence of high-risk cytogenetics, as well as by preferred language and an age cut off of 10 years to evaluate possible surveillance differences by age. Further exploratory analysis was performed using multivariable logistic regression to identify risk factors placing patients at risk for prolonged time to diagnosis longer than 14 days. SES, sex, race/ethnicity, preferred language, vital status, insurance type, age at diagnosis in years, and high-risk cytogenetics were compared using univariate analysis. A priori modeling with race/ethnicity and all variables with \( p < 0.2 \) in univariate modeling were included with stepwise backward elimination for final model building with final model significant only for age at diagnosis and race/ethnicity. We used Cox Proportional hazard modeling with similar model building to evaluate above risk factors for development of hypertension during treatment for ALL and ALLy, with final model significant only for high-risk cytogenetics. All analyses were conducted using Stata (Version 17).

Results:

Among our ALL/ALLy patients, age at diagnosis (years), biologic sex, and high-risk cytogenetics did not differ by race and ethnicity (Table 1). 47% of all patients reported Medicaid insurance, while 36% reported Self-Pay and 17.5% reported having Private insurance. Of those with Private or Self-pay insurance, 67% reported Self-Pay insurance. Non-Hispanic Whites had higher socioeconomic status compared to Hispanics and Non-Hispanic Blacks, while a higher percentage of Hispanics (75%) had Medicaid insurance compared to 59% of Non-Hispanic Blacks and 48% of Non-Hispanic Whites (Table 1). 85% of Hispanics were alive in this cohort, with fewer Non-Hispanic Blacks reported as alive at end of follow up time (69%; \( p = 0.03 \)) (Table 1).

Median time to diagnosis in days for all 274 patients was 11.5 (IQR 7.8, 14.3). Median time to diagnosis of ALL and ALLy in days was similar between Hispanic, Non-Hispanic Black, and Non-Hispanic White racial/ethnic groups (10.5 vs 14 vs 8; \( p = 0.7 \)), but between male and female patients, there was a suggestion of a difference (14 vs 10; \( p = 0.08 \)). Those with Medicaid insurance were diagnosed in less time than those with private or self-pay insurance (median of 10 vs 16 days; \( p = 0.05 \)) (Table 2, Figure 1a). Spanish speakers experienced the most time from symptom onset to diagnosis date compared to English speakers and those speaking other languages (median of 14 vs 11 vs 7 days; \( p = 0.05 \)) (Table 2, Figure 1b). Time to diagnosis
in days was similar both in males and females and in each racial/ethnic group (Figure 1c, 1d). Time to diagnosis in days was similar by vital status and presence of high-risk cytogenetics. Exploratory analyses observed similar time to diagnosis trends among racial/ethnic groups and those with or without presence of high-risk cytogenetics (Supplemental Tables S1, S2). Among Hispanic patients, there was a suggestion that those with Spanish language preference experienced a median 14 days to diagnosis compared to 7 days for Non-Spanish speakers (p=0.08), while median time to diagnosis of pediatric ALL and ALLy was similar between insurance groups (p=0.57) (Supplemental Table S3). Among Non-Hispanic patients, there was a suggestion that those with Private or Self-Pay insurance experienced a median time to diagnosis of 16 days compared to 9 days for those with Medicaid insurance for diagnosis of ALL/ALLy (p=0.08), with time to diagnosis by preferred language similar between groups (p>0.99) (Supplemental Table S3). Of note, preferred language was predominantly English among our Non-Hispanic patients with very few expressing Spanish language preference. Similar results were demonstrated when insurance was evaluated by Private vs. Self-Pay vs. Medicaid insurance. Among Hispanic patients, males experienced a median 18 days compared to 7 days for female patients (p=0.01), however, time to diagnosis was similar between males and females in Non-Hispanics (Supplemental Table S3). Supplemental analyses comparing Non-Hispanic English/Other speakers to Hispanic English/Other and Hispanic Spanish speakers revealed similar findings, with Hispanic Spanish speakers more likely to have prolonged diagnosis time if male. Those Hispanic English/Other speaking patients were as likely to have prolonged diagnosis times as English speakers. Exploratory analysis evaluating effect of age on time to diagnosis demonstrated similar findings as above, with those Hispanic male Spanish speakers more prone to prolonged diagnosis time regardless of age cut off of 10 years. Time experienced for diagnosis of ALL/ALLy was similar for those reported as alive or dead (Table 2). Survival outcomes for ALL/ALLy were similar between racial/ethnic groups (Table 2).

We found that presence of high-risk cytogenetics was associated with a reduced risk of development of hypertension, when adjusting for race/ethnicity and age at diagnosis (HR 0.36; 95% CI 0.14, 0.92). while time to diagnosis was not associated with development of hypertension. Further analysis evaluating variables associated with prolonged times to diagnosis greater than 14 days in multivariable logistic regression analysis found age at diagnosis as the only variable affecting odds of experiencing delays in diagnosis in modeling adjusting for age at diagnosis in years and race/ethnicity.

Discussion:

The results of this study demonstrate that time to diagnosis for pediatric ALL and ALLy differs by both preferred language and insurance type. Those with Medicaid are diagnosed with ALL or ALLy in a median 10 days, while those with private or self-pay insurance experienced a median of 16 days to diagnose the same disease. The majority of non-Medicaid reporting patients had self-pay insurance status, indicating that a large proportion of patients in our cohort were likely uninsured. Among Non-Hispanic patients, there was a suggestion of an observed shift in diagnosis times by insurance status, which was not apparent in the Hispanic patients. Further studies may elucidate whether insurance status may play more of a role in the time Non-Hispanics experience for diagnosis of ALL and ALLy. Common symptoms prior to diagnosis include fever, weight loss, night sweats, leg pain, difficulty walking, and easy bleeding or bruising. These symptoms can begin from 1 month to days prior to presenting to care. When diagnosed at a later stage, pediatric ALL and ALLy can be associated with a more aggressive disease course, placing patients at greater risk for long term complications including chronic kidney disease, hypertension, and neurologic complications from tumor lysis syndrome and uncontrolled disease. These delays may be due to a variety of reasons, including avoidance of emergency rooms, difficulty obtaining a referral to a specialty care provider, or poor anticipatory guidance and education on warning symptoms at home. Current evidence suggests differences exist between patient utilization of Emergency Department (ED) care. Studies have found that uninsured children who were treated in a pediatric outpatient practice were 93% less likely to utilize ED care. Uninsured children were also 4 times more likely to utilize ED care for sick visits than those who were insured. The clinical and social aspects of those in our cohort with self-pay insurance may differ, with individuals likely having no insurance. Those without insurance may have increased difficulty presenting for care, both in outpatient and ED settings, suggesting that utilization of acute care settings does differ by insurance status, with insurance...
status as a driver of differential times to diagnosis of pediatric ALL and ALLy, particularly in Non-Hispanics in our cohort.

We observed differences in time to diagnosis by preferred language, with those speaking Spanish taking a median 14 days for their diagnosis of pediatric ALL or ALLy. Previous studies have suggested that those who speak languages other than English may utilize ED care less than English speaking patients. Differences in ED use in non-English speaking patients are thought to be due to dissatisfaction with the medical system, misunderstanding of diagnoses, and differences in health literacy. We observed differences in time to diagnosis by preferred language, with those speaking Spanish taking a median 14 days for their diagnosis of pediatric ALL or ALLy. Previous studies have suggested that those who speak languages other than English may utilize ED care less than English speaking patients. Differences in ED use in non-English speaking patients are thought to be due to dissatisfaction with the medical system, misunderstanding of diagnoses, and differences in health literacy. In our study, Spanish speaking patients were more likely to take longer to get diagnosed with ALL or ALLy, particularly if male. This difference was observed to be more pronounced in Hispanics, suggesting that Spanish speaking Hispanics may be more prone to delays in diagnosis due to communication and possible cultural barriers than those Hispanic patients who speak English. This may be due to similar factors as seen in previous studies, such as misunderstanding of the medical system and lack of health literacy, but the role of sex in differential times to diagnosis requires further study. Improving the language barrier and understanding cultural norms in pediatric medicine may be beneficial to health practitioners in helping patients understand their health and alter their utilization of healthcare, thereby allowing them to have better outcomes.

This study has demonstrated that differences exist in the length of time for the diagnosis of ALL and ALLy based on preferred language and insurance status. These findings suggest that disparities exist in the care of those who do not speak English as well as those with non-Medicaid insurance, with different ethnicities possibly demonstrating different factors associated with prolonged ALL and ALLy diagnosis time. With many non-Medicaid patients in our cohort reporting self-pay insurance, health literacy and cultural/social barriers are likely playing a role in prolonged diagnosis times for ALL and ALLy. Improved access to health care may affect one’s time to diagnosis of ALL and ALLy, thereby reducing the risk of severe complications from untreated ALL. Our study did not demonstrate increased risk of hypertension with prolonged diagnosis times but further evaluation of severe complications could not be performed. Additional analyses in larger diverse cohorts should be completed to better understand the role of delays in diagnosis in severe complications from untreated ALL and ALLy. While the sample size was limited, a total cohort of 274 patients does represent a large pediatric cohort within an ethnically diverse population base. A particular strength of this study includes this diverse population within MHS, a safety net hospital system that serves a large historically marginalized minority population within the Bronx, NY and provides care for all individuals, regardless of insurance status, representing a medical home in which patients can be assured of continued care regardless of financial or social concerns. Limitations of this study include that preferred language was extracted from EDW which may contain inaccuracies. Previous evidence utilizing EMR based data extraction methods has demonstrated accurate results, however, reaffirming the utility of data extraction methods in retrospective analyses. The use of preferred language does allow us to evaluate this Hispanic subset of patients specifically to determine if there are differences in outcomes in diagnosis of ALL and ALLy based on the ability to speak limited English. Further research is needed to confirm results based on exploratory analyses evaluated in this study in larger populations.

This study demonstrated that those who are not English speaking and those who have Non-Medicaid insurance may be prone to longer diagnosis times of pediatric ALL and ALLy, which may place them at risk for a variety of conditions throughout therapy, including tumor lysis syndrome, stroke, cardiovascular compromise, and kidney damage. Larger studies should be performed to evaluate whether time to diagnosis of ALL and ALLy impacts development of these risk factors. This report suggests that different ethnicities may be prone to delays in time to diagnosis of pediatric ALL based on different social and cultural factors, reflecting the need for further research into the role of social determinants of health on time to diagnosis of ALL.

Conflict of Interest: We know of no conflicts of interest associated with this publication

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References:


TABLE 1. Demographics by Race and Ethnicity in Pediatric Hematologic Malignancies Cohort (PHMC) within Montefiore Health System (MHS)

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TABLE 2. Median Time to Diagnosis in Pediatric Acute Lymphoblastic Leukemia (ALL) and lymphoma associated with insurance status and preferred language in Pediatric Hematologic Malignancies Cohort (PHMC) within Montefiore Health System (MHS)

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SUPPLEMENTAL TABLE 1. Median time to diagnosis of Pediatric Acute Lymphoblastic Leukemia (ALL) and lymphoma stratified by Race and Ethnicity associated with sex in Pediatric Hematologic Malignancies Cohort (PHMC) within Montefiore Health System (MHS)

SUPPLEMENTAL TABLE 2. Median Time to diagnosis of Pediatric Acute Lymphoblastic Leukemia (ALL) and lymphoma stratified by presence of High Risk Cytogenetics within the Pediatric Hematologic Malignancies Cohort (PHMC) within Montefiore Health System (MHS)

SUPPLEMENTAL TABLE 3. Median Time to Diagnosis of Pediatric Acute Lymphoblastic Leukemia (ALL) and lymphoma Restricted by Race and Ethnicity within the Pediatric Hematologic Malignancies Cohort (PHMC) within Montefiore Health System (MHS) demonstrating different Ethnicities at risk of prolonged diagnosis times due to different risk factors

FIGURE 1. Time to Diagnosis of Pediatric Acute Lymphoblastic Leukemia (ALL) and lymphoma in days associated with both Insurance Status and Preferred Language (1a. p=0.05, 1b. p=0.05) but not Sex or Race/Ethnicity (1c. p=0.08, 1d. p=0.70) in the Pediatric Hematologic Malignancies Cohort (PHMC) within Montefiore Health System (MHS)