Incidence and outcomes of treatment-associated hepatotoxicity during pediatric acute lymphoblastic leukemia induction therapy: a Reducing Ethnic Disparities in Acute Leukemia (REDIAL) Consortium report

by Ashley N. Chavana, Emily J. Mason, John P. Woodhouse, Olga A. Taylor, M. Monica Gramatges, Joanna S. Yi, Sandi Pruitt, M. Brooke Bernhardt, Kathleen Ludwig, Laura Klesse, Kenneth Heym, Timothy Griffin, Marley Roberts, Rodrigo Erana, Juan Carlos Bernini, Hong Zhu, Philip J. Lupo, Karen R. Rabin, Michael E Scheurer, Steven D. Mittelman, Van Huynh, Etan Orgel and Austin L. Brown

Incidence and outcomes of treatment-associated hepatotoxicity during pediatric acute lymphoblastic leukemia induction therapy: a Reducing Ethnic Disparities in Acute Leukemia (REDIAL) Consortium report

Running Title: Pediatric ALL Induction Therapy Hepatotoxicity

Ashley N. Chavana[1], Emily J. Mason[1,2], John P. Woodhouse[1,2], Olga A. Taylor[1,2], M. Monica Gramatges[1,2], Joanna S. Yi[1,2], Sandi Pruitt[3,4], M. Brooke Bernhardt[5], Kathleen Ludwig[6], Laura Klesse[4,6], Kenneth Heym[7], Timothy Griffin[1,2], Marley Roberts[1], Rodrigo Erana[8], Juan Carlos Bernini[8], Hong Zhu[9], Philip J. Lupo[1,2], Karen R. Rabin[1,2], Michael E. Scheurer[1,2], Steven D. Mittelman[10], Van Huynh[11], Etan Orgel[12*], Austin L. Brown[1,2*]

1. Baylor College of Medicine, Department of Pediatrics, Division of Hematology/Oncology, Houston, TX, USA

2. Texas Children's Cancer and Hematology Centers, Houston TX, USA

3. University of Texas Southwestern Medical Center, Peter O'Donnell Jr. School of Public Health, Dallas, TX, USA

4. Harold C. Simmons Comprehensive Cancer Center, Dallas, TX, USA

5. St. Jude Children's Research Hospital, Department of Pharmacy and Pharmaceutical Sciences, Memphis, TN, USA

6. University of Texas Southwestern Medical Center, Department of Pediatrics, Dallas, TX, USA

7. Cook Children's Medical Center, Department of Hematology/Oncology, Fort Worth, TX, USA

8. Vannie E. Cook Children Cancer and Hematology Clinics, McAllen, TX, USA

9. University of Virginia School of Medicine, Division of Biostatistics, Charlottesville, VA, USA

10. University of California, Los Angeles, David Geffen School of Medicine, Division of Pediatric Endocrinology, Los Angeles, CA, USA

11. Children's Hospital of Orange County, University of California Irvine College of Medicine, Orange, CA, USA

12. Children's Hospital Los Angeles, Keck School of Medicine of the University of Southern California, Los Angeles, CA, USA

*Authors contributed equally as senior author

Correspondence:

Etan Orgel, MD, MS, Children's Hospital Los Angeles, 4650 Sunset Blvd, MS#54, Los Angeles, CA; Telephone: 323-361-2121, Email: eorgel@chla.usc.edu

Austin L. Brown, PhD., MPH., Baylor College of Medicine, One Baylor Plaza, BCM 622, Houston, TX 77030, Us; Telephone: 713-798-6634; Email: austin.brown@bcm.edu

Conflicts of Interest: SLP reports consulting fees from Pfizer and Gilead outside the present work; the other authors have no conflicts to disclose.

Acute lymphoblastic leukemia (ALL) is the most common malignancy diagnosed in those less than 15 years of age. While five-year overall survival (OS) exceeds 90% with contemporary treatment regimens (1), longstanding racial and ethnic disparities in OS and event-free survival (EFS) remain (2). Achieving remission during the critical initial induction phase of ALL therapy is highly predictive of disease relapse and survival (3); however, induction therapy consists of intensive and potentially toxic chemotherapy which may result in significant treatment-associated hepatotoxicity (TAH) in pediatric patients with ALL (4).

The incidence and precipitating factors for TAH are not well-established, although susceptibility to hepatotoxic chemotherapy may differ by age, obesity, and ethnicity (5, 6). In the general population, nearly one-third of youth are overweight, with some of the highest rates observed among Hispanic children (7). Clinically significant TAH during the induction phase of therapy may necessitate dose reductions or omissions of vital chemotherapeutic agents (8). As a result, ethnic differences in TAH may contribute to observed disparities in ALL relapse and survival. The objectives of this study were to describe the incidence and risk factors for TAH during induction therapy and evaluate the impact of TAH during induction therapy on ALL outcomes in an ethnically diverse cohort of pediatric patients with ALL enrolled in the multi-site Reducing Ethnic Disparities in Acute Leukemia (REDIAL) Consortium.

The REDIAL Consortium includes patients with acute leukemia treated at six childhood cancer centers across the Southwestern US (Texas Children's Cancer Center Houston, Vannie E. Cook Jr. Children's Cancer Center, Cook Children's Medical Center, Children's Hospital of San Antonio, Children's Medical Center at UT Southwestern, and Children's Hospital of Orange County). Institutional review boards at each participating site reviewed and approved the study protocol

for this retrospective chart review and granted a waiver of informed consent. Infants (<1 year) and patients with Down Syndrome were excluded from the analysis.

Patient demographic and clinical parameters were abstracted from electronic medical records (EMR). Body mass index (BMI) in kg/m^2 was calculated from weight (kg) and height (m) at diagnosis. Z-scores were generated based on patient age and gender using Center for Disease Control and Prevention definitions for children (<20 years old) or adult definitions if the patient was ≥ 20 years old (9). BMI percentiles were subsequently used to categorize patients as underweight (<5%), normal weight (5-84.9%), overweight (85-94.9%), or obese (≥ 95%). B-ALL was classified as NCI standard risk if the patient was 1-9 years of age at ALL diagnosis with a white blood cell (WBC) <50,000/μL or NCI high risk if the patient was age ≥10 years of age at ALL diagnosis or presented with a WBC ≥50,000/μL.

The primary endpoint of TAH during induction therapy was clinically assessed through liver function tests (LFTs) including aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (TB), and conjugated bilirubin (CB). Liver labs were assessed at diagnosis and at the end of the induction phase. Additional interval timepoints during the induction phase were collected at the discretion of the treating physician or institution. The highest post-diagnosis value available for each individual was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4: Grade 3 transaminitis if maximum AST or ALT >5-times to 20-times the institutional upper limit of normal (ULN), Grade 4 transaminitis if maximum AST or ALT >20-times the ULN, Grade 3 hyperbilirubinemia if maximum TB >3-times to 10-times the ULN, and Grade 4 hyperbilirubinemia if maximum TB >10-times the ULN. The pragmatic endpoint of CB >3 mg/dL was used to define severe TAH; this is the threshold that

typically necessitates dose reductions or omissions for induction chemotherapy on most contemporary National Clinical Trials Network ALL protocols.

A total of 1,865 eligible patients were identified (Table 1), including 1,099 Hispanic, 505 non-Hispanic White, and 107 non-Hispanic Black patients (Table S1). Nearly a third of the cohort (29.9%) was ≥10 years old at ALL diagnosis and received HR ALL therapy with a four-drug induction inclusive of daunorubicin and overweight/obesity was present in 34.3% of the population at diagnosis. Grade ≥3 ALT was observed in 23.8% of cases, AST in 8.4%, TB in 6.9%, and CB>3 mg/dL occurred in 3.0% of patients through the end of induction therapy (Table S1). Incident cases of Grade ≥3 ALT, Grade ≥3 TB, and CB>3 mg/dL occurred more frequently (p-value<0.05) in Hispanics of all races than non-Hispanics of all races (Table S1) not adjusting for other clinical factors. Because elevated BMI and older age at ALL diagnosis have consistently been implicated in hepatotoxicity (10), statistical interaction between age at ALL diagnosis and BMI category (underweight/normal weight vs overweight/obese) was evaluated in multivariable logistic regression models (Table S2). Statistically significant (p<0.05) interaction was observed between age at ALL diagnosis and overweight/obesity for grade ≥3 AST and CB >3 mg/dL (Table S2). Models stratifying on age (<10 years vs ≥10 years) and BMI status indicate that patients age ≥10 years with overweight/obesity experienced the highest frequency of each outcome (Figure S1): grade ≥3 ALT (34.1%), AST (16.8%), TB (17.0%), and CB >3 mg/dL (11.7%). Among individuals age ≥10 years with overweight/obesity, Hispanics of all races experienced higher rates of TAH (Figure 1) compared to non-Hispanics of all races, with the differences for CB >3 mg/dL reaching statistical significance (14.4% vs 3.6%, p=0.02).

To assess the potential impact of clinically significant hepatotoxicity on treatment outcomes, we compared five-year EFS and OS between individuals with a CB >3 mg/dL during induction therapy and those with a CB ≤3 mg/dL (Table 2). During a median follow-up of 4.6 years, a total of 263 events occurred (relapse or death). In multivariable Cox proportional hazards models accounting for race, ethnicity, age, weight status at diagnosis, and NCI risk group (Table 2), a CB >3 mg/dL during induction remained significantly associated with poorer EFS (HR = 1.89, 95% CI: 1.12-3.17, p=0.017) and OS (HR = 2.43, 95% CI: 1.33-4.33, p=0.004).

Our findings are consistent with prior work identifying overweight/obesity and older age (≥10 years) as risk factors for TAH (5, 6). In an analysis of more than 2,000 patients with high-risk ALL treated on the Children's Oncology Group (COG) CCG1961 protocol, obese patients were 30% more likely to develop TAH during any treatment cycle compared to non-obese patients (11). Extending this work, we provide additional evidence that the incidence of severe TAH (i.e., CB >3 mg/dL), typically necessitating treatment modifications on contemporary ALL treatment protocols, increases with both higher BMI and older age. Notably, the highest rates of TAH were consistently observed among patients with overweight or obesity diagnosed with ALL at >10 years of age.

We also observed suggestive evidence of ethnic differences in TAH incidence during ALL induction therapy. Hispanic patients developing TAH slightly more frequently than non-Hispanic patients (Table S1), although these differences did not retain statistical significance in multivariable models (Table S2). This pattern is consistent with prior work describing disparities in TAH, including higher ALT levels observed among Hispanics compared to those of other ethnic groups (12, 13). To further explore the relationship between age, obesity, and ethnicity,

we compared TAH incidence across combined age, BMI group, and ethnic strata. Hispanic patients age >10 years with overweight/obesity had a higher incidence of CB >3 mg/dL than non-Hispanic patients in the same category (Figure 1), suggesting that ethnic disparities in TAH are not fully explained by racial and ethnic differences in overweight/obesity prevalence alone. Although the biological mechanisms underlying disparities in TAH during ALL therapy are not completely known, ethnic differences in both inherited genetic and non-genetic factors could be partly responsible for variable susceptibility to TAH during ALL therapy (14, 15).

TAH during induction therapy is most often attributed to asparaginase chemotherapy, which has been a component of ALL treatment regimens for decades. Most contemporary ALL protocols require dose reducing asparaginase for patients experiencing severe TAH with a CB >3 mg/dL. In the current study a CB >3 mg/dL during induction therapy was associated with a five-year EFS of 60.5% (95% CI: 43.7-73.7), compared to 83.5% (95% CI: 81.4-85.5) among patient with no evidence of dose-limiting TAH during induction therapy. These findings highlight the potential importance of preventing dose-limiting toxicities such as TAH to reduce morbidity and give patients the best chance for cure.

The strengths of this study lie in its large, multi-site cohort and systematic, comprehensive data collection. However, our results were limited by the data available in the EMR, which may have been incomplete. Additionally, we did not evaluate host genetics, socioeconomic, or environmental factors in the current analysis, although these variables may contribute to TAH susceptibility in this population.

Severe TAH can disrupt the metabolism or delivery of curative therapy during critical phases of therapy and, as shown in this cohort, potentially impact the chances of survival. Identifying at-risk patients at the start of therapy may allow for personalized treatment approaches to mitigate toxicity burden, leading to reductions in relapse and improved survival.

REFERENCES

1.   Hunger SP, Mullighan CG. Acute Lymphoblastic Leukemia in Children. N Engl J Med. 2015;373(16):1541-1552.

2.   Kadan-Lottick NS, Ness KK, Bhatia S, Gurney JG. Survival variability by race and ethnicity in childhood acute lymphoblastic leukemia. JAMA. 2003;290(15):2008-2014.

3.   Coustan-Smith E, Sancho J, Hancock ML, et al. Clinical importance of minimal residual disease in childhood acute lymphoblastic leukemia. Blood. 2000;96(8):2691-2696.

4.   Miller TP, Getz KD, Li Y, et al. Rates of laboratory adverse events by course in paediatric leukaemia ascertained with automated electronic health record extraction: a retrospective cohort study from the Children's Oncology Group. Lancet Haematol. 2022;9(9):e678-e688.

5.   Denton CC, Rawlins YA, Oberley MJ, Bhojwani D, Orgel E. Predictors of hepatotoxicity and pancreatitis in children and adolescents with acute lymphoblastic leukemia treated according to contemporary regimens. Pediatr Blood Cancer. 2018;65(3):e26891.

6.   Hashmi SK, Navai SA, Chambers TM, et al. Incidence and predictors of treatment-related conjugated hyperbilirubinemia during early treatment phases for children with acute lymphoblastic leukemia. Pediatr Blood Cancer. 2020;67(2):e28063.

7.   Ogden CL, Fryar CD, Hales CM, et al. Differences in Obesity Prevalence by Demographics and Urbanization in US Children and Adolescents, 2013-2016. JAMA. 2018;319(23):2410-2418.

8.   Gupta S, Wang C, Raetz EA, et al. Impact of Asparaginase Discontinuation on Outcome in Childhood Acute Lymphoblastic Leukemia: A Report From the Children's Oncology Group. J Clin Oncol. 2020;38(17):1897-1905.

9.   Ogden CL, Flegal KM. Changes in terminology for childhood overweight and obesity. Natl Health Stat Report. 2010;(25):1-5.

10.   Egnell C, Heyman M, Jónsson Ó G, et al. Obesity as a predictor of treatment-related toxicity in children with acute lymphoblastic leukaemia. Br J Haematol. 2022;196(5):1239-1247.

11.   Orgel E, Sposto R, Malvar J, et al. Impact on survival and toxicity by duration of weight extremes during treatment for pediatric acute lymphoblastic leukemia: A report from the Children's Oncology Group. J Clin Oncol. 2014;32(13):1331-1337.

12.   Alqahtani A, Alhousari D, Ali A, et al. Asparaginase toxicity in Hispanic adult and pediatric patients with acute lymphoblastic leukemia: current understanding. Expert Opin Drug Metab Toxicol. 2023;19(6):357-366.

13.   Wu S, Wang M, Alqahtani A, et al. Hispanic ethnicity and the rs4880 variant in SOD2 are associated with elevated liver enzymes and bilirubin levels in children receiving asparaginase-containing chemotherapy for acute lymphoblastic leukemia. Biomed Pharmacother. 2022;150:113000.

14.   Miller KC, Geyer B, Alexopoulos AS, Moylan CA, Pagidipati N. Disparities in Metabolic Dysfunction-Associated Steatotic Liver Disease Prevalence, Diagnosis, Treatment, and Outcomes: A Narrative Review. Dig Dis Sci. 2025;70(1):154-167.

15.   Yang W, Karol SE, Hoshitsuki K, et al. Association of Inherited Genetic Factors With Drug-Induced Hepatic Damage Among Children With Acute Lymphoblastic Leukemia. JAMA Netw Open. 2022;5(12):e2248803.

Table 1. Clinical characteristics of pediatric ALL patients (N=1,865)

| | Overall | Induction Conjugated Bilirubin | | P-val[1] |
		≤3 mg/dL	>3 mg/dL	
Median age at diagnosis, yrs (range)	6.0 (1.0-22.3)	7.6 (1.0-22.3)	13.0 (3.1-19.8)	<0.01
Age Group, n(%)				
1-9 years	1,308 (70.2)	1,086 (70.3)	11 (22.9)	
≥10 years	556 (29.8)	458 (29.7)	37 (77.1)	
Biologic Sex, n(%)				0.39
Male	1,053 (56.5)	870 (56.4)	30 (62.5)	
Female	812 (43.5)	674 (43.7)	18 (37.5)	
Ethnicity, n(%)				<0.01
Non-Hispanic	746 (40.4)	594 (38.9)	8 (17.4)	
Hispanic	1,099 (59.6)	934 (61.1)	38 (82.6)	
Race, n(%)				0.02
White	1,431 (76.7)	1,199 (77.7)	35 (72.9)	
Black	113 (6.1)	80 (5.2)	1 (2.1)	
Other	254 (13.6)	221 (14.3)	7 (14.6)	
Unknown	67 (3.6)	44 (2.9)	5 (10.4)	
Diagnosis and NCI Risk Group, n(%)				<0.01
Standard Risk B-ALL	1,013 (54.4)	837 (54.3)	9 (18.8)	
High Risk B-ALL/T-ALL	849 (45.6)	705 (45.7)	39 (81.2)	
BMI Category at Diagnosis, n(%)				<0.01
Underweight/Normal Weight	1,089 (65.7)	933 (66.6)	16 (34.8)	
Overweight/Obese	568 (34.3)	469 (33.4)	30 (65.2)	

[1]p-value based on t-test for continuous variables and chi-squared or Fisher's exact test for categorical variables

Abbreviations: acute lymphoblastic leukemia, ALL; National Cancer Institute, NCI; body mass index, BMI

Conjugated bilirubin data incomplete or unavailable on n=273 individuals during induction therapy

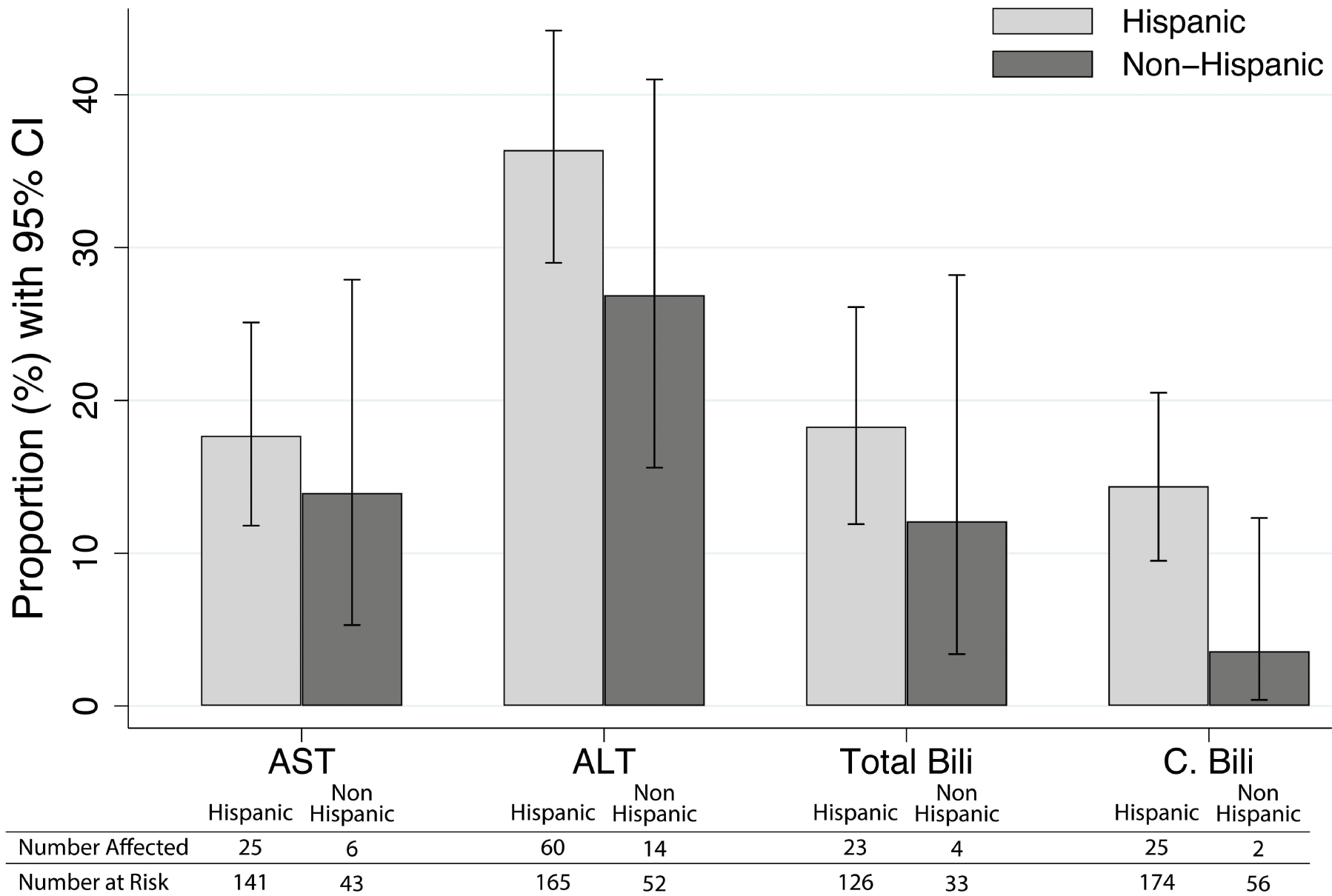Table 2. Factors associated with event-free survival and overall survival among pediatric patients with ALL

Model	Number of Events	Number at Risk	Unadjusted Associations[1]		Adjusted Associations[1]	
Event Free Survival	N=263	N=1,865	HR (95% CI)	P-val	HR (95% CI)	P-val
Conjugated Bilirubin				<0.001		0.017
≤3 mg/dL	215	1,544	Ref		Ref	
>3 mg/dL	17	48	3.06 (1.87-5.01)		1.89 (1.12-3.17)	
Ethnicity				0.003		0.010
Non-Hispanic	83	746	Ref		Ref	
Hispanic	179	1,099	1.50 (1.15-1.94)		1.55 (1.11-2.17)	
Race						
White	202	1,431	Ref		Ref	
Black	14	113	0.94 (0.55-1.62)	0.822	1.19 (0.60-2.37)	0.608
Other	38	254	1.10 (0.78-1.55)	0.603	1.14 (0.77-1.68)	0.511
Unknown	9	67	0.92 (0.47-1.79)	0.799	1.02 (0.45-2.32)	0.971
Diagnosis & NCI Risk Group				<0.001		0.001
B-ALL Standard Risk	83	1,013	Ref		Ref	
B-ALL High Risk/T-ALL	179	849	2.88 (2.22-3.74)		1.91 (1.29-2.82)	
BMI Category at Diagnosis				<0.001		0.058
Under/Normal Weight	123	1,089	Ref		Ref	
Overweight/Obese	108	568	1.77 (1.37-2.29)		1.32 (0.99-1.77)	
Age at diagnosis, years	263	1,865	1.10 (1.07-1.12)	<0.001	1.04 (1.01-1.08)	0.044

Model	Number of Events	Number at Risk	Unadjusted Associations[1]		Adjusted Associations[1]	
Overall Survival	N=144	N=1,865	HR (95% CI)	P-val	HR (95% CI)	P-val
Conjugated Bilirubin				<0.001		0.004
≤3 mg/dL	110	1,544	Ref		Ref	
>3 mg/dL	14	48	4.90 (2.80-8.55)		2.43 (1.33-4.43)	
Ethnicity				0.178		0.098
Non-Hispanic	51	746	Ref		Ref	
Hispanic	93	1,099	1.27 (0.90-1.80)		1.51 (0.93-2.47)	
Race						
White	98	1,431	Ref		Ref	
Black	12	113	1.72 (0.95-3.14)	0.076	2.08 (0.92-4.70)	0.079
Other	26	254	1.47 (0.94-2.30)	0.091	1.53 (0.91-2.55)	0.106
Unknown	8	67	1.70 (0.83-3.50)	0.149	1.85 (0.79-4.36)	0.157
Diagnosis & NCI Risk Group				<0.001		0.004
B-ALL Standard Risk	34	1,013	Ref		Ref	
B-ALL High Risk/T-ALL	110	849	4.17 (2.82-6.17)		2.51 (1.35-4.66)	
BMI Category at Diagnosis				<0.001		0.109
Under/Normal Weight	59	1,089	Ref		Ref	
Overweight/Obese	64	568	2.15 (1.50-3.09)		1.40 (0.92-2.10)	
Age at diagnosis, years	144	1,865	1.14 (1.10-1.17)	<0.001	1.08 (1.02-1.13)	0.009

[1]Unadjusted estimates obtained from Cox proportional hazards model; adjusted estimates obtained from multivariable Cox proportional hazards model, accounting for all other variables included in the table

Abbreviations: acute lymphoblastic leukemia, ALL; hazard ratio, HR; confidence interval, CI; National Cancer Institute, NCI; body mass index, BMI

FIGURE LEGENDS

Figure 1. Incidence of CTCAE grade ε3 aspartate aminotransferase (AST) , alanine aminotransferase (ALT), total bilirubin (Total Bili), and conjugated bilirubin (C. Bili) >3 mg/dL during the induction phase of pediatric ALL therapy among patient >10 years of age with overweight or obesity, stratified by self-reported ethnicity.

	AST		ALT		Total Bili		C. Bili	
	Hispanic	Non Hispanic	Hispanic	Non Hispanic	Hispanic	Non Hispanic	Hispanic	Non Hispanic
Number Affected	25	6	60	14	23	4	25	2
Number at Risk	141	43	165	52	126	33	174	56

SUPPLEMENTAL FIGURES AND TABLES

Table S1. Clinical and demographic characteristics of the study cohort overall and stratifying on self-reported ethnicity

		Self-Reported Ethnicity		
	Overall N=1,865	Hispanic, all races N=1,099	Non-Hispanic, all races N=746	P-value[1]
Median age at diagnosis, yrs (range)	6.0 (1.0-22.3)	6.4 (1.0-22.3)	5.5 (1.0-21.5)	0.003
Age Group, n(%)				0.020
1-9 years	1,308 (70.2)	747 (68.0)	544 (73.0)	
≥10 years	556 (29.8)	352 (32.0)	201 (27.0)	
Biologic Sex, n(%)				0.110
Male	1,053 (56.5)	638 (58.1)	405 (54.3)	
Female	812 (43.5)	461 (41.9)	341 (45.7)	
Race, n(%)				<0.001
White	1,431 (76.7)	924 (84.1)	505 (67.7)	
Black	113 (6.1)	6 (0.6)	107 (14.3)	
Other	254 (13.6)	120 (10.9)	133 (17.8)	
Unknown	67 (3.6)	49 (4.5)	1 (0.1)	
Diagnosis and NCI Risk Group, n(%)				0.631
Standard Risk B-ALL	1,013 (54.4)	588 (54.8)	397 (56.5)	
High Risk B-ALL/T-ALL	849 (45.6)	484 (45.2)	305 (43.5)	
BMI Category at Diagnosis, n(%)				<0.001
Underweight/Normal Weight	1,089 (65.7)	600 (60.7)	477 (73.5)	
Overweight/Obese	568 (34.3)	389 (39.3)	172 (26.5)	
CTCAE AST Grade, n(%)				0.580
Grade <3	1,129 (91.6)	700 (91.9)	412 (90.9)	
Grade ≥3	104 (8.4)	62 (8.1)	41 (9.1)	
CTCAE ALT Grade, n(%)				0.001
Grade <3	1,180 (76.2)	676 (73.2)	489 (80.7)	
Grade ≥3	368 (23.8)	247 (26.8)	117 (19.3)	
CTCAE Total Bilirubin Grade, n(%)				0.036
Grade <3	985 (93.1)	614 (92.0)	356 (95.4)	
Grade ≥3	73 (6.9)	53 (8.0)	17 (4.6)	
Conjugated Bilirubin, n(%)				0.003
≤3 mg/dL	1,544 (97.0)	934 (96.1)	594 (98.7)	
>3 mg/dL	48 (3.0)	38 (3.9)	8 (1.3)	

Table S2. Multivariable logistic regression models[1] for clinical factors associated with treatment-associated hepatotoxicity during induction therapy

	Grade ≥3 AST		Grade ≥3 ALT		Grade ≥3 Total Bilirubin		C. Bilirubin >3 mg/dL	
	OR (95% CI)	P-val	OR (95% CI)	P-val	OR (95% CI)	P-val	OR (95% CI)	P-val
Age at diagnosis, years	0.95 (0.88-1.03)	0.23	1.02 (0.97-1.07)	0.43	1.21 (1.09-1.33)	<0.01	1.07 (0.56-4.88)	0.29
Gender		0.50		0.10		0.71		0.89
Male	Ref		Ref		Ref		Ref	
Female	1.16 (0.74-1.82)		1.24 (0.96-1.60)		0.90 (0.53-1.55)		0.96 (0.50-1.82)	
Ethnicity		0.20		0.09		0.13		0.09
Non-Hispanic	Ref		Ref		Ref		Ref	
Hispanic	0.73 (0.46-1.18)		1.27 (0.96-1.67)		1.66 (0.86-3.19)		2.10 (0.90-4.91)	
Race								
White	Ref		Ref		Ref		Ref	
Black	0.38 (0.08-1.66)	0.20	0.24 (0.10-0.63)	<0.01	1.35 (0.28-6.61)	0.71	0.53 (0.06-4.46)	0.56
Other	1.26 (0.72-2.20)	0.42	1.43 (1.02-2.01)	0.04	1.30 (0.62-2.71)	0.49	1.15 (0.48-2.77)	0.75
Unknown	0.47 (0.06-3.62)	0.47	0.74 (0.33-1.64)	0.46	1.92 (0.48-7.73)	0.36	2.21 (0.59-8.37)	0.24
Diagnosis & NCI Risk Group		0.02		0.03		0.74		0.36
B-ALL Standard Risk	Ref		Ref		Ref		Ref	
B-ALL High Risk/T-ALL	1.94 (1.09-3.47)		0.68 (0.48-0.96)		1.17 (0.48-2.84)		1.66 (0.56-4.88)	
BMI Category at Diagnosis		0.65		0.72		0.90		0.27
Under/Normal Weight	Ref		Ref		Ref		Ref	
Overweight/Obese	0.81 (0.33-2.01)		1.09 (0.67-1.79)		1.09 (0.26-4.66)		0.37 (0.06-2.19)	
Age by BMI Interaction	1.10 (1.01-1.21)	0.03	1.04 (0.99-1.10)	0.09	0.99 (0.89-1.10)	0.83	1.16 (1.01-1.33)	0.04

[1]Logistic regression models adjusted for all variables included in the table

Abbreviations: aspartate aminotransferase, AST; alanine aminotransferase, ALT; odds ratio, OR; confidence interval, CI; National Cancer Institute, NCI; acute lymphoblastic leukemia, ALL; body mass index, BMI
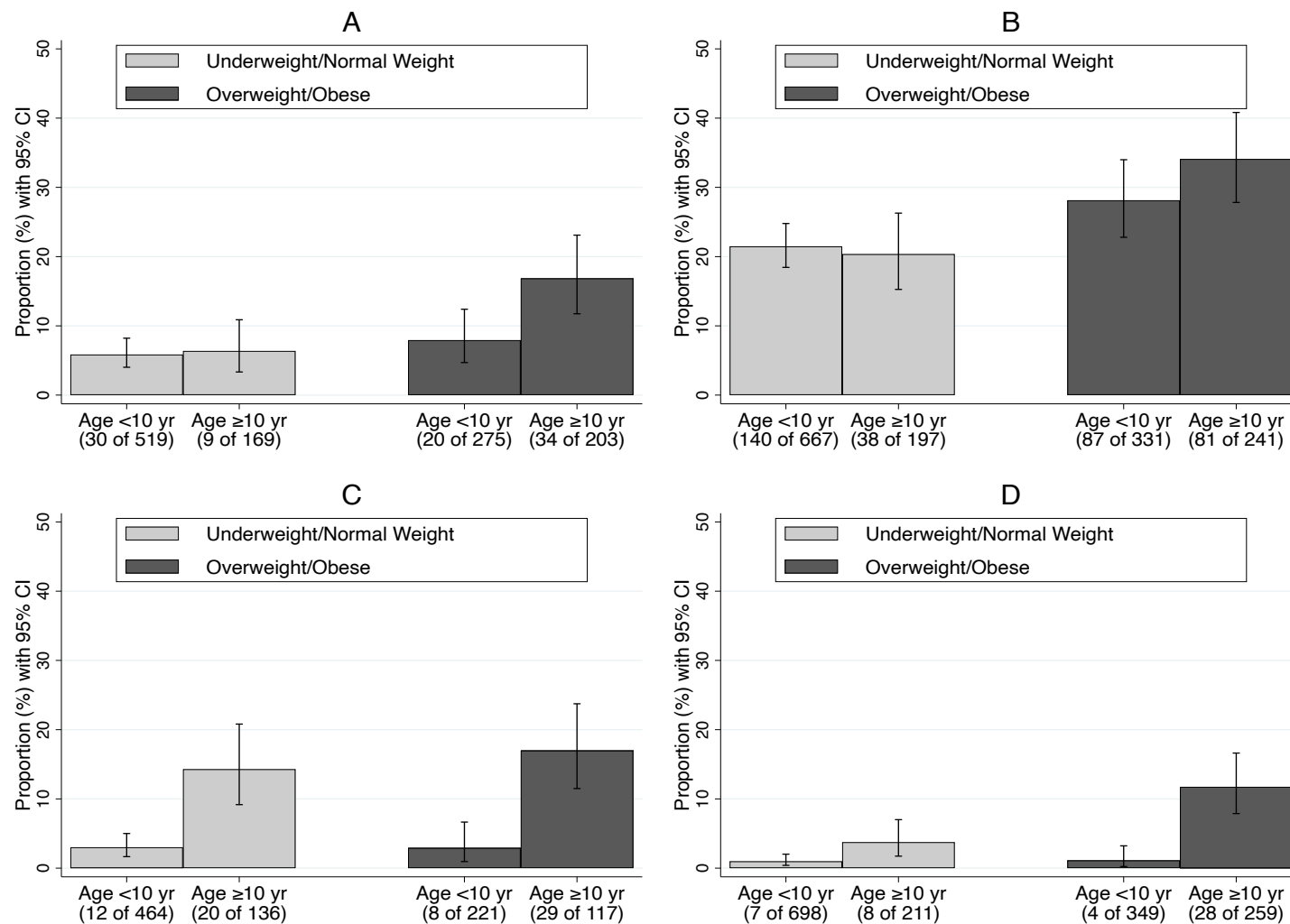
Figure S1. Incidence of CTCAE grade ≥3 aspartate aminotransferase (A) , alanine aminotransferase (B), total bilirubin (C), and conjugated bilirubin >3 mg/dL (D) during the induction phase of pediatric ALL therapy stratified by age group at ALL diagnosis and body mass index group.