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Impaired Neurocognitive Functioning 3 Months Following Diagnosis of High-Risk Acute Lymphoblastic Leukemia: A Report from the Children's Oncology Group (COG)

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Abstract

PURPOSE: Acute lymphoblastic leukemia (ALL) is the most common pediatric cancer diagnosis. Cognitive late effects develop in 20–40% of ALL survivors, but the course of declines is unclear. The aim of this paper is to characterize cognitive functioning, and its association with patient-reported outcomes, early in treatment.

PATIENTS AND METHODS: 483 children with high-risk ALL, aged 6–12 years at diagnosis, consented to the neurocognitive study embedded in a prospective therapeutic trial, Children's Oncology Group (COG) AALL1131. A computerized neurocognitive battery (Cogstate) was administered 3-months post-diagnosis assessing reaction time, visual attention, working memory, visual learning, and executive functioning. Parent-reported executive functioning and patient-reported physical symptoms were also collected.

RESULTS: Data from 390 participants (mean age at diagnosis=9.2 years, 55.4% male) were obtained. Relatively few patients reported pain (16.0%) or nausea (22.6%), but a majority (68.5%) reported feeling at least some fatigue at testing. Mean Cogstate Z-scores were within normal limits across tasks; however, rates of impairment (Z-scores ≤−1.5) for reaction time, working memory, visual learning, and visual attention (were all higher than expected compared to the standardization sample. Patients reporting fatigue were significantly more likely to have impaired reaction time and visual attention compared to those reporting no fatigue.

CONCLUSION: Findings support feasibility of computerized cognitive assessments and suggest higher-than-expected rates of impaired cognitive performance early during treatment for pediatric ALL, notably within 3 months of diagnosis, suggesting intervention efforts may be indicated. These results also highlight acute factors that may impact reliability of "baseline" assessments conducted soon after diagnosis.

Keywords

Acute Lymphoblastic Leukemia; Late effects of cancer treatment; psychology

Introduction

A mainstay of therapy for acute lymphoblastic leukemia (ALL) includes prophylactic therapy targeting central nervous system (CNS)[1] disease. Contemporary regimens achieve CNS protection with intrathecal chemotherapy, avoiding the deleterious effects of cranio/craniospinal irradiation[2]. Nonetheless, children with ALL remain at risk for neurocognitive adverse effects.

Up to 40% of survivors of childhood ALL develop neurocognitive impairments, though the trajectory of these impairments is not well-established[3]. Current literature describes deficits in attention, working memory (WM), processing speed, and executive function (EF)[4–10], which has implications for intellectual functioning, psychosocial adjustment, academic performance, and future employability[11–13]. Demographic risk factors frequently, but not universally, identified in prior studies include female biological sex[14–16], Hispanic/Latino ethnicity[17], lower socioeconomic status (SES)[18], and younger age at diagnosis[18,19]. Most studies have evaluated outcomes in survivors following treatment, when neurocognitive

difficulties have already developed, though some changes have been observed as early as the first year of therapy.[20–24] Despite years of research, however, there remain no reliable prediction models to identify which patients will develop impairments over time[3].

Information about how patient-reported outcomes (PROs) relate to neurocognitive functioning is lacking, particularly for symptoms experienced at time of testing. Fatigue, pain, and nausea are commonly experienced by children with ALL and may vary over the course of therapy[25–29]. Pain is associated with decreased cognitive performance in both healthy individuals and those with medical conditions[30]. There are also data indicating that pain in infancy is associated with reduced structural brain volumes and later cognitive outcomes,[31] suggesting the developing brain may be vulnerable to pain. Although few studies have examined associations between nausea and cognition, nausea perception involves areas of the cerebral cortex recruited during higher-order processing, indicating that nausea may interfere with optimal cognition[32]. Moreover, attention, processing speed, and memory are frequently impacted when individuals are fatigued, even when in good health[33,34]. Given that many “baseline” evaluations of neurocognitive functioning are conducted during the first year after diagnosis[35], and that changes are often benchmarked from this assessment, it is critical to understand how physical symptoms impact neurocognition. Yet very few studies have evaluated symptoms at time of testing, so the extent to which commonly-experienced adverse effects of disease and treatment may impact scores is unclear.

In addition to acute effects of symptoms, there is emerging evidence of an association between later cognitive outcomes and physical symptoms during treatment, particularly fatigue. This could reflect shared neurophysiological mechanisms (e.g., neuroinflammation) underlying both fatigue and impaired cognition[36], or the impact of chronic fatigue on cognition over time. Fatigue has been systematically examined in survivors of pediatric cancer only recently, and findings have varied depending on how, when, and by whom symptoms are reported[29,37–39].

As the early phase of ALL treatment is intensive, many children have difficulty tolerating comprehensive neuropsychological assessments. Such evaluations are also expensive and, in the United States, may not be covered by insurance. Thus, many patients may not be tested even when evaluations are recommended.[40,41] These factors also affect implementation of traditional neuropsychological testing within large, multicenter clinical trials, as many institutes lack resources to conduct testing that cannot be billed as standard-of-care.[41] As such, brief batteries that can be administered during clinic appointments have great potential for routine cognitive monitoring.[42] Recent research demonstrated that administration of Cogstate, a brief computerized assessment battery, is feasible and acceptable to patients and their families, even soon after diagnosis[43]. In the current study, we aimed to characterize neurocognitive functioning in a large, diverse sample of children diagnosed with High-Risk B-cell ALL (HR-ALL) using serial administration of Cogstate along with a measure of parent-reported EF. Here, we report findings for the first assessment, approximately three months post-diagnosis. We also examined whether demographic variables and PROs were associated with cognitive functioning at this early timepoint.

Methods

Participants

Consent for participation in this ancillary study was obtained after induction therapy for children with HR-ALL who enrolled on COG AALL1131 (NCT02883049) and met all inclusion criteria: diagnosis of High or Very High-Risk (VHR) ALL; age 6 to <12 years at diagnosis; fluency in English, French, or Spanish; no history of intellectual disability; and no pre-existing sensory impairment that would preclude computerized assessment. Of 483 enrolled participants enrolled, 390 (80.7%) contributed data from 135 COG institutions across North America, New Zealand, and Australia.

Study Design

COG AALL1131, which included the embedded neurocognitive study described here, was approved by the Pediatric Central Institutional Review Board and open for accrual between February 2012 and August 2019[44,45]. Patients with newly diagnosed HR-ALL were treated with 4-drug induction therapy followed by a modified Berlin-Frankfurt-Münster (BFM) post-induction regimen. Patients with standard-risk B-cell ALL who completed induction therapy on AALL0932 also enrolled on AALL1131 if their risk status changed to HR or VHR at end of Induction. Children on the VHR stratum were randomized to a control arm (consisting of modified BFM with fractionated cyclophosphamide (CPM), fractionated cytarabine, and mercaptopurine) or one of two experimental regimens. Experimental Arm 1 patients were treated with CPM and etoposide, while those on Experimental Arm 2 were treated with clofarabine, CPM, and etoposide during Consolidation and Delayed Intensification phases. Of note, VHR Experimental Arm 2 was closed in September 2014 due to excessive toxicity[45]. For the HR stratum, patients were randomized to either intrathecal methotrexate (IT-MTX) or to intrathecal triple therapy (ITT; methotrexate, hydrocortisone, and cytarabine). HR stratum randomization closed in May 2018 following a futility analysis indicating that ITT could never be statistically superior to IT-MTX. Of note, there were no differences in cognitive outcomes expected or found as a function of randomization to ITT or IT-MTX in the HR stratum[44].

Enrollment on the neurocognitive study embedded within AALL1131 was optional. Participants who opted in completed Cogstate at the end of consolidation therapy (± two weeks), approximately 3 months post-diagnosis, at a routine oncology visit. A primary caregiver simultaneously completed a questionnaire characterizing the child's executive functioning.

Measures

Patient-reported outcomes—To evaluate patients' experience of physical symptoms at the time of assessment, our team developed three questions. Immediately prior to completing Cogstate, participants rated their current *pain, nausea,* and *fatigue* on a 4-point Likert scale ("Not at all", "Just a little", "Pretty much", Very much"). We elected to have patients self-report symptoms, as parents may under- or overestimate symptoms in their children[46].

Cogstate—Cogstate is a computerized cognitive assessment tool that was validated for use in ages 6+ (www.cogstate.com) at the time of this study, though it has since been validated in younger children[47]. It has been included in several recent pediatric oncology studies [43,48,49]. Cogstate tasks were developed for frequent, repeated administration with minimal practice effects[50–54]. The brief battery (20–30 minutes) can be administered by clinic staff (e.g., nurses, research coordinators) after successful completion of online training modules. Tasks include a visually-based card paradigm consisting of colored shapes (e.g., green triangle) designed to be culturally neutral. For the current project, five Cogstate tasks were administered, with practice trials for each task. The first task (Detection) measured reaction time by requiring participants to press a key as soon as the on-screen card turned face up. The second task (Identification), assessing visual attention, instructed participants to press different keys depending on whether a black or red card appeared. The third task (One-Card Learning), assessing visual learning, instructed participants to indicate whether a stimulus card appeared previously during the task. The WM task (One-Back) required participants to indicate if the card presented was identical to the previous card. Finally, the EF task (Groton Maze Learning) instructed participants to identify a set path through a hidden maze by following specific rules over 5 trials. All scores were converted into Z-scores (mean=0, SD=1) using age-based normative data, with lower scores reflecting worse performance.

BRIEF—Parents/caregivers completed the Behavior Rating Inventory of Executive Functioning (BRIEF), an 86-item measure of children's everyday EF[55,56]. Analyses included the Working Memory (WM) subscale and two composite indices: the Behavior Regulation Index (BRI) and Metacognition Index (MI). The BRI reflects the ability to control emotional reactions, inhibit impulses, make transitions, and tolerate change; the MI describes the ability to organize and initiate tasks, as well as self-monitoring and planning skills. Raw scores were converted to age- and sex-based T-scores (mean=50, SD=10), with higher scores indicating greater EF difficulties.

Statistical Analysis

Descriptive statistics were calculated for clinical and demographic characteristics. Continuous means were compared with two-sided t-tests and frequencies with chi-square tests. Impairment was defined as scores falling 1.5 SD or more below (i.e., Cogstate Z-scores ≤ -1.50) or above (i.e., BRIEF T-scores ≥ 65) the mean. One sample Z-tests with one-sided p-values tested whether impairment rates for our sample were higher than those observed in the standardization samples. Multiple regression (continuous scores; F-tests) and multiple logistic (PROs; Chi-square tests) models were used to determine the relative contributions of medical (i.e., ALL risk status) and demographic (i.e., age, biological sex, race/ethnicity, and insurance status) variables to neurocognitive outcomes. All tests used $p<0.05$ to determine significance.

Results

Participants and data collection

Of 722 eligible patients, 483 (66.9%) consented to the neurocognitive study (Fig. 1). Of note, not all eligible patients were treated at institutions who offered this optional

study; 200+ COG institutions enrolled patients on AALL1131, whereas only 150 consented participants to our neurocognitive study. Consenting patients were significantly younger (p=.02) and less likely to be Hispanic/Latinx (p=.04), than patients who did not consent, but did not differ on biological sex, race, or insurance status (Supplemental Table 1). Usable data were obtained from 80.7% of those consented (n=390). Males (p=.02) and non-Hispanic/Latinx (p=.01) participants were more likely to submit data. The mean age at diagnosis of participants submitting usable data was 9.2 years (SD=1.8); 55.4% (n=216) were male; 74.6% (n=291) were White, 7.7% were Black and 2.2% were Asian (Table 1). Twenty-three percent identified as Hispanic/Latino. Half (50.8%; n=198) had US private or military insurance, while 33.6% (n=131) had US public insurance. Tasks were completed validly by 94–99% of participants based on validity criteria defined by the Cogstate software. Importantly, valid task completion did not vary as a function of patient-reported physical symptoms (all ps>0.05).

Comparisons to expected norms

Overall mean Cogstate Z-scores were average (Table 2), ranging from −0.46 (simple reaction time) to 0.52 (visual learning). However, rates of impairment for all outcomes except task-based EF were significantly greater than those obtained for the standardization samples, with impairment rates ranging from 8.5% to 19.1% (Fig. 2). While a small majority (56.8%) performed well on all tasks, 20.8% of participants had two or more impaired scores. Similarly, while mean BRIEF scores (Table 3) were also within normal limits (mean T-score range 51.1 to 52.5), rates of impairment for BRI (15.5%) and WM (14.9%) were significantly greater than those in the standardization sample (p<.001; Fig. 3). Most parents (77.1%) rated their children as having no impairments on BRIEF outcomes, but 12.8% perceived their children as having impaired EF in two or more domains.

Medical and demographic predictors

Neurocognitive functioning did not differ as a function of ALL risk status (HR or VHR) for any of the Cogstate or BRIEF outcomes examined (all ps>0.05). Multiple regression models determined the relative contributions of medical and demographic variables to neurocognitive outcomes (Tables 2 and 3). Controlling for the other variables, insurance status was significant for reaction time (F=3.44, p=.02), visual attention (F=2.89, p=.04), task-based EF (F=5.56, p=.001), performance-based WM (F=2.71, p=.04), and parent-reported behavior regulation (F=3.6, p=.01), with patients with US public insurance generally faring worse than those with US private. Females exhibited worse visual attention (F=4.04, p=.045), but better visual learning (F=9.86, p=.002) and WM (F=4.05, p=.04). Younger age at diagnosis was associated with worse task-based EF (F=7.52, p=.006) and poorer visual learning (F=44.97, p<.001). Race-based differences were observed for performance-based (F=3.84, p=.02) WM with White participants scoring higher than Black, Indigenous, and People of Color (BIPOC). In addition, participants of unknown racial background outperformed White participants in parent-reported WM (F=5.17, p=.006). Finally, no significant relationships were found between Ethnicity and outcomes in the models (all ps>0.05).

Patient-reported physical symptoms

Relatively few participants reported pain (16.0%) or nausea (22.6%) at time of testing, but a majority (68.5%) reported at least some fatigue (Supplemental Fig. 1). Participants who reported at least some pain performed significantly lower on visual learning than those reporting no pain (Mean Z of 0.02 vs. 0.63; p=.004). Additionally, parent-ratings for participants who reported pain reflected greater WM difficulties than for those without pain (Mean T 54.7 vs. 51.2; p=.02). Children reporting fatigue were more likely to have impaired reaction time (21.6% vs. 10.6%; p=.02) and visual attention (21.4% vs. 9.4%; p=.01) compared to those reporting no fatigue. However, participants with fatigue performed significantly better on the visual learning task than those without fatigue (Mean Z of 0.74 vs. 0.17; p=.001). In multivariable logistic regression models, older participants were significantly more likely to report fatigue (Odds Ratio=1.41; Chi-square p<.001) and nausea (Odds Ratio=1.16; Chi-square p=.046). There was no association between patient-reported nausea and neurocognitive outcomes.

Discussion

Our data characterize the early impact of treatment on neurocognitive functioning in a large, diverse sample of children with HR/VHR-ALL. Findings suggest higher-than-expected rates of impaired cognitive performance just three months from diagnosis. Although the majority of participants scored within the average range, a significant minority showed deficits in reaction time, attention, WM, and parent-reported metacognition and behavioral regulation when compared to standardization samples, with over 20% impaired on two or more Cogstate tasks.

We examined the contribution of demographic variables to neurocognitive functioning. Not surprisingly, younger age at diagnosis was associated with worse cognitive outcomes, specifically for EF and visual learning. These findings support the notion that careful monitoring may be especially salient for young children with ALL, for whom early childhood education and intervention efforts may be disrupted during treatment. Unfortunately, we know little about how children with ALL access education, extracurricular activities, or other community services that may support optimal development during treatment[57]. Findings related to biological sex were inconsistent; females performed better in some areas (e.g., visual learning, WM) but weaker in others (e.g., attention). Although it is not yet known whether these results will be stable over time, this pattern parallels recent evidence that some cognitive late effects of ALL treatment may be sex-specific[14,15,58].

Results also suggest that children with fewer economic resources may be at particular risk, given their lower performance in nearly all domains tested. Specifically, differences were seen on measures of reaction time, attention, WM, behavioral regulation, and EF, with greater impairments observed among children from lower SES backgrounds. Differences in SES are known to be associated with neurocognitive and behavioral outcomes in healthy developing children, and our findings likely reflect baseline differences between children from higher- and lower-resourced families prior to being diagnosed with cancer. Even so, SES is emerging as a potentially important factor that interacts with the cancer experience to

predict worse outcomes over time[59]. Torres and colleagues[60] found that SES was associated with IQ, attention, and achievement scores and that higher SES predicted less decline over time in children with brain tumors. In addition, a prior study of pediatric ALL survivors demonstrated a relationship between lower SES and lower estimated IQ scores 8–24 months post-treatment,[18] with differences exceeding that which would be predicted by SES in the general population. These findings highlight the need for more research incorporating comprehensive and multifaceted aspects of SES and material hardship.

Finally, we examined the relationship between patient-reported physical symptoms and performance-based measures of neurocognition. Most participants denied having any nausea, and there was no association between nausea and cognitive outcomes. Although a minority of participants reported pain, pain was associated with impairments in WM and visual learning.

In contrast to low rates of pain and nausea, nearly two-thirds of our cohort reported fatigue, suggesting that fatigue may present earlier and more often than previously reported. A recent article found 28% of pediatric cancer survivors had difficulties with daytime sleepiness, which was also associated with inattention, social difficulties, and mental health issues[61]. Notably, the current assessment was completed shortly after participants were exposed to high-dose steroids. There are data documenting negative impacts of steroids on sleep, although this relationship is poorly understood [62]. These findings suggest that fatigue and sleep should be routinely assessed during therapy and targeted in future intervention studies.

Our results indicate that brief computerized testing is feasible early during ALL treatment in ages ≥6 years. Even so, while there is consensus that early assessment may be useful in tracking changes over time, there is less evidence that testing children soon after diagnosis results in scores that closely approximate their premorbid performance level. Rather, our results suggest children's test performance may fluctuate in part as a function of fatigue, and possibly other physical or emotional symptoms not assessed in our sample. As a result, it may be important to routinely ask children about their symptoms *at the time of neuropsychological evaluation* so these factors can be included in the interpretation of scores. In addition, when children report physical symptoms and also exhibit either parent-reported cognitive difficulties or poor performance on cognitive tasks, it seems reasonable to repeat cognitive testing when symptoms abate, as is frequently done with computerized tools such as Cogstate in youth recovering from concussion[63]. Alternatively, a more detailed assessment could be conducted to better inform decision-making about needed interventions, which is consistent with an approach developed by Jacola and colleagues for monitoring cognitive functioning in pediatric cancer patients[64]. At minimum, these results suggest families may benefit from information about the potential for cognitive disruption early in treatment; even if symptoms are transient, timely intervention may help to alleviate difficulties in the short term.

This is one of the first large, multicenter studies to prospectively collect performance-based neurocognitive data within three months of diagnosis in children with HR/VHR-ALL. Strengths include a large sample size with geographic, socioeconomic, racial, ethnic, and linguistic diversity. Limitations of the study include the absence of a comprehensive

neurocognitive evaluation, including characterization of overall intellectual functioning or additional measures reflecting functional impairment, making it difficult to conclude whether cognitive impairments identified by our measures are associated with real-world difficulties in thinking and learning. However, Cogstate has been used in other pediatric illness groups and has modest to robust concordance with traditional neuropsychological tasks[48,49,65,66]. Moreover, nearly 20% of our sample showed deficits in two or more performance domains, which is consistent with prior data showing a significant minority of survivors with cognitive weaknesses.

An additional limitation is our assessment of physical symptoms using single-item questions rather than validated questionnaires. At the time of study development, there were no published measures of children's in-the-moment symptoms rather than aggregate physical functioning over days or weeks. We also used crude approximations for social determinants of health in our sample. Specifically, insurance status is an imperfect indicator of SES; thus, it is difficult to draw conclusions about elements of economic hardship that may be driving lower performance on our study measures. In addition, we included patient race and ethnicity as predictors in our analyses, though interpretation of results related to these variables– increasingly recognized as proxy variables for the impact of structural racism– is also problematic. Finally, we assessed patients in a narrow age range at diagnosis, missing younger children who are presumably at highest risk for impairments. Importantly, Cogstate is now validated in younger children, and patients aged 4+ are being included in COG's successor study (AALL1731).

This study is an initial report of our prospective, longitudinal study with the aim of developing a model of early detection of functional problems for children with HR-ALL. Based on findings reported here, interventions or increased monitoring may be indicated for at-risk children early in treatment for ALL, particularly for those who are younger at diagnosis, present with lower economic resources, and/or with pain or fatigue. However, it remains unclear whether difficulties identified early in treatment are predictive of lasting cognitive changes or functional impairments throughout survivorship. For example, although sample participants showed higher rates of parent-reported WM problems, rates of overall metacognitive impairment were comparable to expectations. Perhaps the broader metacognition skills assessed by the BRIEF are less salient for children undergoing therapy, or other aspects of early treatment impact WM more specifically. Similarly, elevated rates of behavioral dysregulation in our sample could be explained, at least in part, by the proximity of reporting to high doses of steroids, which are known to be associated with emotional and behavioral lability in children. Thus, future work will include characterization of the trajectory of neurocognitive difficulties in this cohort over time, using both Cogstate and psychologist-administered neuropsychological assessments through five years post-diagnosis. This would permit the development of a proactive approach to reducing morbidity with long-term social, educational, and occupational implications. If a computerized measure can be shown to predict functional impairments at the level of the individual child, we will have identified a safe, feasible, acceptable, and cost-effective strategy to screen and monitor the cognitive functioning of children with cancer. In addition, early detection of disrupted neurocognitive processes will enable us to define the window

during which interventions designed to prevent declines or enhance cognitive functioning can be optimally applied.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Sharing and Availability:

The Children's Oncology Group makes data available in accordance with policies stipulated by the National Institutes of Health. Detailed information on COG data sharing is available at: https://childrensoncologygroup.org/data-sharing

Table of Abbreviations:

ALL	Acute Lymphoblastic Leukemia
BFM	Berlin-Frankfurt-Münster (BFM)
BIPOC	Black, indigenous, and people of color
BRI	Behavior Regulation Index
BRIEF	Behavior Rating Inventory of Executive Functioning
CNS	Central nervous system
COG	Children's Oncology Group
CPM	Cyclophosphamide
EF	Executive functioning
HR-ALL	High-Risk Acute Lymphoblastic Leukemia
IQ	Intelligence Quotient
IT-MTX	Intrathecal methotrexate
ITT	Intrathecal triple therapy
MI	Metacognition Index
NCI	National Cancer Institute
PROs	Patient-reported outcomes

SES	Socioeconomic status
US	United States
VHR	Very high-risk
WM	Working memory

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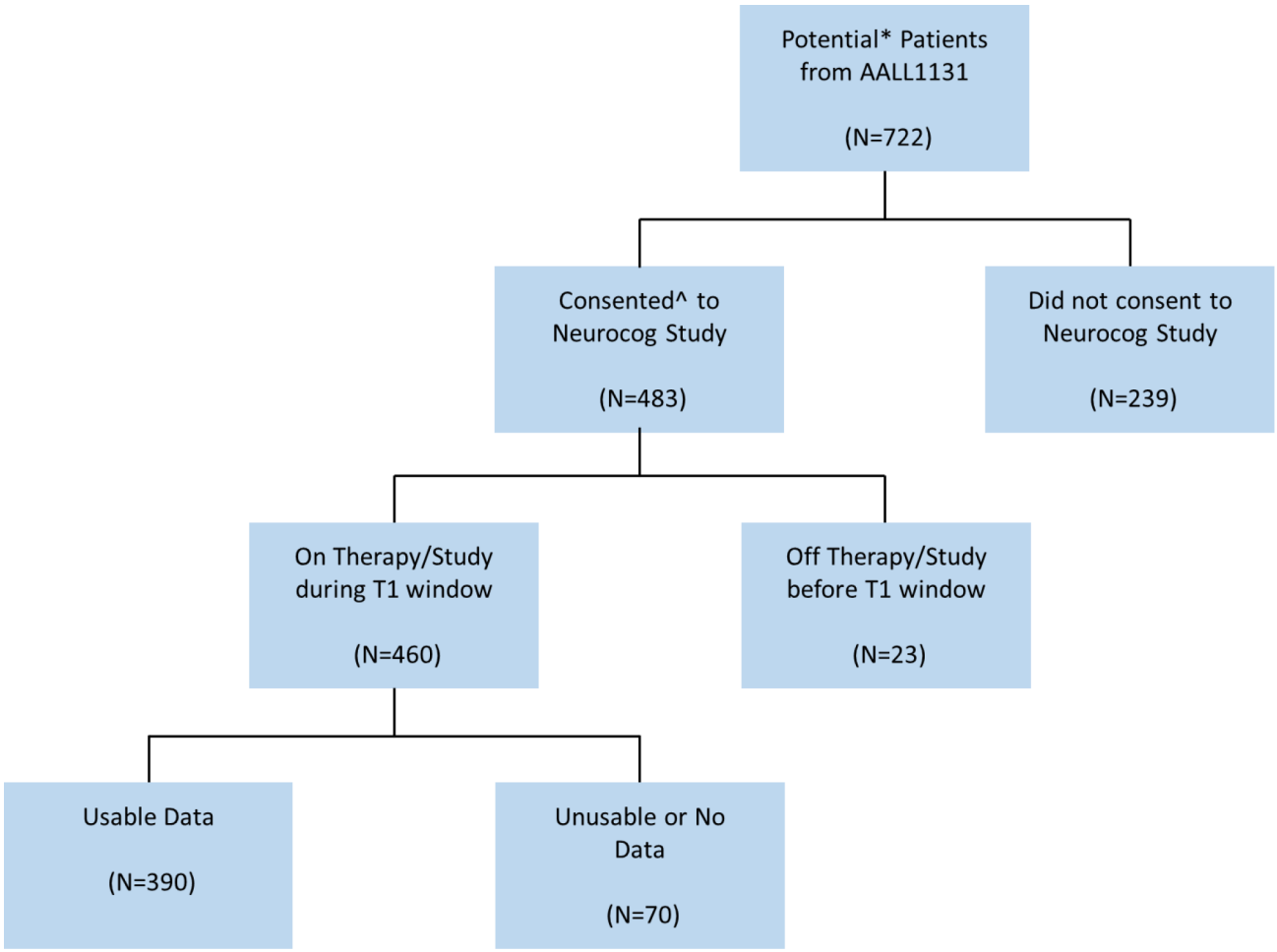

Figure 1.

Consort Diagram

*Potential patients - Aged 6 to < 12 years at time of ALL diagnosis, non-Down syndrome, consented to post induction therapy

^Two patients over 12 years old at diagnosis were consented after the age criteria was relaxed to allow for ages 12–13.

Off Therapy/Study before T1 window includes patients who came off in induction and consolidation and submitted no data

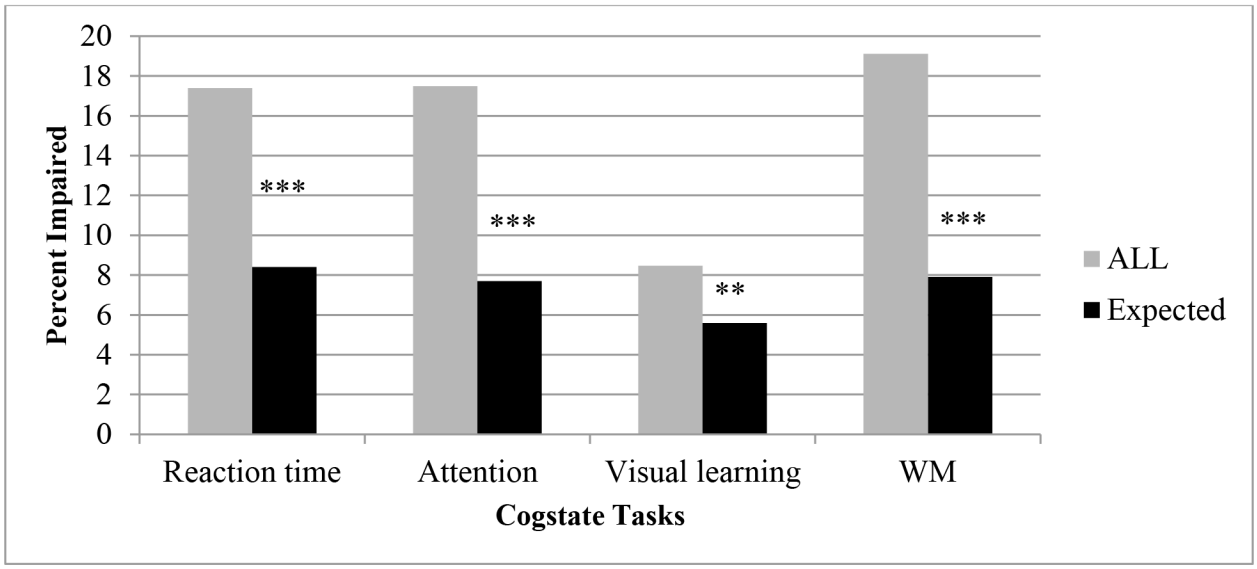

Figure 2.

Percentages of impaired Cogstate scores between ALL patients and expected values.

Note. One-sided, one sample Z-tests versus normative rates with **p < .01; ***p < .001.

ALL = Acute Lymphoblastic Leukemia. WM = Working Memory.

Z-statistics for each outcome are as follows: Reaction Time = 6.18, Attention = 7.02, Visual Learning = 2.45, WM= 7.90.

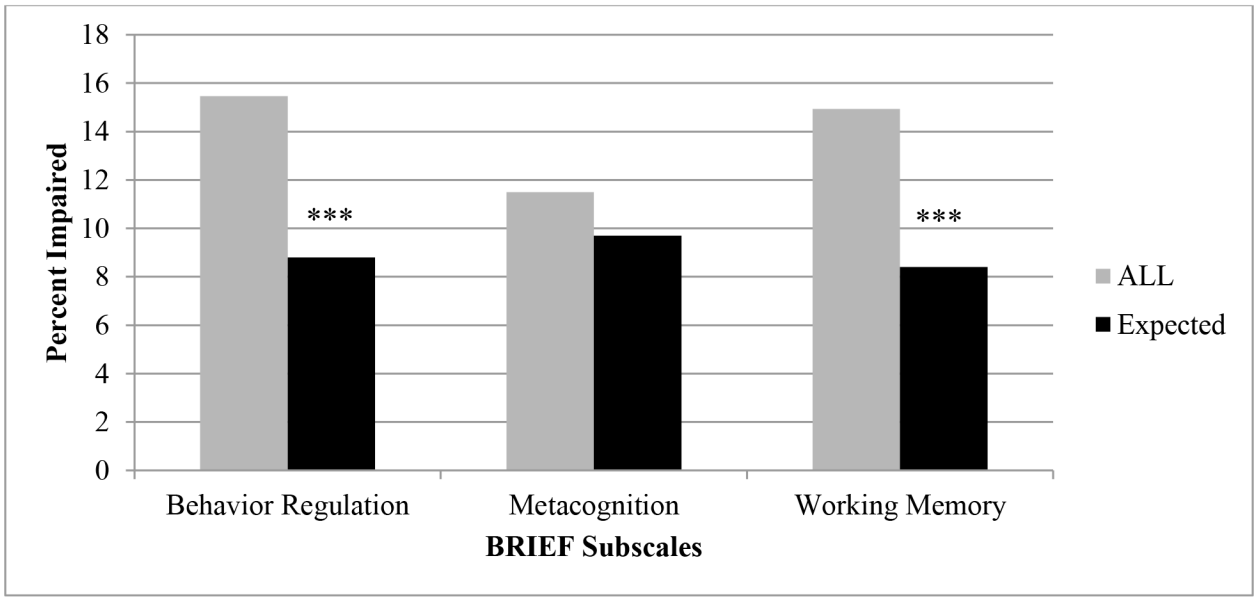

Figure 3.

Percentages of impaired BRIEF scores between ALL patients and expected values.

Note. One-sided, one sample Z-tests versus normative rates with ***p < .001. BRIEF = Behavior Rating Inventory of Executive Function. ALL = Acute Lymphoblastic Leukemia. Z-statistics for each outcome are as follows: Behavioral Regulation = 4.56, Metacognition = 1.17, Working Memory = 4.56.

Table 1.

Summary of Sample Characteristics (n = 390)

	N	%
Age at Diagnosis		
<10 years	212	54.4
≥10 years	178	45.6
Gender		
Female	174	44.6
Male	216	55.4
Race		
American Indian or Alaska Native	4	1.0
Asian	10	2.6
Black or African American	30	7.7
Multi-racial	4	1.0
Native Hawaiian or Pacific Islander	1	0.3
White	291	74.6
Unknown/Missing	50	12.8
Ethnicity		
Hispanic or Latino	91	23.3
Not Hispanic or Latino	282	72.3
Unknown/Missing	17	4.4
Insurance Status		
US Private or Military	198	50.8
US Public	131	33.6
Non-US	38	9.7
Unknown/Self	23	5.9
ALL Risk Status		
High Risk	286	73.3
Very High-Risk	104	26.7

Note: These are the sample characteristics of participants (n=390) who provided any useable Cogstate or BRIEF data. Compared to enrolled participants who provided no data (n=93), those who provided data were more likely to be male (55.4% vs. 41.9%, p=.02) and not Hispanic/Latinx (72.3% vs. 57.0%, p=.01). There were no significant differences in race (p=.54), insurance status (p=.30), or age at diagnosis (p=.22) between groups.

Table 2:

Means and Models for Cogstate Outcomes

	Reaction Time		Visual Attention		Visual Learning		Task-based EF		Working Memory	
Variable	**Mean**	**Adjusted Mean Difference (SE)**	**Mean**	**Adjusted Mean Difference (SE)**	**Mean**	**Adjusted Mean Difference (SE)**	**Mean**	**Adjusted Mean Difference (SE)**	**Mean**	**Adjusted Mean Difference (SE)**
Total sample (SD)	−0.46 (1.27)		−0.34 (1.27)		0.51 (1.47)		0.26 (1.04)		−0.24 (1.32)	
Age at Diagnosis, years		*P* = 0.35		*P* =0.22		***P* <.001**		***P* = 0.006**		*P* = 0.08
		−0.03 (0.04)		−0.05 (0.04)		0.27 (0.04)		−0.09 (0.03)		0.07 (0.04)
Biological Sex		*P* = 0.59		***P* = 0.05**		***P* = 0.002**		*P* = 0.47		***P* = 0.04**
Male	−0.41	Ref	−0.17	Ref	0.26	Ref	0.06	Ref	−0.40	Ref
Female	−0.55	−0.07 (0.13)	−0.51	−0.27 (0.13)	0.72	0.47 (0.15)	0.13	0.08 (0.11)	−0.12	0.28 (0.14)
Ethnicity		*P* = 0.77		*P* = 0.65		*P* = 0.35		*P* = 0.92		*P* = 0.10
Not Hispanic	−0.36	Ref	−0.25	Ref	0.46	Ref	0.17	Ref	−0.18	Ref
Hispanic	−0.79	−0.13 (0.19)	−0.50	0.01 (0.19)	0.45	−0.11 (0.21)	−0.17	0.06 (0.16)	−0.60	−0.34 (0.19)
Unknown	−0.53	−0.12 (0.34)	−0.59	−0.31 (0.34)	0.62	0.51 (0.41)	0.34	−0.05 (0.28)	−0.10	0.35 (0.38)
Race		*P* = 0. 50		*P* = 0.67		*P* = 0.26		*P* = 0.34		***P* = 0.02**
White	−0.47	Ref	−0.35	Ref	0.51	Ref	0.15	Ref	−0.19	Ref
BIPOC	−0.28	0.23 (0.21)	−0.18	0.18 (0.21)	0.15	−0.32 (0.23)	−0.11	−0.10 (0.18)	−0.75	−0.56 (0.21)
Unknown	−0.65	−0.05 (0.21)	−0.31	0.07 (0.21)	0.52	0.16 (0.24)	−0.03	0.23 (0.18)	−0.31	0.07 (0.22)
Insurance status		***P* = 0.02**		***P* = 0.04**		*P* = 0.20		***P* = 0.001**		***P* = 0.04**
Us private or military	−0.33	Ref	−0.23	Ref	0.52	Ref	0.26	Ref	−0.14	Ref
US Public	−0.83	−0.44 (0.17)	−0.62	−0.36 (0.17)	0.34	−0.19 (0.18)	−0.34	−0.53 (0.14)	−0.49	−0.27 (0.17)
Non-US	-0.10	0.20 (0.23)	0.07	0.29 (0.23)	0.79	0.33 (0.25)	0.60	0.10 (0.19)	0.17	0.26 (0.23)
Unknown/Self	−0.29	0.11 (0.29)	−0.14	0.07 (0.29)	0.15	−0.41 (0.32)	0.28	−0.08 (0. 25)	0.28	−0.64 (0.30)

P values are from multivariable models fitted for each of the five outcomes with covariates, including age at diagnosis, biological sex, ethnicity, race, and insurance status. Black, Indigenous, and Person of Color (BIPOC) race categories were combined because of small sample sizes. Adjusted mean difference reflects the model-based regression estimates compared with the reference group or 1-year increase in age. Overall *P* values are given for ethnicity (df = 2), race (df = 2), and insurance status (df = 3).

Table 3:

Means and Models for BRIEF Outcomes

	Behavioral Regulation		Metacogniton Index		Working Memory	
Variable	**Mean**	**Adjusted Mean Difference (SE)**	**Mean**	**Adjusted Mean Difference (SE)**	**Mean**	**Adjusted Mean Difference (SE)**
Total sample (SD)	52.5 (10.5)		51.1 (10.5)		52.0 (10.3)	
Age at Diagnosis, years		*P* = 0.12		*P* =0.93		*P* = 0.86
		−0.47 (0.30)		0.02 (0.30)		0.05 (0.29)
Biological Sex		*P* = 0.52		*P* = 0.36		*P* = 0.24
Male	52.6	Ref	51.4	Ref	52.3	Ref
Female	52.4	−0.71 (1.10)	50.7	−1.01 (1.10)	51.7	−1.26 (1.07)
Ethnicity		*P* = 0.86		*P* = 0.48		*P* = 0.28
Not Hispanic	52.3	Ref	51.1	Ref	51.7	Ref
Hispanic	53.3	0.68 (1.53)	50.7	−0.37 (1.54)	52.7	1.08 (1.50)
Unknown	52.1	1.08 (2.76)	52.9	3.11 (2.76)	53.3	4.13 (2.69)
Race		*P* = 0.21		*P* = 0.13		***P* = 0.006**
White	52.9	Ref	51.6	Ref	52.6	Ref
BIPOC	52.1	−1.11 (1.69)	49.9	−1.83 (1.69)	51.5	−1.25 (1.64)
Unknown	51.1	−3.07 (1.79)	49.3	−3.31 (1.80)	48.9	−5.60 (1.75)
Insurance status		***P* = 0.01**		*P* = 0.10		*P* = 0.09
Us private or military	50.8	Ref	50.3	Ref	51.2	Ref
US Public	54.3	3.64 (1.33)	52.3	2.77 (1.33)	53.8	3.08 (1.30)
Non-US	55.4	4.48 (1.91)	52.8	2.44 (1.91)	51.1	−0.04 (1.86)
Unknown/Self	52.9	2.38 (2.45)	48.4	−0.87 (2.46)	50.2	−0.35 (2.39)

P values are from multivariable models fitted for each of the three outcomes with covariates, including age at diagnosis, biological sex, ethnicity, race, and insurance status. Black, Indegenous, and Person of Color (BIPOC) race categories were combined because of small sample sizes. Adjusted mean difference reflects the model-based regression estimates compared with the reference group or 1-year increase in age. Overall *P* values are given for ethnicity (df = 2), race (df = 2), and insurance status (df = 3).