Adaptive Functioning and Academic Achievement in Survivors of Childhood Acute Lymphoblastic Leukemia: A Report from the Children's Oncology Group

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Abstract

Purpose: To characterize academic and adaptive skill outcomes in survivors of high-risk B-lineage acute lymphoblastic leukemia (HR B-ALL).

Methods: Participants were 178 patients enrolled on a non-therapeutic clinical trial that aimed to characterize neurocognitive and functional outcomes (i.e., academic achievement and adaptive skills) following treatment for childhood HR B-ALL. Eligible patients were treated on Children's Oncology Group AALL0232 clinical trial that included two treatment randomizations: methotrexate delivery (high- or escalating dose) and corticosteroid (dexamethasone or prednisone). Academic achievement and adaptive skills were evaluated at one time point, 8–24 months after completing treatment.

Results: Multivariable logistic regression showed no significant association between treatment variables and outcomes after accounting for age at diagnosis, sex, and insurance status. In multivariable analyses accounting for sex and insurance status, survivors <10 years old at diagnosis had significantly lower scores in math ($p = .02$). In multivariable analyses accounting for sex and age at diagnosis, scores for children with US public health insurance were significantly lower than those with US private or military insurance across all academic and adaptive skill (all p

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values .04). Results from univariate analyses showed that boys had significantly lower scores than girls across all adaptive skill domains (all *p* values .04).

Conclusion: Regardless of treatment randomization, survivors of HR B-ALL <10 years at diagnosis are at risk for deficits in math and overall adaptive functioning; overall adaptive skills for boys were significantly poorer. Screening and early intervention for patients at highest risk, particularly young patients and lower-resourced families, should be prioritized.

Keywords

Childhood ALL; neurocognitive; academic outcomes; adaptive skills

Acute lymphoblastic leukemia (ALL), the most commonly diagnosed childhood malignancy, accounts for over 1 in 4 new diagnoses of childhood cancer, with very young children (ages 2–4) representing the majority of diagnoses.[1] Therapy modifications, such as replacing cranial radiation therapy (CRT) with intensified systemic and intrathecal (IT) chemotherapy for central nervous system (CNS) prophylaxis, have reduced the risk for acute and long-term neurotoxicity without adversely affecting survival.[2] However, survivors treated with contemporary chemotherapy approaches are still at risk for deficits in neurocognitive domains including attention and processing speed.[3,4] Commonly identified risk factors for poorer neurocognitive outcomes include higher intensity of CNS directed therapy, younger age at diagnosis, and female sex. [3,5,6]

Foundational cognitive domains like attention and processing speed are building blocks that support the development of global intelligence [7,8] and higher-order cognitive abilities.[9] In the general population, early onset of attention difficulties predict increased risk for academic failure and reduced social and functional outcomes throughout the lifespan.[10–13] As such, it is reasonable to hypothesize that survivors of childhood ALL, a population with attentional vulnerability, may also struggle with functional outcomes, such as academic achievement and adaptive skills. A better understanding of the early functional implications of neurocognitive deficits is needed to inform strategies for intervention to improve quality of life for survivors.

Findings from the limited number of studies of academic achievement in survivors of childhood ALL treated with contemporary therapy are mixed, with some studies reporting performance within age and grade expectations.[14,15] Other studies describe lower academic achievement and reduced longer-term educational attainment in survivors,[16] with young children being at particular risk.[5] To date, one study has explicitly examined adaptive skills during therapy in a group of preschool age children diagnosed with standard or medium risk ALL.[17] Compared to a control group of healthy children matched for age and sex, children with ALL had significantly lower overall adaptive skill development, with particular deficits in conceptual and social domains. This previous study adds to the literature by describing adaptive skills during treatment, but interpretation is limited by the restricted age range of participants (2.5 – 6 years old), and a lack of information about treatment variables.

The American Association on Intellectual and Developmental Disabilities defines adaptive skills as age appropriate independence in three areas - conceptual (functional academics and

communication), practical (self-care, home and community navigation), and social (social interactions, interpersonal skills). This definition is consistent with the framework of the World Health Organization International Classification of Functioning, Disability, and Health (ICF).[18,19] The ICF model is based on a biopsychosocial approach whereby disability is viewed as a multidimensional construct that includes aspects of biology and individual and societal context. Remediation of disability requires a comprehensive understanding of the risk factors and target outcomes, to design effective intervention to improve the fit between the person and the environment. [20,21]

Accordingly, this study aims to characterize functional outcomes (i.e., academic achievement and adaptive skills) and to identify risk factors for poorer outcome in children treated for high-risk B-lineage ALL (HR B-ALL). All patients included in this study were treated on the Children's Oncology Group (COG) protocol AALL0232, which randomly assigned patients with HR B-ALL to receive therapy that included high-dose methotrexate (HDMTX) with leucovorin rescue, or a lower, escalating-dose MTX without leucovorin rescue, plus asparaginase. Patients were also randomly assigned to corticosteroid therapy that included dexamethasone or prednisone. Academic and adaptive skill outcomes were assessed at one time point, 8–24-months post-completion of treatment. Patients completing the academic and adaptive skill outcome assessment were between ages 1 and 18 years old at diagnosis.

The inclusion of patients that received protocol-directed therapy facilitated examination of clinical variables previously shown to impact neurocognitive outcomes (i.e., younger age at diagnosis, treatment variables). Given findings that female sex is a risk factor for poorer neurocognitive outcomes, we also examined the contribution of patient sex to academic and adaptive skill outcomes in this study, hypothesizing that females would demonstrate lower academic achievement and adaptive skills. Finally, we examined whether outcomes differed by socioeconomic status (SES). Consistent with findings from recent studies that documented an association between SES and neurocognitive outcomes in survivors of childhood cancer,[22] including a study of neurocognitive outcomes from this cohort,[23] we hypothesized that patients with lower SES would have poorer outcomes. Consistent with prior literature, we hypothesized that younger age at diagnosis, female sex, and lower SES would predict lower academic achievement and poorer adaptive skills.

Method

Participants

To evaluate the impact of treatment delivered on Children's Oncology Group (COG) treatment protocol AALL0232 (clinicaltrials.gov: NCT00075725) for HR B-ALL, a companion study (COG AALL06N1) was designed to assess neurocognitive, functional, and behavioral outcomes.[23] AALL0232 opened to accrual in January 2004 and enrolled children with HR B-ALL until January 2011.[24] Slow accrual to AALL06N1 led to several amendments that were designed to facilitate enrollment, including expanding the single assessment time point window from 12 months +/− 4 weeks to 8 to 24 months after completion of AALL0232 therapy and reducing the length of the testing battery. As amended, eligibility criteria for AALL06N1 included enrollment on COG AALL0232, age

of 1 –18 years old at diagnosis, and a primary language of English or Spanish. Exclusion criteria included preexisting neurodevelopmental disability, significant sensory impairment, extensive CNS disease at diagnosis (CNS3), treatment with cranial radiation, or recurrent disease. Informed consent was obtained in accordance with Department of Health and Human Services guidelines. Participants were compensated for time and effort.

Figure 1 depicts the flow of participants through the current study, which enrolled 230 eligible participants, with a final sample of 178 participants (77.4%) who submitted valid data on assessment measures (i.e., measures were completed, within valid ranges and time-frames, and scorable). Demographics of the final sample, including data on health care insurance (proxy for SES) are shown in Table 1. Primary endpoints of neurocognitive abilities (estimated IQ, processing speed, working memory) have been previously reported. [23] The current paper focuses on functional outcomes: academic achievement and overall adaptive functioning.

Treatment

Details of the treatment plan are described elsewhere.[24] Briefly, eligible and consenting participants were randomly assigned to receive dexamethasone (14 days) or prednisone (28 days) during initial induction, and to four courses of high-dose methotrexate (HDMTX) with leucovorin rescue or five doses of escalating dose MTX with PEG asparaginase during interim maintenance. Study randomizations were halted or restricted before study completion based on response data. Excessive toxicities among patients who were age >10 years at diagnosis led to the non–random assignment of these patients to prednisone beginning approximately four years after study activation. Final analysis of the data from AALL0232 demonstrated no improvement in event free survival for patients >10 years who had received dexamethasone. Girls received 23 doses and boys 27 doses of intrathecal MTX, with one dose of intrathecal cytarabine on day 1 of therapy for CNS prophylaxis. Therapy was continued for 2 years for girls and 3 years for boys from the beginning of interim maintenance.

Procedures

Demographic and clinical information was obtained systematically (i.e., trial required case report forms) as part of the clinical treatment trial (AALL0232) or the ancillary study (AALL06N1). Insurance status was used as a proxy for SES, and categories were collapsed as follows for analysis: US public, US private or military, non-US, or unknown. Protocol-directed behavioral assessments were conducted at one time point, 8–24 months after completion of therapy. The Wide Range Achievement Test, 4th edition (WRAT-IV) [25] was administered to survivors aged 6+ by a trained examiner to assess academic achievement. This measure yields scores in three domains: Reading (combination of Word Reading and Reading Comprehension); Math; and Spelling. To assess adaptive functioning, the Adaptive Behavior Assessment System, 2nd edition (ABAS-II) [26] was completed by a parent/legal guardian. The ABAS-II yields sub-scores in 9 skill areas and 3 adaptive domain areas, and an overall Global Adaptive Composite (GAC). The 3 adaptive domain scores (Practical, Social, Conceptual) and GAC were used for primary analyses. Scores for the WRAT-IV and ABAS-II are age-standardized (mean of 100 and standard deviation = 15).

Statistical Analysis

Descriptive statistics (frequencies, means, standard deviations, ranges) were calculated for clinical and demographic characteristics. Initial analyses also examined descriptive statistics (mean, standard deviation, range) and percent at-risk (i.e., 1 standard deviation below the normative mean; age standardized score ≤ 85) for academic and adaptive outcome scores. Frequency comparisons were calculated to test whether observed frequencies of at-risk impairment scores were significantly higher than those expected in a standard population (16th percentile) using 1-sided tests.

Univariate analyses (frequency comparisons, t-tests, ANOVA) were conducted to examine the association among demographic and clinical predictors with academic and adaptive outcomes. Predictor variables for univariate analysis were selected based on the broader research literature in neurocognitive and quality of life outcomes in survivors of childhood ALL, and included treatment randomization, age at diagnosis, patient sex, and insurance status. In separate analyses, age at diagnosis was operationalized as a dichotomous variable (<10; 10 years) to be consistent with age-based criteria for risk stratification from the National Cancer Institute (https://www.cancer.gov/types/leukemia/hp/child-all-treatment-pdq) and as a continuous variable.

We used the results from the univariate analysis to inform multivariable logistic regression models that were used to examine the relative variance in outcomes accounted for by predictors. Specifically, predictor variables from the univariate analysis that showed a significant univariate relationship with outcomes were included in multivariable models. Statistical significance was defined as $p<.05$, unless otherwise specified. All tests of statistical significance were 2-sided unless otherwise noted. Analyses were performed using SAS (Version 9.4; SAS Institute, Cary, NC).

Results

Our previous work reported few demographic differences between potential eligible participants enrolled in AALL0232 (N=1,410), the 247 patients enrolled in ALL06N1, and the 178 patients with usable functional data.[23] Demographics (Table 1) showed that participants were more likely to be female (55.6%), White (80.9%), and not Hispanic or Latino (75.8%). Among participants, 56.7% had US private or military, 25.3% had US public, and 14.6% had non-US Insurance.

Academic Outcomes

The overall group of survivors showed academic achievement scores in the average range, broadly consistent with expectations based on chronological age (Table 2). Rates of at-risk impairment, while clinically meaningful, were not statistically greater than expected for academic outcomes (WRAT-IV).

Results from univariate analyses showed younger age at diagnosis significantly predicted lower math achievement (WRAT-IV Math; $p < .01$: Tables 3 and 4). Compared to individuals with US private or military insurance, patients with US public insurance scored significantly

lower on all domains of academic achievement (WRAT-IV Math, Reading, Spelling; all *p* < .01; Table 3). Treatment variables did not significantly predict academic outcomes.

Multivariable models included age at diagnosis, sex, and insurance considered jointly as predictors on academic and adaptive skill outcomes (Table 5). Compared to those who were older at diagnosis, survivors diagnosed prior to age 10 had significantly increased risk for lower math achievement (WRAT-IV Math, conditional odds ratio (*OR*) = 3.16, *95% CI,* 1.18–8.47, *p* = .02). Compared to those with US private or military insurance, survivors with US public insurance had significantly increased risk for lower math achievement (WRAT-IV Math, *OR* = 3.23, *95% CI,*1.12–9.34, *p* = .03). Compared to those with US private or military insurance, survivors with US public insurance had significantly increased risk for lower spelling and reading achievement (WRAT-IV Spelling *OR* = 8.24, 95% *CI,* 2.60–26.14, *p* <.001; Reading *OR* = 19.11, 95% *CI,* 4.55–80.23, *p* <.001).

Adaptive Skill Outcomes

The overall group of survivors showed adaptive skill scores in the average range, broadly consistent with expectations based on chronological age (Table 2). The rates of at-risk impairment were significantly higher than expected on measures of global adaptive skills (ABAS-II GAC – 21.85%, *p* = .02) and in the practical adaptive skill domain (Practical - 23.7%, *p* =.003). The frequency of scores within the at-risk range did not differ significantly from normative expectations for conceptual and social adaptive scores (Table 2).

Results from univariate analyses examining the contribution of predictor variables to adaptive skill outcomes are depicted in Tables 3 and 4. Adaptive skill ratings varied significantly by patient sex, age at diagnosis, and insurance status. Females had significantly higher ratings of adaptive skills than males in all measured domains (ABAS-II GAC *p* = .02, Practical *p* = .04, ABAS-II Social *p* < .01, ABAS-II Conceptual *p* = .02). Compared to older patients, patients <10 years had significantly poorer ratings of global adaptive skills (ABAS-II GAC *p* = .04). Compared to those with US private or military insurance, survivors with US public insurance had significantly lower adaptive functioning scores on all domains (all *p* < .01). Treatment variables did not significantly predict adaptive skill outcomes.

Results from multivariable models showed that patient sex and insurance status significantly predicted increased risk for adaptive skill deficits. Compared to males, females had significantly decreased risk for deficits in global adaptive, conceptual, and social domains (ABAS-II GAC, *OR* = 0.36, *95% CI,* 0.16–0.81, *p* = .01; Conceptual, *OR* = 0.38, *95% CI,* 0.17–0.89, *p* = .03 ; Social, *OR* = 0.26, *95% CI,* 0.10–0.65, *p* = .004). Compared to survivors with US private or military insurance, survivors with US public insurance had increased risk for adaptive skill deficits in all domains (ABAS-II GAC, *OR* = 4.30, *95% CI,*1.72–10.77, *p* = .002; Conceptual, *OR* = 5.41, *95% CI,* 2.02–14.49, *p* <.001; Social, *OR* = 5.75, *95% CI,* 2.02–16.39, *p* = .001; Practical, *OR* = 2.42, *95% CI,*1.04 – 5.62, *p* = .04). Compared to those with US private or military insurance, survivors with non-US insurance had significantly increased risk for adaptive skill deficits across all domains (ABAS-II GAC, *OR* = 4.84, *95% CI,*1.72–10.77, *p* =.004; Conceptual, *OR* = 6.74, *95% CI,* 2.19–20.79, *p* <.001; Social, *OR* = 3.67 *95% CI,* 1.00–13.46, *p* = .05).

Discussion

The current study examined functional outcomes of survivors of HR B-ALL treated with contemporary therapy (AALL0232) that did not include CRT. To our knowledge, this is the first study to examine adaptive skill outcomes in survivors of childhood ALL post-completion of contemporary therapy. Strengths of the study include relatively large sample size, homogeneous treatment protocol, a focus on functional outcomes (academic achievement and adaptive skills), and the use of psychometrically robust measures.

For the overall group, academic achievement was in the average range (i.e., consistent with age expectations). This is consistent with findings from prior studies of neurocognitive outcomes shortly after completion of treatment. [5,23] In the context of average range academics in the overall group, younger age at diagnosis and lower SES emerged as risk factors for poorer outcomes in both univariate and multivariate analysis. These data suggest that younger children with HR B-ALL with US public insurance are a very high-risk group for academic difficulties, specifically in math.

For adaptive skills, the rates of at-risk impairment were significantly higher than expected in the overall group of survivors. Results from multivariable models suggest that boys and individuals with US public insurance are at particularly increased risk for problems with adaptive skills. Our findings suggest that boys are at greater risk for difficulties with adaptive functioning, compared to girls. This finding contrasts with prior work that identified female sex as a predictor of increased risk for neurocognitive problems. [5,6] It is possible that the additional year of protocol-directed therapy for boys treated on AALL0232 confers additional risk for delayed adaptive development or that boys treated for HR B-ALL are generally more vulnerable to adaptive skill deficits compared to girls.

Importantly, randomized treatment variables did not significantly predict either functional outcomes (academic or adaptive skills). There were no significant differences in outcomes by methotrexate dosing or corticosteroid therapy. This is consistent with findings from the prior study of neurocognitive outcomes in this group. [23] While some previous work had suggested that dexamethasone is associated with greater vulnerability to academic problems, our work did not support this. [27]

The mechanism that confers vulnerability for functional outcomes is likely multifactorial in nature. Attention problems at the end of therapy have been shown to predict reduced academic achievement in early survivorship in a study of survivors of childhood ALL treated on a contemporary therapy protocol. [5] Decreased opportunities for socialization and learning are especially salient for younger children with fewer family resources. It is also feasible that the vulnerabilities we detected are a result of missed opportunities for younger children with HR B-ALL to participate in school (i.e., less environmental stimulation).

Our findings extend those from prior reports of neurocognitive outcomes in this cohort to include heightened vulnerability for children with US public insurance to functional outcomes,[23] specifically academic achievement and adaptive skills. Participants with US public insurance had average academic achievement scores that ranged from 23rd to 27th percentile and adaptive skill ratings that ranged from the 23rd to 34th percentile. Previous

research supports low income as a risk factor, with youth (ages 8–18 years) demonstrating worse adaptive functioning across measures of social competence, academic achievement, problem behaviors, and psychosocial well-being. Future longitudinal work is essential to determine if this identified risk reflects pre-existing deficits linked to general disadvantage and/or greater vulnerability specific to children with ALL. COG is currently conducting longitudinal neurocognitive and adaptive outcomes research with children with ALL to better understand the impact of SES for these children. It seems likely that children with ALL from environments with fewer opportunities for cognitive and environmental stimulation may be at higher risk over time.

Our study is not without limitations. Not all patients enrolled on AALL0232 were eligible to participate in the current study (AALL06N1), which limits the generalizability of our findings. Outcome completion rates varied according to factors related to study design (i.e., amendments to decrease battery size) and measurement characteristics (i.e., lower age limits for some academic tests). The lower completion rates for some study measures increased the variability associated with some outcomes from multivariable analysis (i.e., larger confidence intervals). Finally, we used insurance status as a proxy measure of SES, as this information was available as part of the data collected in the clinical treatment trial. SES is a multidimensional construct defined by characteristics that include parental education and occupation, material and financial resources, and neighborhood variables; these types of data were not feasible to collected within this large cooperative group study. To date, an ideal or gold-standard' approach to measurement has not been developed. Future work should consider more comprehensive measurement of SES.[28] Detection of early signs of morbidity or identification of specific vulnerable children will permit early intervention trials to attempt to mitigate risk. At the community level, strategies to remediate adaptive vulnerabilities include both general social and educational interventions (federally-mandated early intervention programs). Future work is needed to identify programs targeted specifically to improve adaptive skills and academic outcomes in pediatric oncology populations.

Acknowledgments

Data availability:

Deidentified participant data and study protocol will be available to investigators whose proposed use of the data has been approved by an independent review committee identified for this purpose. Requests should be directed to corresponding author; to gain access, data requestor will need to sign a data access agreement.

Abbreviation Key:

ABAS-II	Adaptive Behavior Assessment System, 2nd Edition
ALL	acute lymphoblastic leukemia

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COG	Children's Oncology Group
CNS	central nervous system
CRT	cranial radiation therapy
GAC	Global Adaptive Composite
HDMTX	high-dose methotrexate
HR B-ALL	High-risk acute lymphoblastic leukemia (B-cell)
ICF	International Classification of Functioning, Disability, and Health
MTX	methotrexate
SES	socioeconomic status
WRAT-IV	Wide Range Achievement Test, 4th Edition

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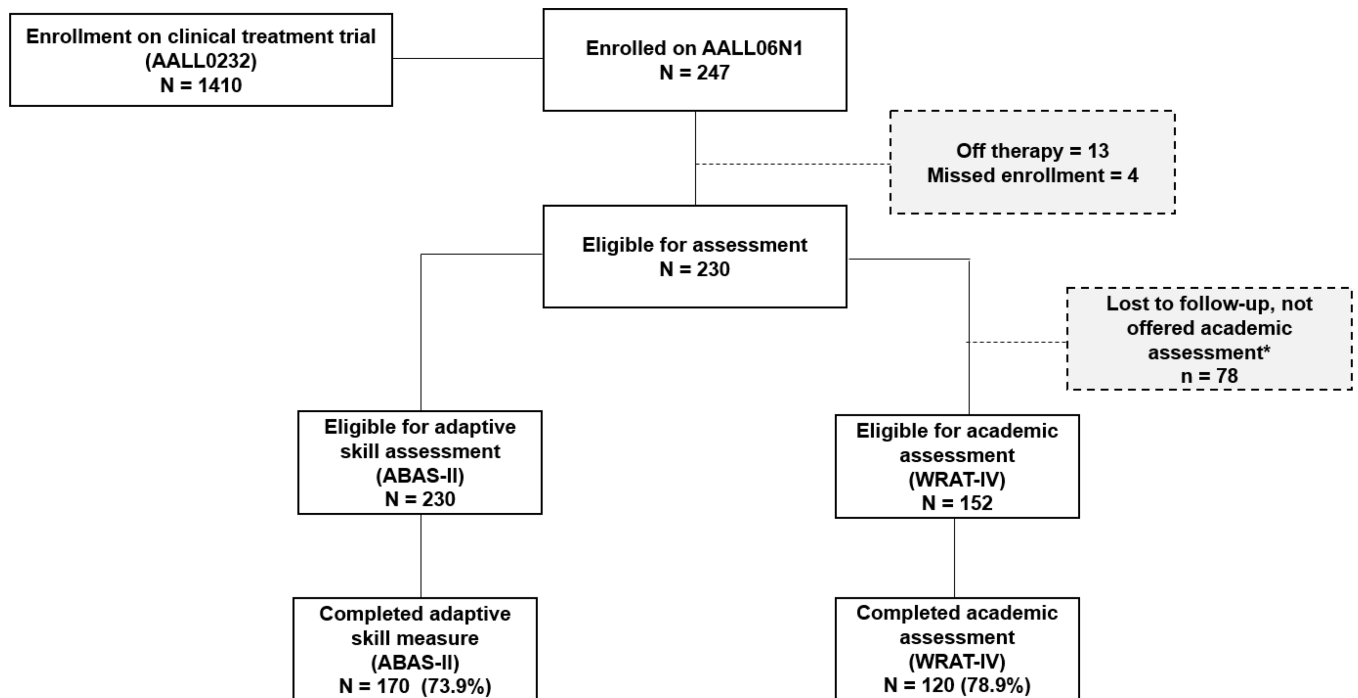
Figure 1.

Participant Flowchart.

Notes: *Some participants were not offered academic assessment after a study amendment that shortened the testing battery. Reasons for missing data were not always consistently documented; when included, generally referred to time constraints.

TABLE 1.

Demographic and clinical characteristics for the overall group (N = 178)

	n	%
Methotrexate Dosing		
High-dose	87	48.9
Escalating dose	91	51.1
Corticosteroid Therapy		
Dexamethasone	80	45.0
Prednisone	98	55.1
Sex		
Male	79	44.4
Female	99	55.6
Race		
White	144	80.9
Asian	6	3.4
Black	5	2.8
Unknown	23	13.0
Ethnicity		
Hispanic or Latino	32	18.0
Not Hispanic or Latino	135	75.8
Unknown	11	6.2
Insurance Status		
US Public	45	25.3
US Private or Military	101	56.7
Non-US	26	14.6
Unknown or Self-Pay	6	3.4
	Mean	*Standard Deviation*
Age at diagnosis (years)	8.5	5.0
Age at assessment (years)		
ABAS-II*	12.5	5.0
WRAT-IV**	12.8	5.1
Time off treatment (months)		
ABAS-II	14.2	3.9
WRAT-IV	13.0	2.9

Abbreviations: ABAS-II: Adaptive Behavior Assessment System, Second Edition (n=170); WRAT-IV: Wide Range Achievement Test, Fourth Edition (n = 120).

TABLE 2.

Descriptive statistics for measures of academic achievement and adaptive functioning

	n	Mean	SD	p [a]	% at risk	p [b]
Academic: WRAT-IV (SS)						
Math Computation	119	99.3	17.5	.65	21.0	.062
Spelling	117	102.4	17.6	.14	17.1	.36
Reading Composite	118	102.7	16.4	.08	13.6	.75
Adaptive Skills: ABAS-II (SS)						
General Adaptive Composite	165	98.4	18.5	.26	21.8	.02
Conceptual Composite	170	100.3	17.2	.82	18.8	.15
Social Composite	166	101.5	16.2	.22	15.7	.53
Practical Composite	169	95.4	18.7	.002	23.7	.003

Abbreviations: WRAT-IV = Wide Range Achievement Test, Fourth Edition; ABAS-II = Adaptive Behavior Assessment System, Second Edition. SS = Standard Scores, normative mean = 100, standard deviation = 15. % at risk. At-risk scores are ≥ 1 SD below the normative mean (≤ 16th percentile).

[a]: 2-sided p-value from one-sample t-test comparing observed versus expected mean and standard deviation.

[b]: 1-sided p-value from frequency comparison of observed versus expected rate of impairment.

TABLE 3.

Univariate comparisons of academic achievement and adaptive skills by demographic and treatment risk factors

	Academics (WRAT-IV)									General Adaptive			Adaptive Skills (ABAS-II)								
	Math			Reading			Spelling						Practical			Social			Conceptual		
	Mean	SD	p	Mean	SD	p	Mean	SD	p	Mean	SD	p	Mean	SD	p	Mean	SD	p	Mean	SD	p
Sex																					
Males	100.0	16.7	0.64	101.7	14.5	0.53	100.6	16.6	0.29	94.7	20.2	**0.02**	92.0	20.4	**0.04**	97.1	17.7	**<.01**	96.7	18.6	**0.02**
Females	98.6	18.4		103.6	17.9		104.1	18.5		101.2	16.7		97.9	17.0		104.9	14.2		103.0	15.7	
Age at diagnosis																					
< 10 years	94.2	15.6	**<.01**	100.1	15.9	0.12	100.0	16.4	0.16	95.3	18.0	**0.04**	93.5	19.0	0.23	100.7	16.6	0.52	98.3	16.3	0.15
10 years	103.7	18.0		104.8	16.5		104.5	18.4		101.3	18.6		97.0	18.4		102.3	15.9		102.1	17.9	
Insurance Status																					
US Public	91.5	15.9	**<.01**	91.1	16.3	**<.01**	89.2	16.3	**<.01**	90.4	21.9	**<.01**	89.2	22.1	**<.01**	94.3	18.4	**<.01**	93.3	19.8	**<.01**
US Private/Military	103.6	17.1		107.6	14.2		108.2	15.8		103.0	14.8		99.4	15.4		105.0	13.4		104.4	14.1	
Non-US	90.5	14.7		97.9	16.2		97.7	13.2		93.2	20.6		88.8	21.2		100.8	17.8		96.0	18.9	
Unknown/self-pay[*]	.	.		.	.		.	.		103.0	16.7		103.3	10.9		101.2	19.5		103.7	18.6	
Methotrexate																					
High-Dose	98.8	15.7	0.77	103.4	15.6	0.63	102.9	16.8	0.78	99.2	17.9	0.57	95.8	17.6	0.75	102.3	15.7	0.54	100.9	17.1	0.68
Escalating	99.7	19.3		101.9	17.1		102.0	18.5		97.6	19.2		94.9	19.8		100.8	16.7		99.8	17.4	
Corticosteroid																					
Dexamethasone	101.0	17.8	0.31	103.8	17.3	0.46	105.6	19.3	0.06	96.1	19.5	0.16	92.2	20.2	0.05	100.2	16.1	0.33	98.9	18.2	0.35
Prednisone	97.7	17.3		101.6	15.5		99.5	15.5		100.2	17.6		97.9	17.1		102.6	16.3		101.4	16.4	

Abbreviations: SD = standard deviation, MTX = methotrexate; WRAT-IV = Wide Range Achievement Test, 4th Edition; ABAS-II = Adaptive Behavior Assessment System, 2nd Edition. Notes: Scores are age-standardized, with a mean of 100 and a standard deviation of 15. 2-sided p-values from mean comparisons.

[*] Unknown/self-pay n = 1 for academic outcomes. Bold font = significant at p<.05.

TABLE 4.

Univariate regression models of academic achievement and adaptive skills by age at diagnosis as a continuous variable

| | Academics (WRAT-IV) | | | | | | | | | Adaptive Skills (ABAS-II) | | | | | | | | | | | |
| | Math | | | Reading | | | Spelling | | | General Adaptive | | | Practical | | | Social | | | Conceptual | | |
	β	SE	p	β	SE	p	β	SE	p	β	SE	p	β	SE	p	β	SE	p	β	SE	p
Age at diagnosis	0.99	0.30	**<.01**	0.52	0.29	0.08	0.50	0.32	0.12	0.69	0.29	**0.02**	0.57	0.29	**<.05**	0.22	0.25	0.39	0.36	0.26	0.17

Abbreviations: WRAT-IV = Wide Range Achievement Test, Fourth Edition; ABAS-II = Adaptive Behavior Assessment System, Second Edition. β = Beta, SE = Standard Error. Notes: 2-sided p-values from univariate regression. Bold font = significant at p<.05.

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Multivariable models of outcomes

Table 5.

| | Academics (WRAT-IV) | | | | | | | | | Adaptive Skills (ABAS-2) | | | | | | | | | | | |
| | Math | | | Spelling | | | Reading | | | General Adaptive | | | Conceptual | | | Social | | | Practical | | |
	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
Sex																					
Male	Ref	.		Ref	.		Ref	.		Ref	.		Ref	.		Ref	.		Ref	.	
Female	1.12	0.4,2.9	0.82	0.95	0.3,2.8	0.93	1.18	0.3,4.0	0.80	0.36	0.2,0.8	0.01	0.38	0.2,0.9	0.03	0.26	0.1,0.7	0.004	0.6	0.3,1.2	0.14
Age at diagnosis																					
< 10 years	3.16	1.2,8.8	0.02	1.71	0.6,5.0	0.33	2.39	0.7,8.1	0.16	0.90	0.4,1.9	0.79	0.92	0.4,2.1	0.85	0.76	0.3,1.9	0.56	1.1	0.5,2.4	0.74
10 years	Ref	.		Ref	.		Ref	.		Ref	.		Ref	.		Ref	.		Ref	.	
Insurance Status																					
US Public	3.23	1.1,9.3	0.03	8.24	2.6,26.1	<0.001	19.11	4.5,80.2	<0.001	4.30	1.7,10.8	0.002	5.41	2.0,14.5	<0.001	5.75	2.0,16.4	0.001	2.4	1.0,5.6	0.04
US Private/ Military	Ref	.		Ref	.		Ref	.		Ref	.		Ref	.		Ref	.		Ref	.	
Non-US	3.85	0.9,16.5	0.07	2.74	0.5,16.1	0.27	5.65	0.8,40.1	0.08	4.84	1.7,14.2	0.004	6.74	2.2,20.8	<0.001	3.67	1.0,13.5	0.05	3.2	1.2,8.6	0.02
Unknown/ Self	*			*			*			1.37	0.1,13.4	0.79	2.06	0.2,20.5	0.54	2.21	0.2,23.1	0.51	*		

Abbreviations: OR = conditional odds ratio estimate; CI = confidence interval

*
could not be estimated due to insufficient cell sizes