Behavioral and Emotional Functioning of Children and Adolescents at the End of Treatment for Acute Lymphoblastic Leukemia Compared to Healthy Peers

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Abstract

This study describes the behavioral and emotional adjustment of 77 children and adolescents 3 months post-treatment for acute lymphoblastic leukemia (ALL), compared to 52 age and sex-matched healthy peers. Parents, teachers, and self-report ratings on the Behavioral Assessment System for Children, Second Edition (BASC-2) were utilized to measure psychological function. While overall mean scores were in the average range for both groups, parents and teachers rated patients higher on behavior symptoms, internalizing problems and adaptive skill difficulties. No significant differences between groups were observed on self-report, and inter-rater correlations were low to moderate. For the ALL group, maternal university completion was associated with elevations on parent report of behavioral problems, while no other factors predicted either parent or teacher report on other scales. Findings indicate that a subset of patients will require specialist psychosocial support to optimise their adjustment following treatment completion.

Keywords Childhood leukemia · Behavior · Adjustment · Chemotherapy · Lymphoblastic leukemia

Introduction

There are numerous factors that may contribute to psychological late effects in children and adolescents treated for acute lymptoblastic leukaemia (ALL), including the challenges associated with a serious medical condition, extended periods of painful therapy, multiple hospitalizations, and disruption to normal developmental experiences. Research focused specifically on patients with ALL, either during treatment or in the survivorship phase (≥ 5 years post treatment) indicates that parents identify between 22 and 47% of children display elevated behavioral and emotional symptoms including social withdrawal, anxiety/depression, somatization, inattention and hyperactivity (Jacola et al., 2016a; Kunin-Batson et al., 2016; Shelby et al., 1998; Waber et al., 2012). In contrast, others have found no difference in psychological adjustment when assessing children and adolescents at various stages post-treatment for ALL and other cancers, compared to healthy controls (Kazak et al., 2010; Nazari et al., 2014; Phipps et al., 2014). Relatively little is known about these childrens' psychological status in the early period following the end of ALL treatment (Kunin-Batson et al., 2016; Moore et al., 2003), despite the fact that the transition from treatment completion back to 'normal' life is recognised as one of the most stressful times for children and families (Wakefield et al., 2012).

Understanding of the psychological effects of pediatric ALL treatment is further limited by a heavy reliance on parent ratings (Jacola 2016a; Waber et al., 2012; Wolfe-Christensen et al., 2009). Parent proxy reports have been found to be complicated by the impact of increased parental vigilance and parental distress (Liu et al., 2018; Malpert et al., 2015), factors that may potentially inflate reported rates of concerning behaviors. Significant discrepancies in rater reports have

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also been identified, with one study, comparing informants for 47 ALL patients who had been receiving treatment for at least 1 year, or were less than 3 years post treatment, finding that children reported fewer problem behaviors than parents and teachers (Moore et al., 2003). Children themselves are thought to under-report difficulties, with young cancer patients often rating themselves similarly to population norms despite known challenges with behaviour and emotions (Carpentieri et al., 2003; Kazak et al., 2010; Waber et al., 2012). Additionally very young children are unable to complete formal questionnaires, limiting the generalizability and power of these data. Teachers have been proposed as providing a more objective depiction of a child's functioning than parents or self-report by allowing for comparison to healthy peers. However, this approach needs to be balanced with an appreciation for how well a teacher may know the child due to the disruption to schooling that often occurs during treatment. Given these complications, obtaining multiple rater reports has been recommended to better inform the degree and frequency of problem behaviors experienced by this patient population (Wolfe-Christensen et al., 2009).

Of further importance, only a handful of studies have incorporated a healthy comparison group when examining psychological outcomes post ALL (Jacola et al., 2016a; Kazak et al., 2010; Nazari et al., 2014; Wolfe-Christensen et al., 2009); thus psychological adjustment for children and adolescents early following ALL treatment remains poorly understood with questions remaining about whether difficulties are present at the end of treatment. Improved understanding of early post-treatment adjustment is important in order to inform evidence-based psychological screening and intervention and direct psychosocial resources where they are needed.

We are conducting a prospective, longitudinal, case-controlled study, the *ALLaboard* study, to investigate the trajectory of psychological adjustment and the cognitive skills underpinning this in pediatric patients following chemotherapy-only treatment for ALL. This paper reports on the first assessment timepoint, 3 months post treatment. We aimed to examine parent, teacher and self-reported behavioral, emotional and adaptive functioning of children and adolescents compared to healthy age and sex-matched children, and explore the correspondence between rater reports. A secondary aim was to explore predictors of rater reports in domains that were found to differ between the ALL group and healthy children. We hypothesized that (i) parents and teachers of patients would identify more difficulties in psychological adjustment than those of healthy comparison children, while both patients and healthy children would self-report few difficulties, (ii) inter-rater correspondence would be low given their observation of behavior in different settings, and (iii) parental mental health would be associated

with higher ratings of problem behaviors and emotional difficulties in their child.

Methods

Design

This study presents data from Wave 1 of a longitudinal, prospective, case-controlled study (*The ALLaboard Study)* that aims to map the developmental trajectory of psychological adjustment and cognition in pediatric patients following chemotherapy-only treatment for ALL. The ALLaboard study involves participants undergoing a total of five assessments at 6-month timepoints. Questionnaire data are collected at time 1 (3 months post-treatment), time 3 (15 months post-treatment) and time 5 (27 months post-treatment). This paper presents time 1 data. ALLaboard is being conducted at the Children's Cancer Centres at The Royal Children's Hospital (RCH) and Monash Children's Hospital (MCH), Melbourne, Australia.

Participants

Patient Group

Patients aged 4–16 years who had completed active chemotherapy-only treatment for ALL between October 2013 and December 2017 were eligible to participate. Participants had completed treatment no more than 3 months prior to enrolment. Participants were ineligible if: they or their parents had insufficient English language ability to complete the assessments; they had a pre-existing neurodevelopmental (e.g., autism spectrum disorder) or neurological (e.g., epilepsy) disorder; they were born prematurely (< 30 weeks); they had a history of radiation treatment; had relapsed or were receiving further treatment; or were in palliative care. Patient participants were treated with intrathecal and intravenous methotrexate (MTX) according to the Children's Oncology Group protocols (AALL0331, AALL0932, standard risk $n=54$; AALL0434, AALL0232, AALL1131 high risk n=23).

Healy Comparison Group

The comparison group comprised a convenience sample of healthy children. Patient participants invited a friend of the same age and sex to participate in the study. A small number of healthy children were recruited through advertising in the Oncology and Psychology Services at The RCH. Comparison participants were ineligible if: they or their parents had insufficient English language ability to complete the

assessments; they had a pre-existing neurodevelopmental or neurological disorder; malignant disease; or were born prematurely (< 30 weeks).

Sample

The study sample included 77 patients (60.1% participation rate) and 52 healthy comparison participants (Table 1). Participants were on average 8 years old (range 4.1–16.3 years); 57% male. Mean time off treatment for patient participants was 3.17 (SD = 0.5) months. There were no significant differences between children and adolescents with ALL and the comparison group on any demographic factors. Parent participants were predominantly mothers (89.61%).

Procedure

The study received ethics approval from The RCH (#33094) and MCH (#13264) Human Research Ethics Committees. Parents were informed of the study by their consultant oncologist at their child's final treatment appointment. Written consent was obtained from parents and children > 12 years with verbal assent from younger children. Assessments of patient and comparison participants were conducted in an outpatient clinic by neuropsychologists or trained research assistants with a minimum undergraduate training in psychology under the supervision of a clinical neuropsychologist. Parents completed questionnaires on the

day of assessment, or within the previous week. Parents were provided with a letter with links to teacher questionnaires on the day of assessment and were asked to pass this on to their child's main teacher for completion. Parents were asked to ensure that the teacher was familiar with their child. In the case that a child had only recently commenced in a new year level, the teacher from the previous year was asked to complete the questionnaire. Reminder emails and telephone calls were made to parents after 2 weeks if either the parent questionnaires or teacher questionnaires were outstanding.

Measures

Patient and family demographic data was obtained via a parent completed questionnaire. Data about diagnosis and treatments were extracted from hospital medical records. All other measures utilized in the study are validated instruments with robust psychometric properties.

Behavioral Assessment System for Children-2nd Edition (BASC-2: Reynolds & Kamphaus, 2004)

Child and adolescent emotional and behavioral functioning was assessed using the BASC-2 (parent, teacher and age appropriate child versions). The BASC-2 is a widely used multidimensional assessment system that evaluates a broad range of problem behaviors and adaptive skills. The BASC-2 has three separate forms based on age which were

Table 1 Sample characteristics

	Children with ALL (N = 77)	Healthy comparison group (N = 52)	p
Age, M (SD), range, years	8.08 (3.15), 4.1–16.3	8.48 (3.48), 4.2–16.0	.55
Boys, N (%)	44 (57.14)	24 (46.15)	.20
Age at diagnosis (years) M (SD), range	5.00 (3.17), 1.3–13.7	–	–
Time since diagnosis (years) M (SD), range	Males: 3.50 (0.87), 3.3–3.7 Females: 2.51 (0.09), 2.4–2.8	–	–
Time since treatment completion (months) M (SD)	3.17 (0.51)	–	–
High risk treatment, N (%)	23 (29.87)	–	–
FSIQ, M (SD), range	102.42 (11.93), 81–136	105.77 (10.09), 83–130	.10
Parent age, M (SD)	39.81 (5.18)	41.70 (5.76)	.06
Mother, N (%)	69 (89.61)	48 (92.31)	.61
Currently employed, N (%)	51 (66.23)	38 (74.51)	.32
Maternal University completion, N (%)	38 (52.78)	30 (60.00)	.43
MFAD total score, M (SD), range	1.72 (0.46), 1.0–2.8	–	–
Distress rating, M (SD), range	3.57 (2.34), 0–8	–	–
PCL-S total score, M (SD), range	31.55 (10.29), 16–59	–	–
DASS depression, M (SD), range	5.26 (6.36), 0–26	–	–
DASS anxiety, M (SD), range	3.55 (4.53), 0–16	–	–
DASS stress, M (SD), range	10.42 (7.14), 0–30	–	–

ALL acute lymphoblastic leukemia, *DASS* depression, anxiety, stress scale, *FSIQ* full scale intelligence quotient, *MFAD* McMaster family assessment device, *PCL-S* posttraumatic checklist—specific version

used in the current study; pre-school (4–5 year old), child (6–11 year old), and adolescent (12–18 year old). Parents and teachers completed the BASC-2 for all children and adolescents enrolled on the study, while children aged 8 years and older completed the age-appropriate self-report form. Items are rated on a 4-point Likert scale for the frequency of each behavior (0 = *Never*, 1 = *Sometimes*, 2 = *Often*, 3 = *Always*). Raw scores are transformed into age and sex adjusted T scores ($M = 50$, $SD = 10$). For the problem scales higher scores represent more symptoms, with T scores of 60–69 indicating the child is *at risk*, and scores ≥ 70 considered *clinically significant*. For the adaptive scales lower scores represent deficits, with T scores of 31–40 indicating the child is *at risk* and ≤ 30 considered *clinically significant*. Composite index scores are generated for each of the rater forms. Many of these are consistent across forms whilst some subscales and composite scales differ based on age (e.g. sensation seeking subscale only generated from the adolescent self report form). N's therefore vary and are noted in the summary tables.

Intelligence

Participants aged 4–5.11 years (ALL $n = 25$; TDC $n = 16$) completed the Wechsler Preschool and Primary Scale of Intelligence—Fourth Edition (WPPSI-IV) to generate a Full Scale Intelligence score (FSIQ) (Wechsler, 2012) ($M = 100$, $SD = 15$). For participants aged 6–16 years (ALL $n = 50$; TDC $n = 36$) FSIQ was estimated using the 4 subtest version of the Wechsler Abbreviated Scale of Intelligence—2nd Edition (WASI-II: 4 subtest version) (Wechsler, 2011) ($M = 100$, $SD = 15$).

McMaster Family Assessment Device (Miller et al., 1985)

Family functioning was measured on the General Functioning scale (GF) of the Family Assessment Device (FAD), which consists of 12 items that measure the overall functioning and health of a family (Miller et al., 1985). Parents rated each item (1–4) depending on how well each statement described their own family. Higher scores reflected poor family functioning. The mean item score was calculated, with scores above 2.0 indicative of unhealthy family functioning (Miller et al., 1985).

The Posttraumatic Stress Checklist—Specific Version (PCL-S)(Weathers, 1993)

The PTSD Checklist—Specific Version is a self-reported scale comprising 17 items that correspond to the key symptoms of post-traumatic stress disorder (PTSD). Parents indicated on a 5 point scale (1 = *Not at all*, 5 = *Extremely*) how much they had been bothered by each symptom over the past

month in relation to their child's cancer. We report the total score (range 17–85) where a total score of 44 or higher is indicative of likely PTSD.

The Depression, Anxiety and Stress Scale-Short Form (DASS) (Lovibond & Lovibond, 1995*)*

Parental depression, anxiety and stress was measured using the 21-item version of the DASS. Parents were asked to indicate on a 4 point scale (0 = *Did not apply to me at all*, 3 = *Applied to me very much, or all the time*) how much each statement applied to them over the past week. Each subscale comprised 7 items with higher scores indicative of more problems.

Statistical Analysis

All data analyses were conducted utilizing STATA version 15.0 (StataCorp, 2019). Mean T scores on the BASC-2 subscales are reported for each group by parent, teacher and self-report. *T* tests were employed to examine differences in group means across each subscale by different reporters. In instances that the data did not meet the assumption of a normal distribution we utilised the Mann–Whitney *U* test to investigate group differences (denoted in tables). Differences in the proportion of participants falling in the 'at risk/clinically significant' range (as defined by normative cut-offs) for each rater were examined using Fisher's exact test of independence.

Intra-class correlations are presented to indicate agreement across respondents. Univariate and multivariate linear regression analyses were used to examine child and parent/family predictors of parent and teacher reported index scores that were found to be significantly different between the ALL group and comparison group. Child and parent/family factors were first examined individually, in univariate analyses. Significant predictors at the 0.10 level were then included simultaneously in a multivariate analysis to examine the strongest predictors of functioning. Due to the number of comparisons we chose a conservative alpha level of 0.01 to denote statistical significance for all analyses.

Results

Child-reported Emotional and Behavioral Functioning

Mean scores for patients and comparison participants fell within the *average* range for all BASC-2 subscales (Table 2). The largest difference between groups in regards to the proportion of children falling within the *at risk/clinically significant* range was found on the attention subscale (30.3%

ALL group compared to 4.2% comparison group, see Supplementary Table 1). Medium effect sizes were reported for attention, as well as internalising symptoms (depression), locus of control and personal adjustment. However, none of the group differences met our conservative 0.01 alpha level for statistical significance.

Parent-reported Emotional and Behavioral Functioning

Parent ratings of emotional, behavioral and adaptive functioning fell within the *average* range on all subscales for both groups. Statistically significant differences were found between groups on the Behavioral Symptoms Index (including withdrawal and attention problems), Internalizing Problems Index (including depression and somatization) and the Adaptive Skills Index (including social skills, leadership, activities of daily living and communication) (Table 3), with medium effect sizes found for these comparisons.

Parents of ALL patients rated 40.3% in the *at-risk to clinically significant* range on Internalizing Problems, compared to 9.6% of the comparison group ($p < .001$, see Supplementary Table 2). Rates around 25–30% in this range were also reported for the ALL group on the attention problems ($p = .004$), depression ($p = .002$), and leadership ($p = .006$) subscales.

Teacher-reported Emotional and Behavioral Functioning

Mean scores for both groups were within the *average* range on all BASC2 subscales for teacher report (Table 4). Statistically significant differences were found on the Behavioral Symptoms Index (including atypicality and withdrawal), Internalizing Problems Index (including depression and somatization), and Adaptive Skills Index between groups.

The proportion of patients falling in the *at-risk to clinically significant* range on teacher report was generally lower than parent-reported outcomes (see Supplementary Table 3). Significantly more children in the ALL group were identified within this range for Internalizing Problems (33.9% v 11.1%, respectively) and Externalizing Problems (15.4% v 0.0%, respectively) than the comparison group.

Table 2 Group comparisons of child-reported emotional and behavioral functioning

	Mean (SD)				
	ALL (*N* = 33)	HC (*N* = 24)	*t* (df)	Cohen's d	*p*
Emotional symptoms index	46.2 (8.6)	43.2 (4.9)	1.57 (55)	0.42	.123
School problems	50.8 (11.6)	47.3 (7.4)	1.31 (55)	0.35	.195
Attitude to school	50.0 (12.4)	46.2 (7.6)	1.34 (55)	0.36	.185
Attitude to teachers	50.5 (10.4)	49.3 (7.4)	0.47 (55)	0.13	.643
Sensation seeking[a]	50.3 (8.8)	47.0 (9.1)	0.78 (16)	0.37	.448
Internalizing problems	46.7 (9.2)	43.0 (5.6)	1.72 (55)	0.46	.091
Atypicality	46.4 (8.5)	45.2 (7.6)	0.56 (55)	0.15	.578
Locus of control	49.8 (11.4)	44.8 (8.2)	1.81 (55)	0.48	.076
Social stress	44.3 (7.7)	42.1 (6.4)	1.11 (55)	0.30	.271
Anxiety	45.5 (7.9)	45.3 (8.7)	0.09 (55)	0.02	.927
Depression	45.7 (5.7)	42.5 (3.1)	2.51 (55)	0.67	.015
Sense of inadequacy	48.5 (9.6)	45.4 (5.9)	1.42 (55)	0.38	.162
Somatization[b]	54.7 (12.7)	45.6 (4.5)	2.05 (17)	0.94	.057
Inattention/hyperactivity	49.6 (9.3)	46.0 (8.0)	1.53 (55)	0.41	.133
Attention problems	50.8 (11.1)	44.7 (6.7)	2.38 (55)	0.64	.021
Hyperactivity	48.8 (7.4)	48.1 (8.7)	0.30 (55)	0.08	.769
Personal adjustment	52.9 (8.7)	56.3 (4.5)	− 1.72 (55)	− 0.46	.092
Relationship with parents	52.4 (9.2)	56.1 (6.2)	− 1.68 (55)	− 0.45	.099
Interpersonal relations	54.2 (6.1)	55.4 (7.3)	− 0.67 (55)	− 0.18	.505
Self esteem	52.5 (6.3)	54.2 (4.0)	− 1.11 (55)	− 0.30	.274
Self reliance	49.7 (10.1)	53.0 (7.6)	− 1.33 (55)	− 0.36	.191

ALL acute lymphoblastic leukemia, *CI* confidence interval, *HC* healthy comparison

[a] ALL *n* = 10, HC *n* = 8 (Only included in adolescent report)

[b] ALL *n* = 10, HC *n* = 9 (Only included in adolescent report)

Table 3 Group comparisons of parent-reported emotional and behavioral functioning

	Mean (SD)		t (df)	Cohen's d	p
	ALL ($N=77$)	HC ($N=52$)			
Behavioral symptoms index	**54.0 (11.2)**	**47.7 (7.4)**	**3.57 (127)**	**0.64**	**.001**
Atypicality	53.1 (11.2)	48.9 (7.8)	2.38 (127)	0.43	.019
Withdrawal	**54.1 (13.9)**	**48.2 (10.1)**	**2.66 (127)**	**0.48**	**.009**
Attention problems	**53.2 (10.3)**	**48.1 (8.5)**	**2.99 (127)**	**0.54**	**.003**
Externalising problems	51.5 (10.5)	48.3 (7.6)	1.86 (127)	0.33	.066
Hyperactivity	52.0 (9.6)	48.7 (7.1)	2.12 (127)	0.38	.036
Aggression	51.2 (9.6)	47.9 (7.9)	2.06 (127)	0.37	.042
Conduct problems[a]	50.1 (11.2)	49.4 (9.4)	0.30 (88)	0.06	.763
Internalizing problems*	**55.8 (14.0)**	**48.4 (8.1)**	**3.03**	**0.61**	**.002**
Anxiety*	53.5 (13.5)	50.7 (7.6)	0.67	0.24	.502
Depression	**54.3 (12.4)**	**47.6 (7.7)**	**3.47 (127)**	**0.62**	**.001**
Somatization	**55.8 (12.2)**	**47.9 (10.3)**	**3.81 (127)**	**0.68**	**<.001**
Adaptive skills index	**46.2 (9.9)**	**51.6 (8.6)**	**−3.20 (127)**	**−0.57**	**.002**
Adaptability	47.6 (10.9)	50.6 (10.4)	−1.57 (127)	−0.28	.118
Social skills	**47.4 (9.7)**	**52.5 (8.8)**	**−3.02 (127)**	**−0.54**	**.003**
Leadership[b]	**48.0 (10.2)**	**53.7 (8.3)**	**−2.84 (89)**	**−0.60**	**.006**
Activities of daily living	**45.7 (9.7)**	**50.5 (8.2)**	**−2.90 (127)**	**−0.52**	**.005**
Functional communication	**46.0 (9.1)**	**50.6 (8.0)**	**−2.98 (127)**	**−0.53**	**.004**

Bold value indicates significant differences at the $p > .01$ level

ALL acute lymphoblastic leukemia, *CI* confidence interval, *HC* healthy comparison

*Mann–Whitney U reported instead of t-test due to non-normality of data

[a]ALL $n=53$, HC $n=37$ (Scales vary based on age)

[b]ALL $n=53$, HC $n=38$ (Scales vary based on age)

Inter-rater Reliability

Supplementary Table 4 presents the intra-class correlations between parent, teacher, and self-ratings for the overlapping subscales. Agreement between reporters was weak to moderate, with the strongest correspondence on externalizing symptoms (0.54), attention problems (0.51) and somatic symptoms (0.67).

Predictors of Parent Reported Child Functioning

Table 5 presents the results of the regression models investigating associations between parent ratings and child, treatment, and parent/family factors. In univariate analysis with the BSI as the outcome, maternal university completion, better family functioning, and fewer posttraumatic stress symptoms (PTSS), depression, anxiety and stress symptoms in parents were associated with fewer reported behavioral symptoms in their child. When these factors were entered into the multivariate model only the association with maternal university completion remained significant. In univariate analysis with the Internalizing Problems Index as the outcome, the same factors were related to better outcomes, however none of these associations were significant in the

multivariate model. With the Adaptive Skills Index as the outcome, maternal university completion, better family functioning, and fewer symptoms of parent PTSS and stress were associated with better adaptive skills, but again these associations attenuated when entered into the multivariate model.

Predictors of Teacher Reported Child Functioning

Table 6 presents the results of the regression models investigating the associations between teacher ratings and child, treatment and parent/family factors. In univariate analyses with the BSI as the outcome, female sex, higher FSIQ and maternal university completion were associated with fewer behavioral symptoms, however these assocations did not remain statistically significant in the multivariate model. For the Internalizing Problems Index, higher FSIQ and maternal university completion were associated with fewer internalizing symptoms in univariate analyses, but no significant factors were identified in the multivariate model. In univariate analyses with the ASI as the outcome, female sex, higher FSIQ, and maternal university completion were associated with fewer behavioral symptoms, although none of these associations remained significant in the multivariate model.

Table 4 Group comparisons of teacher-reported emotional and behavioral functioning

	Mean (SD)		t (df)	Cohen's d	p
	ALL (N=65)	HC (N=45)			
Behavioral symptoms index	**50.2 (11.3)**	**44.4 (5.2)**	**3.19 (108)**	**0.62**	**.002**
Atypicality*	**50.7 (12.2)**	**45.6 (5.8)**	**2.92**	**0.05**	**.004**
Withdrawal	**49.7 (10.7)**	**44.2 (6.3)**	**3.11 (108)**	**0.60**	**.002**
School problems[c]	51.2 (10.3)	45.7 (7.5)	2.56 (77)	0.59	.013
Attention problems[a]	49.5 (9.8)	45.4 (8.1)	2.30 (107)	0.45	.024
Learning problems[b]	52.3 (11.1)	46.6 (7.3)	2.54 (76)	0.58	.013
Externalizing problems*	48.4 (10.1)	45.6 (4.5)	0.54	0.34	.590
Hyperactivity*	49.2 (9.6)	46.2 (5.1)	1.04	0.37	.296
Aggression*	48.9 (10.5)	45.7 (4.4)	1.04	0.38	.297
Conduct problems*[b]	47.8 (10.3)	45.7 (4.9)	− 0.75	0.25	.453
Internalizing problems	**55.6 (12.3)**	**48.1 (7.3)**	**3.65 (108)**	**0.71**	**< .001**
Anxiety	52.9 (11.9)	48.3 (7.7)	2.29 (108)	0.44	.024
Depression	**52.0 (11.6)**	**46.6 (5.6)**	**2.87 (108)**	**0.56**	**.005**
Somatization	**58.3 (11.2)**	**50.6 (8.1)**	**4.00 (108)**	**0.78**	**< .001**
Adaptive skills index	**50.7 (9.6)**	**55.5 (8.2)**	**− 2.73 (107)**	**− 0.53**	**.007**
Adaptability	52.1 (8.9)	54.6 (7.5)	− 1.56 (108)	− 0.30	.122
Social skills	53.1 (10.5)	57.8 (9.3)	− 2.43 (108)	− 0.47	.017
Leadership[b]	51.2 (10.1)	56.8 (8.4)	− 2.59 (76)	− 0.60	.012
Study skills[b]	48.6 (10.1)	53.9 (8.1)	− 2.44 (76)	− 0.56	.017
Functional communication	47.6 (9.5)	51.3 (9.1)	− 2.03 (107)	− 0.39	.045

Bold value indicates significant differences at the $p > .01$ level

ALL acute lymphoblastic leukemia, *CI* confidence interval, *HC* healthy comparison

*Mann–Whitney *U* reported instead of t-test due to non-normality of data

[a] ALL $n=65$, HC $n=44$

[b] ALL $n=46$, HC $n=32$ (Scales vary based on age)

[c] ALL $n=47$, HC $n=32$ (Scales vary based on age)

Discussion

This study represents one of the few controlled trials of emotional and behavioral adjustment in children treated with chemotherapy-only for ALL, that has obtained multiple informant questionnaire data at a stringently defined time point of 3 months post treatment completion. Study findings indicate that the majority of children and adolescents finishing contemporary ALL treatment do not experience psychological difficulties of clinical concern when compared to their age and sex-matched peers, and will likely adjust back to normal routines without specialist intervention. This finding is in keeping with the broader childhood cancer survivorship literature that indicates many patients, across a range of diagnoses and treatment protocols adapt well psychologically following treatment (Kazak et al., 2010; Phipps et al., 2014; Schepers et al., 2019).

Despite these positive findings, approximately 30% of children with ALL were identified as displaying at-risk or clinically significant levels of behavioral, emotional and adaptive skill difficulties in both home and school environments, with reported rates of impairment largely comparable with existing literature (Jacola et al., 2016a, 2016b; Kunin-Batson et al., 2016; Moore et al., 2003). Consistent with Moore et al. (2003), who monitored children both on and recently off treatment, our study found internalizing symptoms (40.3% parent report, 33.9% teacher report), predominantly depressive and somatic symptoms, were elevated post treatment, supporting the pervasiveness of internalizing problems across physical and psychological domains. While an increase in somatic symptoms is understandable in children who have recently completed lengthy cancer treatment, symptoms of depression and anxiety are of concern, particularly if they persist beyond treatment finishing. Of note, Kunin-Batson et al. (2016) found that depression and anxiety ratings at diagnosis closely mirrored those at 3-months post treatment, suggesting that children at-risk of longer-term psychological difficulties may be identified early in treatment.

Attention problems also featured strongly in our study, with approximately one third of patients experiencing difficulties in this domain across informant groups. Whilst not

Table 5 Predictors of parent-reported functioning

	Univariable models			Multivariate model including predictors $p \leq .10$		
	N	B (95% CI)	p	N	B (95% CI)	p
Behavioral symptoms index						
Child age	77	0.28 (−0.54, 1.09)	.503	–	–	–
Child sex	77	3.04 (−2.09, 8.16)	.241	–	–	–
FSIQ	76	−0.14 (−0.36, 0.08)	.200	–	–	–
Treatment intensity	77	−0.87 (−0.646, 4.71)	.756	–	–	–
Maternal university completion	72	−7.87 (−12.95, −2.79)	.003	72	−6.50 (−11.31, −1.68)	**.009**
Family functioning	77	7.49 (2.18, 12.79)	.006	72	4.31 (−1.06, 9.67)	.114
Parental PTSD symptoms	76	0.39 (0.15, 0.62)	.002	72	0.04 (−0.26, 0.34)	.799
Parental depressive symptoms	76	0.50 (0.11, 0.90)	.013	72	−0.13 (−0.68, 0.43)	.652
Parental anxiety symptoms	76	0.77 (0.23, 1.32)	.006	72	0.01 (−0.71, 0.72)	.984
Parental stress	76	0.69 (0.36, 1.01)	<.001	72	0.65 (0.14, 1.16)	.013
Internalizing problems index						
Child age	77	0.04 (−0.99, 1.06)	.943	–	–	–
Child sex	77	5.98 (−0.35, 12.30)	.064	72	8.74 (1.98, 15.51)	.012
FSIQ	76	−0.13 (−0.41, 0.14)	.333	–	–	–
Treatment intensity	77	1.39 (−5.61, 8.38)	.694	–	–	–
Maternal university completion	72	−6.68 (−13.31, −0.06)	.048	72	−6.34 (−12.63, −0.05)	.048
Family functioning	77	9.09 (2.43, 15.75)	.008	72	2.07 (−5.11, 9.26)	.567
Parental PTSD symptoms	76	0.50 (0.20, 0.79)	.001	72	0.34 (−0.07, 0.76)	.105
Parental depressive symptoms	76	0.64 (0.15, 1.13)	.012	72	−0.26 (−0.97, 0.45)	.466
Parental anxiety symptoms	76	1.00 (0.31, 1.68)	.005	72	−0.05 (−0.97, 0.045)	.917
Parental stress	76	0.83 (0.41, 1.24)	<.001	72	0.67 (0.02, 1.32)	.042
Adaptive skills index						
Child age	77	−0.16 (−0.88, 0.56)	.666	–	–	–
Child sex	77	2.42 (−2.12, 6.97)	.291	–	–	–
FSIQ	76	0.19 (−0.00, 0.377)	.051	71	0.18 (−0.01, 0.37)	.058
Treatment intensity	77	2.04 (−2.89, 6.97)	.412	–	–	–
Maternal university completion	72	6.17 (1.75, 10.60)	.007	71	1.97 (−2.76, 6.69)	.409
Family functioning	77	−5.59 (−10.35, -0.83)	.022	71	−3.56 (−8.31, 1.19)	.139
Parental PTSD symptoms	76	−0.40 (−0.60, −0.20)	<.001	71	−0.32 (−0.58, −0.07)	.013
Parental depressive symptoms	76	−0.25 (−0.60, 0.10)	.162	–	–	–
Parental anxiety symptoms	76	−0.29 (−0.79, 0.21)	.248	–	–	–
Parental stress	76	−0.29 (−0.61, 0.02)	.062	71	−0.02 (−0.37, 0.33)	.910

Bold value indicate significant difference at the $p > .01$ level

statistically significant, teachers also identified 28.3% of the ALL group as experiencing clinically significant problems with learning and 21.3% with school problems. This profile is consistent with the findings from Moore et al. (2003), and supports that a subset of children and adolescents are demonstrating functional difficulties maintaining attention and managing learning requirements at the end of treatment. While deficits in attention skills are prevalent in the survivorship population, cognition appears to be relatively intact at the end of chemotherapy-only treatment (Jacola et al. 2016b). Other factors are therefore likely contributing to functional difficulties in this area. These may include

psychological impacts, as well as other neuropsychological limitations, including reduced visuo-motor integration skills and executive deficits, which reduce a child's ability to utilize their cognitive capacity to full effect in everyday situations.

Parents and teachers also identified approximately 15–28% of patients experiencing difficulties in adaptive skills such as self-care activities, interacting with and effectively communicating with peers, and leadership abilities. Difficulties in this domain may reflect altered expectations for behavior, reduced exposure to developmentally appropriate opportunities for independent learning, limited social

Table 6 Predictors of teacher-reported functioning

	Univariable models			Multivariate model including predictors $p \leq .10$		
	N	B (95% CI)	p	N	B (95% CI)	p
Behavioral symptoms index						
Child age	65	0.09 (−0.78, 0.96)	.840	–	–	–
Child sex	65	−6.90 (−12.33, -1.47)	.014	61	−6.42 (−12.00, −0.83)	.025
FSIQ	65	−0.26 (−0.49, -0.03)	.029	61	−0.19 (−0.43, 0.05)	.117
Treatment intensity	65	−0.40 (−6.31, 5.51)	.893	–	–	–
Maternal university completion	61	−8.21 (−13.68, −2.74)	.004	61	−4.54 (−10.62, 1.54)	.140
Family functioning	65	−0.49 (−6.87, 5.88)	.878	–	–	–
Parental PTSD symptoms	65	0.08 (−0.20, 0.36)	.578	–	–	–
Parental depressive symptoms	65	0.05 (−0.39, 0.50)	.815	–	–	–
Parental anxiety symptoms	65	−0.24 (−0.88, 0.40)	.0456	–	–	–
Parental stress	65	0.14 (−0.27, 0.54)	.498	–	–	–
Internalizing summary score						
Child age	65	−0.11 (−1.05, 0.84)	.821	–	–	–
Child sex	65	−3.06 (−9.21, 3.08)	.323	–	–	–
FSIQ	65	−0.32 (−0.56, -0.07)	.012	61	−0.25 (−0.50, 0.01)	.058
Treatment intensity	65	−0.05 (−6.47, 6.36)	.987	–	–	–
Maternal university completion	61	−5.59 (−11.45, 0.28)	.061	61	−3.06 (−9.36, 3.24)	.335
Family functioning	65	−5.03 (−11.84, 1.77)	.144	–	–	–
Parental PTSD symptoms	65	−0.01 (−0.32, 0.30)	.937	–	–	–
Parental depressive symptoms	65	0.09 (−0.40, 0.57)	.719	–	–	–
Parental anxiety symptoms	65	−0.11 −0.80, 0.59)	.760	–	–	–
Parental stress	65	0.25 (−0.19, 0.69)	.256	–	–	–
Adaptive skills index						
Child age	64	0.30 (−0.44, 1.04)	.419	–	–	–
Child sex	64	6.37 (1.77, 10.97)	.007	60	6.04 (1.45, 10.64)	.011
FSIQ	64	0.28 (0.09, 0.47)	.004	60	0.23 (0.03, 0.43)	.024
Treatment intensity	64	0.52 (−4.57, 5.62)	.838	–	–	–
Maternal university completion	60	7.70 (3.01, 12.39)	.002	60	3.67 (−1.40, 8.74)	.153
Family functioning	64	0.61 (−4.90, 6.12)	.825	–	–	–
Parental PTSD symptoms	63	−0.06 (−0.30, 0.19)	.645	–	–	–
Parental depressive symptoms	64	−0.01 (−0.39, 0.37)	.961	–	–	–
Parental anxiety symptoms	64	0.09 (−0.46, 0.64)	.743	–	–	–
Parental stress	64	−0.07 (−0.41, 0.28)	.708	–	–	–

contact during times of immunosuppression and hospitalization, and disruption to school routines and peer activities. The association between perceived school connectedness with behavior and adaptive skills has recently been reported by Dovi et al. (2019), suggesting that incorporating opportunities for ongoing peer contact and remote learning during treatment could form a crucial component of remediation programs focused on improved psychological outcomes (Dovi et al., 2019).

The findings of this study contribute additional novel insights regarding behavioral and emotional adjustment through the inclusion of a closely matched group of healthy comparison children and ratings from multiple informants. The inclusion of a comparison sample for the BASC2 was

considered especially important in this context to ensure appropriate representation of Australian children on this measure which is normed on a North Amercian cohort. While our findings are consistent with non-controlled studies that have reported mean BASC scores in the average range for childhood cancer survivors (Carpentieri et al., 2003; Liu et al., 2018; Shelby et al., 1998; Waber et al., 2012; Wolfe-Christensen et al., 2009), our study identified significant differences in mean scores between the ALL group and healthy age and sex-matched comparison children who were recruited to closely match patients for socio-economic factors such as parent age, maternal education, and geographic location. These findings suggest that for our patient population, comparison to test norms obtained in a North American

setting may not always provide an accurate representation of risk, thus patients obtaining elevated (sub-clinical) scores on multiple subscales may be experiencing difficulties that warrant further specialist evaluation.

Evaluation should include obtaining multiple perspectives regarding patient adjustment and behavior. As our study demonstrates, parents, teachers and children/adolescents contribute unique perspectives that likely reflect the different settings they inhabit, and their expectations for how a child might behave and respond post treatment. Consistent with previous studies (Carpentieri et al., 2003; Moore et al., 2003), our sample of children and adolescents identified no significant problems on self-report. This was in stark contrast to proxy-reports for the patient cohort. The discrepancy between self-report and parent report of psychological adjustment has been suggested to reflect the parent's own distress and experience of their child's cancer diagnosis, as well as increased parental vigilance regarding their child's wellbeing (Liu et al., 2018; Malpert et al., 2015). Parental stress and mental health factors were found to be significant predictors of reported difficulties at a univariate level in this study, however our sample size potentially limited our ability to observe clinically meaningful associations at a multivariate level and only materal university education remained significantly associated with parent ratings of behavioral problems. Further exploration of parent and family factors that place children at higher risk of reported difficulties is warranted given existing evidence of the dynamic relationship between parental and child mental health and adjustment to illness, and possible intervention targets that may result in improved outcomes for both patients and their family.

In this study parent ratings of psychological problems were validated by the elevated rates of internalizing symptoms and problem behaviors identified on teacher report for the ALL group. While teachers corroborated parent concerns, they also contributed unique information regarding the child's psychological and school functioning that was not captured on parent report. These findings highlight the need to include all three informants in any screening protocol to adequately assess risk across multiple settings.

Limitations of the current study need to be considered. The data collected for this study forms part of the longitudinal *ALLaboard* project that included strict timepoints for assessment in the off-treatment phase. The timing of the first assessment at 3 months post-treatment resulted in some families declining involvement due to the proximity to end of treatment. This may have excluded families and patients that were too overwhelmed or distressed to manage the requirements of the study, as well as those focused on returning to normal life and wanting to limit contact with the hospital. The study also excluded children with a pre-existing developmental disorder or neurological insult and families who were not sufficiently proficient in English to complete the questionnaires. We may therefore have underestimated the true prevalence of psychological difficulties at the end of treatment, particularly for children with multiple comorbidities and families who, due to language barriers, may face additional disadvantage in accessing psychological supports. Finally, while not uncommon for pediatric cancer studies that involve face-to-face assessment, this study included a relatively small sample of children and adolescents. This may have particularly impacted child-reported outcomes as self-report questionnaires are only available for children 8 years and above, limiting the power of these findings for this smaller group. Of those families that did participate, parent raters were predominantly mothers, with only eight fathers of patients contributing to the study. This may have been limited by the request that questionnaires be completed by the primary caregiver. Future studies would benefit from employing techniques to increase involvement from both caregivers. These factors limit the generalizability of the study findings.

Clinical Implications

Overall, the results of this study confirm that a subset of patients treated with chemotherapy-only for ALL will experience behavioral and emotional difficulties that warrant monitoring and/or intervention. These findings support the importance of mental health and psychosocial screening to identify patients at risk (Wiener et al., 2015) and to enable targeted interventions aimed at enhancing the wellbeing of patients and their families at the end of treatment. In addition to systematic mental health screening for behavioral and emotional difficulties, our finding that a substantial proportion of children and adolescents experience difficulties with attention, learning problems and reduced adaptive skills, supports the need for a combined intervention approach that also includes school transition support and advocacy in end of treatment monitoring.

While it is difficult to determine ongoing patient needs on the basis of cross-sectional data, this study is part of a longitudinal project which will allow for the identification of those patients who go on to experience persistent behavioral and emotional difficulties. This will provide crucial information to inform a risk-stratified model that addresses service needs and interventions to span the gap between treatment completion and enrolment into survivorship programs.

Currently we can conclude that while most children treated for ALL appear to adjust well at the end of treatment and upon return to more normal life activities, appropriately a third of patients will require support to manage this transition. Surveillance of psychological adjustment is thus required to capture those children who are at risk of chronic problems that will alter their long-term quality of life and independence.

Declarations

Conflict of interest Cinzia R. De Luca, Melissa Mulraney, Vicki Anderson, Peter Downie, Winn Ma, and Maria C. McCarthy disclose no conflict of interest.

Human and Animal Rights The study received ethics approval from The RCH (#33094) and MCH (#13264) Human Research Ethics Committees and performed in accordance with the National Health and Medical Research Council (NHMRC) National Statement on Ethical Conduct in Human Research.

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