ORIGINAL ARTICLE

Neuropsychological Task Performance in Childhood Acute Lymphoblastic Leukemia (ALL) Survivors of the Malay Population

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ABSTRACT

Introduction: Leukemia is one of the most prevalent childhood cancers, accounting for 30% of paediatric cancers globally and 39.1% in Malaysia. This study assesses neuropsychological functioning in childhood Acute Lymphoblastic Leukemia (ALL) survivors, including executive functioning, attention span, working memory, problem solving, processing speed, cognitive flexibility, and inhibitory control. **Methods:** Twenty-seven childhood ALL survivors (12 males, 15 females), aged 8–26 years and in remission for at least one year, were recruited from Hospital Pakar Universiti Sains Malaysia. Participants completed the Wechsler Intelligence Scale: Digit Span and subtests from the Delis-Kaplan Executive Function System: Trail Making Test, Verbal Fluency, Colour-Word Interference, and Sorting Test. **Results:** Results revealed significant neuropsychological deficits compared to normative data. Working memory performance (Digit Span, M = 6.63) was significantly below the mean. Impairments in executive functioning were found in Trail Making Test scores, particularly in Visual Scanning (M = 6.78), Letter Sequencing (M = 4.30), and Number-Letter Sequencing (M = 4.70). Verbal Fluency deficits were most notable in Letter Fluency (M = 4.70). Cognitive flexibility challenges were indicated by Colour-Word Interference scores (Inhibition, M = 8.04; Inhibition/Switching, M = 8.26). Sorting Test scores (M = 7.33) indicated categorization difficulties. Correlations showed that school and post-treatment duration positively affected task performance, while earlier diagnosis negatively affected cognitive flexibility. **Conclusion:** These findings highlight neuropsychological deficits in Malay childhood ALL survivors, emphasizing the need for tailored interventions and screening tools to improve their quality of life and address gaps in understanding long-term effects.
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Keywords: Acute lymphoblastic leukemia, Childhood survivor, Wechsler intelligence scale, Delis-kaplan executive function system, Neuropsychological functioning

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INTRODUCTION

Acute lymphoblastic leukemia (ALL) in children is the most prevalent childhood cancer (6), and it accounts for most of the paediatric cancer cases. In Malaysia, leukemia represents 39.1% of all cancer cases among children aged 0-19 years. Of these, 48% are lymphoid leukemia cases, followed by myeloid (28%) and nonspecific leukemia (24%) (1). The disease often presents nonspecific symptoms and has a bimodal peak occurrence in children aged one to four years and adults over 10 years (6).

Advances in medical treatment, such as risk-targeted chemotherapy and improved supportive care, have significantly enhanced survival to 80-90% in industrialized countries (2,15). Survivors still have long-term consequences, particularly neurocognitive impairment in measures of working memory, attention, and executive function (39,21). These impairments may negatively impact academic achievement, social activity, and quality of life.

Survivors of childhood ALL also frequently report substantial neurocognitive abnormalities resulting from the intense CNS-directed therapies required during therapy. Treatments like intrathecal chemotherapy and, in some cases, cranial irradiation are effective at lowering the rate of relapse but may compromise the growth of the brain during periods of significant growth and development. The neurotoxicity of these treatments, particularly high-dose methotrexate, has been related to the disruption of neuronal function and integrity of white matter. According to research, many survivors have some impairments, 22% of them having processing

speed and 31% executive function deficits relative to controls. These impairments may be present at the time of treatment and continue throughout, significantly affecting survivors' school performance, social function, and quality of life (16,20).

The neurodevelopmental theory provides a framework for understanding why childhood acute lymphoblastic leukemia survivors are particularly vulnerable to these deficits. Critical stages of brain growth and maturation overlap with treatment throughout childhood and adolescence, making regions such as the prefrontal cortex and hippocampus particularly vulnerable to damage. These areas are critical for cognitive functions such as attention, working memory, and executive functioning. CNS-directed therapies' disruption of these developmental trajectories can result in persistent neurocognitive impairments. Additionally, factors such as younger age at diagnosis and higher treatment intensity increase these challenges because the developing brain is less resilient to external insults during the early stages of maturation (7).

Research indicates that ALL survivors frequently exhibit impairments in executive functioning, sustained attention, working memory, and motor processing speed. For instance, Lofstad et al. found pervasive cognitive deficits in ALL survivors despite high survival rates (21). Similarly, Alias et al. reported significant neuropsychological impairments in Malaysian ALL survivors compared to healthy controls, with pronounced deficits in sustained attention, working memory, and attentional flexibility. Additional studies have evaluated specific cognitive domains using standardized tests (3). Campbell assessed executive function using the Delis-Kaplan Executive Function System (D-KEFS) subtests and the Working Memory Index (WMI) from the Wechsler scales. Their findings revealed significant impairments in working memory among ALL survivors, while other executive function domains remained within the average range (5). Furthermore, Peng et al. indicated that 36.2% of survivors had motor processing speed deficiency, and 12.5% had difficulty with attention, which affected their school performance and social adjustment (30). The findings concur with studies by Kadan-Lottick and colleagues, which proved attention problems to be prominent among ALL survivors (17).

According to Kanellopoulos et al., childhood ALL survivors frequently exhibit substantial cognitive deficits, notably in processing speed and executive functioning. This lends support to the notion that CNS-directed therapies, such as high-dose methotrexate, can hurt brain development while undergoing treatment. The research found that a notable percentage of survivors had impaired neurocognitive function, with 22% having processing speed defects and 31% executive function defects when compared to healthy controls. These findings imply that the neurotoxic effects of such treatments alter regular neuronal activity and white matter integrity, resulting in both short-term cognitive problems during treatment and long-term abnormalities that may last for years after treatment completion. Additionally, the diagnosis age and treatment intensity can also influence the degree of such cognitive impairment, with the younger ones being at higher risk since they are still undergoing brain development (18).

This study aims to examine the neurocognitive functioning and clinical characteristics of Malay children who have survived ALL, a group underrepresented in existing research. By addressing this gap, the study seeks to enhance understanding of the long-term neurocognitive impact of ALL within this community. The findings are expected to provide valuable insights for the development of tailored screening tools, intervention strategies, and clinical practices that can better support the specific needs of Malay childhood ALL survivors. Ultimately, this research intends to contribute to strengthening survivorship care and improving the survivor's long-term quality of life.

MATERIALS AND METHODS

Study Design and Participants

This cross-sectional study involved 27 Malay childhood Acute Lymphoblastic Leukemia (ALL) survivors, aged 8 to 26 years, who had completed treatment at least one year prior and were in stable health condition. In this study, neurocognitive assessments and clinical evaluations were performed to examine the participants' current cognitive functioning. Participants were recruited during haematology clinic follow-up appointments at the paediatric outpatient clinic, Hospital Pakar Universiti Sains Malaysia (HUSM). Patients with neurological conditions unrelated to ALL or its treatment and those who were unable to complete neuropsychological testing were excluded from the study. This study was approved by the Research Ethics Committee, Universiti Sains Malaysia (Reference: USM/JEPeM/KK/23030234).

Tools

Demographic data, including years of schooling, age of diagnosis, time since diagnosis, and time since treatment, were gathered via guardian input and review of the patient's medical record. The Digit Span subtest from the Wechsler Intelligence Scales (WISC-IV) and (WAIS-III) were used to measure the participants' cognitive functioning. In addition, the Delis-Kaplan Executive Function System (D-KEFS) with four subtests were used: the Trail Making Test, Verbal Fluency, Colour-Word Interference, and the Sorting Test.

Wechsler Intelligence Test

Digit Span (DS)

The Wechsler Digit Span Test is a commonly employed psychological assessment tool for evaluating working

memory and attentional performance. It is included in the Wechsler Adult Intelligence Scale (WAIS-III) and the Wechsler Intelligence Scale for Children (WISC-IV), making it a core component of the cognitive evaluations. This subtest is well-normed, sensitive, and recognized for its efficacy in assessing auditory attention and short-term memory (29). Participants are tasked with recalling sequences of numbers presented by the examiner, which evaluates their working and short-term memory capacities. The Digit Span Test consists of two main components: Digit Span Forward (DSF) and Digit Span Backward (DSB). In the DSF, participants must repeat a sequence of numbers presented by the examiner in the same order, while in the DSB, participants must repeat the sequence in reverse order (40). The scoring method involves awarding one point for each correctly recalled sequence, with a maximum possible score of nine digits for forward recall and eight digits for backward recall (4). The test is halted if the participant cannot complete both trials at the same span length. In order to compare the raw scores to the participant's age and educational attainment, they are subsequently converted into scaled scores based on normative data (29). Higher scores indicate better working memory and attentional capacity, whereas lower scores may suggest difficulties in working memory, attention, or auditory processing.

Delis-Kaplan Executive Function System (D-KEFS)

Trail Making Test (TMT)

The Trail Making Test (TMT) assesses various high-level cognitive functions, including switching, divided attention, inhibition, updating, cognitive flexibility, and set-shifting (26). The test consists of five conditions: Visual Scanning (Condition 1) evaluates visual search and scanning abilities; Number Sequencing (Condition 2) measures simple visual attention, visual scanning, visual-motor skills, and psychomotor speed; and Letter Sequencing (Condition 3) assesses visual-motor coordination, verbal learning, and processing speed (38). Condition 4, Number-Letter Switching, involves alternating between numbers and letters, measuring divided attention, set-shifting, and cognitive flexibility. Finally, Motor Speed (Condition 5) is responsible for measuring psychomotor speed. Conditions 1, 2, 3, and 5 serve as control conditions to measure visuomotor sequencing and psychomotor speed, while Condition 4 specifically targets executive functions (33). Conditions 2 and 3 are commonly used to evaluate processing speed (38). The scoring focuses primarily on completion time, measured in seconds, across all five conditions, providing a nuanced evaluation of neurocognitive performance. The comparison of completion times across conditions can help determine if switching task limitations are caused by impairments in foundational skills, such as motor speed or visual scanning, or by executive function abnormalities. For example, heightened completion times under Condition 4 relative to less demanding tasks indicate cognitive flexibility difficulties, while comparable performance on all conditions suggests inherent motor or visual processing difficulties (36).

Verbal Fluency

The D-KEFS Verbal Fluency Test (VF) comprises three testing conditions: Letter Fluency, Category Fluency, and Category Switching. The VF measures multiple aspects of verbal behavioural productivity and cognitive flexibility. It evaluates the effectiveness of novel and semantic search strategies and assesses flexibility in implementing them. The process approach enables further evaluation of self-monitoring of information search and difficulties related to initiation and sustaining effort. The VF has three conditions where the examinee must say as many words as possible by letter, category, and category-switching prompts. Heerema mentioned that this test's scoring involves counting the number of correct words produced within defined time limitations with the total number of words generated in each condition recorded and compared to the normative data (13). Higher scores imply better verbal fluency, cognitive flexibility, and executive function, while lower scores may indicate difficulties generating words, cognitive flexibility, or switching between sets of information (26).

Colour-Word Interference

The Stroop test, also known as the D-KEFS Colour Word Interference Test (CWIT), is among the most widely used tools for assessing verbally mediated processing speed and executive functioning (31). Traditionally, the Stroop test consists of three conditions: naming colour patches, reading colour words printed in black ink, and naming the ink colour of words printed in incongruent colours (Interference/Inhibition condition) (9). In the D-KEFS version, a fourth condition, called Inhibition/Switching, requires participants to alternate between colour naming and word reading of colour words printed in discordant ink (36). This task measures executive functions such as inhibition, cognitive flexibility, and switching skills while evaluating participants' perseverance and impulsive tendencies in verbal modality (37). The CWIT is particularly valuable for assessing both processing speed and the ability to manage unplanned responses, making it a comprehensive measure of executive functioning (9). The CWI score primarily involves the completion time for the four conditions: colour naming, word reading, inhibition, and inhibition/switching. The time taken to complete each condition is the primary measure, with shorter times indicating higher performance. Longer completion times in the inhibition condition indicate difficulties with verbal inhibition, as participants struggle to suppress the automatic tendency to read the words rather than name the colours. Similarly, prolonged periods in the inhibition/switching condition indicate impairments in cognitive flexibility and the ability to alternate between tasks. Performance in the inhibition/switching condition is also compared to the inhibition condition to assess task-switching deficiencies (36).

Sorting Test

The Sorting Test (ST) from the Delis-Kaplan Executive Function System (D-KEFS) assesses problem-solving, verbal and nonverbal concept formation, and flexibility of thinking on conceptual tasks. This test explores executive abilities, particularly abstraction, reasoning, categorization, and cognitive flexibility. The test presents the examinee with 16 different sorting concepts across two conditions. According to Shunk et al., Condition 1 is a free sorting condition in which the examinee arranges the cards into various groupings to generate as many categorization rules or concepts as possible. Condition 2 requires the examinee to identify the correct rule or concept for the same sets of cards sorted by the examiner. The examinee is timed and asked to provide a rationale for each sort (33). The test includes a standard form (practice card set, card set 1, and card set 2) and an alternate form (practice card set, card set 3, and card set 4) (24). Only the standard form was used in this study. In the Free Sorting condition, participants receive scores based on the number of correct sorts they independently produce, as well as the clarity and accuracy of their explanations for each sorting concept. The Sort Recognition condition requires participants to recognize and articulate sorting categories presented by the examiner, with scores reflecting their ability to correctly identify and explain these categories (12).

Data Analysis

The data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 27. Descriptive statistics were utilized to categorize and summarize numerical data. This approach allows researchers to describe datasets accurately, quickly, and easily (35). Descriptive statistics were used in this study to analyze the demographic characteristics of ALL childhood survivors and their neurocognitive assessment scores. The means and standard deviations were used to summarize performance on the neurocognitive tasks.

A one-sample t-test is employed to determine if the mean of a single sample is significantly different from the known or hypothesized population mean (25). This test helps identify if the observed sample mean deviates meaningfully from the expected value. This study applied the one-sample t-test to compare the neurocognitive assessment scores. This includes those from the Digit Span, Trail Making Test, Verbal Fluency, Colour-Word Interference, and Sorting Test to normative data or established population means to assess whether childhood ALL survivors exhibit significant neuropsychological deficits.

Pearson Correlation is used to measure the direction, strength and extent of the relationship between the variables (10). Samuels claimed that the p-value produced by Pearson correlation indicates the existence of a linear relationship between two variables, whilst the correlation coefficient, r, indicates the strength of the relationship. This study utilized Pearson correlation to examine the relationships between neurocognitive assessment scores (such as those from the Digit Span, Trail Making Test, Verbal Fluency, Colour-Word Interference, and Sorting Test) and clinical features (including age at diagnosis, treatment duration, and time since treatment completion) (32).

RESULTS

The results of the neurocognitive assessments conducted in this study are presented below. A series of statistical analyses, including one-sample t-tests and correlation tests, were performed to examine the participants' performance on the Digit Span subtest from the Wechsler Intelligence Scale and four subtests from the Delis-Kaplan Executive Function System (D-KEFS). The findings provide insight into the neurocognitive functioning of childhood Acute Lymphoblastic Leukemia (ALL) survivors, with a focus on various cognitive domains such as working memory, attention, and executive functioning.

The cohort included 27 participants, with 15 (55.6%) female participants and 12 (44.4%) male participants (Table I). The ages of participants at the current time ranged between 8 to 26 years, with an average of 15.65 years (SD = 5.07). The mean age at diagnosis was 5.22 years (SD = 2.39), ranging between 1 and 11 years. Years of education received, a measure of educational level, averaged 7.59 years (SD = 4.89) and ranged from 1 to 19 years. Years since diagnosis ranged from 3 to 21 years with an average of 10.37 years (SD = 4.82), while the mean years post-treatment were 7.41 years (SD = 4.83) and ranged from 1 to 19 years. This demographic characteristic provides a description of the sample including key variables like age, treatment history, and education, significant to understanding neuropsychological outcome in this study.

The results of the neuropsychological assessments for childhood Acute Lymphoblastic Leukemia (ALL)

Table I: Descriptive Statistics for Demographic Variables Scores

Demographic Variables	Mean (M)	Standard Deviation (SD)	Minimum (Min)	Maximum (Maz)
Gender Male (n=12) Female (n=15)	-	-	-	-
Age (years)	15.65	5.07	8.00	26.25
School Duration (years)	7.59	4.89	1	19
Age at Diagnosis (years)	5.22	2.39	1	11
Duration since Diagnosis (years)	10.37	4.82	3	21
Duration Post Treatment (years)	7.41	4.83	1	19

Note: N=27

Table II: Descriptive Statistics for Neuropsychological Assessments Scores

Neuropsychological Assessments and Condition	Mean (M)	Standard Deviation (SD)	Minimum (Min)	Maximum (Max)
Digit Span (WISC-IV / WAIS-III)				
Combined Scaled Score	6.63	2.75	3	16
Trail Making Test (TMT)				
Condition 1: Visual Scanning	6.78	3.49	1	12
Condition 2: Number Sequencing	6.15	3.62	1	12
Condition 3: Letter Sequencing	4.30	3.82	1	12
Condition 4: Letter-Number Sequencing	4.70	4.12	1	14
Condition 5: Motor Speed	4.11	3.75	1	12
Verbal Fluency (VF)				
Condition 1: Letter Fluency	4.70	2.45	1	9
Condition 2: Category Fluency	7.22	2.74	1	12
Condition 3: Category Switching - CR	7.04	1.83	4	11
Condition 4: Category Switching - Accuracy	6.85	2.07	3	11
Colour-Word Interference (CWI)				
Condition 1: Colour Naming	7.26	2.88	1	13
Condition 2: Word Reading	7.22	3.57	1	12
Condition 3: Inhibition	8.04	3.29	1	13
Condition 4: Inhibition/ Switching	8.26	3.31	1	14
Sorting Test (ST)				
Condition 1: Free Sorting	7.33	3.44	1	14
Condition 2: Sort Recognition	8.04	3.52	1	15
Combined Condition 1 + 2	7.48	3.58	1	14

Note: N=27

survivors indicate varied levels of cognitive performance across different tasks (Table II). For the Digit Span test, the combined scale score has a mean (M) of 6.63 with a standard deviation (SD) of 2.75, ranging from 3 to 16. This score is considerably lower than the normative mean of 10, showing significant working memory performance deficits for the participants.

On the Trail Making Test (TMT), the participants demonstrated challenges in different conditions. Condition 1 (Visual Scanning) yielded a mean score of 6.78 (SD = 3.49), and Condition 2 (Number Sequencing) has a mean of 6.15 (SD = 3.62). Performance decreased further in Condition 3 (Letter Sequencing), where the mean was 4.30 (SD = 3.82). In Condition 4 (Letter-Number Sequencing), the mean was 4.70 (SD = 4.12), and in Condition 5 (Motor Speed), the mean dropped to 4.11 (SD = 3.75). These results suggest that participants struggled with sequencing and cognitive flexibility tasks, with scores consistently below the expected normative levels.

In the Verbal Fluency (VF) subtests, deficits were most pronounced in Condition 1 (Letter Fluency) (M = 4.70, SD = 2.45), while Condition 2 (Category Fluency) (M = 7.22, SD = 2.74), Condition 3 (Category Switching–CR) (M = 7.04, SD = 1.83), and Condition 4 (Category Switching–Accuracy) (M = 6.85, SD = 2.07) showed comparatively higher, though still below-average, scores. These findings indicate difficulties in verbal production and cognitive flexibility, with particularly low performance in tasks requiring letter-based fluency.

Participants' scores were more variable for the Colour-Word Interference (CWI) test. They scored 7.26 (SD = 2.88) in Condition 1 (Colour Naming), 7.22 (SD = 3.57) in Condition 2 (Word Reading), 8.04 (SD = 3.29) in Condition 3 (Inhibition), and 8.26 (SD = 3.31) in Condition 4 (Inhibition/Switching). Although slightly higher, these scores still reflect challenges in inhibitory control and switching tasks, suggesting ongoing issues with executive functioning.

Lastly, the Sorting Test (ST) showed lower-than-average performance across Condition 1 (Free Sorting) (M = 7.33, SD = 3.44), Condition 2 (Sort Recognition) (M = 8.04, SD = 3.52), and the combined Condition 1+2 (Description Score) (M = 7.48, SD = 3.58) These scores suggest that participants struggled with higher-order executive tasks, such as categorization and problem-solving.

Overall, these results demonstrate a broad pattern of neuropsychological deficits among childhood ALL survivors, with the most prominent weaknesses observed in working memory, sequencing, and verbal fluency, alongside ongoing difficulties in executive functioning.

Pearson correlation analyses revealed several significant associations between neuropsychological performance and demographic characteristics (Table III). For Digit Span, a moderate positive correlation was found with school duration ($r = 0.404$, $p = 0.037$), while no significant correlation was observed with age at diagnosis ($r = 0.060$, $p = 0.767$). Still, a moderate positive correlation was found between duration since diagnosis ($r = 0.342$, $p = 0.081$) and duration post-treatment ($r = 0.368$, $p = 0.059$). This indicates potential trends toward better performance with longer times since diagnosis or treatment.

In the Trail Making Test (TMT), conditions involving sequencing and cognitive flexibility showed the strongest associations. Condition 4 (Letter-Number Sequencing) demonstrated a strong positive correlation with school duration ($r = 0.636$, $p < 0.001$), and moderate correlations with duration since diagnosis ($r = 0.530$, $p = 0.004$) and duration post-treatment ($r = 0.538$, $p = 0.004$). Similarly, Condition 1 (Visual Scanning) and Condition 3 (Letter Sequencing) were

Table III: Pearson Correlations Between Neuropsychological Assessments and Demographic Variables Scores

Neuropsychological Assessments and Condition	School Duration (years)	Age at Diagnosis (years)	Duration since Diagnosis (years)	Duration Post Treatment (years)
Digit Span (WISC-IV / WAIS-III)				
Combined Scaled Score	r = 0.404 p = 0.037	r = 0.060 p = 0.767	r = 0.342 p = 0.081	r = 0.368 p = 0.059
Trail Making Test (TMT)				
Condition 1: Visual Scanning	r = 0.486 p = 0.010	r = 0.250 p = 0.208	r = 0.396 p = 0.041	r = 0.403 p = 0.037
Condition 2: Number Sequencing	r = 0.177 p = 0.376	r = 0.222 p = 0.265	r = 0.074 p = 0.715	r = 0.080 p = 0.692
Condition 3: Letter Sequencing	r = 0.501 p = 0.008	r = 0.203 p = 0.310	r = 0.370 p = 0.058	r = 0.410 p = 0.034
Condition 4: Letter-Number Sequencing	r = 0.636 p < 0.001	r = 0.198 p = 0.322	r = 0.530 p = 0.004	r = 0.538 p = 0.004
Condition 5: Motor Speed	r = 0.034 p = 0.866	r = 0.255 p = 0.200	r = -0.109 p = 0.589	r = -0.173 p = 0.389
Verbal Fluency (VF)				
Condition 1: Letter Fluency	r = -0.056 p = 0.738	r = -0.015 p = 0.942	r = -0.121 p = 0.548	r = -0.116 p =0.563
Condition 2: Category Fluency	r = 0.214 p =0.283	r = -0.108 p = 0.593	r = 0.183 p = 0.361	r = 0.176 p = 0.379
Condition 3: Category Switching - CR	r = 0.040 p = 0.841	r = -0.222 p = 0.266	r = 0.077 p = 0.703	r = -0.028 p = 0.890
Condition 4: Category Switching - Accuracy	r = -0.170 p = 0.397	r = -0.459 p = 0.016	r = -0.029 p = 0.886	r = -0.017 p = 0.934
Colour-Word Interference (CWI)				
Condition 1: Colour Naming	r = -0.052 p = 0.795	r = 0.142 p = 0.479	r = -0.262 p = 0.186	r = -0.235 p = 0.238
Condition 2: Word Reading	r = 0.495 p = 0.009	r = 0.188 p = 0.348	r = 0.357 p = 0.067	r = 0.359 p = 0.066
Condition 3: Inhibition	r = 0.006 p = 0.977	r = -0.133 p = 0.508	r = -0.032 p = 0.872	r = 0.028 p = 0.889
Condition 4: Inhibition/Switching	r = 0.042 p = 0.834	r = 0.240 p = 0.228	r = -0.148 p = 0.460	r = -0.170 p = 0.396
Sorting Test (ST)				
Condition 1: Free Sorting	r = 0.203 p = 0.310	r = 0.388 p = 0.046	r = 0.013 p = 0.948	r = 0.045 p = 0.825
Condition 2: Sort Recognition	r = 0.242 p = 0.224	r = 0.223 p = 0.264	r = 0.085 p = 0.673	r = 0.157 p = 0.433
Combined Condition 1 + 2	r = 0.225 p = 0.259	r = 0.356 p = 0.069	r = 0.032 p = 0.876	r = 0.084 p = 0.677

Note: N = 27; *r* = Pearson correlation coefficient; *p* = significant value. $p < 0.05$ indicates statistical significance

moderately correlated with both school duration and post-treatment duration (r values ranging from 0.486 to 0.501, $p < 0.05$). These findings suggest that educational continuity and time since treatment may positively influence executive functioning. In contrast, Number Sequencing and Motor Speed showed no significant correlations with any variables.

For Verbal Fluency (VF), no significant relationships were found for most conditions, although Condition 4 (Inhibition/Switching) showed a moderate negative correlation with age at diagnosis (r = -0.459, p = 0.016), indicating a potential inverse relationship between age at diagnosis and performance on this task. In contrast, Colour-Word Interference (CWI) revealed a significant positive correlation for Word Reading with school duration (r = 0.495, p = 0.009) but no significant correlations for the other conditions, including Condition 3 (Category Switching-CR) and Condition 4 (Category Switching-Accuracy), where results were non-significant.

Finally, for the Sorting Test (ST), Condition 1 (Free Sorting) showed a significant positive correlation with duration since diagnosis (r = 0.388, p = 0.046) but no significant correlations with other variables. Condition 2 (Sort Recognition) and the combined condition 1 + 2 (Description Score) showed no significant correlations with school duration, age at diagnosis, or duration post-treatment.

The overall correlations indicate that some factors, most notably the school duration and the time since treatment or diagnosis, can impact performance on neurocognitive tests, with significant associations observed in tasks that measure visual scanning, letter-number sequencing, word reading, and sorting skills. The various conditions, however, had no significant correlations, which might mean that further exploration may be needed.

A series of one-sample t-tests were conducted to compare the neuropsychological performance of childhood ALL survivors against the normative benchmark score of 10 (Table IV). Results revealed statistically significant deficits across all assessed domains. Working memory, as measured by the Digit Span subtest, was notably impaired (t = -6.374, p < 0.001, d = -1.23), indicating a large effect size. Executive functioning tasks from the Trail Making Test showed consistent deficits in visual scanning, sequencing, and switching conditions, with effect sizes ranging from moderate to large (d = -0.92 to -1.57).

Verbal fluency was among the most affected domains, particularly in letter fluency (t = -11.249, p < .001, d = -2.16) and category switching - cr (t = -8.418, p < .001, d = -1.62), reflecting severe impairments. Additional deficits were observed in inhibition and processing speed tasks from the Colour-Word Interference (CWI) Test, with Colour Naming (t = -4.950, p < 0.001, d = -0.95) and Word Reading (t = -4.047, p < 0.001 d = -0.78).

Similarly, the Sorting Test revealed marked difficulties in concept formation and cognitive flexibility, with Free Sorting showing a large effect size (t = -4.026, p < 0.001, d = -0.77), and Sort Recognition conditions reflecting moderate deficits (t = -2.894, p = 0.008, d = -0.56).

Across all measures, the mean scores of survivors were significantly lower than normative expectations. These findings underscore the pervasive neurocognitive vulnerabilities in this population and highlight the need for targeted cognitive support in survivorship care.]]

Table IV: One Sample t-Test of Neuropsychological Assessments Scores

Neuropsychological Assessments and Condition	t	p-value	Cohen's d	Mean Difference	95% CI (Lower, Upper)
Digit Span (WISC-IV / WAIS-III)					
Combined Scaled Score	-6.374	<0.001	-1.23	-3.370	(-4.46, -2.28)
Trail Making Test (TMT)					
Condition 1: Visual Scanning	-4.798	<0.001	-0.92	-3.222	(-4.60, -1.84)
Condition 2: Number Sequencing	-5.523	<0.001	-1.06	-3.852	(-5.29, -2.42)
Condition 3: Letter Sequencing	-7.756	<0.001	-1.49	-5.704	(-7.22, -4.19)
Condition 4: Letter-Number Sequencing	-6.677	<0.001	-1.28	-5.296	(-6.93, -3.67)
Condition 5: Motor Speed	-8.171	<0.001	-1.57	-5.889	(-7.37, -4.41)
Verbal Fluency (VF)					
Condition 1: Letter Fluency	-11.249	<0.001	-2.16	-5.296	(-6.26, -4.33)
Condition 2: Category Fluency	-5.275	<0.001	-1.02	-2.778	(-3.86, -1.70)
Condition 3: Category Switching - CR	-8.418	<0.001	-1.62	-2.963	(-3.69, -2.24)
Condition 4: Category Switching - Accuracy	-7.903	<0.001	-1.52	-3.148	(-3.97, -2.33)
Colour-Word Interference (CWI)					
Condition 1: Colour Naming	-4.950	<0.001	-0.95	-2.741	(-3.88, -1.60)
Condition 2: Word Reading	-4.047	<0.001	-0.78	-2.778	(-4.19, -1.37)
Condition 3: Inhibition	-3.103	0.005	-0.60	-1.963	(-3.26, -0.66)
Condition 4: Inhibition/Switching	-2.731	0.011	-0.53	-1.741	(-3.05, -0.43)
Sorting Test (ST)					
Condition 1: Free Sorting	-4.026	<0.001	-0.77	-2.667	(-4.03, -1.31)
Condition 2: Sort Recognition	-2.894	0.008	-0.56	-1.963	(-3.36, -0.57)
Combined Condition 1 + 2	-3.658	0.001	-0.70	-2.519	(-3.93, -1.10)

Note: N = 27, Test Value = 10

In summary, the results revealed that childhood ALL survivors demonstrated the greatest impairments in working memory (Digit Span), sequencing and cognitive flexibility (TMT, Verbal Fluency, and Sorting Test), with somewhat milder but still evident difficulties in inhibitory control (CWI). These findings suggest that deficits are most pronounced in tasks requiring flexible shifting, sequencing, and working memory capacity.

DISCUSSION

This study investigated the neuropsychological performance of childhood Acute Lymphoblastic Leukemia (ALL) survivors within the Malay population. The results indicate that participants exhibit significant deficits in multiple cognitive domains, particularly in working memory, attention, cognitive flexibility, verbal fluency, and executive functioning. These results are in accordance with the literature on the long-term neurocognitive effects of ALL treatment and offer more detailed exploration of the particular challenges of this group. Research consistently shows that childhood ALL survivors experience significant neurocognitive impairments. These deficits frequently affect several cognitive areas, such as executive functioning, memory, and attention. Studies such as by Lofstad et al., support the notion that the effects of ALL treatment on cognitive functioning are significant and pervasive, even in the case of high survival rates (21). Recent research conducted in Malaysia by Alias and colleagues indicated that compared to healthy controls, survivors of childhood ALL show notable neuropsychological impairments. The main areas of deficiency include sustained attention, working memory, and executive functioning, particularly attentional flexibility (3).

Working Memory Deficits

The Digit Span test results showed a significant decline in performance when compared to the normative mean. This finding underscores the persistent working memory impairments among childhood ALL survivors. Cheung and Krull highlighted that working memory is crucial for learning, problem-solving, and daily functioning, and deficits in this area can lead to challenges in the classroom and workplace (7). Furthermore, survivors of childhood acute lymphoblastic leukemia also tend to have attention, working memory, and processing speed deficits, which further leads to deficits in both cognitive and academic performance (11). In addition, attention problems in these survivors are associated with social functioning problems, which adversely affect their capability to interact mutually with others in diverse situations (28). These findings highlight the need for targeted cognitive and behavioural interventions to support both academic achievement and social integration.

Attention and Cognitive Flexibility Challenges

The Trail Making Test (TMT) findings show significant cognitive flexibility and attention challenges. Deficits

were observed across all TMT conditions (Visual Scanning, Number Sequencing, Letter Sequencing, Letter-Number Sequencing, and Motor Speed), with particular vulnerability in motor speed, reflecting broader difficulties in task efficiency and attentional control. According to research, children who survive cancer often have neurocognitive deficits in a number of cognitive areas, with executive functions, including processing speed and cognitive flexibility, being particularly impacted. A study by Kenzik et al., reported that over 40% of childhood cancer survivors reported substantial neurocognitive issues as a result of their treatment, such as attention deficits and task efficiency (19). Similarly, survivors of childhood acute lymphoblastic leukemia (ALL) frequently score worse than the population average on tests measuring executive function and processing speed, according to a thorough analysis by Peng and colleagues (30). This increased vulnerability to cognitive impairments is most likely the result of the effect of treatment regimens, which emphasizes the need for ongoing cognitive monitoring and interventions to address these difficulties. The results underscore the value of early identification and specific intervention for survivors in preventing the long-term impact on cognitive and functional outcomes.

Verbal Fluency Impairments

The verbal fluency (VF) subtests revealed clear deficiencies, particularly in Letter Fluency and Category Switching, indicating difficulties with lexical retrieval, language production, and cognitive flexibility (14). The negative correlation between age at diagnosis and inhibition/switching further suggests that earlier diagnosis may heighten vulnerabilities in cognitive flexibility (23). Hocking et al., further illustrated that childhood ALL survivors have severe impairments on verbal fluency with significant deficits on Letter Fluency and Category-Switching tasks, with scores on each task consistently below expectation. These findings indicate lexical retrieval and cognitive flexibility impairments, both major components of verbal fluency. These deficits are also typically accompanied by more generalized executive function difficulties, including working memory and inhibition that directly related to verbal fluency performance (14). The developmental timing of diagnosis is particularly important, as earlier diagnoses can lead to worse cognitive results. Collectively, these findings underline the significance of regular cognitive examinations and targeted interventions for childhood ALL survivors to minimize the long-term effects of treatment on language and executive functioning skills (14,34).

Executive Functioning Deficits

The Colour-Word Interference (CWI) and Sorting Test (ST) results confirm the presence of executive functioning deficiencies among survivors. Although CWI scores were marginally higher than other tasks, they still show inhibitory control and cognitive switching issues, consistent with prior findings among ALL survivors. The Sorting Test results revealed impairments in categorization and problem-solving, reflecting broader difficulties in cognitive flexibility and strategy formation (5). Together, the findings point to executive functioning deficiencies, particularly in terms of behavioural inhibition and cognitive flexibility, and these are linked to stress management and emotional regulation difficulties after treatment. According to Alias et al., neuropsychological task studies have emphasized impairments in inhibition and cognitive switching among ALL survivors, corresponding to the deficiencies identified in the CWI task. The significant deficiency observed under the Inhibition/Switching condition results from the neurotoxicity of therapies that target the central nervous system, which impair crucial brain regions responsible for executive functions, including the frontal cortex. These deficits not only influence specific task-related results but also extend to more general academic achievement and everyday functioning problems (3). These findings reinforce the fact that Malay childhood ALL survivors face substantial executive function challenges, underscoring the need for targeted cognitive and educational interventions.

Correlation with Demographic Characteristics

A correlation analysis indicated some significant associations between neuropsychological performance and demographic characteristics. School duration was positively correlated with performance in tests such as Digit Span and TMT Letter-Number Sequencing. This suggests that educational attainment may mitigate cognitive deficiencies, possibly through cognitive stimulation and compensatory methods (8). As Luvdйn et al. explained, survivors with more years of schooling, often older participants, demonstrated relatively better cognitive functioning, highlighting education as a potential protective factor against long-term cognitive late effects (22). Similarly, duration since diagnosis and post-treatment showed moderate positive relationships between Trail Making Test and Sorting Test performance. These data indicate that cognitive recovery may continue over time, although slowly. However, the lack of substantial correlations in some settings underscores the variability of recovery trajectories and the necessity for individualized interventions (27). From a practical perspective, these findings support the need to sustain engagement in formal education and providing targeted academic support could play an essential role in enhancing cognitive outcomes and improving long-term quality of life for individuals who have survived childhood ALL (22).

Limitations and Future Directions

Although this research presents valuable information, there are a number of limitations that need to be considered. The sample size is modest (N = 27), which could restrict the findings' generalizability. Future research with larger and varied populations could

provide more generalizable findings. The study also sampled the Malay population, and cross-cultural comparisons could help determine possible cultural or contextual variables affecting cognitive performances. Besides this, additional research must be conducted to ascertain the long-term effect of different treatment modalities on neurocognitive function. Longitudinal investigations that evaluate cognitive function over extended periods can give a more comprehensive picture of recovery patterns and the efficacy of treatment interventions.

CONCLUSION

This study addresses a critical gap in understanding neurocognitive functioning among Malay childhood ALL survivors. The findings revealed significant neuropsychological abnormalities, particularly in working memory, attention, cognitive flexibility, linguistic fluency, and executive functioning. These results align with previous research on the long-term cognitive effects of ALL therapies and provide clearer insight into how such deficits manifest in this population. Importantly, the findings underscore the need for ongoing cognitive follow-up, prompt interventions, and tailored educational support for facilitating childhood ALL survivors towards their enhanced quality of life and subsequent long-term outcomes. By highlighting these specific challenges, this study not only strengthens the field of paediatric cancer survivorship but also emphasizes the importance of strategies that can enhance and improve long-term outcomes and quality of life for childhood ALL survivors.

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