RESEARCH ARTICLE

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DIVERGT screening procedure predicts general cognitive functioning in adult long-term survivors of pediatric acute lymphoblastic leukemia: A PETALE study

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Abstract

Background: Acute lymphoblastic leukemia (ALL) is the most common cancer in children. Because of major improvements in treatment protocols, the survival rate now exceeds 80%. However, ALL treatments can cause long-term neurocognitive sequelae, which negatively impact academic achievement and quality of life. Therefore, cognitive sequelae need to be carefully evaluated. The DIVERGT is a battery of tests proposed as a screening tool, sensitive to executive function impairments in children and adolescent cancer survivors. Our study aimed at verifying the predictive value of the DIVERGT on general cognitive functioning in adult long-term survivors of ALL.

Methods: ALL survivors completed the DIVERGT 13.4 years, on average, after remission (N = 247). In addition, 49 of these survivors (equally selected amongst those with low, average, and high DIVERGT scores) as well as 29 controls completed a more comprehensive neuropsychological evaluation within a 3-year period from DIVERGT administration. Multivariate regression analysis was used to assess the predictive value of the DIVERGT on general intelligence, mathematics, verbal memory, and working memory. As a follow-up analysis, three performance groups were created based on the DIVERGT results. Multivariate analysis of variance (MANOVA) assessed neuropsychological differences between groups.

Results: The DIVERGT accurately predicted General Ability Index (GAI) ($P < 0.0001$), mathematics ($P < 0.0001$) and verbal memory ($P = 0.045$). Moreover, the low-performance group consistently had poorer performance than the high-performance and control groups on the neuropsychological tests.

Conclusion: The DIVERGT is a useful, time-effective screening battery for broader neurocognitive impairments identification in long-term adult ALL survivors. It could be implemented as routine examination in cancer follow-up clinics.

KEYWORDS
acute lymphoblastic leukemia, cognitive dysfunction, follow-up studies, long-term survivors, screening

1 | INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most common cancer type in children. It accounts for 26.8% of childhood cancer diagnoses.[1] Studies showed that the risk of developing ALL during childhood is approximately 1 in 2000[2] and its prevalence is higher in children between 2 and 5 years of age.[3] In the middle of the 20th century, about

Abbreviation: ADHD, attention deficit hyperactivity disorder; ALL, acute lymphoblastic leukemia; CNS, central nervous system; CRT, cranial radiation therapy; GAI, General Ability Index; NPV, negative predictive value; PPV, positive predictive value; PRI, Perceptual Reasoning Index; PSI, Processing Speed Index; VCI, Verbal Comprehension Index; WMI, Working Memory Index

5% of children with ALL survived 5 years or more post diagnosis.[4] Because of major improvements in treatment protocols over the last decades, 5-year-event-free survival rate now exceeds 80%.[5] Treatments for ALL include intravenous and intrathecal chemotherapy and, in some cases, cranial radiation therapy (CRT). Treatments are administered on a time period of about 2 years.[2] Despite their efficacy on survival rates, treatments can cause a range of long-term adverse health outcomes in adult survivors of childhood ALL.

Neurocognitive difficulties are very common treatment-related adverse outcomes amongst childhood cancer survivors. In fact, about 50% of all childhood cancer survivors will experience at least one clinically significant cognitive deficit following treatments.[6] Younger age at diagnosis and female sex can also increase the probability of developing cognitive deficits.[5,7] Neurocognitive impairments are highly deleterious since they can affect academic achievement[4,5,8–10] and quality of life.[11,12]

Many domains of cognitive functioning can be affected by ALL treatments. Studies have reported declines in IQ after CRT or chemotherapy treatments.[13–15] Academic achievement also seems to be poorer. Hence, lowered performance in mathematics[5,8,9,16] and reading comprehension difficulties[4,10] have been reported in ALL survivors. They also show fine dexterity and visuomotor coordination impairment.[17,18] However, the most common neurocognitive sequelae are executive functioning and attentional difficulties. Multiple studies showed that survivors of pediatric ALL have lowered attentional capacities,[8,14,19] working memory,[14,20] processing speed,[7,20,21] and lower performance in different areas of executive functioning like cognitive flexibility, verbal fluency, and inhibition.[10,20,22] Moreover, neurocognitive sequelae persist decades after treatments. Studies even demonstrated that ALL survivors present a greater risk for executive functioning impairments with increased time since diagnosis.[22]

In 2008, Krull and his colleagues[23] created a screening procedure for neurocognitive dysfunctions in pediatric cancer survivors. Their objective was to implement a routine low-cost screening for neurocognitive deficits in cancer survivors. The neurocognitive battery they developed was designed to target specific domains that are sensitive to cancer treatments like processing speed, executive functioning, and working memory. The battery is referred to as the DIVERGT screening procedure and it includes Digit Span,[24,25] Verbal Fluency,[26] Grooved Pegboard,[27] and Trail Making Test.[28] The validation study showed that the DIVERGT had good psychometric qualities, that is, test-retest reliability ($r = 0.72$), discriminative validity, and predictive validity. Overall, the study demonstrated that the DIVERGT was a good predictor of global intellect, reading skills, and mathematics in children and adolescents pediatric cancer survivors, at an average of 6 years after the end of their treatments.

However, it is still unsure whether the DIVERGT remains a good predictor of general cognitive functioning decades after treatments, and if it could be used in long-term follow-up of ALL survivors. Therefore, this study aims at verifying the predictive validity of the DIVERGT screening procedure[23] in adult long-term survivors of ALL. To meet our goal, we first aimed at describing neurocognitive impairment present in our cohort of ALL survivors using the DIVERGT. Based on results, we created three distinct performance groups (low, average, and high

performance). Since young age at diagnosis is a known risk factor in the development of cognitive difficulties,[7] we expected age at diagnosis to be older in the high-performance group. We then used our group classification to conduct follow-up analysis. In follow-up, we first created a mean DIVERGT score and tested if it was associated with age at diagnosis in our cohort. Then, we assessed the predictive validity of the DIVERGT on general intellectual functioning, mathematics, long-term memory, and working memory. We also calculated sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). Since Krull and colleagues[23] already showed that the DIVERGT was a good predictor of general intellectual functioning in children 6 years after treatments, our specific goal was to extend their results to adults ALL survivors more than a decade after treatment. We hypothesized that the DIVERGT would predict general cognitive functioning. If it remains relevant in long-term ALL survivors, it could be implemented as a quick screening tool in cancer follow-up clinics.
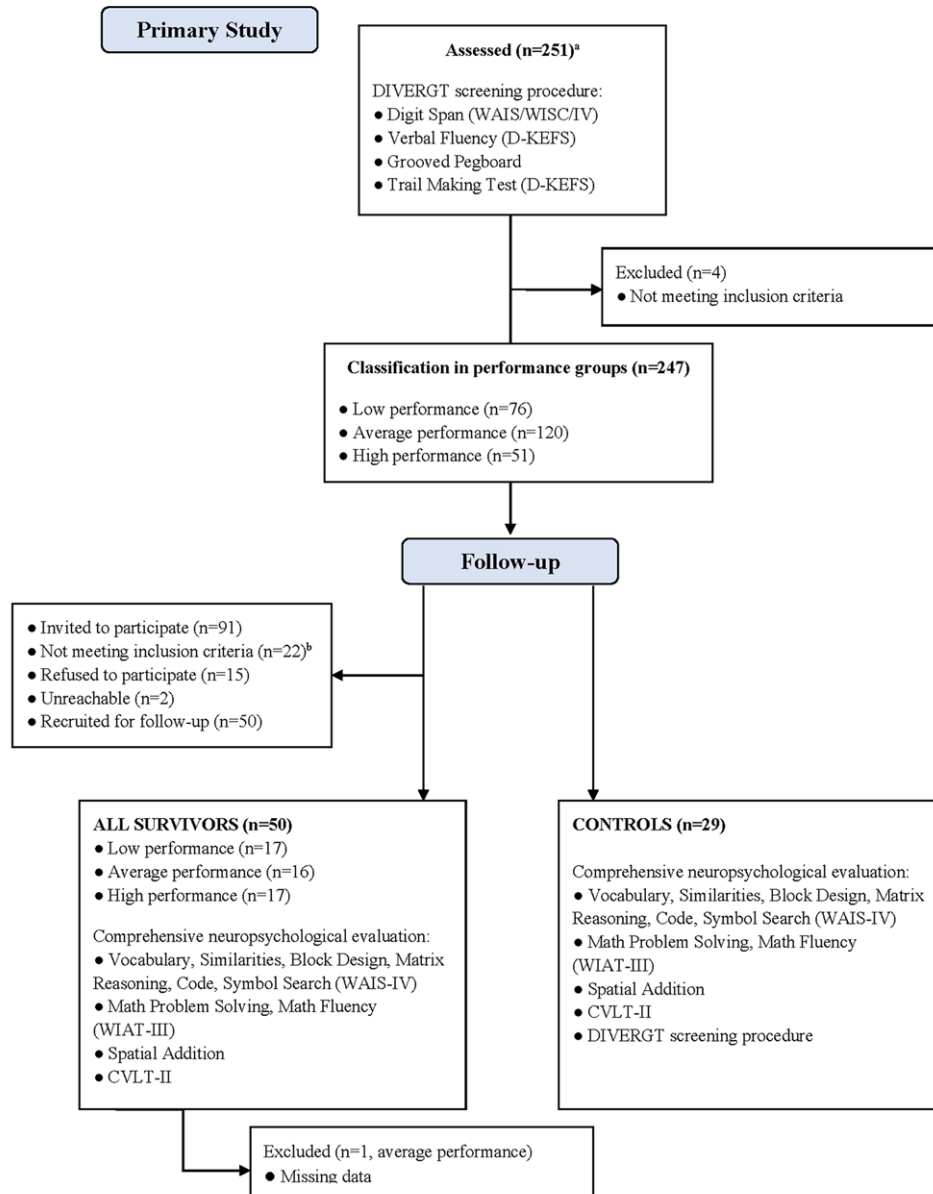
2 | METHODS

2.1 | Participants

This study was included in the PETALE study[29] conducted at Sainte-Justine University Health Center. We recruited ALL survivors who were treated on DFCI-ALL 87-01 to 2005-01 protocols, at least 5 years post diagnosis and with no history of refractory ALL, relapse, or hematopoietic stem cells transplant. A total of 251 ALL survivors participated in the study (Figure 1). Four participants were excluded afterward from the analyses. The remaining 247 ALL survivors were recruited approximately 13.4 years after treatment end (standard deviation = 5.3). Participants were mostly of European descent (95%) and were French-speaking. The study was approved by SJUHC Institutional Review Board. All participants agreed to participate in the study and signed an informed consent form. Compensation for participation included a short report of results with general recommendations, along with covered meals and parking fees.

In follow-up, we recruited 50 adult survivors from the three performance groups that we created using the DIVERGT results (Table 1). A total of 77% of participants who met the inclusion criteria and were invited for follow-up agreed to participate (Figure 1). In each performance group, we attempted to have the male to female ratio of our entire cohort. One participant was removed afterward from the analysis. We also recruited 29 age-matched controls, recruited through social networks, online advertising and posters on hospital billboards. Participants were mostly of European descent (97% of ALL survivors and 90% of controls) and were French-speaking. They agreed to participate in the study and signed an informed consent form.

2.2 | Procedure

The participants completed a neuropsychological evaluation, equivalent to the DIVERGT screening procedure[23] at a standardized moment of the day. Our DIVERGT equivalent battery included the Digit Span (forward and backward conditions for children; forward, backward,

Primary Study

Assessed (n=251)[a]

DIVERGT screening procedure:
- Digit Span (WAIS/WISC/IV)
- Verbal Fluency (D-KEFS)
- Grooved Pegboard
- Trail Making Test (D-KEFS)

Excluded (n=4)
- Not meeting inclusion criteria

Classification in performance groups (n=247)

- Low performance (n=76)
- Average performance (n=120)
- High performance (n=51)

Follow-up

- Invited to participate (n=91)
- Not meeting inclusion criteria (n=22)[b]
- Refused to participate (n=15)
- Unreachable (n=2)
- Recruited for follow-up (n=50)

ALL SURVIVORS (n=50)
- Low performance (n=17)
- Average performance (n=16)
- High performance (n=17)

Comprehensive neuropsychological evaluation:
- Vocabulary, Similarities, Block Design, Matrix Reasoning, Code, Symbol Search (WAIS-IV)
- Math Problem Solving, Math Fluency (WIAT-III)
- Spatial Addition
- CVLT-II

CONTROLS (n=29)

Comprehensive neuropsychological evaluation:
- Vocabulary, Similarities, Block Design, Matrix Reasoning, Code, Symbol Search (WAIS-IV)
- Math Problem Solving, Math Fluency (WIAT-III)
- Spatial Addition
- CVLT-II
- DIVERGT screening procedure

Excluded (n=1, average performance)
- Missing data

[a]For comprehensive information about participant's characteristics and recruitment in primary analysis, see Marcoux et al. (2017).
[b]Follow-up also included magnetic resonance imaging and magnetoencephalography. Exclusion criteria included any metallic foreign body (the most common being metallic dental wired braces).

FIGURE 1 Study flowchart

and sequencing conditions for adults),[24,25] the Grooved Pegboard,[27] and a different version of the Trail Making Test,[30] and Verbal Fluency[30] subtests. The administration lasted about 30 min and measures were administered in a fixed order. The measures were administered in French and were equivalent to English versions (i.e., letters used in the Verbal Fluency test had similar frequency of occurrence in both idioms). All raw scores were converted to age-adjusted scaled scores based on population means (mean [M] = 10, standard deviation [SD] = 3). Based on existing literature regarding common deficits in ALL survivors (i.e., flexibility, verbal fluency, working memory and fine motor dexterity), we a priori selected specific conditions of the DIVERGT tests that would be used to classify participants in performance groups. The selected conditions were: Trail Making Test —

Condition 4, Verbal Fluency—Condition 1, Digit Span—Global Score and Grooved Pegboard—Dominant Hand. According to their DIVERGT results, participants were classified in three performance groups: low, average, and high performance. Criteria for classification in the low-performance group were either one scaled score of 4 or less (below 3rd percentile) or two scores of 6 or less (below 10th percentile). Criteria for classification in high-performance group was either one scaled score of 15 and more (above 94th percentile) or two scores of 12 and more (above 70th percentile). Participants who did not meet any of these criteria were classified in the average performance group. We used this classification to further recruit an equal number of participants from the three performance groups, who completed a more comprehensive neuropsychological evaluation during follow-up.

TABLE 1 Participants' characteristics

	Primary analysis	Follow-up analysis			
		Performance groups			
		Low	Average	High	Controls
Sex, number of patients					
Females	126	5	10	8	16
Males	121	12	5	9	13
Age at testing, years					
Mean	21.6	24.2	24.6	27.4	25.5
Standard deviation	6.3	6.1	4.3	6.0	4.6
Range	8–38	18–38	18–35	19–37	18–34
Education, years[a]					
Mean	11.2	11.4	12.1	14.4	14.0
Standard deviation	2.5	1.5	1.5	2.0	2.4
Age at diagnosis, years					
Mean	6.1	5.2	4.3	9.4	
Standard deviation	4.6	4.7	3.9	5.3	
Treatment, number of patients					
Chemotherapy only	100	3	4	5	
CRT and chemotherapy	147	13	11	12	
IV MTX cumulative doses, mg/m^2					
Mean	6,268.1	5,781.7	5,361.0	6,230.5	
Standard deviation	1,458.1	2,439.5	1,351.2	1,471.6	
IT MTX cumulative doses, mg/m^2					
Mean	149.5	146.9	136.2	118.9	
Standard deviation	53.2	58.6	43.3	49.7	
Time since treatment end, years					
Mean	13.4	14.9	17.1	14.4	
Standard deviation	5.3	5.4	3.3	5.9	
Time between testings, years					
Mean		1.6	1.4	1.8	
Standard deviation		0.5	0.5	0.6	

[a]Mean education years must be interpreted with caution because our sample included adults who already completed their highest education level and young adults or adolescents who were still in school.

Follow-up evaluation included French-Canadian versions of Similarities, Vocabulary, Block design, Matrix Reasoning, Code and Symbol Search (WAIS-IV),[25] Math Problem Solving and Math Fluency (WIAT-III),[31] Spatial Addition (WMS-IV)[32] and CVLT-II.[33] Follow-up evaluation was completed within a 3-year period from DIVERGT administration. The administration lasted about 2.5–3 hr. Measures were administered in a fixed order, at a standardized moment of the day. All raw scores were converted to age-adjusted standard scores based on population means (M = 100, SD = 15), and followed a normal distribution.
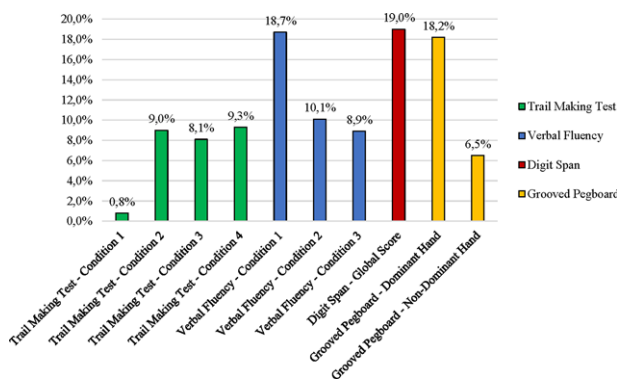
2.3 | Statistical analyses

We first plotted occurrences of deficits (scores at least 1.5 SD below norm) on each DIVERGT subtest amongst our cohort. Further, we classified our participants in three performance groups (low, average,

high performance). We performed an analysis of variance (ANOVA) to investigate if age at diagnosis differed amongst groups. Our patient classification was used to perform subsequent analyses.

To investigate the predictive value of the DIVERGT on our follow-up measures, we computed an average of the four DIVERGT variables of interest (in scaled scores, M = 10, SD = 3) for each participant. To verify the relevance of this score for further analyses, we performed a linear regression investigating the effect of age at diagnosis on the mean DIVERGT score. We then performed a multivariate regression analysis to investigate the predictive value of DIVERGT performance on our cognitive measures. Afterward, we calculated sensitivity, specificity, PPV, and NPV of the DIVERGT on our follow-up measures. Participants in the low-performance group were defined as having impairment on the DIVERGT (cut-off score was either one scaled score of 4 or less or two scores of 6 or less). Finally, we conducted a multivariate analysis of variance (MANOVA) to assess differences between our

TABLE 2 Mean results of the DIVERGT tasks (in scaled scores)

	Mean	Standard deviation
Trail Making Test		
Condition 1—Visual Scanning	11.1	1.8
Condition 2—Number Sequencing	9.7	3.1
Condition 3—Letter Sequencing	10.0	3.1
Condition 4—Number-Letter Switching	9.4	3.0
Verbal Fluency		
Condition 1—Letter Fluency	7.9	2.8
Condition 2—Category Fluency	9.7	3.4
Condition 3—Category Switching	9.8	3.3
Digit Span	8.0	2.9
Grooved Pegboard		
Dominant Hand	9.1	3.5
Non-dominant Hand	9.6	2.6

FIGURE 2 Occurrences of deficits (scores below 1.5 SD)

performance groups. In both multivariate regression and MANOVA analyses, Pillai's trace statistic was used. Pillai's trace is a positive-valued multivariate test statistic ranging from 0 to 1, which has adequate power and robustness.[34] Follow-up analysis assessed verbal comprehension, perceptual reasoning, processing speed, general intelligence, visual working memory, long-term memory, and mathematical abilities. Specific measures were WAIS-IV Verbal Comprehension Index (VCI), Perceptual Reasoning Index (PRI), Processing Speed Index (PSI) and General Ability Index (GAI), WIAT-III Math Problem Solving and Math Fluency, WMS-IV Spatial Addition, CVLT-II Combined Trial 1 to 5, and Long-Delay Free Recall conditions.

3 | RESULTS

3.1 | Occurrences of deficits

Table 2 presents the mean scores of the DIVERGT subtests amongst our ALL survivor cohort. Figure 2 presents occurrences of deficits on the same subtests. The previously chosen conditions for group classification turned out to be the most sensitive (i.e., the conditions with the highest deficit occurrences).

3.2 | Participants classification in performance groups

Low-performance group included 76 survivors (30.8%), average performance group included 120 survivors (48.6%), and 51 survivors (20.6%) were classified in the high-performance group. As expected, age at diagnosis differed amongst groups, $F(2,244) = 5.1$, $P = 0.007$, $R^2 = 0.2$. Post hoc analysis using Tukey honest significant difference (HSD) test revealed that age at diagnosis was older in the high-performance group (M = 7.9, SD = 5.0), compared to the low-performance group (M = 5.3, SD = 4.3), $P = 0.006$, and to the average performance group (M = 5.9, SD = 4.4), $P = 0.027$. The group classification was then used to recruit a subsample of participants, and conduct supplementary analyses to verify the predictive value of the DIVERGT on general cognitive functioning.

3.3 | Predictive validity of the DIVERGT

As expected, the mean DIVERGT score was associated with age at diagnosis, $F(1,246) = 23.3$, $P < 0.0001$, $R^2 = 0.09$, confirming the relevance of this score for further analyses.

Then, using Pillai's trace, multivariate regression analysis revealed that the mean DIVERGT score was strongly associated with follow-up measures, V = 0.67, $F(9,39) = 8.96$, $P < 0.0001$, $\eta_p^2 = 0.67$. Further univariate analyses revealed that the mean DIVERGT performance was associated with all WAIS-IV indexes. The mean DIVERGT performance was associated with GAI, $F(1,47) = 24.0$, $P < 0.0001$, $\eta_p^2 = 0.35$ (Figure 3A). Sensitivity of the DIVERGT on GAI impairment was 80%. Specificity was 70%. PPV and NPV were 24% and 97%, respectively. GAI was used instead of Full IQ because the Digit Span subtest, which is part of the calculation of Full IQ, was used to create the mean DIVERGT score. Working Memory Index (WMI) was not included because it also includes Digit Span. Precisely, the mean DIVERGT score was associated with VCI, $F(1,47) = 13.08$, $P = 0.001$, $\eta_p^2 = 0.22$, PRI, $F(1,47) = 8.43$, $P = 0.006$, $\eta_p^2 = 0.15$, and with PSI, $F(1,47) = 21.65$, $P < 0.0001$, $\eta_p^2 = 0.32$.

The mean DIVERGT performance was also associated with mathematical reasoning (Math Problem Solving), $F(1,47) = 26.8$, $P < 0.0001$, $\eta_p^2 = 0.36$ (Figure 3B) and to verbal memory (CVLT-II—Combined Trials 1 to 5), $F(1,47) = 4.23$, $P = 0.045$, $\eta_p^2 = 0.08$. Sensitivity of the DIVERGT on mathematics reasoning impairment was 58%, and specificity was 69%. PPV and NPV were respectively 24% and 91%. Sensitivity and specificity of the DIVERGT on verbal memory impairment were respectively 75% and 69%. PPV was 18%, and NPV was 97%. Association between the mean DIVERGT performance and Spatial Addition approached trends level of significance, $F(1,47) = 3.8$, $P = 0.057$, $\eta_p^2 = 0.08$. Math Fluency subtest, and CVLT-II Delayed Free-Recall were not related to DIVERGT performance.

3.4 | DIVERGT and group classification

According to results on the DIVERGT procedure, survivors were classified in distinct performance groups: low, average, and high performance. MANOVA using Pillai's trace showed that there were
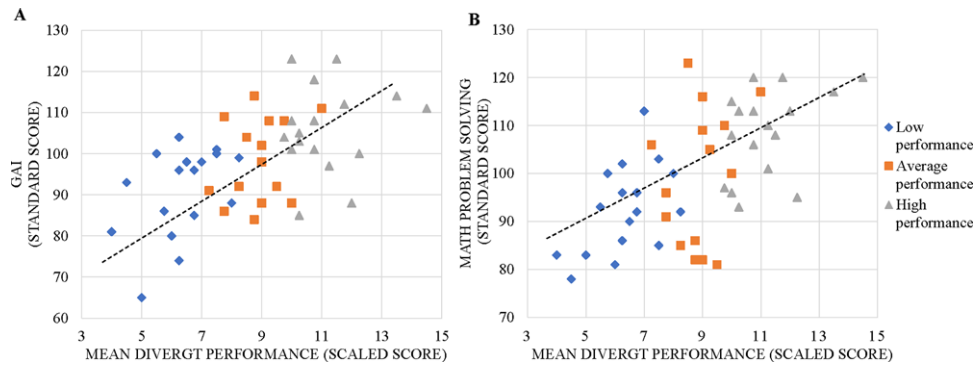
FIGURE 3 Association between the mean DIVERGT score and 3A) WAIS-IV GAI (panel A), and 3B) WIAT-III Math Problem Solving (panel B)
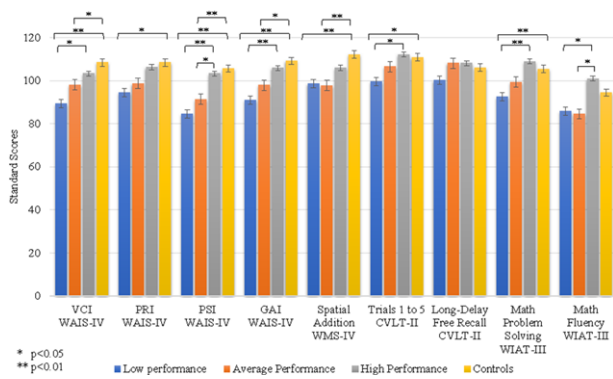

FIGURE 4 Differences between performance groups on follow-up neuropsychological measures

significant differences between groups on our follow-up neuropsychological measures, $V = 0.79$, $F(9,66) = 2.7$, $P < 0.0001$, $\eta_p^2 = 0.26$. Further univariate tests using Tukey HSD analysis revealed significant differences between groups on all subtests (Figure 4), except on long-term memory delayed recall (CVLT-II Long-Delay Free Recall). Differences between groups were also calculated using Sidak's correction for multiple comparisons. Since results were equivalent with both methods, we only reported Tukey HSD analyses.

Groups differed on VCI, $F(3,74) = 10.35$, $P < 0.0001$, $\eta_p^2 = 0.30$. Post hoc comparisons revealed that the low-performance group (M = 89.41, SD = 13.27) differed significantly from the high-performance group (M = 102.56, SD = 11.78), $P = 0.004$, and from the controls (M = 108.31, SD = 12.79), $P < 0.0001$. Moreover, the average performance (M = 98.00, SD = 9.78) group differed significantly from the controls, $P = 0.029$.

Group also differed significantly on PRI, $F(3,74) = 4.19$, $P = 0.009$, $\eta_p^2 = 0.15$. Post hoc comparisons showed that the low-performance group (M = 94.41, SD = 13.26) differed from the controls (M = 107.52, SD = 13.60), $P = 0.01$.

There was a significant difference between groups on PSI, $F(3,74) = 14.9$, $P < 0.0001$, $\eta_p^2 = 0.38$. Post hoc comparisons revealed that the low-performance group (M = 84.65, SD = 13.14) differed from the high-performance group (M = 103.13, SD = 12.64), $P < 0.0001$, and from the controls (M = 105.62, SD = 11.94), $P < 0.0001$. Furthermore, the average performance (M = 91.33, SD = 8.27) group differed from the high-performance group, $P = 0.016$, and from the controls, $P = 0.001$.

There were also significant differences on GAI, $F(3,74) = 10.40$, $P < 0.0001$, $\eta_p^2 = 0.30$. Post hoc comparisons showed that the low-performance group (M = 90.82, SD = 10.9) differed significantly from the high-performance group (M = 105.76, SD = 10.74), $P = 0.002$, and from the control group (M = 109.07, SD = 12.76), $P < 0.0001$. The average performance group (M = 97.80, SD = 9.86) differed from the controls, $P = 0.014$. WMI was not included in the analyses because the Digit Span was used in primary analysis to create performance groups.

Groups differed significantly on Spatial Addition subtest, $F(3,74) = 7.15$, $P < 0.0001$, $\eta_p^2 = 0.23$. Post hoc comparisons revealed that the low-performance group (M = 98.53, SD = 10.72) results were different from the controls (M = 112.07, SD = 12.14), $P = 0.002$. The average performance group (M = 97.67, SD = 14.00) was also significantly different from the control group, $P = 0.001$.

There were also significant differences between groups on verbal memory (CVLT-II—Combined Trial 1 to 5), $F(3,74) = 3.77$, $P = 0.014$, $\eta_p^2 = 0.12$. Post hoc comparisons showed that the low-performance group (M = 99.47, SD = 13.21) differed from the high-performance (M = 112.69, SD = 14.15), $P = 0.021$, and the control groups (M = 110.83, SD = 12.90), $P = 0.024$.

Last, there were differences between groups on Math Problem Solving, $F(3,73) = 6.19$, $P = 0.001$, $\eta_p^2 = 0.20$ and Math Fluency subtests, $F(3,74) = 3.90$, $P = 0.012$, $\eta_p^2 = 0.14$. Post hoc comparisons showed that the low-performance group (M = 92.53, SD = 9.3) differed from the high-performance group (M = 109.00, SD = 9.27), $P = 0.001$, and from the control group (M = 105.41, SD = 12.61), $P = 0.004$ on the Math Problem Solving Task. On the Math Fluency Index, the low-performance group (M = 85.71, SD = 11.49) differed from the high-performance group (M = 100.63, SD = 22.42), $P = 0.037$. The average performance (M = 84.47, SD = 19.38) and high-performance groups also differed significantly from each other, $P = 0.026$.

4 | DISCUSSION

Our first objective was to identify prevalence of deficits in long-term ALL survivors, using the DIVERGT screening procedure.[23] We found high prevalence of deficits (1.5 SD below norm). Multiple ALL survivors had impairments in cognitive flexibility (approximately 10%), visual attention and processing speed (approximately 8%), verbal fluency (close to 20%) working memory (close to 20%), and fine

motor dexterity (approximately 18%). This may be contrasted with the general population, where approximately 6% of the population would be expected to perform 1.5 SD below the norm (according to the normal curve). Based on the DIVERGT results, we also created three performance groups (low, average, high performance). Almost a third (30.8%) of our cohort was classified in the low-performance group.

Our results highlight the necessity of maintaining a rigorous follow-up of these patients after remission, since a high percentage of them are at risk of developing long-term neurocognitive sequelae following treatments.

Our primary aim was to investigate the predictive validity of the mean DIVERGT score on global cognitive functioning in adult, long-term ALL survivors. Since the mean DIVERGT was related to age at diagnosis in our cohort, we showed that such a score was relevant for subsequent analysis. Hence, literature reviews show that age at diagnosis is strongly related to cognitive performance.[7,35]

The DIVERGT score predicted multiple neurocognitive functions: verbal comprehension, processing speed, GAI and mathematical reasoning. Moreover, the DIVERGT showed acceptable sensitivity (approximately 60–80%) and specificity (approximately 70%). NPV was also excellent (above 90%). Our results suggest that chances of presenting impairment in other cognitive domains are scarce if DIVERGT screening is normal. The DIVERGT could thus help identify the individuals who would benefit from a more comprehensive evaluation.

Despite the strong association between essential cognitive functions and the DIVERGT, we found no relation with delayed memory. Recent studies showed that survivors of childhood cancer may present early aging signs.[36,37] Moreover, evidence suggests that ALL survivors treated with high-dose CRT show reduced integrity in brain regions responsible for memory formation.[38] Therefore, ALL survivors may be particularly vulnerable to neurodegenerative pathologies, such as early dementia. An association between the DIVERGT score and delayed memory performance in our cohort would have suggested that it could be useful to screen for age-related cognitive impairment and dementia. However, our participants were young adults, and the absence of relation between the two measures may not be definitive. Future work could investigate the association between the DIVERGT and memory in aging ALL survivors. Assessing older ALL survivors with the DIVERGT would confirm the validity of this screening procedure through all lifespan.

After confirming the validity of the DIVERGT in our cohort, we also assessed differences in general cognition performance between groups. Across multiple tests, the low-performance group consistently had poorer performance than the high-performance group. Therefore, the DIVERGT screening procedure is a quick and useful way of discriminating participants with the lowest performance, who are more at risk of presenting neurocognitive sequelae and related functional impairment, from participants with the highest performance, who should not present any cognitive impairment in everyday life.

In sum, the DIVERGT permits a reliable and quick assessment of general cognitive difficulties in long-term ALL survivors. The original DIVERGT validation study[23] found that the DIVERGT accurately predicted global intellectual functioning, reading skills, and mathematics. The DIVERGT screening battery was administered to children and adolescents, approximately 6-year post-treatments and multiple cancer types were included (leukemia, lymphoma, Central Nervous System (CNS) tumors, non-CNS tumor). We, therefore, did not only replicate and confirm their results, but also brought new knowledge about the predictive validity of the DIVERGT. Indeed, we showed that the DIVERGT still predict general cognitive functioning and mathematics in adult long-term survivors of ALL (approximately 15 years after treatment). The DIVERGT then remains a useful screening procedure, more than a decade after the end of treatments for pediatric cancer. As such, a recent study regarding guidelines for neuropsychological services in pediatric oncology suggests the systematic use a screening procedure like the DIVERGT in clinical follow-up after pediatric cancer.[39]

Last, it is important to mention that DIVERGT was specifically designed for cancer survivors, and is specific to that population. It targets mainly executive functioning and working memory deficits. Some other clinical populations show such impairment, but generally have a more preserved general cognitive functioning. For instance, a great proportion of individuals presenting attention deficit hyperactivity disorder (ADHD) or learning disabilities (dyslexia, dyscalculia) have specific executive functioning and working memory impairment, but normal or high IQ.[40–44] Therefore, the DIVERGT would not necessarily be a good predictor of general cognitive abilities and mathematical skills in other clinical populations.

Some limitations of this study must be acknowledged. First, the sample of participants included only ALL survivors, so the conclusions may not be generalizable to all childhood cancer survivors. However, the DIVERGT predictive validity was already demonstrated in a mixed sample of childhood cancer survivors.[23] Second, this study should be replicated in other clinical populations (ADHD, learning disorders), to confirm the specificity of the conclusions to cancer survivors. Last, equivalence between males and females in follow-up group was not achieved. Nevertheless, we attempted to follow the male-to-female ratio of our entire cohort in each performance group. Literature has shown that females tend to be at greater risk of cognitive impairment following treatments against ALL.[45–47] Our cohort seemed to differ from these findings, since a higher ratio of males was found in the low-performance group. Moreover, exploratory analyses revealed no effect of sex on any of our measures of interest. We posit that the male-to-female ratio difference did not affect our conclusions.

To conclude, the DIVERGT was proved to be a useful and personalized tool for cancer survivors, which could easily be used for a quick screening of neurocognitive sequelae. DIVERGT assessment in ALL survivors could be used to provide an overview of cognitive functioning and determine which individuals would benefit from a more comprehensive neuropsychological evaluation. A better knowledge of strengths and impairments through neuropsychological testing could provide tools to improve academic or professional achievement and general quality of life in adult ALL survivors.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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