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Cognitive Function in Patients with Chronic Lymphocytic Leukemia: a Cross-Sectional Study Examining Effects of Disease and Treatment

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Abstract

Cancer-related cognitive impairment (CRCI) has not been objectively assessed in chronic lymphocytic leukemia (CLL). It is currently unclear how much of CRCI is attributable to disease, treatment, or both. We used CLL as a novel model to study the differential roles of disease and treatment in CRCI. 150 CLL patients (100 treatment-naïve and 50 chemotherapy-treated) including 84 patients with higher-risk of CLL progression completed objective neuropsychological tests. Sociodemographic-adjusted linear regression models examined cognitive outcomes in relation to risk and treatment. Higher-risk patients recalled 2 fewer words on a memory task (β= −1.8, 95%CI-3.3,−0.3) and took 15 seconds longer on an executive function task (β=15.4, 95%CI 3.1,27.6) than lower-risk patients, independent of treatment. Treated patients reported greater cognitive difficulties than treatment-naive patients (β=−6.1, 95%CI-10.1,−2.2) but did not perform worse on objective measures. Higher-risk patients experienced impairments in executive function and memory suggesting that disease biology contributes to CRCI independent of treatment.

Keywords

Chronic lymphocytic leukemia; cognitive impairment; chemotherapy; treatment naïve

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Disclosure of Interest

The authors report no conflicts of interest.

Introduction

Cancer-related cognitive impairment (CRCI) affects up to 10 million cancer survivors and is associated with decreases in quality of life, social engagement, and occupational and educational success.[1,2] CRCI is also associated with decreased treatment adherence and poorer overall survivors in older hematological malignancy patients.[3,4] Most studies of CRCI have been conducted in cancer patients treated with chemotherapy which is believed to be an important cause of this condition. In contrast, the literature is not conclusive about the role of other factors including cancer biology in the etiology of CRCI.[5] Longitudinal studies have reported that cancer survivors decline on tests of attention, memory, executive function, and processing speed during chemotherapy, implicating these agents in CRCI.[6,7] In these studies, 30% of survivors were impaired prior to adjuvant chemotherapy treatment, suggesting that their malignancy could be associated with CRCI which is then exacerbated by chemotherapy. Possible mechanisms for CRCI include pro-inflammatory or oxidative stress pathways stimulated either by disease processes or treatment that lead to neurotoxicity and cognitive impairment.[8,9] Understanding the etiology and mechanisms of CRCI has been limited by the paucity of data from treatment naïve populations.

We chose chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL) as a novel approach to study the role of disease effects and treatment in the etiology of CRCI. CLL is a common lymphoid malignancy with well-characterized biology and has effective and tolerable but non-curative treatment, and a relatively long median survival. Little data on the effect of disease on cognitive function exists and no data regarding cognitive function assessed via objective cognitive testing has been published to date specifically in CLL. Less than 10% of patients with this non-curable indolent B-cell malignancy present with constitutional symptoms or cytopenias that require immediate treatment. The remainder are monitored closely and only treated upon disease progression, with a median time from diagnosis to first treatment between 5 and 7 years, resulting in a large treatment naïve population of CLL patients. [10,11] The use of flow cytometry, fluorescence in situ hybridization (FISH) and gene sequencing has identified several molecular prognostic markers including interstitial chromosomal deletions of chromosomes 17 (del17p13) and 11 (del11q22.3), absence of *IGHV* somatic hypermutation, dysfunction mutations in genes including *TP53*, *NOTCH1,* and *SF3B1* and increased expression of ZAP70 or CD38. These prognostic biomarkers reflect underlying disease biology, allow for more accurate risk stratification, and can inform surveillance, treatment practices, and risk of progression. [11,12] Patients with CLL thus provide a unique opportunity to understand the impact of a systemic malignancy in treatment naïve patients.

We examined the effects of CLL and its treatment on cognitive function by dichotomizing patients for biological risk (higher-risk vs. lower-risk disease) and treatment (treatment-naïve vs. treated). To our knowledge, this is the first objective cognitive assessment study of CRCI in CLL. We hypothesized that patients with higher-risk disease would perform worse on neurocognitive tests than those with lower-risk disease and that patients previously treated with chemotherapy would perform worse than treatment naïve patients.

Methods

Patients and Study Procedures

We recruited eligible CLL patients enrolled in the University of Rochester (UR) Wilmot Cancer Institute (WCI) CLL Registry. This study was approved by the UR Institutional Review Board, conformed to the standards set by the Declaration of Helsinki, and all participants provided written informed consent. Eligibility criteria included: diagnosis of CLL based on standard criteria[11], age ≥21 years, no neurodegenerative disorders or major psychiatric illness (e.g. hospitalization within the past five years), and English fluency. Treatment naïve CLL patients had to be diagnosed with CLL for ≥3 months and have had no prior systemic treatment (e.g. chemotherapy, immunotherapy, etc.) for any malignancy. Previously-treated patients had completed ≥1 chemotherapy regimen ≥3 months before study entry and achieved a sustained complete or partial remission. Patients previously treated with a chemotherapy agent but currently on the BTK inhibitor ibrutinib ≥1 year and in a stable remission were also eligible for the treated group.

Patients were further classified as at higher- or lower-risk of disease progression requiring treatment using validated standard clinical biomarkers abstracted from patient medical records.[11,12] If a patient had one or more of the following prognostic markers they were considered higher-risk: somatically unmutated *IGHV (<2%)*, deletion 17p13, deletion 11q22.3, ZAP70 positivity, CD38 positivity, or deleterious *NOTCH1*, *SF3B1*, or *TP53* mutation. Patients without any of these markers including those whose markers were not measured (based on clinical judgment of necessity) were defined as lower-risk for the purposes of this study. Target enrollment of 50 higher- and 50 lower-risk treatment naïve patients was met.

Study Measures and Outcomes

Cognitive Function—Participants completed a 1.5 hour comprehensive cognitive function test battery on the same day as their regularly scheduled apppointment in the lymphoma clinic. The neuropsychological battery assessed domains commonly reported to be impaired in cancer survivors including executive function, attention, episodic memory, language, working memory, processing speed, and verbal fluency.[13] Specific validated tests used in this study were the NIH Toolbox for the Assessment of Neurological and Behavior Function Cognition (NIH-TB[14]), Comprehensive Trail Making Test (TMT A/B; representing Trails 1 and 5 respectively[15]), Hopkins Verbal Learning Test-Revised (HVLT-R[16]), and the Controlled Word Association Test (COWA[17]).

The NIH-TB is an iPad-administered battery of seven individual neuropsychological tests of executive function, attention, memory, language, and processing speed.[14] The NIH-TB yields fully-adjusted scores (age, gender, race, and education) for the total composite score of global cognition as well as for each of the seven Individual tests. In addition, we utilized the following paper-based tests: HVLT-R immediate recall summed over the first three trials (range 0–36), HVLT-R delayed recall (trial 4, range 0–12), TMT-A and TMT-B time to completion in seconds, and COWA total number of correct words averaged across three trials. Finally, self-reported cognitive function was measured using the perceived cognitive

impairment subscale of the Functional Assessment after Cancer Therapy Cognition questionnaire (FACT-Cog version 3).[18] Scores of one standard deviation (SD) below the age-adjusted normative mean on the NIH Toolbox outcomes are considered impaired.[29,19] In addition to reporting mean age-adjusted scores, we applied this criterion to all cognitive outcomes based on the T-score conversion to derive the percent impaired compared to population norms, as 1 SD is within the range of what is considered clinically meaningful in CRCI research.[14,20]

Other Patient-Reported Outcomes—Within one-week of neurocognitive testing, participants also completed questionnaires for fatigue[21], anxiety[22], and depression[23] that are frequently co-occurring symptoms of CRCI.[24]

Statistical Analysis

All analyses were completed using SAS 9.4 (SAS Institute, Cary, N.C.). Statistical significance was assessed at the two-sided 0.05 level. Descriptive statistics for covariates were calculated overall and according to risk status and treatment history. We evaluated our hypotheses using linear regression models that included risk (model 1), treatment (model 2), and a model that included both risk and treatment (model 3), for each cognitive outcome, adjusting for *a priori* defined covariates age, gender, race, and education. *A priori,* we planned to run an additional model with an interaction term between treatment and risk for any cognitive outcome that showed an association ($p<0.10$) with treatment or risk. In additional exploratory analyses, anxiety, depression, and fatigue were included as covariates.[24] All models were assessed for appropriate model fit. Several potentially influential outliers were identified through residual plots (conservatively, a cook's distance of >0.5 indicated an influential outlier) but all data points were deemed to be valid. Thus, results including these data points are presented here and estimates omitting these data points are noted in table footnotes. Given the large number of hypothesis tests, p-values were adjusted for the false discovery rate (FDR)[25].

Sample Size and Power—The sample size for this study was determined to estimate a clinically meaningful difference on the NIH Toolbox Total Composite Score (15 points) between higher- and lower-risk patients and between treated and treatment-naive patients (Models 1 and 2). An alpha of 0.025 was used to calculate the required sample size to account for these two primary hypotheses. All other analyses are considered exploratory and were corrected for multiple comparisons using the false discovery rate as described above. With a 1:1 ratio of higher- and lower-risk patients in the treatment naïve sample and a 2:1 ratio of treatment naïve to treated patients, and a power of 80% we estimated at least 90 treatment naïve (45 higher- and 45 lower-risk) and 45 previously treated patients were required. We planned to recruit 10% more patients in each group to account for potential missing data and non-compliance.

Results

Participant Characteristics

Of the 196 patients contacted, 150 agreed to participate in the study (76.5%). Primary reasons participants declined were lack of time (n=28, 61%), and lack of interest (n=7, 15%). %). Among patients who declined, 36% had been previously treated and 52% were high risk, similar to the overall distribution in the final sample (33% and 56% respectively). Patients who refused were, on average, older (median age 72 vs. 65 in the study sample), however, the age of our study sample is consistent with the age of patients routinely seen in our CLL clinic. [26] Demographic and clinical characteristics of the participants are presented in Table I.

Overall Cognitive Impairment

The percent of patients impaired on each neurocognitive assessment based on NIH-TB impairment criteria of 1 SD is reported in Table II. Overall, 8.7% of patients were impaired on the NIH-TB total composite score. Of note, approximately 20% of patients were impaired on tests of executive function, attention, and processing speed (NIH Flanker Inhibitory Control & Attention, NIH Pattern Comparison). Twenty-eight and 36% of patients were impaired on immediate and delayed memory recall, respectively (HVLT-R).

Cognitive Function in Higher- vs. Lower-Risk Patients

Higher-risk patients, on average, performed worse on tests of memory, attention, and executive function (Model 1, Table III) compared to those with lower-risk disease. Executive function and memory associations remained statistically significant after adjustment for treatment (Model 3, Table III). Higher-risk patients recalled almost two fewer words than lower-risk patients on the HVLT-R immediate recall (β=−1.79, 95%CI −3.30 to −0.28) and performed 15 seconds slower than lower-risk patients on the TMT-B, a measure of executive function (β=15.37, 95%CI 3.10 to 27.65). Higher-risk patients performed 6.5 seconds slower on the TMT-A, a test of attention/processing speed, compared to lower-risk patients (β=6.54, 95%CI −0.20 to 13.28). After adjustment for multiple comparisons (FDR), these associations lost statistical significance at the two-sided 0.05 level (both p=0.145, Supplemental Table I). There were no statistically significant interactions between treatment and risk status for the FACT-Cog, HVLT-R immediate recall, TMT-A, and TMT-B (Supplemental Table II). Anxiety, depression, and fatigue did not significantly predict cognitive outcomes other than the FACT-Cog.

Cognitive Function in Treated vs Treatment Naïve Patients

Treated patients, on average, performed worse than treatment-naïve patients on all tests across all domains with the exception of the COWA. However, the differences were small and not statistically significant (Model 2, Table III). These findings did not change even after controlling for anxiety, depression, and fatigue. However, treated patients self-reported significantly more cognitive impairment, scoring six points worse on the FACT-Cog perceived impairment scale than treatment naïve patients (β= −6.12, 95%CI −10.07 to −2.17). This difference remained statistically significant after adjustment for multiple

comparisons (p=0.033, Supplemental Table I) and additional adjustment for anxiety, depression, and fatigue scores (β= −5.06, 95%CI −5.58 to −1.54).

Discussion

In this the first study of objective CRCI in CLL patients, we report that up to 20 to 30% of patients experience cognitive impairment in the domains of memory, processing speed, attention, and executive function. In this study, we have to the best of knowledge determined objectively for the first time that higher-risk CLL patients performed significantly worse on objective tests of executive function and memory compared to low-risk patients, independent of treatment status. Overall, our findings suggest that disease biology may play a role in the etiology of CRCI in CLL. These associations remained after adjustment for demographic and psychosocial factors. However, when we adjusted for multiple comparisons our findings were no longer significant. Further research is needed to confirm these findings and clarify if high-risk patients should be monitored for cognitive impairment prior to treatment. . Additionally, treated CLL patients self-reported significantly more cognitive impairments than treatment naïve CLL patients despite little difference in objective tests, potentially due to the contribution of disease on cognitive functioning. These results remained statistically significant after adjustment for multiple comparisons, anxiety, depression and demographic factors increasing our confidence that CRCI remains an important issue for those treated with chemotherapy.

To our knowledge, only one other study has examined associations between tumor characteristics (other than stage) and CRCI. Using a population of breast cancer survivors, Koleck and colleagues report patients who were HER2 positive performed worse on visual and verbal memory than HER2 negative patients.[27] In our study, higher-risk patients performed worse than lower-risk patients on tests of executive function and memory, independent of treatment. Both studies suggest a role for tumor biology in CRCI. It is also possible, given the chronic and systemic nature of CLL, that the biological processes of disease play a more important role than previous chemotherapy treatment. Among the higher-risk markers used in this study, there is significant variability in associations with treatment response and overall survival, therefore further research is needed, in larger prospective cohorts, to determine which of these higher-risk prognostic markers may best predict CRCI.[12]

Similar to a longitudinal study of CLL patients randomized to varying chemotherapy regimens[28], we report that treated patients self-report more cognitive impairment than treatment-naïve patients. Recent work suggests that the difference presented here (5 points) is clinically meaningful.[29] Nonetheless, only small differences were observed on objective measures comparing those treated to treatment naïve. It is possible our study was not powered to find a treatment association given the heterogeneity in treatment history. In sensitivity analyses of treated patients (n=50), we did not see any indication that type of treatment (bendamustine-rituximab vs fludarabine-cyclophosphamide-rituximab) or time since treatment was predictive of CRCI. This suggests that heterogeneity in the treated group is unlikely to explain the small effect sizes in our study. In sensitivity analyses excluding patients currently on ibrutinib (n=18), associations remained unchanged with the exception

of TMT-B which inverted (β=−5.50, 95%CI −15.50, 4.50). These patients were the most heavily previously treated patients (>3 regimens) suggesting that our original findings may be attributable to cumulative chemotherapy exposures. Unfortunately, only 18 participants were on ibrutinib at the time of the study and all were previously treated, limiting our ability to examine the individual effects of ibrutinib. As the treatment for CLL moves away from chemoimmunotherapy in the U.S. it will be important to see what, if any, effect ibrutinib and other targeted agents have on cognition, particularly in previously treatment naïve populations. However, chemoimmunotherapy remains important in the treatment of many B cell malignancies and the role of these regimens in the etiology of CRCI requires further evaluation because of patient self-report of CRCI and evidence suggesting that non-Hodgkin lymphoma patients experience CRCI after bendamustine-rituximab.[30]

In addition to the novelty of this study, strengths include an objective analysis of CLL biology, a comprehensive cognitive battery of both objective and subjective assessments, covering a range of cognitive domains, and analyses that accounted for anxiety, depression, and fatigue. We were also able to provide novel data to inform on cognitive function in aging cancer patients, larger studies are needed to examine these effects across the full age distribution of CLL (e.g. 50 to 85+) while accounting for comorbidities. This study is cross-sectional; therefore, we cannot determine the true trajectory of CRCI CLL patients. Inherent limitations to neuropsychological testing may have restricted our ability to detect associations. Neurocognitive tests were originally designed to detect overt neurological injury in specific locations. *A priori*, this study was powered to find a large association (e.g. 15 point difference on the NIH toolbox), and it is becoming clear that in CLL, like much of the other cancer types, CRCI is more often a mild to moderate condition. For example, despite high proportions of those with CLL classified as impaired on domain-specific tasks of executive function and memory (20.7% to 36.7%), the frequency of global impairment was similar to population based studies of elderly populations (8.7% impaired on the NIH-TB Composite Score) (Table II). [31] It should be noted that that our sample was highly educated (43% college degree or more); however, our results also suggests a domain-specific tasks of CRCI in those with CLL which should be examined further. Even small changes or deficits in cognitive function can impact quality of life and should not be disregarded. Future research using assessments based in cognitive neuroscience focused on executive function, attention, processing speed, and memory may be warranted to enhance our ability to detect mild to moderate effects.[32] Additionally, future research should be expanded to assess the risks of dementia in this older population using clinical screening measures (e.g. MMSE, MOCA, Blessed).[33,34] Lastly, only 19/66 (29%) of patients classified as lower-risk CLL had all biomarkers tested (Supplemental Table III). Most of the missing markers were *IGHV* mutation status and *TP53*, *SF3B1*, and *NOTCH1* mutation analysis which have only more recently become routine clinical tests in determining CLL prognosis at diagnosis. Lower-risk patients without complete testing were older (median age 67 vs 62, $p<0.035$) but did not differ on other demographic variables (Supplemental Table IV). The median time from diagnosis to study entry for lower-risk patients with incomplete testing was >4 years suggesting that fewer of these patients had higher-risk disease compared to published data. [35] It is likely that clinicians did not complete full testing because the patient was diagnosed several years prior to the tests becoming available which diminishes the

prognostic value. To test for the potential impact of any misclassification, regression models were run that omitted any lower-risk patient without complete biomarker testing which produced attenuated but similar results (Supplemental Table V). Collectively, these analyses indicate that misclassification in this study likely had minimal effect on our overall findings. Additionally, the statistical significance of these higher-risk associations was lost after adjustment for multiple comparisons. Therefore, further research in larger longitudinal cohorts of treatment-naïve patients is warranted to confirm the higher-risk association and determine which clinical biomarkers may best predict CRCI (e.g. deletion 11q22).

In conclusion, our findings suggest that disease biology contributes to CRCI, independent of treatment. Larger longitudinal studies with complete prognostic biomarker data are needed to fully examine the risk of CRCI associated with higher-risk disease, characterize the trajectory of CRCI in CLL in both chemoimmunotherapy and targeted agent treated patients, and explore any potential interactions between treatment and risk. Understanding the trajectory of CRCI in CLL and its predictors will allow us to design targeted interventions to preserve cognitive function and mitigate any further dysfunction in an elderly population of cancer patients that may already be experiencing cognitive decline due to normal aging and aging-related conditions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table I:

Demographic and clinical characteristics.

Patient characteristics	Total	Treatment Naive	Treated	p-value	Lower-risk	Higher-risk	p-value
N	150	100	50		66	84	
Age (median (min, max))	65 (33,91)	64 (45,91)	68 (33,85)	0.139	64.5 (47,89)	65 (33,91)	0.829
Male	88 (58.7)	58 (58.0)	30 (60.0)	0.815	38 (57.6)	50 (59.5)	0.810
Race							
White	144 (96.0)	96 (96.0)	48 (96.0)	1.00	65 (98.5)	79 (94.0)	0.169
Black	6 (4.0)	4 (4.0)	2 (4.0)		1 (1.5)	5 (6.0)	
Non-Hispanic	149 (99.3)	100 (100.0)	49 (98.0)	0.333	66 (100.0)	83 (98.8)	0.374
Education							
≤High School Graduate/GED	29 (19.3)	17 (17.0)	12 (24.0)	0.313	9 (13.6)	20 (23.8)	0.308
Some College	57 (38.0)	37 (37.0)	20 (40.0)		24 (36.4)	33 (39.3)	
College Graduate	30 (20.0)	19 (19.0)	11 (22.0)		15 (22.7)	15 (17.9)	
Graduate/Professional Degree	34 (22.7)	27 (27.0)	7 (14.0)		18 (27.3)	16 (19.0)	
ECOG PS							
0	98 (65.3)	72 (72.0)	26 (52.0)	0.021	47 (71.2)	51 (60.7)	0.180
1	51 (34.0)	27 (27.0)	24 (48.0)		19 (28.8)	32 (38.1)	
2	1 (0.7)	1 (1.0)	0 (0.0)		0 (0.0)	1 (1.2)	
Rai stage[a]							
0		51 (51.0)	N/A		27 (54.0)	24 (48.0)	0.757
I		36 (36.0)			17 (34.0)	19 (38.0)	
II		9 (9.0)			5 (10.0)	4 (8.00)	
III		2 (2.0)			0 (0.0)	2 (4.00)	
V		2 (2.0)			1 (2.00)	1 (2.00)	
Time since diagnosis (years)							
Median (min, max)	3.18 (0.25,19.74)	2.04 (0.25,19.74)	7.89 (0.85,17.64)	<0.001	3.86 (0.27,13.73)	2.75 (0.25,19.74)	0.669
Disease Risk Group (overall)							
Low-Risk Disease	66 (44.0)	50 (50.0)	16 (32.0)	0.036			
High-Risk Disease	84 (56.0)	50 (50.0)	34 (68.0)				

[a]Treated patients were in a stable partial or complete remission and were unstaged.

Table II:

Age adjusted mean cognitive test scores and percent of patients impaired on each cognitive test.

Test	N	Direction Of Better Score	Age Adjusted Score[a] (mean (SD))	% Impaired[b]
NIH-TB Total Composite Score (global cognition)	150	Higher	106.81 (14.13)	8.7
Dimensional Change Card Sort (executive function)	150	Higher	108.81 (15.84)	3.3
Oral Reading Recognition Test (reading decoding)	150	Higher	110.35 (17.37)	8.0
Picture Vocabulary Test (vocabulary comprehension)	150	Higher	108.43 (12.56)	3.3
Flanker Inhibitory Control & Attention (attention & executive function)	150	Higher	93.59 (10.67)	20.7
List Sorting Working Memory (memory)	150	Higher	104.74 (13.78)	8.0
Pattern Comparison (processing speed)	150	Higher	98.65 (17.74)	23.3
Picture Sequence Matching (memory)	150	Higher	100.82 (14.85)	12.0
COWA (verbal fluency)	148[e]	Higher	42.61 (10.49)[f]	13.3
HVLT-R Total Correct Immediate Recall (memory)	150	Higher	46.19 (11.68)	28.0
HVLT-R Total Correct Delayed Recall (memory)	150	Higher	43.91 (12.34)	36.7
TMT-A (attention)	148[e]	Lower	51.70 (8.89)	7.3
TMT-B (executive function)	148[e]	Lower	51.22 (9.96)	11.3
FACT-Cog Perceived Cognitive Impairment Subscale (self-report)	149[c]	Higher	58.21 (11.68)	N/A[d]

NIH-TB: National Institutes of Health Toolbox Cognition Battery; FACT-Cog: Functional Assessment After Cancer Treatment Cognition; COWA: Controlled Word Association Test; HVLT-R: Hopkins Verbal Learning Test Revised; TMT-A/B: Trail Making Test A or B.

[a] NIH Toolbox outcomes are age adjusted scaled scores (μ=100), paper tests are age adjusted T-scores (μ=50),

[b] impairment defined as an age-adjusted score >1 SD below the normative mean,

[c] one participant did not return study questionnaires,

[d] normative mean unavailable,

[e] two participants did not complete these tests due to time constraints,

[f] mean COWA score adjusted for age and education

Table III:

Estimated mean difference in cognitive test scores (and 95% confidence intervals).

		Model 1[a]	Model 2[a]	Model 3[a,b]	
		Higher-risk vs. Lower-risk	Treated vs. Treatment Naïve	Higher-risk vs. Lower-risk	Treated vs. Treatment Naïve
	Direction Of Better Score	β (95%CI)	β (95%CI)	β (95%CI)	β (95%CI)
NIH-TB Total Composite Score[c] (primary outcome)	Higher	−1.96 (−4.94,1.01)	−0.38 (−3.53,2.77)	−1.96 (−4.99,1.07)	−0.03 (−3.22,3.16)
Dimensional Change Card Sort	Higher	−2.05 (−5.34,1.23)	−0.58 (−4.06,2.90)	−2.01 (−5.36,1.33)	−0.22 (−3.74,3.31)
Oral Reading Recognition	Higher	−3.22 (−6.78,0.34) *	0.82 (−2.97,4.61)	−3.45 (−7.08,0.17) *	1.44 (−2.37,5.26)
Picture Vocabulary Test	Higher	−2.20 (−4.76,0.36) *	−0.41 (−3.13,2.31)	−2.19 (−4.80,0.41) *	−0.01 (−2.76,2.73)
Flanker Inhibitory Control & Attention	Higher	−0.17 (−2.46,2.13)	−0.81 (−3.23,1.61)	−0.04 (−2.37,2.30)	−0.80 (−3.26,1.66)
List Sorting Working Memory	Higher	0.41 (−2.46,3.27)	−0.48 (−3.50,2.54)	0.50 (−2.42,3.42)	−0.57 (−3.64,2.50)
Pattern Comparison	Higher	0.35 (−3.49,4.19)	−0.80 (−4.84,3.24)	0.50 (−3.41,4.41)	−0.89 (−5.01,3.23)
Picture Sequence Matching	Higher	0.66 (−2.68,4.01)	−0.69 (−4.21,2.83)	0.80 (−2.61,4.20)	−0.83 (−4.42,2.75)
HVLT-R Total Correct Immediate Recall	Higher	**-1.81 (−3.29,−0.32)**[e]	−0.44 (−2.04,1.15)	**-1.79 (−3.30,−0.28)**[e]	−0.14 (−1.73,1.45)
HVLT-R Total Correct Delayed Recall	Higher	−0.38 (−1.19,0.44)	−0.10 (−0.96,0.76)	−0.37 (−1.20,0.46)	−0.04 (−0.91,0.84)
TMT-A time in seconds[d]	Lower	**6.89 (0.24,13.54)**[e]	3.46 (−3.59,10.51)	6.54 (−0.20,13.28) *	2.43 (−4.63,9.50)
TMT-B time in seconds[d]	Lower	**15.41 (3.32,27.51)**[e]	2.69 (−10.26,15.65)	**15.37 (3.10,27.65)**[e]	0.28 (−12.59,13.15)
COWA total correct words	Higher	0.21 (−0.96,1.38)	0.66 (−0.57,1.89)	0.11 (−1.07,1.30)	0.64 (−0.61,1.89)
FACT-Cog	Higher	−0.08 (−3.96,3.80)	**-6.12 (−10.07,−2.17)**[f]	0.84 (−2.98,4.66)	**-6.26 (−10.27,2.25)**[f]

NIH-TB: National Institutes of Health Toolbox Cognition Battery; FACT-Cog: Functional Assessment After Cancer Treatment Cognition; COWA: Controlled Word Association Test; HVLT-R: Hopkins Verbal Learning Test Revised; TMT-A/B: Trail Making Test A or B.

Boldindicates statistical significance p<0.05,

*indicates p<0.10, prior to adjustment for multiple comparisons. False discovery rate adjusted p-values are available in Supplemental Table 1.

[a]Model adjusted for age, gender, race, and education,

[b]model mutually assessed both treatment and risk status,

[c]fully adjusted NIH toolbox scores are t –scores,

[d] these models had three potential influential outliers, estimates upon removal: TMT-A Model 1 β =4.16 95%CI −0.21 to 8.52; TMT-B Model 1 β =11.63 95%CI 2.82 to 20.45; TMT-A Model 3 β =4.07 95%CI −0.37 to 8.52; TMT-B Model 3 β =13.20 95%CI 1.70 to 24.69,

[e] after adjustment for multiple comparisons trends remained (P<0.2) but were no longer significant,

[f] after adjustment for multiple comparisons effect remains significant (p=0.030).