Longitudinal exploration of cancer-related cognitive impairment in patients with newly diagnosed aggressive lymphoma: protocol for a feasibility study

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ABSTRACT

Introduction Cancer-related cognitive impairment (CRCI) is a distressing and disabling side-effect of cancer treatments affecting up to 75% of patients. For some patients, their cognitive impairment may be transient, but for a subgroup, these symptoms can be long-standing and have a major impact on the quality of life. This paper describes the protocol for a study: (1) to assess the feasibility of collecting longitudinal data on cognition via self-report, neuropsychological testing, peripheral markers of inflammation and neuroimaging and (2) to explore and describe patterns of cancer-related cognitive impairment over the course of treatment and recovery in patients with newly diagnosed, aggressive lymphoma undergoing standard therapy with curative intent.

Methods and analysis This is a prospective, longitudinal, feasibility study in which 30 newly diagnosed, treatment-naive patients with aggressive lymphoma will be recruited over a 12-month period. Patients will complete comprehensive assessments at three time points: baseline (time 1, pre-treatment) and two post-baseline follow-up assessments (time 2, mid-treatment and time 3, 6–8 weeks post-treatment completion). All patients will be assessed for self-reported cognitive difficulties and objective cognitive function using Stroop Colour and Word, Trail Making Test Part A and B, Hopkins Verbal Learning Test-Revised, Controlled Oral Word Association and Digit Span. Blood cell-based inflammatory markers and neuroimaging including a positron emission tomography (PET) with 18F-labelled fluoro-2-deoxyglucose (18F-FDG) and CT (18F-FDG-PET/CT) and a MRI will explore potential inflammatory and neuroanatomical or functional mechanisms and biomarkers related to CRCI. The primary intent of analysis will be to assess the feasibility of collecting longitudinal data on cognition using subjective reports and objective tasks from patients during treatment and recovery for lymphoma. These data will inform the design of a larger-scale investigation into the patterns of cognitive change over the course of treatment and recovery, adding to an underexplored area of cancer survivorship research.

Strengths and limitations of this study

We have developed a workable schedule of assessments to support the collection of multiple sources of information that will help characterise and understand the nature of cognitive changes over the course of treatment and recovery.

We have been able to develop processes and procedures to accommodate the rapidity with which treatment has to commence and the intensity of treatment.

We may be limited in our ability to achieve exploratory aims; this, of course, will be dependent on the success of recruitment, compliance with assessments and attrition.

Ethics and dissemination Ethical approval has been granted by Austin Health Human Rights Ethics Committee (HREC) in Victoria Australia. Peer reviewed publications and conference presentations will report the findings of this novel study.

Trial registration number Australian New Zealand Clinical Trials Registry (ACTRN12619001649101).

INTRODUCTION

Cancer-related cognitive impairment (CRCI) is a recognised and adverse consequence of cancer and its treatment and can occur in up to 75% of patients. For some people cognitive impairment may be transient, but for a subgroup these symptoms can be long-lasting after treatment, drastically impacting on the quality of life and ability to function.

Aggressive lymphomas, including Hodgkin lymphoma (HL) and non-Hodgkin’s lymphoma, such as diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma, transformed follicular lymphoma and grade 3b
of developing CRCI or serve as a useful diagnostic tool.25 Signatures may provide insight regarding individuals at risk for cognitive changes, and approaches to improve the quality of life, work, learning capacities and many aspects of social life.7 Clinical and preclinical studies have implicated inflammation in the pathophysiology of CRCI in non-CNS solid tumours, and in response to chemotherapy in these populations.20–24 It is plausible that peripheral inflammatory signatures may provide insight regarding individuals at risk of developing CRCI or serve as a useful diagnostic tool.25 Structural differences in the brain have also been identified in patients with solid tumours using brain imaging.26 However, there is no longitudinal data investigating either of these biomarkers in newly diagnosed aggressive non-CNS lymphoma.

In 2006, the International Cognition and Cancer Task Force (ICCTF) was established. Subsequently, it developed recommendations for a core set of neuropsychological tests, standard criteria for defining cognitive impairment and cognitive changes, and approaches to improve the quality of study methodology.36 As 30% of people have been shown to have lower than expected cognitive performance prior to cancer treatment,37 the ICCTF strongly recommends longitudinal studies with repeated measures, including a pretreatment baseline assessment and comparison to a non-cancer control group.38

The feasibility of collecting comprehensive longitudinal cognitive data including self-report, neuropsychological assessment, biomarkers and brain imaging over the course of treatment and recovery in patients with newly diagnosed aggressive non-CNS lymphoma undergoing standard treatment with curative intent is currently unknown and potentially challenging. Establishing feasibility in people with suspected aggressive lymphoma as they undergo an urgent comprehensive diagnostic workup and rapid commencement of chemotherapy is an important goal. Nonetheless, a longitudinal exploration of the pattern of CRCI over the course of treatment and recovery has not been described in this population and is an important precursor to the development of supportive care services.

For the first time, we will conduct a prospective longitudinal comprehensive assessment using repeated measures of cognition in patients with non-CNS aggressive lymphoma as supported by International guidelines.38 At the completion of this study, we will understand the feasibility of conducting a comprehensive longitudinal study on CRCI in this population to describe patterns of CRCI over time. This novel study will address a deficit in the evidence, before embarking on a large-scale study to comprehensively describe the cognitive outcomes and trajectory of this cohort of patients.

AIMS

This study has two main aims. The first is to assess the feasibility of collecting longitudinal data on cognition using self-report and objective assessments in people with newly diagnosed, aggressive lymphoma undergoing standard therapy with curative intent. The second is to explore and describe patterns of CRCI in the population of interest as measured by self-report, neuropsychological assessment, peripheral markers of inflammation and neuroimaging.

OBJECTIVES

The primary feasibility objectives are to: estimate the recruitment rate to the study; describe reasons for ineligibility; assess retention of participants at follow-up assessments; assess compliance with scheduled neuropsychological assessments; assess compliance with patient-reported study measures at scheduled assessments; assess the acceptability of study measures as reported by participants; assess the practicability of blood collection; estimate the proportions of patients who are willing to have positron emission tomography (PET)/CT brain acquisition studies at each assessment; estimate the proportions of patients who have scheduled PET/CT brain acquisition studies; estimate the proportions of patients who are willing to have MRI scans at each assessment and estimate the proportions of patients who have scheduled MRI scans.

Exploratory objectives relate to the assessment of changes in measures of cognition over time. Relevant objectives are to: describe changes in neuropsychological functioning from baseline at follow-ups; changes in self-report cognitive functioning from baseline at follow-ups; changes on PET/CT brain scans from baseline at follow-ups and, changes on MRI scans from baseline at follow-up.

METHODS

Design and setting

This single-site longitudinal, feasibility study will be conducted in the specialised haematology department of...
Participants

Thirty newly diagnosed, treatment-naïve patients with aggressive lymphoma undergoing curative-intent combination chemotherapy will be recruited over a 12-month period. Each participant will be followed up to 6-months from enrolment.

Eligibility

The study will enrol people aged 18 years or older with newly diagnosed aggressive lymphoma (HL, DLBCL, Burkitt lymphoma, transformed follicular lymphoma or grade 3b follicular lymphoma); scheduled to undergo Burkitt lymphoma, transformed follicular lymphoma or newly diagnosed aggressive lymphoma (HL, DLBCL, aggressive lymphoma undergoing curative-intent chemotherapy will be recruited over a 12-month period. Each participant will be followed up to 6-months from enrolment.

Sample size

The target sample of 30 participants is pragmatic. If 30 patients are accrued in 12 months, the expected monthly accrual rate is 2.5 patients per month with a 95% CI of 1.7–3.6 patients per month; the corresponding CI for the accrual rate over 12 months is 20.2–42.8 patients (confidence limits calculated in R V.3.5.1 using the ‘epitools’ package).39

Procedures

Consented participants will undergo comprehensive assessments, including neuropsychological testing, self-report questionnaires, blood cell-based inflammatory markers and neuroimaging at three pre-specified time points. Time 1 (T1): pre-treatment (treatment naïve), time 2 (T2): mid-treatment (that is after cycle 2, and before cycle 3 of chemotherapy) and time 3 (T3): 6–8 weeks post-treatment completion.

The neuroimaging (¹⁸F-FDG PET/CT brain acquisition study and MRI scan) will be offered as an optional substudy. The brain MRI substudy will occur in the first 15 participants willing to participate at two time points only (T1 and at T3). The flow of participants through the study is described in figure 1.

VARIABLES, DATA SOURCES AND MEASUREMENT

Demographic Information

Demographic and clinical information will be gathered via a medical record review at baseline. Current medications, including psychoactive and complementary medications, will be documented. Comorbidities will be collected using the Colinet Morbidity Index40 and ECOG performance status.41

Treatment details

Chemotherapy regimens, including agents delivered, dose-intensity, duration and number of cycles, as well as amendments to planned treatment, will be collected from the participants medical record.

Neuropsychological assessment

Standard neuropsychological testing will be used to assess cognitive domains of memory, information processing speed, verbal fluency, attention and executive function. Table 1 depicts the domains assessed and tests used. These tests cover the cognitive domains most commonly impaired in cancer survivors, are widely used, validated and include those recommended as part of a core battery of tests by the ICCTF.44 Normative data for each neuropsychological test are available for comparison to determine similarities or differences between the lymphoma group and a healthy population.

The Stroop colour and word test measures executive function, based on the observation that individuals can read words much faster than they can identify and name colours.42 The Trail Making Test is an assessment of visual attention and task switching. It consists of two parts in which the subject is instructed to connect a set of 25 dots as quickly as possible while still maintaining accuracy. The test can provide information about visual search speed, scanning, speed of processing, mental flexibility, as well as executive functioning and is sensitive to detecting cognitive impairment.43 The Hopkins Verbal Learning Test assesses verbal memory and involves participants being asked to remember a list of 12 words with three semantic categories. Three learning trials are followed by an unprompted delayed recall and a 24-word list in which participants are asked which words are the target words and which are distractors.44 The Controlled Oral Word Association test is a verbal fluency test measuring spontaneous production of words belonging to the same category or beginning with the same designated letter.45 The Digit Span Wechsler Adult Intelligence Scale measures auditory focused attention and working memory by having the participant repeating back number sequences of increasing length in the same order or in reverse order.46

Patient-Reported Outcome Measures (PROMs)

A set of self-report measures will be used to assess cognitive functioning, fatigue and emotional distress. All measures are appropriate for use in cancer populations and have evidence supporting their measurement properties.47 Subjective cognitive functioning will be assessed with The European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life questionnaire for cancer (QLQ-C30) Cognitive functioning scale (EORTC QLQ-C30 CF).48 The Functional Assessment of Cancer Therapy (FACT)-Cognitive Function scale (FACT-COG)49 and The Cognitive Failures Questionnaire (CFQ).50
The 2-item EORTC QLC-C30 CF assesses the extent to which participants have experienced each cognitive condition (attention and memory) within the last week. Respondents use a 4-point Likert-type scale ranging from ‘0’ (Not at all) to ‘3’ (Very much) to rate each item. Item review involved patients and psychometric evidence support its use in patients with cancer.48 51 Responses are summed to create a total score (possible
range: 0–6) and higher scores reflect higher levels of cognitive condition.

The 37-item FACT-COG assesses perceived cognitive functioning including mental acuity, attention and concentration, memory, verbal fluency, functional interference, deficits observed by others, change from previous functioning and impact on the quality of life within the last week. Respondents use a 5-point Likert-type scale ranging from ‘0’ (Never) to ‘4’ (Several times a day) to rate each item. Item generation and review involved patients and oncology specialists and psychometric evidence support its use in patients with cancer. The FACT-COG includes negatively worded (eg, I have had trouble concentrating) and positively worded (eg, My mind is as sharp as it has always been) items. Responses are summed to create a total score (possible range: 0–148). Negatively worded items are reverse scored to create subscale scores, with higher scores reflecting fewer cognitive problems and better quality of life, consistent with the FACT scoring system.

The 25-item COG assesses perceived cognitive condition, including self-mindness, everyday life-slips and errors of perception, memory and motor functioning in the past 6 months. It will be completed at two time points only (T1 and T3) and will provide data on self-reported capacity in the 6 months leading up to diagnosis, through treatment and into recovery. Respondents use a 5-point Likert-type scale ranging from ‘0’ (Never) to ‘4’ (Very often) to rate each item, and psychometric evidence support its use in patients with cancer. Responses are summed to create a total score (possible range: 0–100). Higher scores reflecting higher levels of cognitive failures.

Fatigue is strongly associated with self-reported cognitive declines and is considered a contributor to decline in cognitive function. Fatigue will be assessed with the Functional Assessment of Chronic Illness Therapy-Fatigue scale (FACT-Fatigue). This 13-item questionnaire used with the 28-item FACT-G quality of life instrument assesses the intensity and impact of fatigue on daily life in the last 7 days. Respondents use a 5-point Likert-type scale ranging from ‘0’ (Not at all) to ‘4’ (Very much) to rate each item. Item generation and review involved patients and oncology specialists and psychometric evidence supports its use in patients with cancer. Responses are summed to create a total score (possible range: 0–52), with higher scores reflecting higher levels of fatigue. We have healthy normative data collected using the FACT-G questionnaire in an Australia population available for comparison.

Depression and anxiety have been associated with CRCI, thus these outcomes will be assessed using the Patient-Reported Outcomes Measurement Information System (PROMIS) Emotional Distress-Depression 8b and Anxiety 7a short forms. The 7-item PROMIS Anxiety 7a short form will assess the frequency of emotions such as fear, stress and anxiety in the last 7 days. Respondents use a 5-point Likert-type scale ranging from ‘1’ (Never) to ‘5’ (Always) to rate each item. Item review involved patients and psychometric evidence supports its use in patients with cancer.

Responses are summed to create a total score (possible range: 35.2–82.7), and higher scores reflect higher levels of anxiety.

The 8-item PROMIS Depression 8b short form will assess the frequency of emotions such as worthlessness, hopelessness and sadness in the last 7 days. Respondents use a 5-point Likert-type scale ranging from ‘1’ (Never) to ‘5’ (Always) to rate each item. Item review involved patients and psychometric evidence supports its use in patients with cancer.

Responses are summed to create a total score (possible range: 35.2–82.4), and higher scores reflect higher levels of depression.

Average testing time is 10–12 s per item on each questionnaire, giving a total time per assessment for all questionnaires of 25 min.

**Participant burden interview (initial pilot)**

In addition to neuroimaging requirements, it is anticipated study measures may take between 60 and 70 min to complete. It is important to explore the acceptability and feasibility of this set of measures in a population for whom there is no reported data of acceptability for this battery of tests. We will therefore ask the first five participants enrolled to describe their experience of completing the assessments, including time commitment, repetition of measures, burden and recommended changes. This brief, face-to-face interview using a semi-structured interview schedule, will take place 1 week after the participants have completed the T1 self-report measures and neuropsychological testing.

**Laboratory tests**

We hypothesise that inflammatory markers in the blood are positively associated with CRCI. As an initial exploration of this association, we will use full blood examination (FBE) counts that are inexpensive and standard of care in treating patients with lymphoma. These include:

- Neutrophil to lymphocyte ratio (NLR).
- Platelet to lymphocyte ratio (PLR).
- Systemic Immune-Inflammation Index (SII).

Participants will have blood tests collected as part of standard care. This will occur prior to each cycle of chemotherapy, and at the end of therapy to ensure blood count recovery. The blood cell-based inflammatory markers will be calculated from readily available results of FBE. These
data will be available at each of the three time-points. The NLR and PLR will be calculated as the ratio of neutrophil count to lymphocyte count, and as the ratio of platelet count to lymphocyte count, respectively. The SII will be defined as platelet count times the NLR. We recognise that lymphoma and cancer treatment can modify NLR, PLR and SII, and other markers of inflammation such as CRP, ESR or cytokine analysis may show a stronger association between inflammation and CRCI. However, these markers are not always included in the standard of care assessment in patients with lymphoma. The aim of this study is to explore whether standard of care blood cell counts may serve as a cost-effective biomarker for CRCI that requires no additional labour or tests.

Neuroimaging substudy

Neuroimaging will be performed using both ¹⁸F-labelled fluoro-2-deoxyglucose (¹⁸F-FDG) PET/CT and MRI examinations to explore potential structural and functional changes associated with CRCI.

¹⁸F-FDG PET/CT brain acquisition study: a dedicated brain acquisition study will be undertaken to explore changes in glucose metabolism and signs of acute metabolic effects at all three time points. As it is an optional sub-study, it will be undertaken with the subset of participants willing to take part. The whole-body ¹⁸F-FDG PET/CT scans will be performed as standard of care. As part of this scan, an additional 10-minute brain PET emission scan, 30-min post-injection and a low dose head CT will be acquired.

Consenting participants will be assessed on the same PET scanner (Philips Ingenuity scanner), in the hospital’s Molecular Imaging department. The brain PET emission scan will not expose participants to additional radiation above the standard of care whole-body PET emission scan. The low dose brain CT scans (for localisation and attenuation correction of PET emission scan) will include low additional radiation exposure to participants. Based on the estimated dose, the level of risk is described as very low, and is within an allowable annual dose to the public from controlled sources.

MRI scan: an MRI scan of the brain will be performed to explore changes in regional cortical volumes. This will be performed only in the first 15 patients who consent to the MRI sub-study, at two time points only (T1 and T3), due to the costs of the scans.

Consenting participants will be imaged on a 3T scanner (Siemens Magnetom Skyra) with a 64-channel phased-array head coil in the radiology department. The MRI acquisition will include 3D magnetisation prepared - rapid gradient echo (MP-RAGE) T1, 3D fluid attenuation inversion recovery (FLAIR) and diffusion tensor imaging (DTI) sequences. A T1-weighted three-dimensional magnetisation prepared rapid gradient echo (T1 MP-RAGE) sequence with 1mm isotropic voxels will be used for structural/morphometric analyses. FLAIR images will be used for quantitative measures of white matter (WM) hyperintensity burden.

MP-RAGE images will be acquired with the following parameters: repetition time (TR)=2300 ms, echo time (TE)=2.98 ms, field of view (FOV)=256mm, fractional anisotrophy (FA)=<9°, number of slices=192, 1.0 mm thickness, 256×256 matrix, in plane resolution of 1.0 mm². 3D FLAIR sampling perfection with application optimised contrasts using different flip angle evolution (SPACE) will be acquired using the following parameters: TR=5000 ms, TE=91 ms, FOV=256mm, number of slices=192, 1.0 mm thickness, 256×256 matrix, in plane resolution of 1.0 mm². DTI acquisition will be conducted using a whole brain two-dimensional spin-echo sequence with an echo-planar readout and a pair of diffusion weighting gradients positioned symmetrically around the 180° pulse. DTI parameters: TE=92 ms, TR=2400 ms, 30 axial slices interleaved with 4 mm slice thickness, field of view=220 mm, voxel size 1.7×1.7×4.0 mm. Diffusion gradients will be applied along 64 non-collinear directions with a b value of 1000 s/mm²; one non-diffusion-weighted set of images will be acquired.

DATA ANALYSIS

Feasibility outcomes

The main feasibility outcomes are recruitment, retention, compliance with study measures, as well as acceptability and practicability of subjective and objective study measures. Recruitment data will be summarised using a rate and 95% CI using the Poisson distribution. Compliance with assessments, as well as adherence and retention data, will be summarised using a proportion and 95% CI; the latter will be estimated using the Wilson method. Relevant analyses will be performed in R.

Acceptability of the assessments will be explored through one-on-one, face-to-face, semi-structured participant burden interviews in the first five participants. Content analysis will be used to analyse the responses and identify recommendations for modifications to improve the acceptability of study assessments.

Patient characteristics, patient-reported outcomes and neuropsychological test outcomes

Analysis will include all available data and will be performed in R. Responses to patient-reported outcome measures and neuropsychological tests will be scored according to author guidelines. Values for missing measures and tests will not be imputed.

Descriptive statistics will be used to summarise patient characteristics and missing data. Descriptive statistics will include counts and percentages, and means and SD or medians and interquartile ranges, as appropriate.

Continuous patient-reported and neuropsychological test outcomes will be summarised descriptively (means and SD) at each time point. Changes from baseline at follow-up time points will also be analysed descriptively (means and SD). Effect size estimates (ie, standardised measures of change from baseline; in this case, mean change divided by the baseline SD), as described by Kazis et al, will be used to characterise the size of observed differences. If appropriate,
a secondary analysis of continuous patient-reported and neuropsychological test outcomes will be carried out by fitting a linear mixed model to each outcome separately using the ‘lmerTest’ package. Models will be estimated via maximum likelihood and include a fixed effect for time and a random participant effect.

**Neuroimaging**

We will be using a Tukey-Kramer HSD test to establish longitudinal changes in regional tracer uptake as well as in cortical volumes and thickness over the course of the treatment and recovery. False discovery rate correction for multiple comparisons will be performed on the regional comparisons and correlations.

\[^{18}\text{F-FDG PET/CT brain acquisition study analysis: all brain study scans, and MRI image sets are aligned using CapABIL.\textsuperscript{65}}\] Standardised uptake values (SUV) will be calculated for all brain regions examined and SUV ratios (SUVR) will be generated by dividing all regional SUV by the cerebellar cortex SUV. Neocortical glycine hypometabolism will be expressed as the average SUVR of the mean of frontal, superior parietal, lateral temporal, lateral occipital and anterior and posterior cingulate regions. We will also compute the frontal and anterior cingulate SUVRs and the FDG posterior cortical index as the average SUVR of the lateral temporal, parietal and posterior cingulate/precuneus cortices.

Voxel-wise analyses: Statistical brain mapping (SPM8) strategies\textsuperscript{66} will be used to analyse the variation of the continuous PET measurements during treatment and recovery on a voxel-by-voxel basis, thus providing regional information that is independent of any pre-specified cortical region. Difference in SUVR images between the different PET scan visits will first be computed. We will then perform straightforward SPM on the difference SUVR images to define the pattern of tracer retention changes over the course of treatment and recovery.

**MR analysis:** Volumetric estimates (hippocampus, cortical grey matter (GM), WM and ventricular volumes), expressed in cm\(^3\), will be obtained from T1 MP-RAGE images using computational quantification of MRI from AIBL (CurAIBL).\textsuperscript{57} CurAIBL implements an Expectation Maximisation approach for the segmentation of GM, WM and cerebrospinal fluid, and a segmentation propagation approach to define smaller regions of interest (ROIs) including hippocampus and ventricles. The hippocampus ROI is extracted using a multi-atlas approach based on the Harmonised Hippocampus Protocol.\textsuperscript{68} Cortical volumes will be corrected for intracranial volumes.

Once pure tissue segmentation and partial tissue classification are performed, the cortical thickness estimation of the resulting GM will be computed using a combined voxel-based approach. Cortical thickness will be estimated in the anterior middle frontal gyri, in the cerebellum and in the posterior parietal cortex.

**Patient and public involvement**

This study explores the feasibility of collecting longitudinal data on cognition in patients with newly diagnosed aggressive lymphoma. However, no patients or members of the public were included in the design of the study. The results will be disseminated to participants after the study on request, which will be completed by the study team. The participant burden interview will not be analysed by patients themselves, but inclusion of the burden interviews speaks to this limitation as they will generate patient feedback on feasibility of the study.

**DISCUSSION**

For the first time, we will conduct a prospective longitudinal comprehensive assessment using repeated measures of cognition in patients with newly diagnosed aggressive lymphoma undergoing standard therapy with curative intent. At the completion of this study, we will understand feasibility of collecting longitudinal data on cognition, and will describe patterns of CRCI in the population of interest as measured by self-report, neuropsychological assessment, peripheral markers of inflammation and neuroimaging.

This novel study will address a deficit in the evidence, to inform the planning of a larger-scale longitudinal cohort study, to comprehensively describe the cognitive outcomes and trajectory of this cohort of patients, and ultimately lead to intervention studies in the future.

**Ethics and dissemination**

Ethical approval was granted by the Austin Hospital Human Research Ethics Committee (HREC) approval number HREC.55582/Austin-2019. The study is registered at the Australian and New Zealand Clinical Trials Registry. The trial is open to patient recruitment. Participants will not be exposed to any undue risks or harm by participation. The estimated risk of the additional radiation exposure from the neuroimaging is classified as very low risk and covers the allowable annual dose to the public from controlled sources. This trial will be conducted in compliance with the principles of the Declaration of Helsinki (2013) and the principles of Good Clinical Practice and the Australian National Statement on Ethical Conduct in Human Research.\textsuperscript{59}

We anticipate the study will be completed in April 2021 and report results in 2021–2022. Future publications and presentations will explore feasibility outcomes and patterns of cognitive function over time in this cohort of patients, and relationships between outcomes.

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