CANCER-RELATED COGNITIVE IMPAIRMENT IN OLDER ADULTS WITH ACUTE MYELOID LEUKEMIA RECEIVING CHEMOTHERAPY: PERSPECTIVES FROM PATIENTS AND THEIR CAREGIVERS

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A dissertation submitted to the faculty at the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the School of Nursing.

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ABSTRACT

Ya-Ning Chan: Cancer-related Cognitive Impairment in Older Adults with Acute Myeloid Leukemia Receiving Chemotherapy: Perspectives from Patients and their Caregivers
(Under the direction of Ashley Leak Bryant)

Acute Myeloid Leukemia (AML), an aggressive cancer of blood and bone marrow, is a disease of older adults, with a median diagnosis age of 68 years. Chemotherapy is the standard treatment for AML. Unfortunately, chemotherapy may impact cognitive function, also known as cancer-related cognitive impairment (CRCI), which impacts survivors across illness journey. Current literature on CRCI focuses mainly on survivors with a solid tumor diagnosis; consequently a knowledge gap exists for older adults with AML. Hence, this dissertation aims to 1) systematically explore current literature on cognitive function in adults with AML; 2) examine trajectory of CRCI and identify its correlates from 1st to 4th cycle of chemotherapy in older adults with AML; and 3) describe CRCI experiences of older adults with AML and their caregivers up to 4th cycle of chemotherapy.

This dissertation is guided by the Dynamic Symptoms Model. Chapter 2 systematically examines cognitive function literature in adults with AML treated with chemotherapy. Chapter 3 and Chapter 4 are based on a prospective, longitudinal study. Chapter 3 presents the quantitative data of 14 older adults with AML. The findings show that cognitive function remain stable over time; however, 63.64% and 75% of older adults with AML experience subjective and cognitive impairment respectively after initiating chemotherapy. In particular, impaired verbal learning/memory and executive function are found in a greater number of older adults with AML. Additionally, potential correlates of cognitive function include: disease burden, insomnia,

emotional distress, and hemoglobin. Chapter 4 presents the qualitative data from 11 older adults with AML and 8 caregivers. The findings show: 1) CRCI symptom experience, such as memory, language, and concentration; 2) impact of CRCI on emotion and the disruption of life; 3) CRCI problem-solving and emotional coping strategies; and 4) perceived demographic, physical/clinical, psychological, environmental, and other risk factors of CRCI.

Findings from this dissertation provide an in-depth and comprehensive preliminary understanding of CRCI in older adults with AML, which provides fundamental knowledge for future sufficiently-powered quantitative studies. Additionally, understanding caregivers' experiences provides a critical foundation for future intervention development to involve caregivers in managing CRCI in older adults with cancer.

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LIST OF ABBREVIATIONS

AML	Acute Myeloid Leukemia
Borg CR-10	Borg Category Ratio Scale
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CML	Chronic Myeloid Leukemia
CogOth	Functional Assessment of Cancer Therapy-Cognitive Function Comments From Others Subscale
CogPCA	Functional Assessment of Cancer Therapy-Cognitive Function Perceived Cognitive Ability Subscale
CogPCI	Functional Assessment of Cancer Therapy-Cognitive Function Perceived Cognitive Impairments Subscale
CogQOL	Functional Assessment of Cancer Therapy-Cognitive Function Impact Of Quality Of Life Subscale
COVID-19	Coronavirus Disease 2019
CRCI	Cancer-related Cognitive Impairment
Ara-c	Cytarabine
D-KEFS	Delis–Kaplan Executive Function System
DS	Digit Span
Embase	Excerpta Medica database
EORTC QLQ-C30	European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire
FACT-Cog	Functional Assessment of Cancer Therapy-Cognitive Function
FACT-Leu	Functional Assessment of Cancer Therapy-Leukemia

Hgb	Hemoglobin
HVLT-R	Hopkins Verbal Learning Test-Revised
HMA	Hypomethylating Agents
ICCTF	International Cognition and Cancer Task Force
LEUS	Functional Assessment of Cancer Therapy-Leukemia Leukemia subscale
JBI	Joanna Briggs Institute
LDH	Lactate Dehydrogenase
LDSB	Longest Digit Span-backward
LDSF	Longest Digit Span-forward
MCID	Minimal Clinically Important Differences
MDS	Myelodysplastic Syndrome
NCCH	North Carolina Cancer Hospital
NCCN	National Comprehensive Cancer Network
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCI	Reliable Change Index
PRO-CTCAE	Patient Reported Outcomes-Common Terminology Criteria for Adverse Events
QOL	Quality of Life
TMT	Trail Making Test
VEN	Venetoclax
WAIS	Wechsler Adult Intelligence scale
WBC	White Blood Cell Count

CHAPTER 1: INTRODUCTION

Background and Significance

Acute Myeloid Leukemia

Acute myeloid leukemia (AML), a cancer of the blood and bone marrow, is a disease that primarily affects older adults, with a median age at diagnosis of 68 years (National Cancer Institute, nd). The 5-year survival rate was 28% during the period of 2011 through 2015 (National Cancer Institute, nd). In 2022, an estimated 20,050 new cases of AML will be diagnosed, accounting for 33.06% of the leukemia population (Siegel et al., 2022).

Chemotherapy is the standard treatment for AML. Adults with a diagnosis of AML will first receive intensive induction chemotherapy (such as 7+3 regimen) that typically requires a 4-6 week hospital stay (National Comprehensive Cancer Network, 2018). Providers then rely on a bone marrow biopsy to determine remission status; based on those results, people with AML will either be re-induced or discharged to their home setting with additional brief hospitalizations for consolidation chemotherapy, which is typically 4-6 cycles over a 6-month period (National Comprehensive Cancer Network, 2018). However, due to the poor tolerance of intensive treatment in older adults (>60 years old) with AML and adults with comorbidities (Forsythe et al., 2019), other treatment options have been developed.

On November 21, 2018, the Food and Drug Administration approved Venetoclax (VEN) in combination with hypomethylating agents (HMA: azacytidine or decitabine) or low-dose cytarabine (ara-c) [VEN+HMA/low-dose ara-c] for use in adults ≥75 years with newly diagnosed

AML or those with comorbidities who are precluded for intense chemotherapy (Food and Drug Administration, 2018). Clinical trials indicated benefits on tumor response rate and overall survival in older adults with AML who were treated with VEN+HMA/low-dose ara-c (Guerra et al., 2019).

Cancer-related Cognitive Impairment

Impaired cognitive function, also known as cancer-related cognitive impairment (CRCI), "chemobrain," or "chemo fog," has been widely reported in cancer survivors during or post-chemotherapy. Cancer survivors with CRCI may experience different levels and domains of cognitive deficits. A meta-analysis of 13 CRCI studies found deficit domains of executive function (effect size=-0.27, 95% CI -0.44– -0.09), memory (effect size=-0.21, 95% CI -0.36– -0.07), verbal function and language skills (effect size=-0.17, 95% CI -0.33– -0.00), construction (effect size=-0.12, 95% CI -0.28–0.04), concept formation and reasoning (effect size=-0.10, 95% CI -0.30–0.10), perception (effect size=-0.06, 95% CI -0.38–0.26), and orientation and attention (effect size=-0.02, 95% CI -0.16–0.12) (Hodgson et al., 2013). With these deficits, survivors may face difficulties maintaining their social roles and daily activities (Selamat et al., 2014), have decreased work ability and productivity (Von Ah et al., 2018), and have a lower quality of life (Klemp et al., 2018).

Cancer-related cognitive impairment in solid tumors

Approximately 17% to 94% of cancer survivors experience CRCI after initiation of chemotherapy (Hermelink et al., 2007; Hess et al., 2015; Janelsins et al., 2017; Stouten-Kemperman et al., 2015; Von Ah & Tallman, 2015). CRCI was assessed both during and after completing chemotherapy, with mixed results. For survivors with a solid tumor diagnosis, Janelsins et al. (2017) found a statistically significant decrease in cognitive function from pre-

chemotherapy to post-chemotherapy in 581 breast cancer survivors. This significant decrease from baseline remained until 6 months post-chemotherapy (Janelsins et al., 2017). Similar results were found among 49 breast cancer survivors, who showed significant deterioration from pre-chemotherapy at four months and at eight months post-chemotherapy ($p=0.046$) (Moore et al., 2019). Moreover, CRCI also exists in long-term survivors. Stouten-Kemperman et al. (2015) assessed 51 testicular cancer survivors at an average of 14 years post-treatment and found that survivors who received chemotherapy reported a lower cognitive function than those who did not receive chemotherapy ($p=0.03$). However, Khan et al. (2019) tested cognitive function immediately after administration of a cycle of chemotherapy in 144 breast and colorectal cancer survivors, and their results complicated the findings of Janelsins et al. (2017), Moore et al. (2019), and Stouten-Kemperman et al. (2015). Khan et al. (2019) found significantly slower orientation and attention ($p=0.01$), suggestive of cognitive decline, but they also found an improvement in executive function ($p=0.03$). This evidence of potential improvement in cognitive function during and after chemotherapy is not isolated. Similar results were found that showed a significant improvement in delayed memory (95% CI 5.7–21.8, $p=0.023$) and perceived cognitive function ($p<0.05$) from pre-chemotherapy to 6 months follow-up in 75 breast cancer survivors (Debess et al., 2010), whereas a statistically significant decrease was identified in executive function (95%CI 7.7–25.0, $p=0.002$) (Debess et al., 2010). Another study reported no significant change in cognitive function ($p=0.37$) from pre-chemotherapy to the end of treatment among 102 breast cancer survivors (Iconomou et al., 2004). Thus, the results of CRCI during and post chemotherapy remains mixed in solid tumor cancers such as breast and colorectal cancer survivors.

Cancer-related cognitive impairment in hematological malignancies

Research on CRCI in hematological cancers remains limited, but several studies provide a foundation for future work in patients with hematological cancers, such as lymphoma, chronic myeloid leukemia (CML), myelodysplastic syndrome (MDS), or AML. Kotb et al. (2019) reported a prevalence of CRCI of 62% among 150 patients with mixed diagnoses of hematological malignancies. One study of 30 survivors with B-cell non-Hodgkin's lymphoma reported a significantly lower perceived cognitive function three months after chemotherapy ($p=0.013$, 95%CI -42.4– -5.4) and executive function and attention ($p=0.003$, 95% CI -67.8– -15.3) when compared to healthy controls (Zimmer et al., 2015). However, Meadows et al. (2013) found significant improvement in executive function ($p<0.01$) and memory ($p<0.01$) from pre-treatment at 12 and 18 months in 106 survivors with CML or MDS. In terms of the AML population, two studies, which focused on exploring CRCI using batteries of neuropsychological assessment, were identified. One study including 54 adults with AML or MDS found an increased prevalence of decline in attention, memory, executive function, verbal function, psychomotor speed, and dexterity from pre-chemotherapy to one month later; however, the only statistically significant decline was dexterity (Meyers et al., 2005). Another longitudinal study of 20 adults with AML receiving cytarabine found mixed results of changes of cognition during the six months study follow-up (Modzelewski et al., 2011). Although AML is mainly diagnosed in older adults with a median age of 68 years, these two studies included samples with relatively younger mean ages (38–60 years), which is not representative. Hence, CRCI remains understudied in adults with AML, especially the older adult population.

Gaps in Research

CRCI is a treatment-related side effect that has a negative impact on cancer survivors during and after chemotherapy. Considering that chemotherapy is the standard treatment for adults with AML, it is crucial to understand CRCI in this patient population. However, to the best of our knowledge, only a few studies aimed to study CRCI in adults with AML. Additionally, the study samples were relatively younger than the general AML population.

Although prior studies have assessed CRCI (Hutchinson et al., 2012; Li & Caeyenberghs, 2018; Simó et al., 2013), identified potential factors and biomarkers related to CRCI (Castel et al., 2017; Henneghan, 2016), and tested interventions on CRCI (Cifu et al., 2018; Kim & Kang, 2019; Zimmer et al., 2016), the majority of these studies included only adults with solid tumors—in particular, women with breast cancer. Regarding hematological malignancies, studies mainly focused on pediatric populations with acute lymphoblastic leukemia or primary central nervous system lymphoma diagnosis (Williams et al., 2016). With different patient characteristics (older age, both male and female gender) and chemotherapy plans, it is difficult to generalize findings from other cancer types to the AML population. Hence, in order to fill the gap in the current CRCI literature, this dissertation aims to explore CRCI trajectories in older adults with AML.

Purpose

This dissertation synthesizes current knowledge of cognitive function in adults with AML and explores the CRCI trajectory among older adults with AML from the initiation of chemotherapy to 3 months later. In order to have an in-depth and comprehensive understanding of CRCI in older adults with AML, we collected quantitative data using patient-reported questionnaires and a battery of neuropsychological assessments and qualitative data from both

older adults with AML and their caregivers using semi-structured interviews. The specific aims were:

Aim 1 (manuscript 1): Systematically explore current literature on cognitive function in adults with AML.

Aim 2 (manuscript 2): Examine the development and trajectory of CRCI severity from initiating chemotherapy to 3 months later in adults with AML over 60 years of age.

Aim 3 (manuscript 2): Identify factors (demographic, physiologic/clinical, and psychological, environmental factors) associated with CRCI in adults with AML over 60 years of age.

Aim 4 (manuscript 3): Describe the CRCI experiences of adults with AML over 60 years of age and their caregivers up to 3 months after initiating chemotherapy.

Conceptual Framework

This dissertation is guided by the conceptual model of CRCI in older adults with AML (Figure 1.1), adapted from the Dynamic Symptoms Model (Brant et al., 2016). This model was built upon the appraisal and comparison of four symptom models and theories (Brant et al., 2010), which were the Theory of Symptom Management (Dodd et al., 2001), the Theory of Unpleasant Symptoms (Lenz et al., 1997), the Symptoms Experience Model (Armstrong, 2003), and the Symptom Experiences in Time Theory (Henly et al., 2003). The model has primarily been used in research focusing on cancer-related symptoms (Brant et al., 2016), which aligns with the proposed dissertation.

This model (Figure 1.1) identifies four antecedents that may impact cognitive function: demographic (age, gender, education level), physiologic/clinical (treatment regimen, comorbidity, fatigue, sleep disturbance, hemoglobin, white blood cell count, neutrophil count,

lactate dehydrogenase), psychological (anxiety, depression), and environmental (in-hospitalization). Symptom experience focuses on patients' and caregivers' interpretation of CRCI through qualitative interviews. Symptom trajectories are measured over time at different time points using patient-reported questionnaires and a neuropsychological assessment.

Outline of Dissertation

This dissertation is formatted as a three-manuscript dissertation. The title and focus of each chapter are as follows:

Chapter 1 highlights the significance of this dissertation. In this chapter, the background of CRCI, conceptual framework, and aims of the dissertation are presented.

Chapter 2 (Manuscript 1), titled "Cognitive Function in Adults with Acute Myeloid Leukemia: A Systematic Review," is a systematic review of cognitive function in adults with AML. The aim of this review is to 1) describe cognitive function in adults with AML, 2) identify potential factors associated with poor cognitive impairment in adults with AML, and 3) explore how cognitive impairment impacts adults with AML.

Chapter 3 (Manuscript 2), titled "Cancer-Related Cognitive Impairment and Its Factors in Older Adults with Acute Myeloid Leukemia: A Prospective Longitudinal Study," describes the trend and development of CRCI from initiating chemotherapy (baseline) and up to 3 months post-enrollment. In addition, potential associated factors (demographic, physiologic/clinical, psychological, and environmental) of CRCI are examined.

Chapter 4 (Manuscript 3), titled "Experiences of Cancer-Related Cognitive Impairment in Older Adults with Acute Myeloid Leukemia and their Caregivers: A Qualitative Analysis," uses a qualitative descriptive approach to describe the experiences of older adults with AML and

the challenges posed by CRCI. The study also describes the experiences of these adults' caregivers.

Chapter 5 summarizes the main findings of Chapter 2, Chapter 3, and Chapter 4. The implications in research and clinical practice, strengths and limitation of this dissertation are also presented.

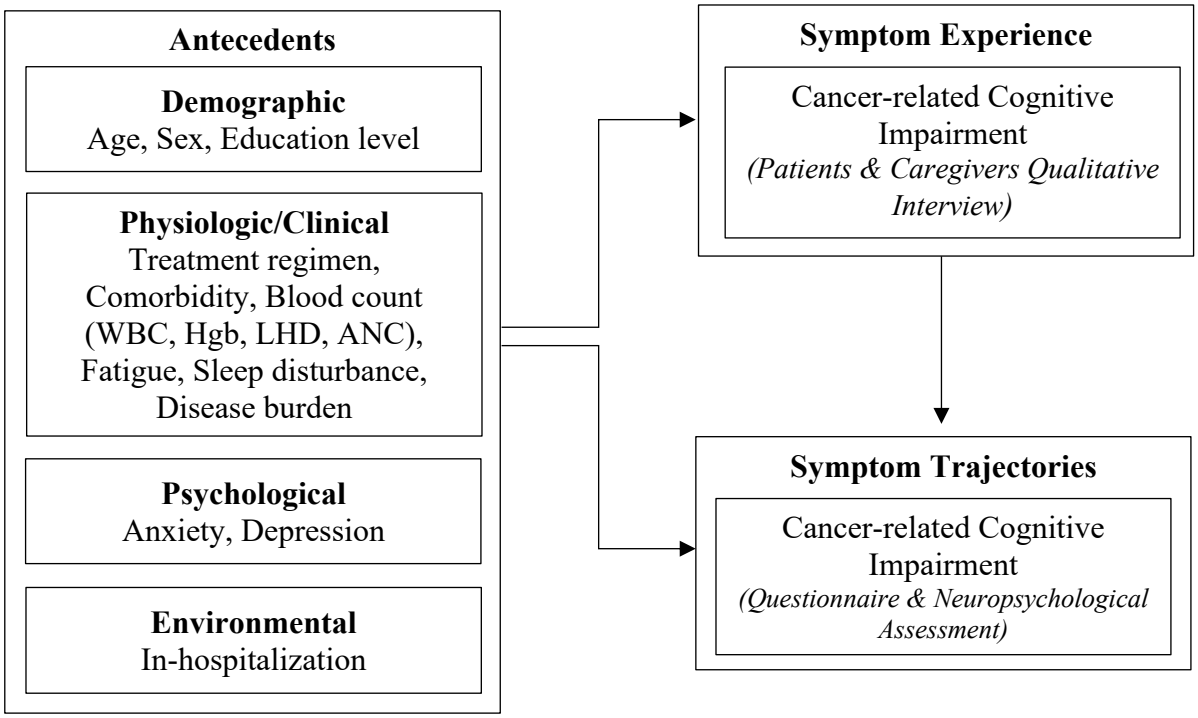

Figure 1.1. **Conceptual framework of CRCI among adults with AML who have received chemotherapy [adapted from Brant et al. (2016)]**

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CHAPTER 2: COGNITIVE FUNCTION IN ADULTS WITH ACUTE MYELOID LEUKEMIA TREATED WITH CHEMOTHERAPY: A SYSTEMATIC REVIEW

Introduction

Cognitive impairment has been reported in survivors of cancer and involves deficits in memory, attention, executive function, and processing speed (Deprez et al., 2018; Lange et al., 2019b). With these deficits, survivors of cancer may experience social isolation (Selamat et al., 2014), decreased working capacity (Selamat et al., 2014), lower quality of life (QOL) (Lycke et al., 2019), and increased mortality risk (Robb et al., 2010). According to Lange et al. (2019a), cognitive impairment may result from various factors, such as aging, cancer itself, genes and biomarkers, and toxicities of specific cancer treatments. Regardless of causality, cognitive function decline in survivors of cancer is known as cancer-related cognitive impairment (CRCI) (Lindner et al., 2014).

CRCI—which has been colloquially labeled as "chemobrain" or "chemo fog"—has been reported in survivors of cancer undergoing anticancer therapy, during or after treatment completion (Hess et al., 2015; Moore et al., 2019) and during long-term survivorship (Stouten-Kemperman et al., 2015). Existing research focuses primarily on survivors of cancer with a solid tumor diagnosis, such as breast cancer (Bray et al., 2018). Prior studies of hematological cancers focused on pediatric populations with acute lymphoblastic leukemia or primary central nervous system lymphoma (Williams et al., 2016).

For survivors with a diagnosis of acute myeloid leukemia (AML), chemotherapy is a standard treatment (National Comprehensive Cancer Network, 2018). In the United States, AML

is the most common acute leukemia, with over 20,050 new cases anticipated in 2022 (Siegel et al., 2022). AML is especially common in older adults as the median age at diagnosis of 68 years (National Cancer Institute, nd-b). Because a large percentage of adults with AML receive chemotherapy and are older, it is important to understand the CRCI in this population. Furthermore, because radiation and surgery are rarely employed in adults with AML, cognitive impairment in this population after therapy may be due either to chemotherapy, the existential trauma of the diagnosis, biologic consequences of the leukemia, and aging.

The aims of this systematic review were to 1) describe cognitive function pre-, during, or post-chemotherapy; 2) identify potential correlates of cognitive function; and 3) explore how cognitive function predicts other outcomes in adults with AML.

Methods

This review was guided by the Preferred Reporting Items for Systematic reviews and Meta-Analyses (Moher et al., 2009). The review protocol is registered in PROSPERO (protocol # CRD CRD42020170338).

Search Strategy

The PubMed, CINAHL Plus with Full Text (EBSCO*host*), APA PsycInfo (EBSCO*host*), and Embase databases were searched by a health science librarian (Ms. Jamie L. Conklin) on November 17, 2021. The search included a combination of key words and subject headings for AML, chemotherapy, and CRCI (Appendix 2.1). No date restrictions or limitations were set except for the Embase database. During the Embase database search, we limited the search by including only articles as the publication type. All articles were imported into EndNote; after removing duplicates, the articles were then imported into Covidence for screening.

Data Extraction and Synthesis

The authors (Ms. Ya-Ning Chan & Ms. Stephanie Betancur & Dr. Ashley Leak Bryant) independently screened the title/abstract and full-text articles to identify studies for inclusion. Discrepancies were resolved by the third author. The inclusion criteria were: 1) full-text articles published in English, 2) included participants' ≥18 years old, and 3) reported cognitive function in adults with AML or a mixed sample of adults with AML or myelodysplastic syndromes (MDS) who were treated with chemotherapy. We considered the studies eligible if they included participants with MDS because those with high-risk MDS have an increased risk of progressing to AML and may be considered for intensive chemotherapy or stem cell transplant (Bewersdorf et al., 2020). We excluded studies including survivors who received chemotherapy and those who did not receive chemotherapy but did not separately report cognitive function in participants who received chemotherapy.

Data were extracted using an Excel template created by the authors (Ms. Ya-Ning Chan & Ms. Stephanie Betancur) and included purpose, study design, sample size and characteristics, measure tool and time points, main findings, strengths and weaknesses, and implications. Findings were synthesized based on the aims of this review.

Quality Assessment

One author (Ms. Ya-Ning Chan) assessed the quality of the included articles using the Joanna Briggs Institute (JBI) Systematic Reviews Critical Appraisal Tools (Moola S, 2020). Specifically, for articles using longitudinal or cohort study design, we used the Checklist for Cohort Studies. For articles using cross-sectional design, we used the Checklist for Analytical Cross Sectional Studies. Each item was assessed using "Yes," "No," "Unclear," or "Not Applicable." We did not exclude any articles based on the quality assessment results.

Results

The initial search identified 1,114 articles. After excluding duplicates and screening title/abstract, 65 articles were identified. After full-text screening, 10 articles were retained in the final synthesis (Figure 2.1).

Study Characteristics and Study Quality

The 10 articles, from eight independent studies, were published between 2009 and 2021 across six countries (Table 2.1). Four were prospective longitudinal, four were prospective cohort, and two were cross-sectional. These studies used repeated assessments over time, and intervals ranged from a month to a couple cycles of chemotherapy, with total study duration over 12 months. In the five studies for which cognitive function was not the main outcome, cognitive function was measured exclusively at baseline. The majority of studies focused on geriatric assessment. Three studies had cognitive function as the main outcome.

All articles focused on recruiting a single group of participants with exposure of AML or MDS treatment (i.e. chemotherapy or supportive care). The majority of the articles (70%) pre-identified and managed confounding factors by using statistical methods or publishing normative data. The quality of the included articles, appraised using the JBI Systematic Reviews Critical Appraisal Tools, can be found in Table 2.2.

Sample Characteristics

Study sample sizes ranged between 20 and 397. Two studies included participants with a diagnosis of MDS; one recruited participants with other types of malignant hematological disease. Most studies included participants with intensive chemotherapy only. Two studies also included participants who were treated with supportive care or immunomodulatory agents (for MDS), which did not include chemotherapy. Across studies, similar numbers of men and women

were included; participant mean age ranged from 38–72 years, and median age ranged from 69–77 years. For studies reporting race, White was predominant (95.9%–96.3%). For studies reporting education level, college degree or above was predominant (51.4%–57.5%).

Main Findings

Change in cognitive function across chemotherapy continuum

Various approaches (patient-reported questionnaires, neuropsychological assessments, and neuroimaging) were used across studies to measure cognitive function. Two studies reported subjective or perceived cognitive function, eight studies reported neuropsychological assessment, and one study used additional neuroimaging to capture objective data. Of studies with subjective measures, all assessed cognitive function using the EORTC QLQ-C30 two-items cognitive function subscale with an aim to explore QOL among an AML population and reported mean or median cognitive function scores (Alibhai et al., 2009; Oliva et al., 2011). Specifically, one longitudinal study further examined the change of cognitive function over time and found a stable cognitive function across the treatment continuum up to 12 months (Alibhai et al., 2009) (Table 2.3).

Among the eight studies using objective assessment tools, two used the Mini-Mental State Exam (MMSE), three used the Modified Mini-Mental State Examination (3MS), one used the Montreal Cognitive Assessment (MOCA), and two used a battery of neuropsychological assessments. For the six studies using the MMSE, 3MS, and MOCA to assess overall cognitive function, two longitudinal studies assessed the change of cognitive function using the MMSE and 3MS, respectively, from diagnosis of AML up to the end of consolidation chemotherapy and found that cognitive function remained stable over time ($p=0.55$; $p=0.72$) (Jouzier et al., 2021; Klepin et al., 2016). In addition to reporting mean or median score, a specific cut-off score for

cognitive impairment was defined and the prevalence of cognitive impairment was further identified. Three articles from the same study included the 3MS as part of the geriatric assessment and found the prevalence of cognitive impairment ranged from above 20% to 31.5% prior to induction chemotherapy/within 5 days of initial hospitalization for AML (Klepin et al., 2011; Klepin et al., 2013; Klepin et al., 2016) and less than 20% after induction chemotherapy (Klepin et al., 2016). One study conducted the assessment using the MMSE at AML diagnosis and reported that 16% of participants had cognitive impairment (Jouzier et al., 2021). A cross-sectional study assessed cognitive function at six months to two years after chemotherapy using the MOCA and observed 62.2% prevalence of cognitive impairment (Kotb et al., 2019). These studies concluded that although cognitive function remained stable over time; the prevalence of cognitive impairment was 16%–31.5% at the initiation of chemotherapy and up to 62.2% after starting chemotherapy.

CRCI shows impairment in different cognitive domains; therefore, researchers in two studies used batteries of neuropsychological assessments to better understand how each domain is impacted (Meyers et al., 2005; Modzelewski et al., 2011). Specifically, in one study, mixed results were identified in severity of impairment related to hand dexterity, attention, working memory, verbal memory, and global efficiency between time points across the treatment continuum (Modzelewski et al., 2011). However, the other study identified a non-significant increase in prevalence of impairment related to attention, psychomotor speed, total recall, immediate recognition, delayed recall, verbal fluency, visual scanning, and executive function between pre- and post-induction chemotherapy (Meyers et al., 2005) and a significant increase in prevalence of impaired dexterity (Meyers et al., 2005). Unfortunately, with only two studies using batteries of neuropsychological assessment with a follow-up time frame between one and

six months, we had limited evidence for drawing a powerful conclusion on how chemotherapy impacts domains of cognitive function in the AML population. These findings highlight the necessity for using batteries of neuropsychological assessments in future CRCI research.

Neuroimaging is an evolving method to understand cognitive function. In addition to the neuropsychological assessments, one study further used single-photon emission computerized tomography (SPECT) to measure brain perfusion and indicated non-significant differences between pre-chemotherapy and post-chemotherapy (Modzelewski et al., 2011). However, with this single study, we are hesitant to draw conclusions.

Potential correlates of cognitive function

The following potential correlates were tested across studies:

Age. The relationship between age and cognitive function was tested in two studies; both reported non-significant findings (Jouzier et al., 2021; Meyers et al., 2005). Specifically, one study found that age did not correlate with the change of cognitive function over time (Jouzier et al., 2021). Another study found a non-significant relationship between age and cognitive function (Meyers et al., 2005).

Gender. One study observed no significant difference in the change of cognitive function over time between genders (Jouzier et al., 2021).

Education. One study found a significant positive association between years of education and cognitive function (Meyers et al., 2005).

Biomarkers. One study examined the relationship between biomarkers and cognitive function and reported mixed findings (Meyers et al., 2005). For inflammatory cytokine, the study found a significant negative association between IL-6 and executive function and a positive association between IL-8 and memory at pre-chemotherapy (Meyers et al., 2005). Yet, no significant

relationship was found between hemoglobin and cognitive function at pre-chemotherapy (Meyers et al., 2005).

Disease characteristics. Relationships between disease characteristics and cognitive function were assessed in two studies that included: cytogenetics (favorable to intermediate vs. unfavorable) (Klepin et al., 2011) and remission status at 6 months (p=0.88) (Alibhai et al., 2009); however, no significant relationships were identified.

Chemotherapy regimens. Comparisons in cognitive function across different AML chemotherapy regimens were made in two studies; both generated no significant findings (Jouzier et al., 2021; Oliva et al., 2011). One cross-sectional study reported no difference in cognitive function at AML diagnosis between patients receiving intensive and palliative treatment (p=0.524) (Oliva et al., 2011). Similarly, the other longitudinal study reported that receiving lomustine during induction and post-induction chemotherapy was not associated with a change in cognitive function over time (p=0.61) (Jouzier et al., 2021).

Time of induction. Jouzier et al. (2021) further tested the relationship with time of induction and discovered non-significant findings.

Fatigue. In one study, no significant relationship between fatigue and cognitive function was found prior to starting chemotherapy (Meyers et al., 2005).

Functional status. Jouzier et al. (2021) reported a 16% and 34% prevalence of cognitive impairment in participants with the Eastern Cooperative Oncology Group (ECOG) performance status 0–1 and those with the ECOG performance status 2, respectively (no p-value tested). This same study also found a non-significant relationship between the ECOG performance status and the change of cognitive function over time (Jouzier et al., 2021).

To summarize, only education and cytokines were identified to significantly correlate with cognitive function. However, these findings were only reported in one study. In contrast, age, gender, hemoglobin, cytogenetics, remission status, treatment regimens, hemoglobin, fatigue, and functional status were not significantly associated with cognitive function.

Prediction of cognitive function on other outcomes

Cohort studies with a focus on geriatric assessments examined the prediction of cognitive function on disease status, treatment plan, symptoms, and physical performance among adults with AML. One study found that cognitive function at initiation of chemotherapy had a non-significant effect on remission (3MS>77 vs. 3MS<77= 67% vs. 57%, p=0 .41) (Klepin et al., 2013). Another study reported that participants with cognitive impairment at pre-chemotherapy completed significantly fewer cycles of azacytidine chemotherapy than those without cognitive impairment at pre-chemotherapy (MMSE<24 vs. MMSE≥24: 3.5 ± 2.1 vs. 10.9 ± 7.9; p = 0.03) (Molga et al., 2020). Using six cycles of azacytidine chemotherapy as a cut-off point, this same study also found that a significantly higher percentage of participants with cognitive impairment at pre-chemotherapy were not able to complete the six cycles than those without cognitive impairment at pre-chemotherapy (MMSE<24 vs. MMSE≥24: 75% vs. 24%, p=0.05) (Molga et al., 2020).

In contrast, another cohort study identified that cognitive function at diagnosis did not predict the occurrence of grade 3–4 toxicities during induction chemotherapy (MMSE≥26 vs. MMSE<26: no toxicities number= 83.3% vs. 16.7% & toxicities number= 78.7% vs. 21.4%, p=0.31) (Jouzier et al., 2021). In terms of the prediction on physical performance, one longitudinal study identified a significant positive relationship between baseline cognitive function and the improvement of physical performance from pre- to post-induction

chemotherapy, after adjusting for cytogenetic risk, depression, balance, and performance status (p=0.05) (Klepin et al., 2016). Also, this same study reported that participants with cognitive impairment (3MS<77) at both pre- and post-induction chemotherapy had a significant decrease in physical performance (Short Physical Performance Battery: 8.0±1.7 vs. 3.6±1.7, p=0.07) compared to those without cognitive impairment (Short Physical Performance Battery: 8.4±0.7 vs. 6.9±0.7, p=1.12) (Klepin et al., 2016). However, all these findings were tested in only one study. We are therefore unable to surmise a definitive conclusion about the prediction of cognitive function on disease, treatment plan, symptoms, and physical performance.

Findings about the prediction of cognitive function on mortality were tested in one study (Klepin et al., 2013). Klepin et al. (2013) found a non-significant higher percentage of 30-day mortality (within 30 days of starting induction chemotherapy) in participants with cognitive impairment than those who did not have cognitive impairment (3MS<77: 23.8%, [95%CI=8.2–47.2] vs. 3MS≥77: 9.6%, [95%CI=3.0–21.0], p=0.14). However, this same study also discovered a significant positive relationship between cognitive impairment and risk of death after adjusting for covariates (HR 2.5, [95%CI=1.2-5.5]) (Klepin et al., 2013). The prediction of cognitive function on survival were mixed across three studies (Jouzier et al., 2021; Klepin et al., 2013; Molga et al., 2020). Klepin et al. (2013) discovered that participants with cognitive impairment within 5 days of initial hospitalization had a significantly lower median overall survival than those without cognitive impairment (3MS<77: 5.2 months vs. 3MS≥77: 15.6 months, p=0.002). However, Jouzier et al. (2021) found that there was non-significant prediction of cognitive function at diagnosis on both overall survival (MMSE≥26 vs. MMSE<26: median overall survival= 26 months [95%CI=22.4–31.2] vs. 21 months [95%CI=13.1–36.8], p=0.67) and event-free survival (MMSE≥26 vs. MMSE<26: median event-free survival=16 months [95%CI=12.5–

19] vs. 13 months [95%CI=9.7–22.5], p=0.81). Similarly, another study also identified that there was no significant difference in survival between participants who received azacytidine chemotherapy with and without cognitive impairment (12 months vs. 19 months, p=1) (Molga et al., 2020). Although these longitudinal or cohort studies with a focus on geriatric assessments emphasize the comprehensive domains of aging—such as functional status, mobility, nutrition, and cognition—these exploratory findings reinforce the importance of understanding cognition in this patient population because of its potential prediction on multiple aspects of adults with AML.

Discussion

In our systematic review of extant AML research, we found that cognitive function was studied as one of the components of QOL and as an important factor of geriatric assessment. Our review concluded that up to 62.2% of adults with AML experienced cognitive impairment; however, stable cognitive function after initiating chemotherapy was identified when measured either using patient-reported questionnaires or objective assessments.

Although chemotherapy is a standard treatment for adults with AML, we identified limited research focusing on the impact of AML chemotherapy on CRCI. Of the two studies including patient-reported questionnaire, both used the EORTC QLQ-C30 cognitive function subscale (Alibhai et al., 2009; Oliva et al., 2011). However, considering the EORTC QLQ-C30 is a QOL measure and the cognitive function subscale only measures two cognitive domains (European Organisation for Research and Treatment of Cancer, nd.), it might not be sensitive enough to capture changes in cognitive function following chemotherapy. Additionally, EORTC QLQ-C30 provides different information about cognitive function compared to neuropsychological assessments. Consequently, we identified a gap in researchers'

understanding of perceived cognitive function as reported via cognitive function-specific self-reported questionnaires. Perceived cognitive function is critically important (Savard & Ganz, 2016) to facilitate early recognition of declines in cognitive function (Lai et al., 2009) and increase clinicians' ability to detect CRCI (Isenberg-Grzeda et al., 2017). Hence, these findings highlight a necessity for researchers to understand CRCI in the AML population and use cognitive function-specific patient-reported measures.

Objective assessments were widely used in CRCI studies. The MMSE and 3MS (which was expanded from the MMSE) (Teng & Chui, 1987) were the most commonly used objective assessments in our review, specifically in studies focusing on geriatric assessment (Jouzier et al., 2021; Klepin et al., 2011; Klepin et al., 2013; Klepin et al., 2016; Molga et al., 2020). However, the MMSE may not be sensitive enough to detect cognitive changes in cancer populations (Isenberg-Grzeda et al., 2017) because it is a screening measure of cognitive function and thus provides limited information. Although batteries of neuropsychological assessments and neuroimaging are recommended by the International Cancer and Cognition Task Force (Deprez et al., 2018; Wefel et al., 2011), only two studies used them (Meyers et al., 2005; Modzelewski et al., 2011). With this small number of studies, we were unable to conclude how chemotherapy impacts cognition domains in adults with AML. To address this gap, we highlight a need for researchers to use batteries of neuropsychological assessment to understand CRCI in AML.

Understanding the correlates of cognitive function will enable early identification and intervention. Lower education correlated with worse cognitive function (Meyers et al., 2005), which was consistent with findings of a prior study of lymphoma survivors (Wouters et al., 2016). Although aging may contribute to a lower cognitive function in some domains, our review found no relationship between age and cognitive function (Jouzier et al., 2021; Meyers et al.,

2005). One study included in our review found no relationship between fatigue and cognitive function (Meyers et al., 2005), which was different from the results of a prior study reporting fatigue as a predictor of decreased cognitive function in survivors of cancer (Oh, 2017). This inconsistency might be due to the measures used: Meyers et al. (2005) used a battery of neuropsychological assessments, while Oh (2017) used the MMSE and a patient-reported questionnaire. The differences between patient-reported cognitive function and neuropsychological assessments have been identified in prior research. Specifically, O'Farrell et al. (2017) found that patient-reported cognitive function was negatively associated with anxiety and fatigue; while objective cognitive function measured by a battery of neuropsychological assessments was not. In addition, survivors of cancer with a low hemoglobin level may experience symptoms (i.e. fatigue, dizziness, headache) which might contribute to cognitive decline (Cunningham, 2003). However, no significant relationship was found between hemoglobin level and cognitive function in our review (Meyers et al., 2005). Researchers proposed that inflammation is a possible etiology of CRCI (Lange et al., 2019a). A prior study also identified a significant negative relationship between cytokines (IL-1β, TNF-α and IL-4) and cognitive function (Zhao et al., 2020). However, the identified cytokines were different from the ones identified in our review (Meyers et al., 2005). Finally, no psychological correlates were tested. A recent systematic review of 19 studies focusing on survivors of breast cancer concluded that survivors with higher levels of psychological distress indicated worse cognitive function (Yang & Hendrix, 2018). Therefore, the relationship between emotional distress and cognitive function should be further studied in AML survivors. To summarize, the small number of studies testing each correlate and their inconsistent use of cognitive function measures limits the power

of our findings. The lack of strong evidence reinforces the importance of using cognitive function-specific measures and further testing the correlates in future studies.

Limited studies included in our review found that worse cognitive function contributes to poorer outcomes in adults with AML. In our review, one study found worse cognitive function causes an early cessation of azacytidine therapy (Molga et al., 2020). Azacytidine, one of the hypomethylating agents, was prescribed in combination with Venetoclax to treat AML survivors who are precluded from intensive chemotherapy (Food and Drug Administration, 2018). This treatment plan includes daily oral medication, Venetoclax, which requires AML survivors to adhere to their treatment protocol. Unfortunately, prior research found that poor cognitive function may lead to a nonadherence to oral cancer treatment over time (Bender et al., 2014). Another study reported that adults with AML experiencing worse cognitive function have poorer chances of survival (Klepin et al., 2013). This finding aligned with prior studies, which indicated a significant positive relationship between decreased cognitive function and mortality in community-dwelling older adults (Lv et al., 2019). Studies focusing on other cancer diagnoses found that survivors of cancer with CRCI may experience social isolation (Selamat et al., 2014), poor working capacity (Selamat et al., 2014), and decreased QOL (Lycke et al., 2019). Considering differences in patients' characteristics, how CRCI impacts survivors of cancer may vary. For example, Boykoff et al. (2009) found that the symptoms of CRCI made survivors of breast cancer easily distractible and decreased work efficiency, forcing them to switch to jobs with lighter workloads. However, survivors of breast cancer have a median age of diagnosis of 62 years (National Cancer Institute, nd-a), while AML is 68 years, which is over standard retirement age (National Cancer Institute, nd-b). Hence, work capacity might not be the focus in the AML population. Instead, AML survivors may be more focused on other tasks, so

researchers cannot assume that CRCI has the same impact in AML survivors as it does in different cancer populations. A research gap exists and qualitative studies are needed to understand the experiences of older adults with AML with CRCI.

Our review included ten articles reporting cognitive function; because we did not restrict to CRCI studies, we obtained a broader understanding of current cognitive function study in AML population. However, the sample sizes were varied across studies and some major findings were only tested in a single study, which made it hard to draw conclusions on the cognitive function in this population. In addition, the three studies on CRCI were not representative of the general AML population because the age of their samples (mean age: 38–60 years) were younger than the median age of diagnosis (68 years) (Meyers et al., 2005; Modzelewski et al., 2011) and did not focus exclusively on AML survivors (Kotb et al., 2019; Meyers et al., 2005). Due to these weaknesses in the sample ages and diagnosis, we know little about CRCI in older adults with AML. Thus, older adults should be recruited in future CRCI research in the AML population.

This review is not without limitation. First, no gray literature was searched. Therefore, unpublished reports and conference proceedings related to CRCI in AML survivors were missed during the searching process. Second, due to the limited research about CRCI in hematological malignancies, studies that recruited samples with an MDS or AML diagnosis were included in the review. Consequently, the results we captured might not be solely representative of the experiences of AML survivors.

Conclusion

Our review provided a thorough understanding of current research on cognitive function in adults with AML who were treated with chemotherapy. Cognitive function may impact

survivors in different aspects. However, stable cognitive function was identified after initiating chemotherapy. Furthermore, some potential correlates of cognitive function—education and cytokines—were identified.

Our review identified several CRCI research gaps in the AML population. First, a lack of using cognitive function-specific measures limited the power of findings related to understanding experiences and correlates of CRCI. Second, there is no research exploring how CRCI impacts adults with AML. Lastly, CRCI studies included a variety of diagnoses and relatively younger samples. Therefore, future researchers should use patient-reported questionnaires and objective assessments (such as a battery of neuropsychological assessments) to explore CRCI and correlates in adults with AML—in particular, older adults. Furthermore, given the emergence of newer treatments for AML in older adults, there will be more choices in therapies, and the risks of CRCI with such therapies (both new and old treatments) need to be consistently defined in order to empower patients to choose according to their goals. Finally, considering differences in patients' characteristics (i.e., age), how CRCI impacts survivors of cancer may vary. It is also crucial to use a qualitative approach to explore how CRCI impacts this patient population. Once a preliminary understanding is obtained, quantitative studies with fully powered sample sizes and intervention development can be further conducted. By doing so, we will have an in-depth and comprehensive understanding of CRCI in adults with AML.

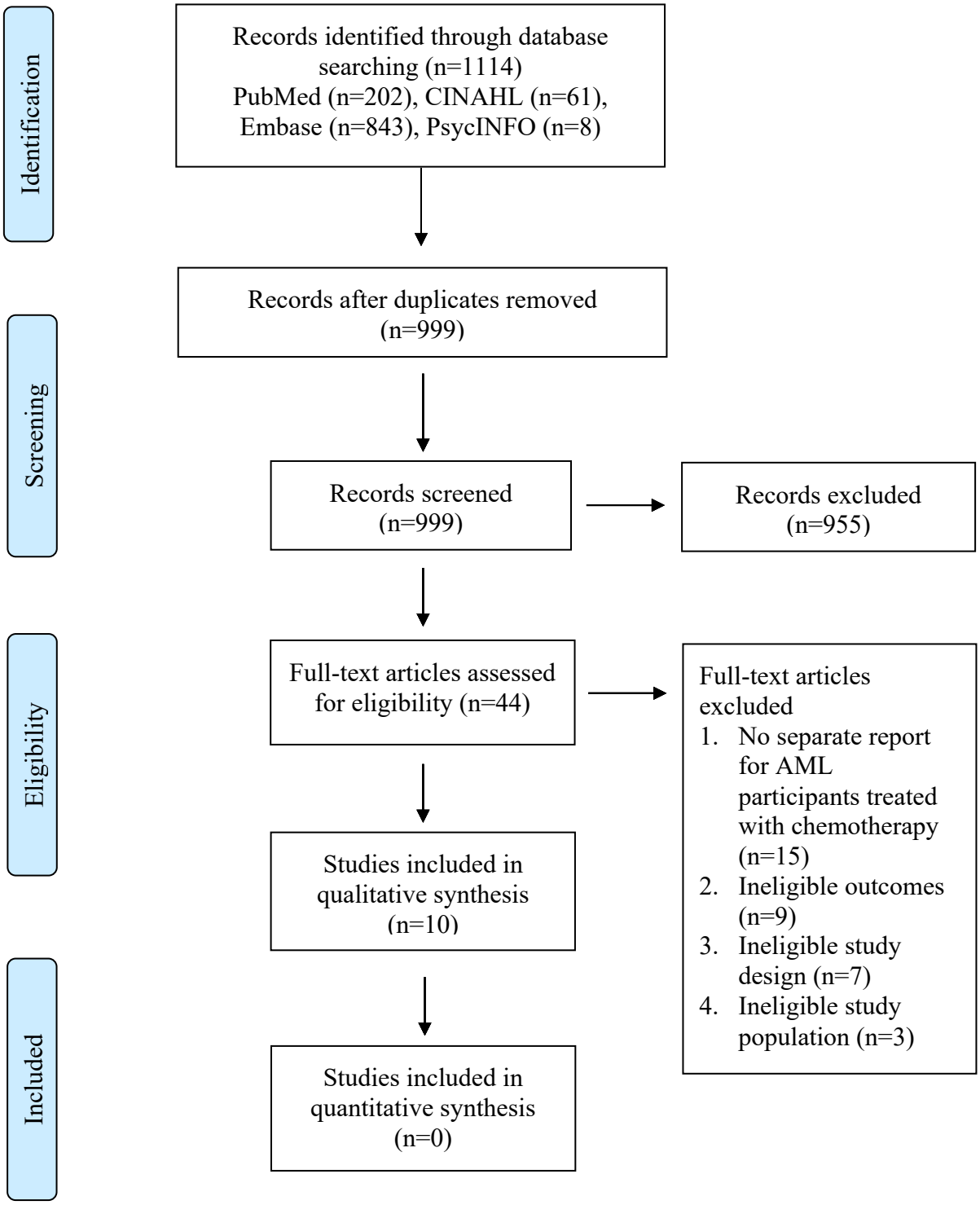

Figure 2.1. **PRISMA flowchart of study selection process**

Table 2.1. **Characteristics of the included studies (n=10)**

Authors (Year)	Design	n	Treatment	Male (%)	Age in Years, Mean(SD)/Median	Length of Study
Alibhai et al. (2009)	L	20	CT	55	70 (NS)	12m
Jouzier et al. (2021)	C	397	Intensive CT	57	69 (NS)	>12m
Klepin et al. (2011)[a]	CS	54	Intensive CT	59	71 (6)	N/A
Klepin et al. (2013)[a]	C	74	Intensive CT	54	70 (6) or 69	?
Klepin et al. (2016)[a]	L	49	Intensive CT	57	69	≈3–4m
Kotb et al. (2019)	CS	45[b]	CT	NS	NS	N/A
Meyers et al. (2005)	L	54[c]	CT	56	60 (NS)	1m
Modzelewski et al. (2011)	L	20	Intensive CT	45	38 (12)	6m
Molga et al. (2020)	C	98[c]	CT & non-CT	63	77	?
Oliva et al. (2011)	C	113	CT & non-CT	51	72 (6)	12m

Note:

[a] The articles were from the same study.

[b] The sample included other malignant hematological disease and only presented the number of adults with AML.

[c] The sample included adults with myelodysplastic syndromes.

≈ means approximately

? means not able to determine.

Abbreviation: L, longitudinal; CS, cross-sectional; C, cohort; CT, chemotherapy; non-CT, non-chemotherapy; NS, non-specified; SD, standard deviation; m, months; N/A, not applicable.

Table 2.2. **Quality assessment of the included studies using the JBI (n=10)**

Authors (Year)	Were the two groups similar and recruited from the same population?	Were the exposures measured similarly to assign people to both exposed and unexposed groups?	Was the exposure measured in a valid and reliable way?	Were confounding factors identified?	Were strategies to deal with confounding factors stated?	Were the groups/ participants free of the outcome at the start of the study (or at the moment of exposure)?	Were the outcomes measured in a valid and reliable way?	Was the follow up time reported and sufficient to be long enough for outcomes to occur?	Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	Were strategies to address incomplete follow up utilized?	Was appropriate statistical analysis used?	Were the criteria for inclusion in the sample clearly defined?	Were the study subjects and the setting described in detail?	Were objective, standard criteria used for measurement of the condition?
Alibhai et al. (2009)	Yes	NA	NA	No	No	NA	Yes	Yes	Yes	No	Yes	-	-	-
Jouzier et al. (2021)	Yes	NA	NA	Yes	Yes	NA	Yes	Yes	Yes	Yes	Yes	-	-	-

Klepin et al. (2011)	-	-	NA	Yes	Yes	-	Yes	-	-	-	Yes	Yes	Yes	Yes
Klepin et al. (2013)	Yes	NA	NA	Yes	Yes	NA	Yes	Unclear	Yes	Yes	Yes	-	-	-
Klepin et al. (2016)	Yes	NA	NA	Yes	Yes	NA	Yes	Yes	Yes	No	Yes	-	-	-
Kotb et al. (2019)	-	-	NA	No	No	-	Yes	-	-	-	Yes	Yes	Yes	Yes
Meyers et al. (2005)	Yes	NA	NA	Yes	Yes	NA	Yes	Yes	Yes	No	Yes	-	-	-
Modzelewski et al. (2011)	Yes	NA	NA	Yes	Yes	NA	Yes	Yes	Yes	No	Yes	-	-	-
Molga et al. (2020)	Yes	NA	NA	No	No	NA	Yes	Unclear	Yes	Yes	Yes	-	-	-
Oliva et al. (2011)	Yes	NA	NA	Yes	Yes	NA	Yes	Yes	Yes	Yes	Yes	-	-	-

Abbreviation: NA,not applicable.

Table 2.3. **Main cognition outcome of the included studies (n=10)**

Authors (Year)	Measures	Assessment Time Points	Reported Format / Time Point	Change Overtime	Correlates Tested
Cognition assessed more than once					
Alibhai et al. (2009)	2 items	pre-CT, 1m, 4m, 6m, 9m, 12m	mean score / all time points	Stable (no p-value)	remission status at 6m
Jouzier et al. (2021)	MMSE (<26 CI)	at dx, 3rd cycle re-ICT, 6th cycle re-ICT, end-CCT	mean score / at dx P of CI at dx: 16%	NS	gender, performance status, age, grade 3-4 toxicity during induction, time of induction, lomustine during induction and postinduction therapy
Klepin et al. (2016)	3MS (<77 CI)	pre-ICT, post-ICT	mean score / all time points P of CI: ≈> 20%→≈< 20%	NS	-
Meyers et al. (2005)	Digit Span, Digit Symbol, HVLT, COWA-verbal fluency, TMT, GPT	pre-CT, 1m	mean score / pre-CT P of impaired domains- attention: 7%→8% psychomotor speed: 8%→13% total recall: 44%→58% immediate recognition: 7%→25% delayed recall: 41%→58% verbal fluency: 17%→25% visual scanning: 28%→38%	P of impaired dexterity: S↑ P of other impaired domains: NS	age, education, hemoglobin, fatigue, cytokines

Authors (Year)	Measures	Assessment Time Points	Reported Format / Time Point	Change Overtime	Correlates Tested
			executive function: 29%→46% dexterity: 37%→54%		
Modzelewski et al. (2011)	SPECT, ICARS, BI, TMT, 9HPT, DRS, Digit Span, GBVLT	at dx, pre-CCT, 2nd cycle CCT, during CCT, post-CCT, 6m	mean score / all time points P of normal test score: 100%	SPECT at dx vs. pre-CCT vs. 2nd cycle CCT: NS R't hand dexterity: S↑ during CCT–post-CCT L't hand dexterity: S↓ 2nd cycle CCT–during CCT & S↑ post-CCT–6m attention: S↑ post-CCT–6m working memory: S↑ post-CCT–6m & S↑ at dx–pre-CCT verbal memory: S↑ at dx–6m global efficiency: S↑ at dx–6m	-
Cognition assessed once					
Klepin et al. (2011)	3MS (<80 CI)	within 5d of initial hospitalization	mean score P of CI: 31.5%	N/A	cytogenetics

Authors (Year)	Measures	Assessment Time Points	Reported Format / Time Point	Change Overtime	Correlates Tested
Klepin et al. (2013)	3MS (<77 CI)	within 5d of initial hospitalization	median score P of CI: 28.8%	N/A	-
Kotb et al. (2019)	MOCA (<26 CI)	6m–2y post-CT	mean score of each domain P of CI: 62.2%	N/A	-
Molga et al. (2020)	MMSE (<24 CI)	pre-treatment	N/A	N/A	-
Oliva et al. (2011)	2 items	at dx	**IC group** median score	N/A	treatment

Note: 2 items= cognitive function domain from the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), ≈ approximately, ↑ increased, ↓ decreased, S significant, S- significant negative relationship

Abbreviation: 3MS, Modified Mini-Mental State Examination; HVLT, Hopkins Verbal Learning Test; COWA, Controlled Oral Word Association; TMT, Trail Making Test; GPT, Grooved Pegboard Test; SPECT, single-photon emission computerized tomography; ICARS, International Cooperative Ataxia Rating Scale; BI, Barthel Index; 9HPT, Nine Hole Peg Test; DRS, Mattis Dementia Rating Scale; GBVLT, Grober and Buschke Verbal Learning test; MMSE, Mini-Mental State Exam; MOCA, Montreal Cognitive Assessment; CT, chemotherapy; ICT, induction chemotherapy; CCT, consolidation chemotherapy; IC, intensive chemotherapy; dx, diagnosis; m, months; d, days; y, years; N/A, not applicable; p, prevalence; CI, cognitive impairment; CF, cognitive function; NS, non-specified.

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CHAPTER 3: CANCER-RELATED COGNITIVE IMPAIRMENT AND ITS FACTORS IN OLDER ADULTS WITH ACUTE MYELOID LEUKEMIA: A PROSPECTIVE LONGITUDINAL STUDY

Introduction

Acute myeloid leukemia (AML) is most commonly diagnosed in older adults, with around 60% of newly diagnosed cases in adults aged 65 years or older (National Cancer Institute, nd). In 2022, there will be approximately 20,050 new cases diagnosed with AML, accounting for one-third of the total leukemia population (Siegel et al., 2022). Chemotherapy which includes induction, reinduction, and consolidation chemotherapy, is the standard treatment for adults with AML (National Comprehensive Cancer Network, 2018). However, not every adult with AML is able to tolerate this intensive treatment. Studies show that adults with an older age, poor functional performance, comorbidities, or unfavorable cytogenetics may experience poorer treatment outcomes (Forsythe et al., 2019). Therefore, as an alternative treatment option, Venetoclax (VEN), in combination with hypomethylating agents (HMA) or low-dose cytarabine chemotherapy [VEN+HMA/low-dose ara-c], has been used in adults with AML who are precluded from intensive treatment (Mukherjee & Sekeres, 2019).

Unfortunately, people who have received chemotherapy treatment have been found to report an impaired cognitive function, which is also known as cancer-related cognitive impairment (CRCI), “chemo brain,” or “chemo fog.” Cancer survivors with CRCI may show deficits in executive function, memory, verbal function/language skills, construction, concept formation and reasoning, perception, and orientation/ attention (Hodgson et al., 2013).

Furthermore, the deficits were found in survivors both during and after completing chemotherapy in survivors with breast cancer, testicular cancer, and lymphoma (Janelsins et al., 2017; Moore et al., 2019; Stouten-Kemperman et al., 2015; Zimmer et al., 2015). Survivors with CRCI had a hard time maintaining social connection, conducting daily activities (Selamat et al., 2014), and retaining work capacity (Von Ah et al., 2018). All these problems may further lead survivors to a lower quality of life (Klemp et al., 2018). Therefore, it is essential to understand the extent of CRCI problem in the AML population since chemotherapy is the standard treatment.

There is a lack of research on CRCI in adults with AML—in particular, older adults. In our systematic review in Chapter 2, a limited amount of CRCI research on adults with AML was identified. The CRCI studies on adults with AML included samples with relative younger mean ages (38-60 years) (Meyers et al., 2005; Modzelewski et al., 2011). Furthermore, in addition to AML, several studies also included participants with other types of hematological malignancies (Kotb et al., 2019; Meyers et al., 2005), such as myelodysplastic syndromes (MDS), chronic lymphoid leukemia, or lymphoma. Therefore, a research gap is identified in understanding CRCI exclusively in older adults with AML.

Current research assessed CRCI using varied measures and time intervals. The International Cognition and Cancer Task Force (ICCTF) suggests using batteries of neuropsychological assessments to measure domains of cognitive function (Wefel et al., 2011). However, only two studies evaluated CRCI using batteries of neuropsychological assessments in adults with AML (Meyers et al., 2005; Modzelewski et al., 2011). One study reported a significant increase in the prevalence of impaired dexterity and no significant changes in the prevalence of impaired attention, psychomotor speed, memory, verbal fluency, visual scanning,

and executive function after induction chemotherapy (Meyers et al., 2005). Another study assessed multiple time points across the treatment continuum up to six months and found mixed results in the change of dexterity, attention, memory between time points (Modzelewski et al., 2011). Because of the difference in results reporting formats (prevalence vs. severity) and AML treatment regimens (high-dose cytarabine vs. induction chemotherapy), we were unable to synthesize the results and draw conclusion about the CRCI problem in adults with AML.

In addition to objective assessment, researchers recommended incorporating patient-reported questionnaires, such as the Functional Assessment of Cancer Therapy-Cognitive Function (FACT-Cog) (Wagner, 2008), when assessing cognitive function in cancer populations (Isenberg-Grzeda et al., 2017). By doing so, an early recognition of declines in cognitive function can be facilitated (Lai et al., 2009). However, to the best of our knowledge, no studies have used cognitive function-specific measures in adults with AML. Therefore, a gap is identified in understanding CRCI using a battery of neuropsychological assessments and cognitive function-specific patient-reported questionnaires in the AML population.

Understanding factors associated with CRCI enables us to identify high risk patients earlier. Prior reviews identified that lower education (Li et al., 2015), higher fatigue (Ehlers et al., 2017), poor sleep quality, higher emotional distress, lower exercise level (Henneghan, 2016), lower hemoglobin, and genes (such as APOE-4, COMT-Val) (Castel et al., 2017) are associated with worse cognitive function in cancer survivors, such as breast cancer. Although several correlates of cognitive function were identified in our systematic review in Chapter 2, the limited research is not established enough to guide identification of high-risk patients.

To summarize, there are gaps in CRCI research in older adults with AML: using a battery of neuropsychological assessments and patient-reported questionnaires and identifying

associated factors. Hence, the current study explores CRCI at pre-chemotherapy and over the AML treatment continuum in older adults with AML. Specifically, this study aims to: 1) examine the development and trajectory of CRCI severity from prior to initiating chemotherapy to 3 months follow-up using both patient-reported questionnaires and a battery of neuropsychological assessments; and 2) identify factors (demographic, physiological/clinical, and psychological, environmental factors) associated with CRCI.

Methods

Study Design and Sample

This study was a prospective, longitudinal study conducted in the North Carolina Cancer Hospital (NCCH). A purposive sampling strategy was applied. The inclusion criteria of the participants were: 1) aged over 60 years and older, 2) diagnosed with AML and planning to get VEN+HMA/low-dose ara-c chemotherapy, 3) able to read and speak English, and 4) able to provide their consent to participate in the study. Older adults with AML who were 1) unable to participate per their oncology provider or 2) referred to hospice care were excluded.

Study Recruitment and Study Procedure

The study, an ancillary study of a larger clinical trial (#NCT04570709), was approved by the Institutional Review Board of the University of North Carolina at Chapel Hill (#20-2614) and registered on clinicaltrial.gov (#NCT04644419). Recruitment took place between November 2020 to September 2021. Potentially eligible patients were referred by a clinical pharmacist and nurse navigators. After confirming eligibility of older adults by reviewing the electronic medical record, older adults with AML were approached by introducing both a clinical trial about developing a nurse-led RN-Led Palliative and Supportive Care Intervention for older adults with AML (#NCT04570709) and the current study. Eligible older adults with AML were provided

with time to ask clarifying questions and consider if they would like to participate; the decision had to be made before or within two days of initiating VEN+HMA/low-dose ara-c chemotherapy. After obtaining written informed consent from patients, demographic characteristics were collected.

Prior studies suggested that it is important to have a baseline assessment prior to the initiation of chemotherapy because cognitive impairment has been observed at cancer diagnosis (Vega et al., 2017). In addition, VEN+HMA/low-dose ara-c chemotherapy were administered according to DiNardo et al. (2020) and Wei et al. (2020). Considering there is limited symptom research in older adults with AML receiving VEN+HMA/low-dose ara-c chemotherapy, data were collected at the following three time points: seven days before or within three days of initiation of the 1st cycle of chemotherapy (T1); before the 2nd cycle of chemotherapy (approximately 30 days) (T2); before the 4th cycle of chemotherapy (approximately 90 days) (T3). The actual start date of each cycle is based on the blood results of each individual participant. At each data collection encounter, older adults with AML were asked to complete a packet of questionnaires and a battery of neuropsychological assessments (described below). Clinical characteristics and lab data were collected through electronic medical record review.

In order to decrease attrition and participants' burden, all data collection was performed during hospitalization, at outpatient visits, or through phone call. These follow-up appointments were scheduled by phone call or text prior to their outpatient visit. The entire data collection procedure was conducted in a quiet and separate room in the clinic, infusion unit, or inpatient unit to protect participants' privacy and avoid external disturbances. Because VEN+HMA/low-dose ara-c has been primarily scheduled as an outpatient treatment, older adults with AML need to travel daily to the clinic for infusion. There were scenarios which older adults with AML

received their 1st cycle of chemotherapy at the NCCH and then transferred to other local private practice or community hospital for future chemotherapy infusion for transportation convenience. Therefore, if the older adults with AML changed their treatment location, we scheduled a phone call to finish the electronic questionnaire only.

Measures

Electronic medical record review

Clinical characteristics and biomarkers were collected by reviewing the electronic medical record; we collected leukemia type, cancer treatment, comorbidity, remission status, hemoglobin (Hgb), white blood cell count (WBC), neutrophil count (ANC) and lactate dehydrogenase (LDH).

Patient-reported questionnaire

The FACT-Cog version 3 was used to assess patient-reported cognitive function. The FACT-Cog is a 37-item tool, which has been widely used for assessing self-reported cognitive function in cancer populations. It consists of 4 subscales, including perceived cognitive impairments (CogPCI) (score 0–72), comments from others (CogOth) (score 0–16), perceived cognitive abilities (CogPCA) (score 0–28), and impact of quality of life (CogQOL) (score 0–16) (Wagner, 2008). The higher the score, the better the cognitive function. The FACT-Cog has indicated a good test-retest reliability (intra-class coefficient=0.79-0.86), convergent validity, and discriminant validity (Wagner, 2008).

The Patient Reported Outcomes-Common Terminology Criteria for Adverse Events (PRO-CTCAE) was used to assess symptom burden. Developed by the National Cancer Institute, the PRO-CTCAE is a tool that focuses on assessing toxicity among cancer population. Participants responded whether they experienced the symptom, the symptom's frequency, the

symptom's severity, and how much the symptom interferes with usual or daily activities. The seventeen symptoms include: diarrhea, chills, heartburn, nausea, appetite, mouth sores, vomiting, constipation, cough, rash, shortness of breath, fatigue, anxiety, sad feeling, nothing can cheer me up, pain, and insomnia. Each item is assessed using a 5-point Likert scale, and higher scores indicate more severe symptoms. A total score was calculated. Moreover, fatigue severity, insomnia severity, anxiety frequency, sad feeling frequency, and nothing can cheer me up frequency were calculated to generate an individual score. The PRO-CTCAE has shown its content validity (Hay et al., 2014), construct validity, and test-retest reliability (intra-class coefficient=0.53–0.96) in cancer survivors (Dueck et al., 2015).

The Leukemia subscale (LEUS) from the Functional Assessment of Cancer Therapy-Leukemia (FACT-Leu) was used to assess disease burden. The LEUS is a 17-item tool that asks individuals with leukemia their leukemia-specific concerns and symptoms during the past seven days (Functional Assessment of Chronic Illness Therapy group, nd). Each item was scored using a five-point Likert scale with total score ranges from 0 to 68. The higher the score, the lower the disease burden. The LEUS has indicated a good test-retest reliability (intra-class coefficient=0.89), convergent validity, and divergent validity in individuals with leukemia (Cella et al., 2012).

Neuropsychological Assessments

A battery of neuropsychological assessments was used to measure objective cognitive function. The included assessments (Table 3.1) have been widely used in studies measuring cognitive function in cancer survivors (Olson et al., 2016). The Hopkins Verbal Learning Test-Revised (HVLT-R), which can be used for individuals aged 16 years and older, includes three components: total recall (trial 1, trial 2, trial 3), delayed recall (trial 4), and delayed recognition

(Brandt & Benedict, 2001). Due to time constraints in the clinic, we only performed total recall and delayed recall components to assess memory and verbal learning ability. The higher the total recall and delayed recall score, the better the memory and verbal learning ability. The HVLT-R has demonstrated good test-retest reliability (Benedict et al., 1998), construct and concurrent validity (Shapiro et al., 1999). The alternative forms were used at each time point (T1: Form1, T2: Form2, T3 or early end-of-study: Form 3).

The Wechsler Adult Intelligence scale (WAIS)-IV can be used to assess cognitive function for individuals aged between 16 and 90 years (Wechsler, 2008a). The digit span (DS) includes forward, backward, and sequencing subtest. We used the DS forward and backward to assess working memory. Score of DS forward and backward, longest DS forward (LDSF) and longest DS backward (LDSB) were documented. The higher the score, the better the working memory. The DS forward and backward assessments have excellent reliability and test-retest stability (Wechsler, 2008b). The WAIS-IV has also been tested for convergent validity and discriminant validity (Wechsler, 2008b).

The Delis–Kaplan Executive Function System (D-KEFS), which is appropriate to use for assessing individuals aged between 8 and 89 years, verbal fluency test consists of letter fluency, category fluency, and category switching (Delis et al., 2001). Only the letter fluency component was used in the current study for speeded lexical fluency. The total correct raw score was recorded. The higher the score, the better the speeded lexical fluency. An alternative form was used to reduce practice effect (T1: FAS, T2: BHR, T3 or early end-of-study: FAS). The D-KEFS has demonstrated good test-retest reliability, internal consistency, and validity (Delis et al., 2001).

The Trail Making Test (TMT)-A and B were used to assess processing speed and executive function. TMT-A sample and TMT-B sample were also used as practice for participants at each time points. The seconds of completing TMT-A sample, TMT-B sample, TMT-A, and TMT-B were documented. The longer the completion time, the lower the processing speed and executive function. The assessment has been tested for test-retest reliability (Levine et al., 2004).

Lastly, the Borg Category Ratio Scale (CR-10) was used to assess cognitive workload after each assessment by asking "how much effort did you need to complete this assessment?" The participants could choose their perceived cognitive workload using the Borg CR10 ranging from 0 to 10, and maximum (Borg, 1982). The tool has been used to assess subjective workload assessment (DiDomenico & Nussbaum, 2008).

The data collector was trained by a researcher with experiences using this battery of neuropsychological assessments. Standardized assessment procedures (Appendix 3.1) and instruction scripts were used when conducting each data collection. The battery of neuropsychological assessments took a total of around 25-45 minutes to complete.

Data Analysis

All the collected data were included for data analysis. We used the SAS 9.4 software to analyze data and Microsoft Excel to create figures. We conducted descriptive analysis to explore the distribution of sample characteristics, symptom, disease burden, remission status, setting, and cognitive function at each time point. Then, we used the Wilcoxon signed rank test to examine the change of trajectory of subjective and objective cognitive function across different measurement time points.

To characterize the individual changes over time, we defined the individual change in cognitive function as "improved," "stable," and "declined." We used minimal clinically important differences (MCID) of the FACT-Cog and the CogPCI tested by Bell et al. (2018) using anchor method. Specifically, Bell et al. (2018) identified a clinically meaningful change with a change of 10.0 points for the FACT-Cog (7.6% of the FACT-Cog score) and a change of 5.9 points for the CogPCI (8.4% of the CogPCI score). For neuropsychological assessments, we used reliable change index (RCI) (Jacobson & Truax, 1992) to define clinically significant change recommended by the ICCTF (Wefel et al., 2011). RCI can be applied to research with a small sample size and a focus on individual changes (Zahra & Hedge, 2010). Moreover, because of the short assessment interval (as short as 21 days for T1-T2) and recommendations from previous CRCI research in breast cancer population (Cerulla et al., 2019), we used the RCI with 90% confidence interval and adjusted for practice effect (Chelune et al., 1993). The formula of practice effects adjusted RCI for calculating clinically significant change has been used in CRCI research in cancer populations (Cerulla et al., 2019; Jenkins et al., 2006; Jones et al., 2013; Wefel et al., 2010).

$$SE_m = SD_1 \left(\sqrt{1 - r_{xx}}\right)$$

$$SE_{diff} = \sqrt{2(SE_m)^2}$$

$$\text{Practice Effects adjusted RCI} = (SE_{diff}) \times (\pm 1.64) + (M_2 - M_1)$$

Note: SE_m = standard error of measurement, SD_1 = standard deviation of the baseline score, r_{xx} = test-retest reliability of the measure, SE_{diff} = standard error of the difference between scores, M_2 = mean follow-up score, M_1 = mean baseline score.

However, there is a lack of control group for the current study and literature in older AML populations. Therefore, based on previous CRCI studies in adults with breast cancer

(Wefel et al., 2010), glioblastoma (Armstrong et al., 2013), and multiple myeloma (Jones et al., 2013), we used the published normative data (Benedict et al., 1998; Delis et al., 2001; Levine et al., 2004; Wechsler, 2008a) as a control group to calculate the RCI.

Using the published normative standard score (t-score, percentile, scaled score) adjusted for age and education as applicable (Brandt & Benedict, 2001; Delis et al., 2001; Tombaugh, 2004; Wechsler, 2008a), we transformed the raw score of each neuropsychological assessment into z-scores (Strauss et al., 2006). Specifically, we applied the criteria of cognitive impairment defined by the ICCTF: 1) two or more assessments show a z-score ≤ -1.5 or 2) one single assessment shows a z-score ≤ -2.0 (Wefel et al., 2011). In terms of the FACT-Cog, we used the cut-off point of 54 for the 18-item CogPCI to define cognitive impairment (Dyk et al., 2020).

To test the potential correlation of cognitive function, we used the Fisher-Freeman-Halton Exact Test to examine the correlation between sample characteristics (i.e., age, sex, educational level, comorbidity, cytogenetic, and treatment regimen) and change of cognitive function (improved, stable, or declined). Finally, we used Spearman's Rank Correlation Coefficient to examine the relationship of biomarkers, remission status, setting and cognitive function at each time point.

Results

Sample Characteristics and Study Follow-ups

Among the 22 older adults with AML referred by a clinical pharmacist and nurse navigators, two had schedule conflicts and were not approached. Six older adults with AML declined due to feeling overwhelmed, fatigue, and not interested in spending time for research activities. A total of 14 provided their consented and finished T1 assessment. During the study follow-up, one withdrew consent because of unwillingness to spend extra time participating, four

died, four had changes in their treatment plan, and one was excluded from the analysis due to prolonged postponement of treatment, which resulted in four participants who finished all T1, T2, and T3 assessments. Specifically, for those who changed their treatment plans (three proceeded to stem cell transplant and one changed chemotherapy regimen), we did an early end-of-study assessment.

An average follow-up was 92.09 days (standard deviation=34.92, range 37–127 days). The mean follow-up from T1 to T2 was 38.27 days (standard deviation=10.32, range 28–65 days); T2 to T3 was 87.0 days (standard deviation=9.20, range 78–98 days); T2 to early end-of-study was 61 days (standard deviation=27.77, range 21–84 days). The retention rate was 79% and 57.14% at T2 and T3/early end-of-study, respectively (Figure 3.1).

The mean age of the study sample was 73.57 years (standard deviation=8.03; median=72 years), with age ranging between 64 and 89 years. The majority of the sample were male (78.57%), non-Hispanic White (92.86%), high school graduates (64.29%), married/partnered (64.29%), living with others (64.29%), and receiving a VEN+Azacitidine regimen (85.71%). All of them had insurance coverage (Table 3.2).

Changes in Subjective and Objective Cognitive Function Over Time

Level of cognitive function

For subjective cognitive function measured by the FACT-Cog (Figure 3.2 & Table 3.3), the mean score of the FACT-Cog total score, CogQOL, and CogPCA gradually improved over time. On the other hand, the mean score of the CogPCI decreased from T1 to T2; then increased from T2 to T3. The CogOth remained stable over time. Non-statistically significant change was identified in the FACT-Cog total score and the four subscales between time points.

For objective cognitive function measured by a battery of neuropsychological assessments, the HVLT-R total recall and delayed recall, the D-KEFS letter fluency test, and the TMT-A&B increased from T1 to T2; but decreased from T2 to T3. In contrast, both the DS forward and the DS backward increased gradually over time. In terms of the Berg CR-10, other than the Berg CR-10 for the TMT-B, all other Berg CR-10 (for the HVLT-R total recall and delayed recall, the DS forward and backward, the TMT-A&B) increased gradually over time. Still, no significant difference was found in the mean score of all the neuropsychological assessments and the Berg CR-10 between time points.

In terms of individual change of cognitive function between time points (Figure 3.3), the majority of participants experienced a stable cognitive function from T1 to T2 using both patient-reported questionnaires (FACT-Cog: n=6 of 11, 54.55%; CogPCI: n=5 of 11, 45.45%) and a battery of neuropsychological assessments (n=4-9 of 11, 50%-90%). As shown in Figure 3.3-(a), 20%-30% of participants were found to have improved in the FACT-Cog, CogPCI, HVLT-R total recall and delayed recall as well as DS-forward from T1 to T2, while no participants showed improvement in the DS-backward, TMT-A, and TMT-B. In contrast, over 20% of participants (20%-40%) showed a decline in the CogPCI and HVLT-delayed recall, TMT-A, and TMT-B from T1 to T2; no decline was found among participants in the HVLT-total recall, DS-forward, and D-KEFS letter fluency test.

In terms of the change from T2 to T3, except for the CogPCI (n=1 of 3; 33.33%) and the HVLT-delayed recall (n=1 of 3, 33.33%), other assessment results were found to be stable in the majority of participants (50%-100%). Additionally, Figure 3.3-(b) indicated that above 25% of participants (25%-66.67%) showed an improvement in the FACT-Cog, CogPCI, HVLT-delayed recall, DS-forward and backward, D-KEFS letter fluency test, and TMT-A; however, no

participants show an improvement in the HVLT-total recall and TMT-B. Only the HVLT-R total recall and delayed recall and DS-backward showed a decline in 25%-33% (n=1 of 3 or n=1 of 4) of participants.

For the change from T2 to early end-of-study, 25% (n=1 of 4) and 50% of participants (n=2 of 4) showed a stable FACT-Cog and CogPCI respectively; and 50%-100% (n=2-4 of 4) showed stable neuropsychological assessments. As shown in Figure 3.3-(c), no participants were found to have an improvement in the HVLT-R total recall and delayed recall, DS forward, D-KEFS letter fluency test, TMT-A, or TMT-B. Additionally, no participants were found to have a decline in the DS forward, D-KEFS letter fluency test, or TMT-A.

Prevalence of cognitive impairment

In terms of the prevalence of cognitive impairment (Figure 3.4), ≥50% of participants were cognitively impaired using the CogPCI at T1 (n=7 of 14; 50%), T2 (7 of 11; 63.64%), and early end-of-study (n=2 of 4; 50%). However, only 1 participant (33.33%) at T3. Using the battery of neuropsychological assessments, an increased percentage of participants met the criteria of overall cognitive impairment defined by the ICCTF from T1 (n=6 of 14; 42.86%), T2 (n=5 of 10; 50%), to T3 (n=2 of 4; 50%). For each assessment, the HVLT-R delayed recall was found to have the highest percentage of participants (25%-50%) with a z score ≤ -2.0 across all time points. In contrast, the DS forward and backward were found to have the lowest percentage of participants (0%-7.14%) with z score ≤ -2.0 across all time points.

Potential Correlation of Subjective and Objective Cognitive Function

The relationships between cognitive changes and baseline sample characteristics were tested. For the cognitive change between T1 and T2 (Table 3.5), findings indicated that participants with an age ≥72 years experienced either a stable or declined FACT-Cog or CogPCI,

while those with an age <72 years reported either a stable or improved FACT-Cog or CogPCI. Still, no significant findings were identified (p=0.156; p=0.058). Moreover, participants with one or no comorbidities experienced a stable or decline in FACT-Cog or CogPCI; those with two or more comorbidities had a mainly increased FACT-Cog or CogPCI. The only significant relationship identified was between the number of comorbidities and change in FACT-Cog (p=0.041). The relationship between cognitive changes between T2-T3, T3-early end-of-study and baseline sample characteristics was detailed in Table 3.6 and Table 3.7; no significant findings were identified.

The PRO-CTCAE, the LEUS, biomarkers, remission status, and setting were assessed at each time point (Table 3.4). The relationship between these variables and cognitive function were further tested (Table 3.8, Table 3.9, Table 3.10, Table 3.11). For the FACT-Cog and its subscales, no significant correlate was identified at T1, T2, and T3; it only showed in early end-of-study. Specifically, the CogPCI was significantly correlated with the symptom score (rho=-1, p<0.0001) and the LEUS (rho=-1, p<0.0001).

For the neuropsychological assessments, findings indicated that the HVLT-R Total Recall had a significant strong correlation with insomnia (rho=-0.634; p=0.018) and Hgb (rho=0.664, p=.008) at T1; however, no significant correlation relationship was identified at T2 and T3. For early end-of-study, although correlations between the HVLT-R total recall, insomnia and Hgb (rho=-0.949; rho=-0.600) were strong, they were not statistically significant. In addition, the HVLT-R delayed recall was significantly correlated with insomnia (rho=0.694, p=0.015; rho=-0.838, p=0.003) and sad feeling (rho=-0.713, p=0.012; rho=-0.794, p=0.008) at both T1 and T2. Significant findings were also identified between HVLT-R delayed recall and symptom score (rho=-0.654, p=0.027), anxiety (rho=-0.656, p=0.026), and Hgb (rho=0.671,

p=0.015) at T1; nothing can cheer me up (rho=-0.855, p=0.001) at T2. For DS forward, the only significant relationships identified were with Hgb (rho=0.663, p=0.035) and WBC (rho=0.694, p=0.024) at T2. Finally, for the TMT, the TMT-A had a significant relationship with Hgb (rho=-0.721, p=0.016) at T2. In terms of the TMT-B, it was significantly correlated with anxiety (rho=0.553, p=0.049) at T1, Hgb (rho=-0.745, p=0.011; rho=1, p<0.0001) at both T1 and early end-of-study, WBC (rho=1, p<0.0001), and ANC (rho=1, p<0.0001) at early end-of-study.

Discussion

To the best of our knowledge, this prospective, longitudinal study is the first study exploring the trajectory of CRCI and its correlates in older adults with AML receiving VEN+HMA/low-dose ara-c chemotherapy. Our findings suggested that the trend toward change in overall subjective and objective cognitive function did not meet statistical significance during study follow-up, though participants showed clinically significant changes on the individual level. Up to 63.64% and 75% of participants were identified as cognitively impaired after initiating VEN+HMA/low-dose ara-c chemotherapy using a patient-reported questionnaire and a battery of neuropsychological assessments, respectively. In addition, physiological/clinical and psychological factors were potential correlates of cognitive function.

Our current study identified a non-significant change in overall cognitive function and cognitive domains during the study follow-up between cycle 1, cycle 2, and cycle 4/early end-of-study. Our findings aligned with prior studies showing stable cognitive function during chemotherapy with a three to over 12-month follow-up in adults with AML (Alibhai et al., 2009; Jouzier et al., 2021; Klepin et al., 2016) and adults with a mixed cancer diagnosis (Moore et al., 2019). In terms of cognitive domains, our findings were similar to the results from Modzelewski et al. (2011), which indicated no significant changes in attention and working memory in adults

with AML who were receiving high-dose ara-c. Current CRCI studies mainly performed their assessments one to six months post-chemotherapy to assess acute changes (Deprez et al., 2018). Compared to other CRCI studies, our study has a relatively short assessment time interval and follow-up; therefore, the change in cognitive function might have not occurred or influenced by practice effects. However, longitudinal studies of cognitive function of older adults with AML are challenging due to attrition from mortality (current sample: 21.43%), AML relapse or progression, and frequent changes in therapy. Considering the complexity of this population, the short assessment time interval was reasonable and allowed us to have a preliminary understanding of the cognitive function of this specific patient population. Still, we recommend that future studies have a longer follow-up and larger sample size to explore further cognitive changes. We also recommend including a control group to assist in mitigating or permit analyzing the influence of practice effects.

Although no significant changes were identified in a group level, 0%–66.67% and 0%–50% of older adults with AML showed clinically meaningful individual increase or decline in their cognitive function, respectively, between time points. The FACT-Cog with MCID as a cut-off score has been used in CRCI research in cancer survivors, such as breast cancer (Rodriguez et al., 2021) but not older adults with AML. Rodriguez et al. (2021) found a subjective cognitive decline around 35.7%–36.7% during the first 12 months of nonmetastatic breast cancer treatment. In comparison, our study identified around 0%–27.27%, which is lower than the findings from Rodriguez et al. (2021). This difference might result from the short follow-up time interval, treatment plan, and cancer diagnosis. For neuropsychological assessments, we used the RCI to determine clinically significant change in older adults with AML, which provided us a chance to focus on the individual change of older adults with AML and explore changes over

time in small sample size research. This method has been used in other hematological malignancies. Specifically, Jones et al. (2013) indicated that the majority of the adults with multiple myeloma showed stable or improved neuropsychological assessments and reported that the decline was mainly in verbal learning/memory, working memory, and executive function (20%-29.3%) during the three month follow-up after hematopoietic stem cell transplant. Similarly, our findings identified 50–100% stable or improved neuropsychological assessments in the neuropsychological assessment from cycle 1, cycle 2, to cycle 4. The decline was mainly identified in verbal learning/memory and executive function, not in working memory. However, due to the small sample size, the percentage should be interpreted conservatively.

To the best of our knowledge, this is the first CRCI study in older adults with AML using RCI method. Collins et al. (2013) claimed that using published normative data as a control group might be adequate to longitudinally explore CRCI in cancer survivors using proper measures with practice effects, demographic characteristics, and baseline assessment in consideration. In addition, Cerulla et al. (2019) emphasized the importance of addressing practice effects when examining CRCI in breast cancer survivors. Therefore, due to a lack of control group and the difficulty of finding a published existing study with similar demographic characteristics, our study used the published normative data (Benedict et al., 1998; Delis et al., 2001; Levine et al., 2004; Wechsler, 2008a) to calculate RCI. However, compared to the published normative data (Benedict et al., 1998; Delis et al., 2001; Levine et al., 2004; Wechsler, 2008a), our study includes an older sample with a mean age of 73.57 years and has a shorter assessment time interval ranging from 21 to 98 days. Additionally, we collected educational level rather than years of education from older adults with AML. Hence, we suggest future research should

include a control group and collect the data of years of education so that an accurate RCI can be generated from a sample with similar demographic characteristics.

Our study found both subjective and objective cognitive impairment at all time points with a prevalence of subjective cognitive impairment of 33.33%–63.64% and objective cognitive impairment of 42.86%–75%. This prevalence fell within the prevalence range (17%-94%) from prior studies focusing on survivors with breast cancer, ovarian cancer, and testicular cancer who received chemotherapy (Hermelink et al., 2007; Hess et al., 2015; Janelsins et al., 2017; Stouten-Kemperman et al., 2015; Von Ah & Tallman, 2015). In addition, our study found that CRCI was found in older adults with AML prior to initiating chemotherapy/at diagnosis that was aligned with prior CRCI research in breast cancer survivors (Vega et al., 2017). However, the prevalence of CRCI in the current study was higher than the findings from prior AML studies identified in Chapter 2 of the systematic review, which was 16%–31.5% at the initiation of chemotherapy and up to 62.2% after starting chemotherapy. This difference might result from the measures. Specifically, prior AML studies used the MMSE, 3MS, and MOCA; however, the MMSE might not be sensitive enough to detect CRCI in cancer survivors (Isenberg-Grzeda et al., 2017). In terms of each neuropsychological assessment, the current study found that a higher number of older adults with AML showed an impaired verbal learning/memory (10%–50%) and executive function (10%–25%) but a lower number of older adults with AML experienced an impairment in working memory/attention (0%–7.14%). This aligned with the findings from Meyers et al. (2005) focusing on exploring CRCI in adults with 54 AML or MDS receiving induction chemotherapy. Although a percentage of cognitively impaired participants presented in the current study, the small sample size might exaggerate the actual percentage. Hence, the results

should be interpreted cautiously. We recommend that future studies include a sufficient sample size to better understand the prevalence of CRCI in older adults with AML.

Although results were mixed across time points, our study identified the following possibly significant correlates of cognitive function and cognitive domains (verbal learning/memory, working memory/attention, letter fluency, processing speed, and executive function) at some time points: number of comorbidity, symptom burden, insomnia, emotional distress, disease burden, Hgb and WBC. Similarly, prior research has found that breast cancer survivors with a comorbidity have significantly higher odds of experiencing cognitive impairment than those who did not have comorbidity prior to cancer treatment (Mandelblatt et al., 2014). In addition, aligned with the findings from Jouzier et al. (2021) and Meyers et al. (2005), we found that age did not have a significant relationship with cognitive function. However, different from Meyers et al. (2005), our results did not show any relationship between educational level and cognitive function. This difference might result from the way education was assessed. Specifically, Meyers et al. (2005) collected the years of education and had a wide range between 5 and 18 years; our study collected education level, and 92.86% of the participants received a high school degree or above. In terms of symptoms, current finding showed that insomnia and emotional distress were significantly correlated with cognitive domains (i.e.: verbal learning/memory and executive function), which aligned with previous studies focusing on adults with breast cancer (Carroll et al., 2019; Yang & Hendrix, 2018). In addition, similar to prior CRCI studies in adults with colorectal cancer and AML (Cruzado et al., 2014; Meyers et al., 2005), fatigue did not correlate with cognitive function. However, the current study used the PRO-CTCAE, which assesses each symptom using a single item to avoid

participant burden. We would suggest that future studies use a brief but structured questionnaire to assess and validate each symptom.

Disease burden were negatively correlated with cognitive function in the current study. Rodin et al. (2009) found that disease burden is the major predictor of depression in advanced cancer survivors. Hence, considering that emotional distress was related to cognitive function, the finding that disease burden was a correlate of cognitive function is expected. For biomarkers, Hgb was found to be positively correlated with verbal learning/memory, working memory, verbal fluency, and executive function in the current study, which is different from the findings from Meyers et al. (2005). However, Cunningham (2003) suggested that cognitive decline could result from low Hgb because of anemia symptoms, such as fatigue, dizziness, headache. Therefore, the finding was reasonable. Although several possible correlates were identified from the current study, our results needed to be interpreted conservatively due to a small and highly homogeneous sample. For some sample characteristics, the number of participants in each category were too small (less than 5) to be examined statistically. Hence, we suggest future research to include a sufficient number of older adults with AML with diverse sample characteristics to better identify potential correlates of CRCI.

This study is not without limitations. First, the sample size is very small; therefore, the results should be interpreted conservatively. Secondly, the characteristics are homogeneous within the sample—the majority were male, White, and highly educated; therefore, the results of correlates could not be well identified. Thirdly, there are incomplete data in some neuropsychological assessments due to hearing problems and scheduling limitations. Specifically, one participant showed severe hearing problems during study follow-up; therefore, the HVLT-R total recall and delayed recall were not able to be performed. Moreover, in order to

decrease participants' burden and avoid the delay of participants' treatment scheduling, we conducted the data collection during the wait time between clinic appointments and stopped study activity once participants were called for infusion at the clinic in the NCCH. Therefore, some participants were not able to complete the HVLT-R delayed recall due to the time constraints, and one participant did not receive the battery of neuropsychological assessments at T2 because of a change in treatment location. Finally, in order to increase the flexibility of data collection time frame and participant recruitment, we performed the baseline assessment at seven days before or within three days of 1st cycle of VEN+HMA/low-dose ara-c infusion and also recruited patients who were treated for relapse AML. Hence, the baseline assessment results were not from all older adults who had never been treated with chemotherapy.

This prospective, longitudinal study has some strengths. First, the current study provides a comprehensive understanding of CRCI using both patient-reported questionnaires and a battery of neuropsychological assessments in older adults with AML, which addresses the current knowledge gap in CRCI research in the AML population and older adults with cancer. Secondly, our study also shows the acceptability and barriers (i.e.: time burden, hearing problem) of using patient-reported questionnaires and neuropsychological assessments in older adults with AML, which informs future research to consider an alternative way to assess objective function when choosing their assessment tools. Finally, by identifying potential correlates, the study not only identifies potential high-risk older adults with AML for clinicians and oncology nurses to give extra attention, but also allows future research to identify potential covariates when conducting CRCI research.

Conclusion

The study concluded that older adults showed clinically significant changes in both subjective and objective cognitive impairment, especially the decline in verbal learning/memory and executive function. Additionally, about 63.64% and 75% of participants experienced subjective and cognitive impairment, respectively, after initiating VEN+HMA/low-dose ara-c chemotherapy. Finally, although findings were mixed across time points, symptom and disease burden were potential correlates of perceived cognitive function; insomnia, emotional distress, and hemoglobin were potential correlates of verbal learning/memory and executive function.

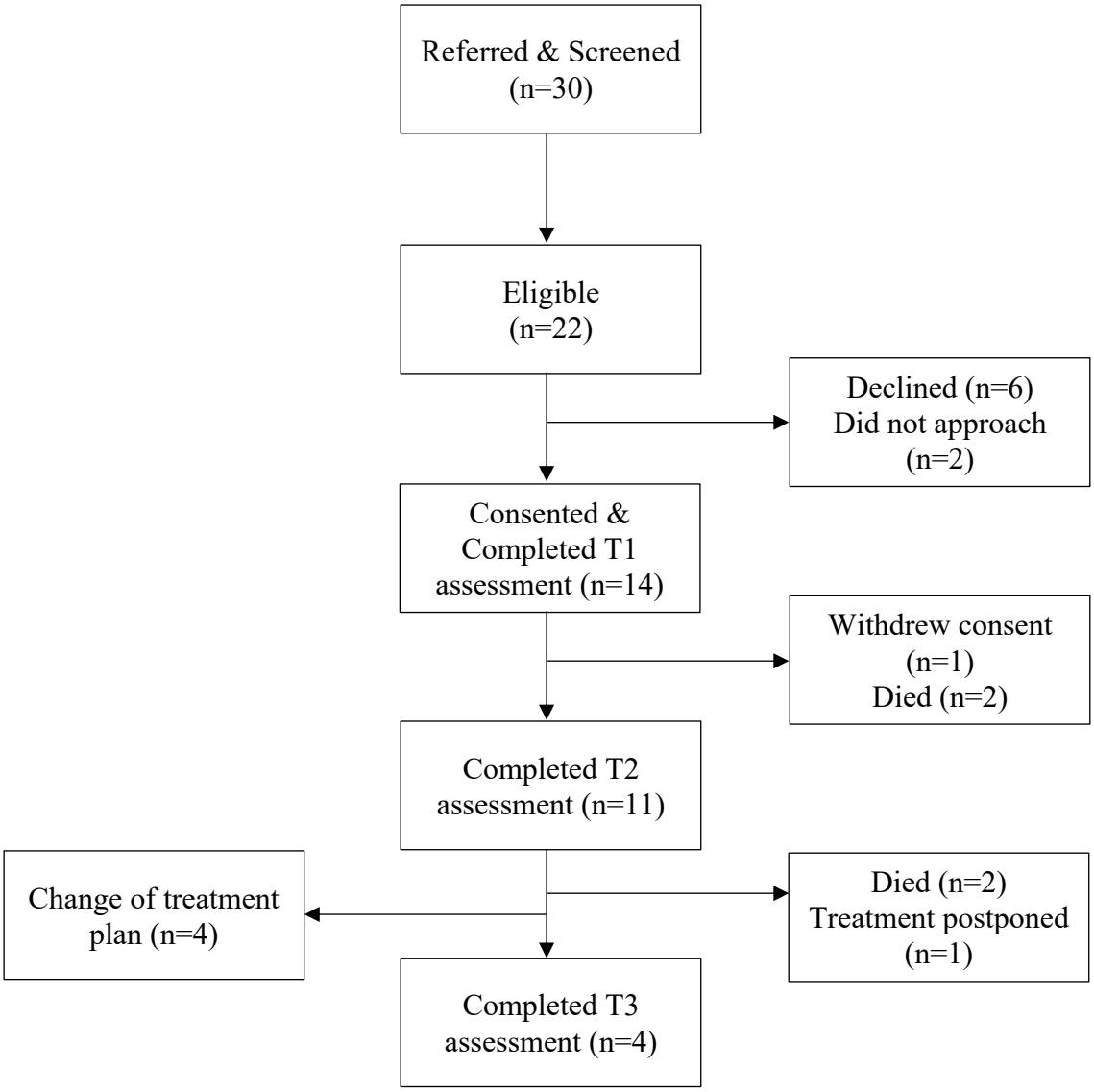
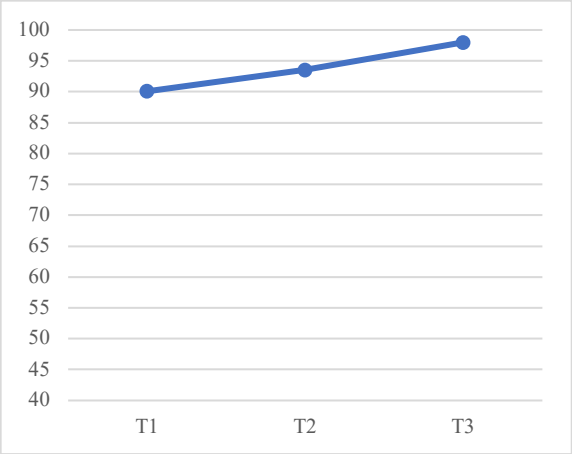
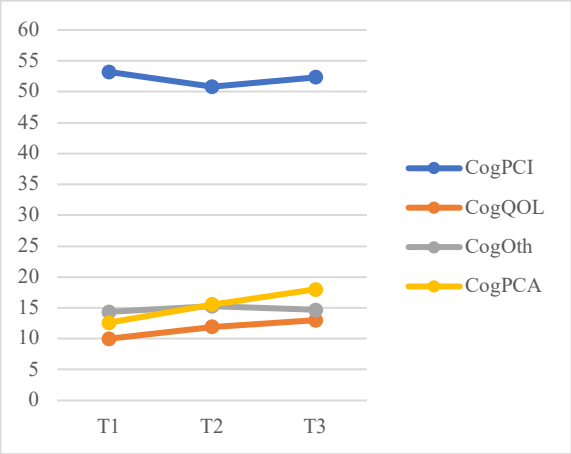


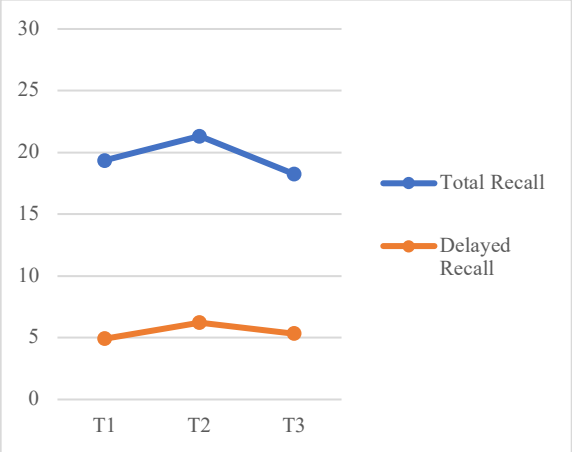
Figure 3.1. **Flowchart of sample recruitment and follow-up**



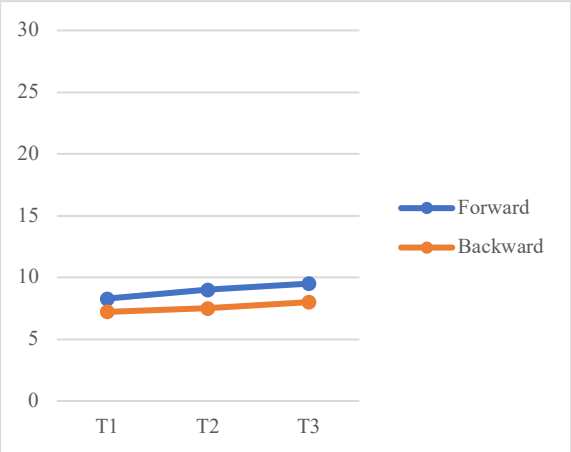
(a) Functional Assessment of Cancer Therapy-Cognitive Function Total Score



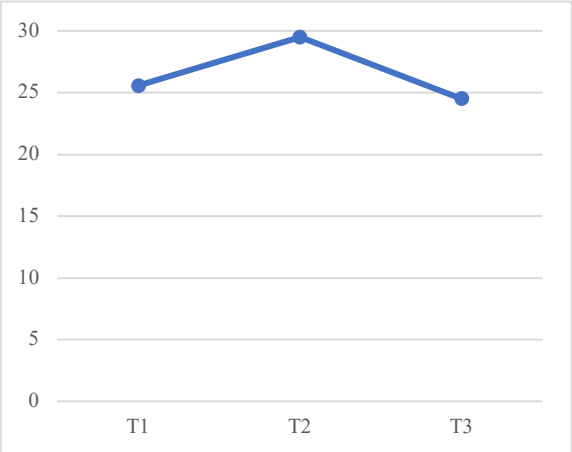
(b) Functional Assessment of Cancer Therapy-Cognitive Function Subscales



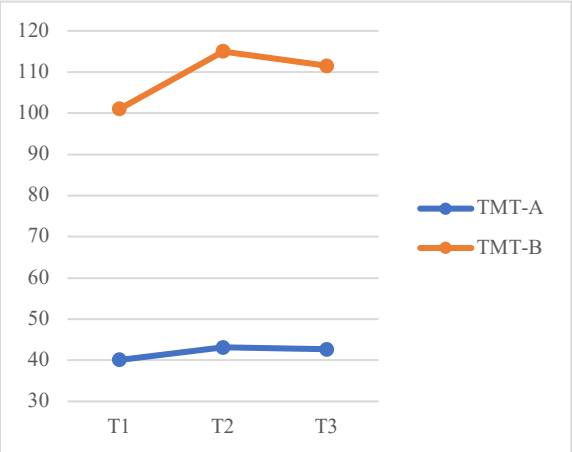
(c) Hopkins Verbal Learning Test-Revised



(d) Digit Span



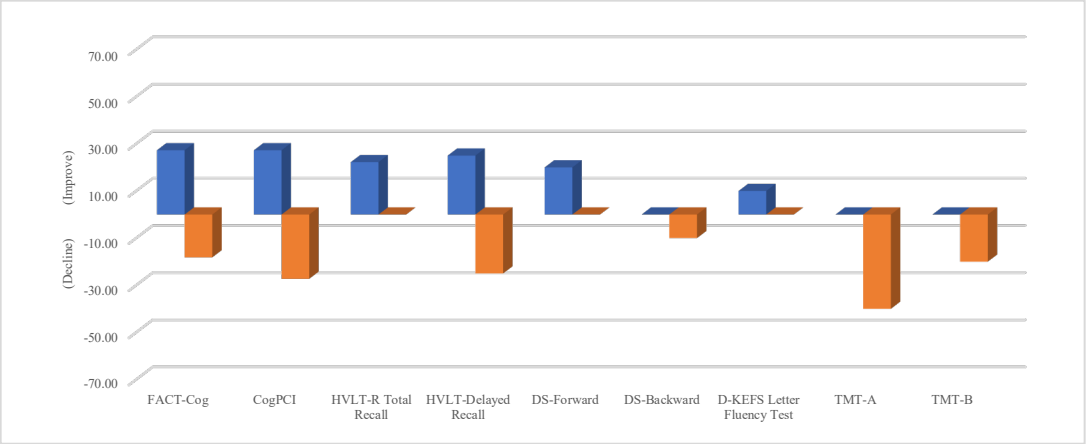
(e) Delis–Kaplan Executive Function System (D-KEFS) Letter Fluency test



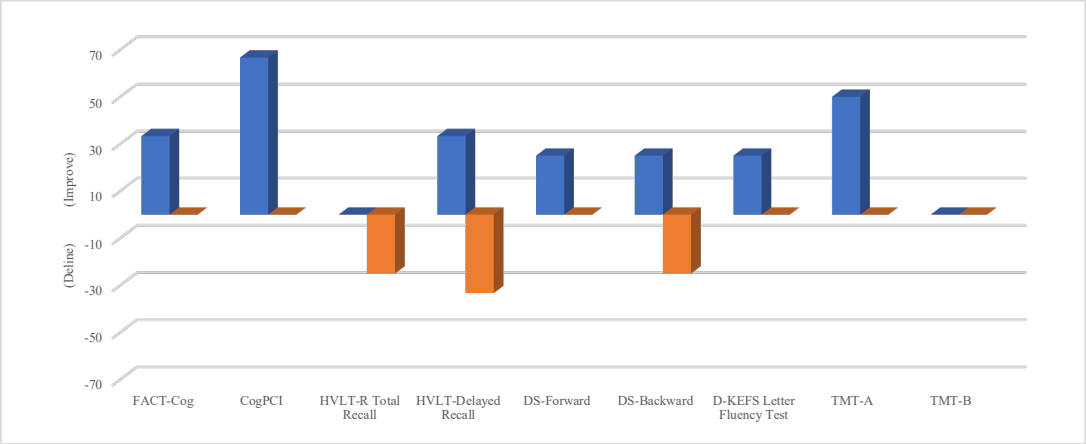
(f) Trail Making Test

Figure 3.2. **Trajectory of subjective and objective cognitive function over time**

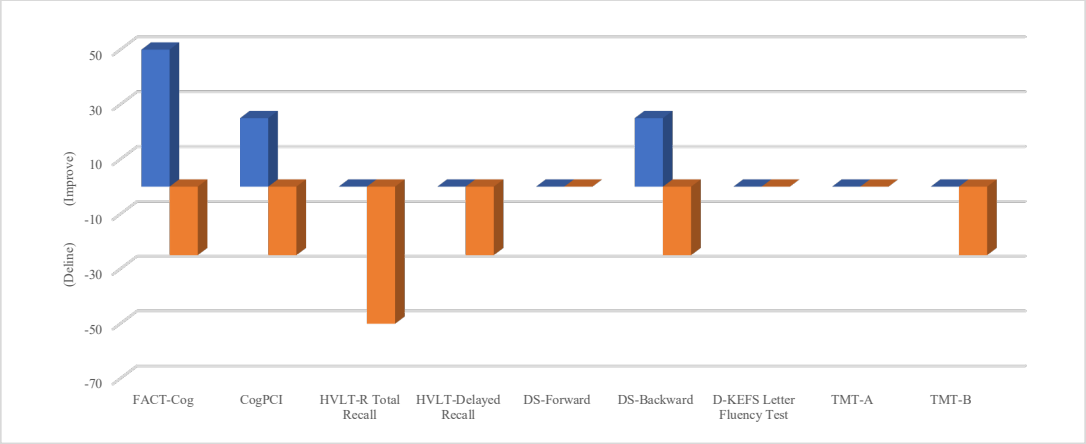
Note: At T1 (cycle 1), T2 (cycle 2), and T3 (cycle 4), n=14, 11, and 4, respectively. However, for the HVLT-R delayed recall at T1, n=12. For the HVLT-R total recall and delayed recall at T2, n=9. For the DS-forward and backward, D-KEFS Letter Fluency Test, and TMT-A&B at T2, n=10. For the FACT-Cog Total Score, CogPCI, CogQOL, CogOth, CogPCA, and HVLT-R delayed recall, at T3, n=3.



(a) T1–T2



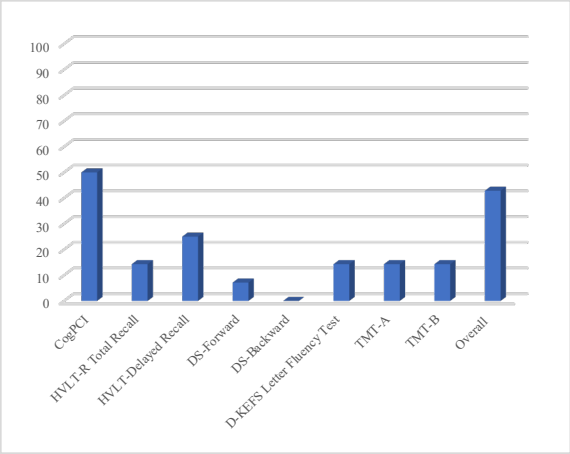
(b) T2–T3



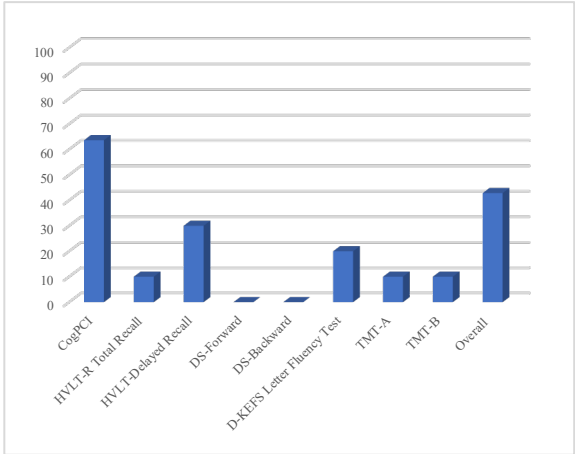
(c) T2–Early end-of-study

Figure 3.3. **Percentage of change of cognitive function between each time point**

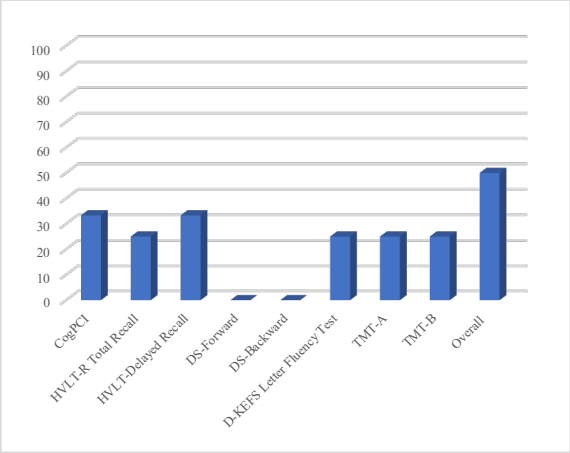
Note: For T1–T2 (cycle 1–cycle 2) , T2–T3 (cycle 2–cycle 4), and T2–Early End-of-study (cycle 2–Early end-of-study), n=11, 4, and 4, respectively. However, for the HVLT-R total recall and delayed recall of T1–T2, n=9. For the DS-forward and backward, D-KEFS Letter Fluency Test, and TMT-A&B of T1–T2, n=10. For the FACT-Cog Total Score, CogPCI, and HVLT-R delayed recall of T2–T3, n=3.



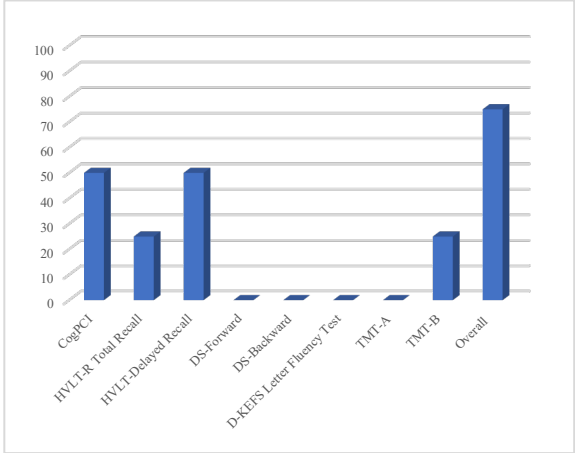
(a) T1



(b) T2



(c) T3



(d) Early end-of-study

Figure 3.4. **Percentage of cognitive impairment at each time point**

Note 1: For each neuropsychological assessment, the figure presents the percentage of sample who had a z≤ -2.0 for that specific assessment. For overall, the figure presents the percentage of sample whose battery of neuropsychological assessments met the criteria of cognitive impairment defined by the International Cognition and Cancer Task Force.

Note 2: At T1, T2, T3, and early end-of-study, n=14, 11, 4, and 4, respectively. However, for the HVLT-R delayed recall at T1, n=12. For the HVLT-R total recall and delayed recall at T2, n=9. For the DS-forward and backward, D-KEFS Letter Fluency Test, and TMT-A&B at T2, n=10. For the CogPCI and HVLT-R delayed recall, at T3, n=3.

Table 3.1. **List of neuropsychological assessments and published normative data resource**

Domain	Assessment	Reliable Change Index (RCI)			
		N	Age	Assessment Interval (days)	Resource
Memory, verbal learning ability	Hopkins Verbal Learning Test-Revised (HVLT-R)	40	68.8±5.8 (Range: 56-82)	46.6±30.1 (Range: 14-134)	Benedict et al. (1998)
Working memory	Wechsler Adult Intelligence scale (WAIS) IV-digit span forward & backward	298	52.6±23.6	Mean 22 (Range: 8-22)	Wechsler (2008b)
Speeded lexical fluency	Delis–Kaplan Executive Function System (D-KEFS) letter fluency test	38	Range: 50-89	N/A	Delis et al. (2001)
Processing speed, executive function	Trail Making Test (TMT) A & B	344	41.4±9.3	235±127	Levine et al. (2004)

Table 3.2. **Sample characteristics of older adults with AML(n=14)**

Characteristics		Mean	SD
Age		73.57	8.03
		n	%
Sex	Male	11	78.57
	Female	3	21.43
Gender	Male	11	78.57
	Female	3	21.43
Race	White	13	92.86
	Black or African American	1	7.14
Ethnicity	Non-Hispanic	14	100.00
Education level	High school graduate/ Graduate equivalency degree	9	64.29
	College degree	3	21.43
	Advanced degree	1	7.14
	Prefer not to answer	1	7.14
Annual household income	<$20,000	1	7.14
	$20,001-40,000	2	14.29
	$40,001-60,000	3	21.43
	$60,001-80,000	3	21.43
	$80,001-100,000	1	7.14
	>$100,001	2	14.29
	Prefer not to answer	2	14.29
Marital Status	Married/Partnered	9	64.29
	Divorced	2	14.29
	Widowed	3	21.43
Living with Others	Yes	9	64.29
	No	5	35.71
Employment prior to diagnosis	Yes	7	50.00
	No	7	50.00
Comorbidities			
Arthritis	Yes	3	21.43
Lung disease	Yes	1	7.14
Diabetes	Yes	2	14.29
Cardiac disease	Yes	6	42.86
Cancer	Yes	6	42.86
Renal disease	Yes	0	0

Liver disease	Yes	0	0
Mental health problem	Yes	3	21.43
Cytogenetics	Undetermined	1	7.14
	Intermediate	3	21.43
	Adverse	10	71.43
Treatment regimen	Venetoclax+Azacitidine	12	85.71
	Venetoclax+Decitabine	2	14.29

Table 3.3. **Distribution of main outcomes (raw score) and changes between time points**

Variables	Time points				Change between time points				
	T1 (n=14)	T2 (n=11)	T3 (n=4)	Early end-of-study (n=4)	T1-T2	T2-T3	T1-T3	T2-Early end-of-study	T1-Early end-of-study
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	p value	p value	p value	p value	p value
Main Outcomes: Cognitive Function									
Functional Assessment of Cancer Therapy-Cognitive Function (FACT-Cog) version 3									
FACT-Cog	90.07 (18.01)	93.55 (22.67)	98 (20.81)[d]	100.25 (21.42)	p=0.504	p=0.5	p=0.75	p=1.0	p=0.25
CogPCI	53.21 (12.42)	50.82 (13.49)	52.33 (11.59)[d]	56.75 (10/81)	p=1.0	p=0.25	p=1.0	p=1.0	p=0.25
CogQOL	10 (4.02)	11.91 (3.73)	13.0 (2.0)[d]	8.25 (5.56)	p=0.438	p=1.0	p=0.25	p=0.25	p=0.25
CogOth	14.36 (1.78)	15.27 (1.01)	14.67 (2.31)[d]	13.75 (1.7)	p=0.125	p=1.0	p=1.0	p=0.5	p=1.0
CogPCA	12.6 (7.37)	15.55 (7.76)	18.0 (5.29)[d]	21.5 (4.43)	p=0.438	p=1.0	p=0.75	p=0.25	p=0.25
Hopkins Verbal Learning Test-Revised (HVLT-R)									
Total Recall	19.36 (5.97)	21.33 (6.60)[b]	18.25 (6.08)	21.5 (6.19)	p=0.195	p=0.625	p=0.625	p=0.5	p=0.75
Delayed Recall	4.92 (2.87)[a]	6.22 (4.66)[b]	5.33 (6.11)[d]	6.75 (4.27)	p=0.75	p=1.0	p=1.0	p=1.0	p=0.75
CR-10 (Total Recall)	3.5 (1.99)	3.83 (1.66)[b]	4.75 (1.26)	3.38 (2.14)	p=0.906	p=1.0	p=1.0	p=1.0	p=0.5
CR-10 (Delayed Recall)	3.73 (2.61)[a]	4 (2.40)[b]	7.67 (4.04)[d]	4.13 (2.72)	p=0.813	p=0.5	p=1.0	p=0.5	p=0.25
Digit Span (DS)-Forward									

Variables	Time points				Change between time points				
	T1 (n=14)	T2 (n=11)	T3 (n=4)	Early end-of-study (n=4)	T1-T2	T2-T3	T1-T3	T2-Early end-of-study	T1-Early end-of-study
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	p value	p value	p value	p value	p value
Total Forward Item Score	8.29 (2.09)	9 (1.83)[c]	9.50 (2.52)	8.75 (2.22)	p=0.117	p=1.0	p=0.5	p=0.25	p=1.0
LDSF CR-10 (DS-Forward)	5.57 (1.40)	5.9 (0.99)[c]	6.25 (1.5)	5.25 (1.71)	p=0.656	p=1.0	p=1.0	p=0.5	p=1.0
	3.5 (1.74)	3.15 (1.83)[c]	4.5 (1.91)	2.38 (1.25)	p=0.469	p=0.5	p=1.0	p=-	p=0.5
Digit Span (DS)-Backward									
Total Backward Item Score	7.21 (1.37)	7.5 (1.96)[c]	8.0 (2.16)	7.75 (3.5)	p=0.438	p=0.75	p=0.5	p=1.0	p=1.0
LDSB CR-10 (DS-Forward)	4 (0.88)	4.2 (1.14)[c]	4.5 (1.29)	5.0 (2.16)	p=0.406	p=1.0	p=0.5	p=0.75	p=0.75
	4.11 (1.69)	3.75 (1.51)[c]	5.50 (1.73)	4.5 (2.52)	p=0.57	p=0.125	p=1.0	p=0.5	p=0.75
D-KEFS Letter Fluency Test									
Total Responses	29.43 (13.74)	30.8 (13.82)[c]	28.0 (12.11)	41.0 (18.89)	p=0.854	p=0.375	p=0.25	p=0.125	p=0.125
Total Correct Raw Score	25.57 (12.61)	29.5 (12.96)[c]	24.5 (9.68)	38.75 (17.56)	p=0.059	p=1.0	p=0.125	p=0.125	p=0.25
CR-10 (Letter	4.43 (2.14)	4.4 (1.65)[c]	5.5 (1.91)	3.13 (1.93)	p=0.766	p=0.625	p=1.0	p=0.75	p=0.5

Variables	Time points				Change between time points				
	T1 (n=14)	T2 (n=11)	T3 (n=4)	Early end-of-study (n=4)	T1-T2	T2-T3	T1-T3	T2-Early end-of-study	T1-Early end-of-study
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	p value	p value	p value	p value	p value
Fluency Test)									
Trail Making Test (TMT)									
TMT-A	40.06 (12.61)	43.14 (17.04)[c]	42.63 (18.27)	28.0 (5.65)	p=0.232	p=0.125	p=0.625	p=0.875	p=0.875
CR-10 (TMT-A)	1.25 (1.34)	1.35 (1.20)[c]	1.5 (1.73)	0.63 (0.95)	p=0.453	p=1.0	p=0.5	p=0.5	p=0.5
TMT-B	101.01 (45.94)	114.98 (61.56)[c]	111.5 (50.89)	76.04 (20.78)	p=0.432	p=0.375	p=1.0	p=0.125	p=0.875
CR-10 (TMT-B)	3.25 (1.78)	2.75 (1.69)[c]	4.0 (1.15)	3.88 (2.25)	p=0.328	p=1.0	p=0.75	p=0.25	p=0.5

Note:

[a] For the HVLT-R delayed recall and CR-10 (delayed recall) at T1, n=12.

[b] For the HVLT-R total recall and delayed recall, CR-10 (total recall), and CR-10 (delayed recall) at T2, n=9.

[c] For the DS-forward and backward, CR-10 (DS-forward and backward), D-KEFS Letter Fluency Test, CR-10 (D-KEFS Letter Fluency Test), TMT-A&B, and CR-10 (TMT-A&B) at T2, n=10.

[d] For the FACT-Cog Total Score, CogPCI, CogQOL, CogOth, CogPCA, HVLT-R delayed recall, and CR-10 (delayed recall) at T3, n=3.

Abbreviation: CogPCI, perceived cognitive impairments; CogOth, comments from others; CogPCA, perceived cognitive abilities; CogQOL, impact of quality of life; CR-10, Borg Category Ratio Scale; LDSF, longest Digit Span forward; LDSB, longest Digit Span backward.

Table 3.4. **Distribution of symptoms, biomarkers, remission status, and setting over time**

Variables	T1 (n=14)	T2 (n=11)	T3 (n=4)	Early end-of-study (n=4)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Patient Reported Outcomes-Common Terminology Criteria for Adverse Events				
Symptom score	7.77 (5.78)[a]	6.36 (4.13)	4.0 (2.71)	7.25 (4.27)
Fatigue	1.5 (1.09)	1.18 (0.75)	0.75 (0.5)	0.75 (0.96)
Insomnia	0.92 (1.32)[a]	0.55 (0.69)	0 (0)	0.75 (0.96)
Anxiety	0.62 (0.87)[a]	0.55 (0.82)	0.25 (0.5)	0.75 (0.96)
Sad feeling	0.54 (0.78)[a]	0.36 (0.67)	0.25 (0.5)	0.5 (0.58)
Nothing can cheer me up	0.15 (0.38)[a]	0.45 (0.69)	0 (0)	0.5 (1.0)
LEUS	46.43 (8.16)	49.73 (9.87)	53.67 (3.51)[d]	54 (9.2)
Biomarkers				
Hemoglobin	8.56 (1.58)	10.28 (1.71)[b]	11.98 (2.52)	11.23 (2.53)
White Blood Cell Count	5.35 (6.47)	2.95 (2.8)[b]	3.05 (0.99)	2.93 (2.41)
Neutrophil Count	2.06 (2.34)	1.78 (2.49)[b]	1.68 (0.75)	1.85 (1.84)
Lactate Dehydrogenase	580.43 (272.89)	457[c]	-	156[c]
	n (%)	n (%)	n (%)	n (%)
Remission Status				
Yes	0 (0)	5 (45.45)	4 (100)	3 (75)
No	14 (100)	6 (54.55)	0 (0)	1 (25)
Setting				
In-Clinic	12 (85.71)	14 (100)	4 (100)	1 (25)
In-Patient Unit	2 (14.29)	0 (0)	0 (0)	3 (75)

Note:

[a] *For the symptom score, insomnia, anxiety, sad feeling, and nothing can cheer me up at T1, n=13.*

[b] *For the hemoglobin, white blood cell count, and neutrophil count at T2, n=10.*

[c] *For the lactate dehydrogenase at T2 and early end-of-study, n=1.*

[d] *For the LEUS at T3, n=3.*

Abbreviation: LEUS, Functional Assessment of Cancer Therapy-Leukemia Leukemia subscale.

Table 3.5. **Correlation between change of cognitive function from T1 to T2 and baseline sample characteristics**

	Age		Sex/Gender		Education level		Number of Comorbidity		Cytogenetics		Treatment Regimen	
	≥72	<72	Male	Female	High School	College or above	One or less	Two or more	Inter-mediate	Adverse	VEN+ AZA	VEN+ DEC
	n	n	n	n	n	n	n	n	n	n	n	n
FACT-Cog												
Improved	**0**	**3**	2	1	2	1	0	3	0	3	3	0
Declined	**2**	**0**	1	1	1	1	1	1	1	1	2	0
Stable	3	3	5	1	4	1	5	1	1	4	4	2
CogPCI												
Improved	**0**	**3**	2	1	2	1	0	3	0	3	3	0
Declined	**3**	**0**	2	1	2	1	2	1	1	2	2	1
Stable	2	3	4	1	3	1	4	1	1	3	4	1
HVLT-R Total Recall												
Improved	0	2	2	0	2	0	1	1	1	1	2	0
Declined	0	0	0	0	0	0	0	0	0	0	0	0
Stable	4	3	5	2	4	2	4	3	1	5	6	1
HVLT-R Delayed Recall												
Improved	0	2	2	0	2	0	1	1	1	1	2	0
Declined	1	1	2	0	2	0	1	1	1	0	2	0
Stable	2	2	2	2	2	1	2	2	0	4	3	1
DS-Forward												
Improved	1	1	2	0	1	1	1	1	0	1	2	0
Declined	0	0	0	0	0	0	0	0	0	0	0	0
Stable	4	4	6	2	6	1	5	3	2	6	6	2
DS-Backward												
Improved	0	0	0	0	0	0	0	0	0	0	0	0
Declined	0	1	1	0	1	0	0	1	0	0	1	0

	Age		Sex/Gender		Education level		Number of Comorbidity		Cytogenetics		Treatment Regimen	
	≥72	<72	Male	Female	High School	College or above	One or less	Two or more	Inter-mediate	Adverse	VEN+ AZA	VEN+ DEC
	n	n	n	n	n	n	n	n	n	n	n	n
Stable	5	4	7	2	6	2	6	3	2	7	7	2
D-KEFS Letter Fluency Test												
Improved	0	1	1	0	1	0	0	1	0	1	1	0
Declined	0	0	0	0	0	0	0	0	0	0	0	0
Stable	5	4	7	2	6	2	6	3	2	6	7	2
TMT-A												
Improved	0	0	0	0	0	0	0	0	0	0	0	0
Declined	3	1	4	0	3	1	3	1	1	3	3	1
Stable	2	4	4	2	4	1	3	3	1	4	5	1
TMT-B												
Improved	0	0	0	0	0	0	0	0	0	0	0	0
Declined	0	2	2	0	1	1	2	0	0	2	1	1
Stable	5	3	6	2	6	1	4	4	2	5	7	1

Abbreviation: FACT-Cog, Functional Assessment of Cancer Therapy-Cognitive Function; CogPCI, perceived cognitive impairments; HVLT-R, Hopkins Verbal Learning Test-Revised; DS, Digit Span; D-KEFS, Delis–Kaplan Executive Function System; TMT, Trail Making Test; AZA, Azacitidine; DEC, Decitabine.

Table 3.6. **Correlation between change of cognitive function from T2 to T3 and baseline sample characteristics**

	Age		Sex/Gender		Education level		Number of Comorbidity		Cytogenetics		Treatment Regimen	
	≥72	<72	Male	Female	High School	College or above	One or less	Two or more	Inter-mediate	Adverse	VEN+ AZA	VEN+ DEC
	n	n	n	n	n	n	n	n	n	n	n	n
FACT-Cog												
Improved	1	0	1	0	1	0	0	1	0	1	1	0
Declined	0	0	0	0	0	0	0	0	0	0	0	0
Stable	0	2	2	0	1	1	2	0	1	1	2	0
CogPCI												
Improved	1	1	2	0	2	0	1	1	1	1	2	0
Declined	0	0	0	0	0	0	0	0	0	0	0	0
Stable	1	0	1	0	0	1	1	0	0	1	1	0
HVLT-R Total Recall												
Improved	0	0	0	0	0	0	0	0	0	0	0	0
Declined	0	1	1	0	1	0	0	1	0	1	1	0
Stable	3	0	3	0	2	1	3	0	1	2	2	1
HVLT-R Delayed Recall												
Improved	1	0	1	0	1	0	1	0	1	0	1	0
Declined	1	0	1	0	1	0	1	0	0	1	0	1
Stable	1	0	1	0	0	1	1	0	0	1	1	0
DS-Forward												
Improved	1	0	1	0	1	0	1	0	0	1	0	1
Declined	0	0	0	0	0	0	0	0	0	0	0	0
Stable	2	1	3	0	2	1	2	1	1	2	3	0
DS-Backward												
Improved	1	0	1	0	1	0	1	0	1	0	1	0

	Age		Sex/Gender		Education level		Number of Comorbidity		Cytogenetics		Treatment Regimen	
	≥72	<72	Male	Female	High School	College or above	One or less	Two or more	Inter-mediate	Adverse	VEN+ AZA	VEN+ DEC
	n	n	n	n	n	n	n	n	n	n	n	n
Declined	1	0	1	0	0	1	1	0	0	1	1	0
Stable	1	1	2	0	2	0	1	1	0	2	1	1
D-KEFS Letter Fluency Test												
Improved	1	0	1	0	1	0	1	0	0	1	0	1
Declined	0	0	0	0	0	0	0	0	0	0	0	0
Stable	2	1	3	0	2	1	2	1	1	2	3	0
TMT-A												
Improved	2	0	2	0	1	1	2	0	0	2	1	1
Declined	0	0	0	0	0	0	0	0	0	0	0	0
Stable	1	1	2	0	2	0	1	1	1	1	2	0
TMT-B												
Improved	0	0	0	0	0	0	0	0	0	0	0	0
Declined	0	0	0	0	0	0	0	0	0	0	0	0
Stable	3	1	4	0	3	1	3	1	3	1	3	1

Abbreviation: FACT-Cog, Functional Assessment of Cancer Therapy-Cognitive Function; CogPCI, perceived cognitive impairments; HVLT-R, Hopkins Verbal Learning Test-Revised; DS, Digit Span; D-KEFS, Delis–Kaplan Executive Function System; TMT, Trail Making Test; AZA, Azacitidine; DEC, Decitabine.

Table 3.7. **Correlation between change of cognitive function from T2 to early end-of-study and baseline sample characteristics**

	Age		Sex/Gender		Education level		Number of Comorbidity		Cytogenetics		Treatment Regimen	
	≥72	<72	Male	Female	High School	College or above	One or less	Two or more	Inter-mediate	Adverse	VEN+ AZA	VEN+ DEC
	n	n	n	n	n	n	n	n	n	n	n	n
FACT-Cog												
Improved	0	2	2	0	2	0	1	1	1	0	2	0
Declined	0	1	1	0	1	0	0	1	0	1	1	0
Stable	0	1	0	1	0	0	1	0	0	1	1	0
CogPCI												
Improved	0	1	1	0	1	0	1	0	1	0	1	0
Declined	0	1	1	0	1	0	0	1	0	1	1	0
Stable	0	2	1	1	1	0	1	1	0	1	2	0
HVLT-R Total Recall												
Improved	0	0	0	0	0	0	0	0	0	0	0	0
Declined	0	2	1	1	1	0	2	0	1	1	2	0
Stable	0	2	2	0	2	0	0	2	0	1	2	0
HVLT-R Delayed Recall												
Improved	0	0	0	0	0	0	0	0	0	0	0	0
Declined	0	1	1	0	1	0	1	0	1	0	1	0
Stable	0	3	2	1	2	0	1	2	0	2	3	0
DS-Forward												
Improved	0	0	0	0	0	0	0	0	0	0	0	0
Declined	0	0	0	0	0	0	0	0	0	0	0	0
Stable	0	4	3	1	3	0	2	2	1	2	4	0
DS-Backward												
Improved	0	1	0	1	0	0	1	0	0	1	1	0

	Age		Sex/Gender		Education level		Number of Comorbidity		Cytogenetics		Treatment Regimen	
	≥72	<72	Male	Female	High School	College or above	One or less	Two or more	Inter-mediate	Adverse	VEN+ AZA	VEN+ DEC
	n	n	n	n	n	n	n	n	n	n	n	n
Declined	0	1	1	0	1	0	1	0	1	0	1	0
Stable	0	2	2	0	2	0	0	2	0	1	2	0
D-KEFS Letter Fluency Test												
Improved	0	0	0	0	0	0	0	0	0	0	0	0
Declined	0	0	0	0	0	0	0	0	0	0	0	0
Stable	0	4	3	1	3	0	2	2	1	2	4	0
TMT-A												
Improved	0	0	0	0	0	0	0	0	0	0	0	0
Declined	0	0	0	0	0	0	0	0	0	0	0	0
Stable	0	4	3	1	3	0	2	2	1	2	4	0
TMT-B												
Improved	0	0	0	0	0	0	0	0	0	0	0	0
Declined	0	1	1	0	1	0	1	0	1	0	1	0
Stable	0	3	2	1	2	0	1	2	0	2	3	0

Abbreviation: FACT-Cog, Functional Assessment of Cancer Therapy-Cognitive Function; CogPCI, perceived cognitive impairments; HVLT-R, Hopkins Verbal Learning Test-Revised; DS, Digit Span; D-KEFS, Delis–Kaplan Executive Function System; TMT, Trail Making Test; AZA, Azacitidine; DEC, Decitabine.

Table 3.8. **Correlation between cognitive function and symptoms, biomarkers, remission status, and setting at T1**

	FACT-Cog	CogPCI	CogQOL	CogOth	CogPCA	Total Recall	Delayed Recall	DS-Forward	DS-Backward	Letter Fluency	TMA-A	TMT-B
Symptom	-0.403	-0.355	-0.216	-0.197	-0.296	-0.468	**-0.654***	-0.077	-0.134	-0.413	0.152	0.279
Fatigue	-0.114	-0.036	-0.193	-0.164	-0.207	-0.009	0.057	-0.111	0.302	-0.426	-0.186	-0.166
Insomnia	-0.1	-0.087	-0.136	-0.274	-0.154	**-0.634***	**-0.694***	-0.226	-0.284	-0.452	0.349	0.403
Anxiety	-0.198	0.008	-0.309	-0.042	-0.229	-0.460	**-0.656***	0.233	-0.284	-0.19	0.158	**0.553***
Sad feeling	-0.06	-0.055	-0.224	-0.127	0.022	-0.519	**-0.713***	0.078	-0.314	-0.307	0.420	0.443
Nothing can cheer you up	-0.06	-0.229	0.20	0.151	-0.029	-0.114	-0.226	0	0.088	0.456	-0.057	0.114
LEUS	0.055	0.088	0.237	0.134	-0.115	-0.028	0.145	-0.04	-0.38	0.296	0.172	0.113
Hgb	0.515	0.485	-0.171	0.226	0.507	**0.664***	**0.671***	0.384	0.479	**0.559***	-0.392	-0.348
WBC	-0.171	-0.129	0.039	-0.047	0.011	-0.207	-0.062	0.047	-0.41	-0.414	0.525	0.235
ANC	-0.192	-0.097	-0.093	-0.157	-0.054	-0.095	0.145	-0.011	-0.474	-0.428	0.436	0.009
LDH	-0.421	-0.485	0.241	-0.207	-0.148	0.055	0.053	-0.16	-0.023	-0.321	-0.037	-0.112
Setting (0=in clinic)	-0.279	-0.127	-0.127	-0.053	-0.279	-0.432	-0.457	0.054	-0.364	-0.507	0.304	0.354

*Note: *p≤0.05; **p≤0.01; ***p≤0.005; ****p≤0.001*

Abbreviation: FACT-Cog, Functional Assessment of Cancer Therapy-Cognitive Function; CogPCI, perceived cognitive impairments; CogOth, comments from others; CogPCA, perceived cognitive abilities; CogQOL, impact of quality of life; DS, Digit Span; TMT, Trail Making Test; LEUS, Functional Assessment of Cancer Therapy-Leukemia Leukemia subscale; Hgb, hemoglobin; WBC, white blood cell count; ANC, neutrophil count, LDH, lactate dehydrogenase.

Table 3.9. **Correlation between cognitive function and symptoms, biomarkers, remission status, and setting at T2**

	FACT-Cog	CogPCI	CogQOL	CogOth	CogPCA	Total Recall	Delayed Recall	DS-Forward	DS-Backward	Letter Fluency	TMA-A	TMT-B
Symptom	-0.188	-0.415	-0.367	-0.30	0	-0.277	-0.64	0.041	0.328	0.256	-0.049	0.232
Fatigue	-0.029	-0.096	0.117	0.078	-0.172	-0.194	-0.099	-0.161	0.200	-0.237	-0.026	0.224
Insomnia	-0.357	-0.511	-0.5	-0.225	-0.229	-0.373	**-0.838****	0.014	0.204	0.201	-0.228	0.013
Anxiety	-0.018	-0.531	-0.205	-0.429	0.048	0.01	-0.361	0.127	0.377	0.275	0.275	0.523
Sad feeling	-0.348	-0.471	-0.414	-0.301	-0.308	-0.398	**-0.794****	0.034	-0.068	0.090	0.022	0.112
Nothing can cheer you up	-0.458	-0.668	-0.342	-0.370	-0.352	-0.458	**-0.855****	-0.078	-0.021	-0.021	0.049	0.298
LEU	0.064	0.274	0.151	0.143	-0.159	0.276	0.504	-0.009	-0.392	-0.207	-0.097	-0.347
Hgb	-0.03	0.231	-0.23	0.072	0.188	0.30	0.128	**0.663***	0.142	0.224	**-0.721***	**-0.745***
WBC	-0.139	-0.182	-0.205	-0.374	0.188	0.30	-0.034	**0.694***	0.203	0.418	-0.188	-0.139
ANC	-0.116	-0.29	-0.125	-0.256	0.073	-0.025	-0.462	0.469	0.204	0.322	-0.122	0.012
Remission (0=not in remission)	0.115	-0.029	0.06	0.095	0.173	0.173	-0.31	0.534	0.424	0.383	-0.244	-0.174

*Note: *p≤0.05; **p≤0.01; ***p≤0.005; ****p≤0.001*

Abbreviation: FACT-Cog, Functional Assessment of Cancer Therapy-Cognitive Function; CogPCI, perceived cognitive impairments; CogOth, comments from others; CogPCA, perceived cognitive abilities; CogQOL, impact of quality of life; DS, Digit Span; TMT, Trail Making Test; LEUS, Functional Assessment of Cancer Therapy-Leukemia Leukemia subscale; Hgb, hemoglobin; WBC, white blood cell count; ANC, neutrophil count.

Table 3.10. **Correlation between cognitive function and symptoms, biomarkers, remission status, and setting at early end-of-study**

	FACT-Cog	CogPCI	CogQOL	CogOth	CogPCA	Total Recall	Delayed Recall	DS-Forward	DS-Backward	Letter Fluency	TMA-A	TMT-B
Symptom	-0.949	**-1.00******	-0.400	-0.800	-0.632	-0.400	-0.800	-0.632	-0.200	-0.400	-0.800	-0.400
Fatigue	-0.833	-0.949	-0.105	-0.632	-0.500	-0.211	-0.738	-0.500	0.105	-0.211	-0.632	-0.632
Insomnia	0	-0.105	-0.211	0.105	-0.833	-0.949	-0.632	-0.833	-0.738	-0.949	0.105	0.738
Anxiety	0.500	0.738	-0.316	0.211	0.500	0.211	-0.738	0.500	-0.316	0.211	0.211	0.632
Sad feeling	0.707	0.447	0.894	0.894	0	0	0	0	0.447	0	0.894	0
Nothing can cheer you up	0	-0.258	0.258	0.258	-0.817	-0.775	-0.775	-0.817	-0.258	-0.775	0.258	0.258
LEUS	0.949	**1.00******	0.400	0.800	0.632	0.400	0.800	0.632	0.200	0.400	0.800	0.400
Hgb	0.316	0.400	-0.400	0.200	-0.316	-0.600	0	-0.316	-0.800	-0.600	0.200	**1.00******
WBC	0.316	0.400	-0.400	0.200	-0.316	-0.600	0	-0.316	-0.800	-0.600	0.200	**1.00******
ANC	0.316	0.400	-0.400	0.200	-0.316	-0.600	0	-0.316	-0.800	-0.600	0.200	**1.00******
Remission (0=not in remission)	0.817	0.775	0.258	0.775	0	-0.258	0.258	0	-0.258	-0.258	0.775	0.775
Setting (0=in clinic)	0.817	0.775	0.258	0.775	0	-0.258	0.258	0	-0.258	-0.258	0.775	0.775

Note: $^{*}p\leq0.05$; $^{**}p\leq0.01$; $^{***}p\leq0.005$; $^{****}p\leq0.001$

Abbreviation: FACT-Cog, Functional Assessment of Cancer Therapy-Cognitive Function; CogPCI, perceived cognitive impairments; CogOth, comments from others; CogPCA, perceived cognitive abilities; CogQOL, impact of quality of life; DS, Digit Span; TMT, Trail Making Test; LEUS, Functional Assessment of Cancer Therapy-Leukemia Leukemia subscale; Hgb, hemoglobin; WBC, white blood cell count; ANC, neutrophil count.

Table 3.11. **Correlation between cognitive function and symptoms, biomarkers, remission status, and setting at T3**

	FACT-Cog	CogPCI	CogQOL	CogOth	CogPCA	Total Recall	Delayed Recall	DS-Forward	DS-Backward	Letter Fluency	TMA-A	TMT-B
Symptom	0	0	0	-0.500	-0.866	-0.316	-1.00	0	-0.316	-0.500	0.632	0.632
Fatigue	0	0	0	-0.500	-0.866	-0.775	-0.866	0	-0.258	-0.817	0.775	0.258
Insomnia	-	-	-	-	-	-	-	-	-	-	-	-
Anxiety	-0.866	-0.866	-0.866	-1.000	-0.866	-0.258	0	0.817	0.775	0	-0.258	-0.775
Sad feeling	0.866	0.866	0.866	0.500	0	-0.775	-	-0.817	-0.775	-0.817	0.775	0.258
Nothing can cheer you up	-	-	-	-	-	-	-	-	-	-	-	-
LEUS	-0.500	-0.500	-0.500	0	0.500	1.000	1.000	0.500	0.500	1.000	-1.000	-0.500
Hgb	-0.500	-0.500	-0.500	-0.866	-0.500	-0.600	0.500	-0.316	0.400	-0.316	0	-0.800
WBC	0.500	0.500	0.500	0	-0.500	-0.800	0.500	-0.316	-0.200	-0.632	0.400	-0.400
ANC	0.500	0.500	0.500	0	1.00	-0.800	0.500	-0.316	-0.200	-0.632	0.400	-0.400

Note: rho value with grey shading indicated no p value could be generated from analysis.

Abbreviation: FACT-Cog, Functional Assessment of Cancer Therapy-Cognitive Function; CogPCI, perceived cognitive impairments; CogOth, comments from others; CogPCA, perceived cognitive abilities; CogQOL, impact of quality of life; DS, Digit Span; TMT, Trail Making Test; LEUS, Functional Assessment of Cancer Therapy-Leukemia Leukemia subscale; Hgb, hemoglobin; WBC, white blood cell count; ANC, neutrophil count.

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CHAPTER 4: EXPERIENCES OF CANCER-RELATED COGNITIVE IMPAIRMENT IN OLDER ADULTS WITH ACUTE MYELOID LEUKEMIA AND THEIR CAREGIVERS: A QUALITATIVE ANALYSIS

Introduction

Acute Myeloid Leukemia (AML) is an older adult cancer with a median age of 68 years at diagnosis (National Cancer Institute, nd). More than 59% of newly diagnosed AML survivors are aged equal to or over 60 years (National Cancer Institute, nd). Typically, adults with AML are treated with chemotherapy (National Comprehensive Cancer Network, 2018). Unfortunately, due to comorbidity, reduced function, and adverse cytogenetics, older adults with AML may have a lower tolerance for intensive AML treatment—such as the standard three days of anthracycline and seven consecutive days of cytarabine (7+3 regimen) induction chemotherapy—which may lead to a poor outcome (Estey, 2018; Etienne et al., 2007; Klepin et al., 2013). Therefore, Venetoclax (VEN), in combination with hypomethylating agents (HMA) or low-dose cytarabine [VEN+HMA/low-dose ara-c], has recently been approved as a well-tolerated and alternative chemotherapy option for older adults with AML (Jonas & Pollyea, 2019).

The impact of chemotherapy on cognitive function has been documented among survivors with various cancer diagnoses (Hodgson et al., 2013). Cancer-related cognitive impairment (CRCI) may involve impaired executive function, memory, verbal function/language skills, construction, concept formation and reasoning, perception, and orientation/ attention (Hodgson et al., 2013). In order to understand cancer survivors' perspectives of CRCI and how

CRCI may impact survivors, several qualitative studies have been conducted. For example, Selamat et al. (2014) performed a meta-ethnography of seven qualitative studies focusing on breast cancer survivors, which synthesized their CRCI experiences, coping, and impacts. By interviewing 31 cervical cancer survivors, Zeng et al. (2017) found that having difficulty concentrating was the most common problem and that impaired cognition mainly impacted daily activities. By understanding how survivors cope with CRCI and how CRCI affects survivors' life, researchers and health care providers can have a better understanding on the focus of future CRCI interventions development and potential effective coping strategies to better support cancer survivors. Still, qualitative studies focusing on breast cancer survivors are predominant. Compared to AML, breast cancer has a younger median age at diagnosis, which is 62 years. With a relatively younger cancer population that is predominantly female, there may be differences in the survivors' perspectives of CRCI and how CRCI may have an impact survivors. Therefore, an understanding of the AML patient experience of CRCI is needed to inform the knowledge gap in older adults with AML.

Having a caregiver is indispensable for cancer survivors during their illness journey, especially in older adults with cancer. Caregivers not only provide support but also play a vital role in assessing and managing cancer survivors' uncomfortable symptoms at home (Ullgren et al., 2018). Using data from a national survey of 1,182 AML survivors and caregivers conducted by the Leukemia & Lymphoma Society, Crossnohere et al. (2019) found that the prevalence of CRCI in AML survivors was 78%. Specifically, the severity of CRCI was reported by both people with AML and caregivers; and no significant difference was identified ($p=0.43$) (Crossnohere et al., 2019). In addition, rather than providing intervention only to the survivors, a growing number of interventions focused on incorporating caregivers or family members as well.

A prior systematic review identified 10 studies using caregiver or family interventions on cancer symptom control and management; however, the significant effect was limited (Griffin et al., 2014). Still, the caregiver is an important component in cancer survivorship. Hence, it is critical to understand caregivers' perspectives on CRCI, which will provides valuable information for CRCI management intervention development.

There are few studies focused on CRCI among the hematological malignancy population. Furthermore, although caregivers engage in cancer survivors' symptom assessment and management, to the best of our knowledge, there is no prior qualitative research exploring older adults with AML and their caregivers' perspectives on CRCI. To fill this research gap, the current study aims to provide an in-depth and comprehensive understanding of how older adults with AML and their caregivers view CRCI. Specifically, we hope to gain both patients' and caregivers' perspectives on the CRCI experience, changes in cognition, coping strategies, and how CRCI affects their lives.

Methods

Study Design and Approach

This is a qualitative descriptive analysis of a prospective, longitudinal study. The qualitative descriptive approach is used to describe or summarize certain phenomena and the characteristics experienced by individuals (Lambert & Lambert, 2012), using straight and everyday language (Sandelowski, 2010). The study was approved by the Institutional Review Board of the University of North Carolina at Chapel Hill (IRB. No. 20-2614).

Participants

The recruitment and consent procedure can be found in detail in the Chapter 3. Eligible older adults with AML who participated in the study of the Chapter 3 (n=14), recruited from the

North Carolina Cancer Hospital (NCCH), were invited to participate in this qualitative study. These older adults with AML were asked to identify one caregiver. Caregivers were eligible if they were 1) aged 18 years and older and 2) able to read and understand English.

Data Collection

Interview-Guide Development

The interview guides for older adults with AML and caregivers were drafted by the lead author (Ms. Ya-Ning Chan), who was guided by the Dynamic Symptoms Model (Brant et al., 2016); it was further reviewed and revised by the research team (Drs Aaron Piepmeier, Ashley Leak Bryant, Catherine Bender, Matthew C. Foster, Rachel Hirschey, Ruth A. Anderson). In order to capture the CRCI experiences over time, the interview guides asked whether survivors experienced any changes in cognitive function compared to prior interviews. Additionally, after conducting interviews on two older adults with AML and two caregivers, the transcripts were reviewed by an expert in CRCI (Dr. Catherine Bender) to identify if further modification of the interview guides was needed. After reviewing the transcripts by the expert (Dr. Catherine Bender), no changes were made. Table 4.1 shows the example interview questions for older adults with AML and caregivers. Completed interview guides for older adults with AML and caregivers can be found in Appendix 4.1 and Appendix 4.2.

Procedures

After identifying one caregiver, the author (Ms. Ya-Ning Chan) approached the identified caregiver and explained the study. Caregivers were also provided with time to ask questions and consider their participation. Interviews were conducted after written consent was obtained.

Interviews with older adults with AML and caregivers were conducted at 1) 2nd cycle of chemotherapy (around 30 days after initiating chemotherapy) (T1) and 2) 4th cycle of

chemotherapy (around 90 days after initiating chemotherapy) (T2). The author (Ms. Ya-Ning Chan) scheduled the interviews at a time good for participants beforehand through a phone call or text message to ensure their availability and decrease attrition. Depending on their schedule constraints, older adults with AML and caregivers were interviewed either in-person or over the phone in a private room to protect their confidentiality and avoid external distraction. Each recording was sent to the transcription service to transcribe verbatim; then, all transcripts were de-identified and checked for accuracy by the author (Ms. Ya-Ning Chan).

Data Analysis

Process

We used an inductive approach and thematic analysis (Hsieh & Shannon, 2005; Sandelowski, 2000a, 2000b) to capture older adults' with AML and caregivers' descriptions of CRCI experiences, how CRCI affects life in general, how to cope with CRCI, and potential related factors of CRCI. Transcripts were coded by two authors (Ms. Ya-Ning Chan & Mr. Youngmin Cho) separately using the ATLAS.ti software.

We conducted coding in three level. For the first level of coding, we used holistic coding to organize the transcripts. Then, in the second level of coding, we used descriptive coding or in-vivo coding to code 2–5 older adults' with AML and caregivers' transcripts separately. After separately identifying the common codes, two authors (Ms. Ya-Ning Chan & Mr. Youngmin Cho) then met to discuss and develop a codebook with a definition of each code (Appendix 4.3). Then, feedback was provided by coauthors (Drs. Aaron Piepmeier, Ashley Leak Bryant, Catherine Bender, Matthew C. Foster, Rachel Hirschey, Ruth A. Anderson) on the codebook to clarify the definition of each code and modify codes and definitions accordingly. After finalizing the codebook, the two authors (Ms. Ya-Ning Chan & Mr. Youngmin Cho) proceeded to code the

transcripts using the codes from the codebook. Any meaningful quotes that could not be coded using the existing codes were discussed; these additional codes were also added to the codebook. Finally, for the third level of coding, similar codes were grouped to generate themes and subthemes. During all the coding phases, the authors (Ms. Ya-Ning Chan & Mr. Youngmin Cho) used memos to document decisions made during analysis of the interviews and reflect on biases or preconceived notions of the coders that may influence data-analysis (Sandelowski, 2000a, 2000b, 2010). Any discrepancies were discussed to reach consensus. The authors met weekly to discuss codes, patterns, emergent codes, themes, and any discrepancies. Lastly, we organized and synthesized the findings within older adults with AML and within caregivers at each time point using data matrix.

Rigor

We applied the shared standard of rigor in qualitative research, which was developed by Lincoln (1985), to ensure the rigor of this study. For credibility, the data were collected using semi-structural interview guides developed by the research team, which includes qualitative methodology experts and cancer and cognition content experts, to ensure that the interview questions could capture the data we aimed to study. The interviews were audiotaped, transcribed verbatim, and checked for accuracy before data analysis to ensure that we kept participants' original words. Although the study recruited only older adults with AML and their caregivers, the transferability of their responses about CRCI experiences, how CRCI affects lives, their coping strategies, and perceived CRCI related factors might be similar across older cancer survivors. Therefore, the study findings could provide valuable insight and guidance for future CRCI survey or intervention development research targeting older cancer survivors and caregivers. For dependability, we applied a standard procedure for data analysis—holistic

coding, descriptive/in-vivo coding, and codes grouping/subthemes and themes generalization—to ensure that the study is replicable. Memos were used to facilitate data analysis. In addition, the research team reviewed the coding process and preliminary results. For confirmability, two coders (Ms. Ya-Ning Chan & Mr. Youngmin Cho) separately coded the transcripts, constantly compared and discussed to solve coding discrepancies and reach consensus, and regularly met with the research team to get feedback.

Results

Sample Characteristics and Study Follow-ups

A total of 25 participants (14 older adults with AML and 11 caregivers) were consented to participate in the study (Figure 4.1). During the study follow-ups, two participants withdrew consent due to limited time, three older adults with AML died, and three caregivers were removed from the study because their loved one (older adults with AML) died. Due to the constant postponing of cycle 4 treatment, two participants (one older adult with AML and one caregiver) were excluded for follow-up interview from the current dissertation analysis. Additionally, four older adults with AML completed an early end-of-study interview because the change of their AML treatment plan (three proceeded to peripheral blood stem cell transplantation and one changed their chemotherapy regimen). In total, 19 participants completed the T1 interview; seven participants completed the T2 interview; and seven participants completed an early end-of-study interview.

For older adults with AML, the average total follow-up time was 74 days for the entire study. The average was 87 days for those who completed the T2 interview and 61 days for those who completed the early end-of-study interview. For caregivers, the average total follow-up time was 82.67 days. The average was 91 days for those who completed the T2 interview and 74.33

days for those who completed the early end-of-study interview. The retention rates for the T1, T2/early end-of-study interviews were 76% and 56%, respectively (Figure 4.1).

The 11 older adults with AML who participated in the interview were aged 64 to 89 years. The majority of them were White (90.91%), male (72.73%), with a high school/GED degree (63.64%), and married/partnered (54.55%). The eight caregivers were aged from 45 to 83 years. The majority of them were White (87.5%), female (87.5%), and married/partnered (87.5%) (Table 4.2). Five of the caregivers were spouses (62.5%) and three were children (37.5%).

Common Themes in Older Adults with AML

We identified four main themes: CRCI experiences, the impact of CRCI, CRCI coping strategies, and perceived CRCI related factors; we also noted subthemes within each main theme of older adults with AML (Table 4.3).

CRCI experience

We identified four subthemes, which included ***domains***, ***frequency***, ***ways to notice CRCI***, and ***trajectory of CRCI***. Older adults with AML expressed cognitive changes in various domains. Specifically, they noticed a change in memory and became forgetful. Some found they could not recall the things they had been trying to remember in their mind; some mentioned that they could not remember occasions/events they had been through, such as the day they were admitted for AML treatment or the process of a bone marrow biopsy. Moreover, some older adults with AML, who had pre-existing problems in memorizing names, emphasized their increased difficulties in remembering names of people to whom they had been introduced previously.

I can't remember names. Then, I think about it and then after a while, it come to me, but I just can't pull it up. I don't know how to explain it. I don't have to tell you all this because you see what I -- I just can't remember. I can remember some things good but a lot of things, I just cannot. (Male, 80-84 years old, T1 interview)

Older adults with AML also mentioned that they struggled to remember where they put their "stuff" (i.e., car keys) or recall what others told them to do or what they intended to do when they walked into a room. They needed to spend extra time to locate the items they were looking for or had to walk back and forth to be able to finish the tasks.

Sometimes you'd walk in a room and you'd say why did I come in there and you stand there for a few minutes and then you'd say, okay, I'm going out. (Male, 65-69 years old, Early end-of-study interview)

Additionally, some of them found they had difficulty remembering conversations they had with others previously or even just minutes ago. One described that his memory became "foggy" in general and was unsure whether he could remember or recall in the short-term.

Memory is still pretty good. Remembering things is a little foggy, but if somebody brings up a conversation, I can remember the majority of it. But if somebody asks me something, sometimes, it's there. Sometimes, it's not, so I guess recent memory is not really there, but long term is pretty good, yeah. (Male, 65-69 years old, Early end-of-study interview)

In addition to the memory problem, some noticed the change in language—they struggled to find words when talking to others. Some mentioned specifically that they could not recall words they rarely used during everyday conversation or they could not think of the object's name until they actually saw the object, while others claimed that the problem happened during everyday conversation without identifying any specific scenario.

Finding the words seems to be my biggest thing at times. I used to not have that big of a problem finding the words to say. And now sometimes I have struggled finding the right words to express myself at that point. (Male, 65-69 years old, Early end-of-study interview)

The last domain we identified was concentration. Several older adults with AML noticed that their attention/concentration became diminished. They did not do things in a sequential way or became easily distracted.

I've noticed a couple of times where I've set out to do something, and then I kind of get sidetracked, and I forget all about it until I see it and I go, "Oh, that's right. I was going to go do that, or I was going to go do this." (Male, 65-69 years old, T1 interview)

On the other hand, some older adults with AML claimed their concentration changes were voluntary. Specifically, some mentioned that they did not need to stay as focused as when they were young because they were unemployed or did not have a lot of things to think about. One mentioned that his concentration depended on his interest toward a specific area of focus. Some expressed that their concentration and priority switched after they got cancer that led them to pay less attention on other aspects of their lives.

Once you receive a diagnosis for acute myeloid leukemia, as they say about a man who's going to the gallows, it focuses your attention not necessarily on other things but on your life. So in that sense, it's changed… Well, what I have time to do and what remains to be done, on the other hand there, I think that I should often feel that I should be doing. …. And I'm not enthusiastic about doing that anymore. (Male, 85-89 years old, T1 interview)

Older adults with AML also identified the frequency of their problem in memory, language, and concentration. Although several of them identified the problem as an "everyday

thing," they generally claimed the problem happened "infrequently" or "off and on" depending on the day or occasions.

> *Depends on the day. I don't know. I'd say I'd go through a phase like that at least once a day, maybe twice a day (having a difficulty remembering the words). But, and some days I don't, but it all depends on the activity I'm doing that day to be honest and who I'm talking to. (Male, 65-69 years old, T1 interview)*

In terms of how they noticed these cognitive changes, several of them mentioned that others, such as their caregivers, pointed out or brought up the problems. Some realized their problems by themselves when they encountered challenges.

> *It (having difficulty finding words) just seemed to slowly happen. One day, you're good to go and then the next day, you notice there's a little bit of a difference. Well, a few more days down the road, there's a little more difference and then finally you realize that hey, this isn't the way it was a week or two ago. (Male, 65-69 years old, Early end-of-study)*

Finally, older adults with AML had experienced varied trajectories of perceived cognitive changes. Several older adults with AML described their cognitive function decreasing or remaining the same after being diagnosed with AML and starting their VEN+HMA/low-dose ara-c chemotherapy. However, some had received other cancer treatment (for AML or myelodysplastic syndrome) and thought the decline in cognitive function started when they were first diagnosed with cancer or received more intensive treatment. Compared to previous intensive treatment (i.e., peripheral blood stem cell transplantation or clinical trial), they perceived VEN+HMA/low-dose ara-c chemotherapy as less intensive. Therefore, they did not experience further decrease in cognitive function or actually felt better.

I think it actually has gotten better to where when I first started all this chemo and everything, there was a lot of things I was forgetting and having problems remembering. Now not so much. It's not as bad as it used to be… That (first start chemotherapy) would have been back in June of 2019. I went ahead and signed up for a clinical study, so I got extra chemo. That's probably where it all started. It was an extra couple of days, and it was pretty radical. There were days I would wake up and go where am I, oh yeah, yeah. And then the next couple of them weren't so bad. And then the one chemo that I got before my transplant in December of 2019 really wiped me out. I don't think I ever recovered from that one. But I did go into remission for about six months, and then I relapsed. It's been kind of mild chemo since then. And this, what I'm going through right now, isn't so bad. (Male, 65-69 years old, T1 interview)

Compared to prior to being diagnosed of AML, some older adults with AML experienced poorer cognitive function at the diagnosis or the initiation of VEN+HMA/low-dose ara-c chemotherapy and gradually improved afterwards; but was still worse than the time before diagnosis.

Probably during that first seven days of chemo is where it (changes in cognition) really came into play because I was overwhelmed. I was getting accustomed to the hospitals and treatments, and it's the difficulties of just keeping up with everything became a little more than I anticipated. Now that I'm more accustomed to it, and understand the hospital, understand the timing, and I'm doing better. (Male, 75-79 years old, T1 interview)

In addition, older adults transitioning from cycle 2 to cycle 4/early end-of-study identified no further change in cognitive function.

I don't think I've seen any difference in my memory. I haven't seen much change in it. No… (It) Stayed the same. (Male, 65-69 years old, T2 interview)

To summarize, either noticing by themselves or pointed out by others, older adults with AML mentioned their difficulties in memory, language, and concentration throughout the study follow-up, although these problems did not happen on a daily basis. Moreover, older adults with AML either experienced 1) a decrease in cognitive function at diagnosis and initiating VEN+HMA/low-dose ara-c chemotherapy and an improvement afterwards; 2) a decrease in cognitive function after the initiation of VEN+HMA/low-dose ara-c chemotherapy with no later improvement, or 3) no change in cognitive function after the initiation of VEN+HMA/low-dose ara-c chemotherapy. Then, they felt that there was no change in cognitive function between T1 and T2/early end-of-study.

Impact of CRCI

Older adults with AML identified the impact of changes in memory, language, and concentration on various aspects of their lives. We identified three subthemes, including ***impact on emotion***, ***disruptions of life***, and ***no impact***. Frustration and being upset were common emotions expressed by older adults with AML.

Sometimes, I can't (remember things), and it's just it gets frustrating because I know it's there. I know I've lived it, but it could be a day. It could be a week. It could be two weeks, but a month, a year, two years, 10 years, no problem whatsoever. (Male, 65-69 years old, T1 interview)

They felt awkward, uncomfortable, and embarrassed when encountering difficulties finding words or recalling people's names when talking to people and being unable to retrieve the words or names from their memory immediately.

Well, sometimes, it's embarrassing. I can't recall a name, but I about got used to it. It don't really bother me that bad. People look at me and say, "Well, he's an old, sick man," so they overlook me. (Male, 80-84 years old, T1 interview)

Rather than being frustrated and upset about their difficulties, older adults were concerned more about how their caregivers worried over the survivor's disease condition. For example, one expressed his worry toward his wife when thinking about her concern about his changes in cognitive function.

I worry about my wife all the time because she's scared, very scared [about older adults with AML's condition]. (Male, 75-79 years old, T1 interview)

Changes in cognitive function also disrupted older adults' with AML daily lives. They mentioned that they could not perform daily tasks or work on the stuff they used to enjoy as before because they were not like they used to be and needed to be extra careful. They also noticed that they needed much time when doing daily tasks due to the change in cognitive function.

It (difficulty concentrating and memory slows down) just slows everything down, yeah. It's just where I used to be able to get a lot of things accomplished, and now it's just a much slower process. (Male, 75-79 years old, T1 interview)

Moreover, several older adults with AML identified challenges in talking with others during social activities due to their difficulty in finding words that further led to isolating themselves from family, friends, and others.

I was talking to my daughter the other day and about 15 minutes into the conversation, I started stumbling over words, trying to find words that I needed to use, so I gave the

phone to my wife and let her do the talking. It's just chalk one off for chemo brain, I guess. (Male, 65-69 years old, Early end-of-study interview)

The impact of changes in cognition was not only on older adults with AML, but they also pointed out how this problem disrupted their caregivers' lives. Specifically, older adults with AML identified how their caregivers provided them support, such as finding words while talking and scheduling clinic appointments, and they acknowledged that caregivers had increased caregiving responsibilities. Older adult with AML stated "*Because she's [daughter] there now a lot with me and she's my eyes, ears. So, I've learned to shift the responsibility I hate to say." (Female, 85-89 years, T1 interview)*

Although some older adults with AML experienced the impact on emotion and disruption of life, several older adults with AML claimed that the change in cognitive function seldom happened and did not cause any impact on them.

It's [changes in memory] just that little moment and that was it, so I don't think I have much trouble, do I? No. (Male, 60-64 years old, T1 interview)

To summarize, the data showed that CRCI impacts survivors' emotions and disrupted their lives over time. Some older adults with AML claimed that CRCI did not have an impact at all during the study follow-up. No new impacts emerged during study follow-up.

CRCI coping strategies

In order to reduce or manage changes in cognition, older adults with AML identified various coping strategies. We identified three subthemes, including ***problem-solving coping strategies***, ***no problem-solving coping strategies***, and ***emotional coping strategies***. Problem-solving coping strategies referred to behaviors or actions the older adults with AML took to reduce and manage CRCI. Taking notes or written reminders was one of the most common

problem-solving coping strategies. Specifically, older adults with AML mentioned that they wrote down the names of peoples they met during clinic visit or things they needed to take care of; some wrote down the time of every clinic appointment and made a list for grocery shopping.

> *Sometimes I'll write it down. Like before I go to the store for something, I'll write it down because I know by the time I get to the store, I'll get a few things, and then I'll get home and I'll go, "Oh geez, I needed to get that too." So, I started making little lists and stuff for grocery shopping, [grocery store name], things like that. It helps me to remember, and it works out okay. (Male, 65-69 years old, T1 interview)*

Other than writing down on paper, several older adults with AML also used technical support, such as the appointment function in My Chart, calendar function on the phone, and reminder from their voice assistant devices.

> *I use Alexa a lot… She helps me a lot… Talks to you. Alexa, tell me in ten minutes I need to turn the water off...We have a discussion about I wonder how deep [lake name] is..."Alexa, how deep is [lake name]?" 1,150 feet. It's like...She knows everything…She'll tell you whatever you to tell her. She's like an encyclopedia. (Male, 75-79 years old, T2 interview)*

Some older adults with AML pointed out that their lives were very regular and structured. They had activities scheduled at certain times. This clear routine helped them remember things such as notice any physical changes or taking medications.

> *I do the same thing. I get up 5:30 in the morning, whether I got to be somewhere or not. I go downstairs. I have pretty much the same kind of stuff for breakfast. I come back upstairs. I do my reading. I send texts to a couple of people and about six o'clock I turn the news on and it's not that I'm rigid, but structure gives you a sense of security and it*

also helps you remember to do things. So it's like, okay, I get my water. And then I got some pills I have to take. (Female, 65-69 years old, T1 interview)

One even tried to do some cognitive exercises, which included crossword puzzles and reading, to reduce her changes in cognitive function. Moreover, older adults with AML also actively sought assistance or understanding from others. For example, some had their caregivers help or took full charge of scheduling and keeping track of all the clinical appointments, while some had others do the talking for them when they encountered difficulty finding words. In addition, one explicitly told people he talked to others about his difficulty in finding words to have their understanding.

So, in conversation, you talk a long way, just talk, talk, talk, and then you stop and you've got to think. And then I would go, "Chemo brain" and everybody would go, okay, whatever. (Male, 65-69 years old, T1 interview)

Some older adults with AML, on the other hand, did not use any problem-solving coping strategies pro-actively to manage their changes in cognitive function. They just took some time to pause and think when they could not recall names, events, or things they were supposed to do; some claimed that they were able to get the memory back.

I just have to take a minute and kind of. Take pause and kind of talk to myself and try to get the word in. Most of the time it comes to me, but it's a lot slower than it was. (Male, 65-69 years old, T1 interview)

Some thought of a connection between an item and person's name to try remembering names of people they were introduced. Some just paused and thought when they could not find the right words. They used the words they wanted to use if they could think of; if not, they chose to come up with different words with the same meaning.

There were times when I'd have a conversation with somebody and then I would stop, and I would have to think of the word that I want to use, and sometimes it would be there or otherwise I would just seek out another word that means the same thing, a more simpler word. (Male, 65-69 years old, T1 interview)

In addition to problem-solving coping strategies, older adults demonstrated emotional coping strategies—the attitude and perspective on CRCI. Older adults with AML noticed the change in cognitive function during daily lives and the problem did not cause any concern and worry to them. Instead, they considered the change in cognitive function as a normal aging process, expecting they would not be as sharp as they were when young. Some accepted the change in cognitive function, did the best they could, and lived with it since they did not think they could control over the change.

It [forgetting names] doesn't worry me, I have accepted one thing. You don't worry about what you don't have control of. (Male, 65-69 years, T1 interview)

Moreover, some dealt with the difficulties they encountered with a sense of humor or relying on praying and their personal religion to support them while they encountered difficulties.

I feel it's a challenge. Something to press through. I truly believe once I able to get through all the treatments and, praise God, put the cancer behind me, I believe it'll get better because I'll get back more into my routine and doing what I'm been used to doing. (Male, 65-69 years old, Early end-of-study interview)

To summarize, we saw no problem-solving coping strategies, emotional coping strategies, and no coping strategies in T1, T2 or early end-of-study interviews. We identified no changes related to coping strategies across the study follow-up.

Perceived CRCI related factors

Older adults with AML identified potential related factors they thought might contribute to the change in memory, language, and concentration. We generated five subthemes: ***demographic***, ***physiologic/clinical***, ***psychological***, ***environmental***, and ***other factors***. Some of older adults with AML identified age as a demographic factor, connecting the cognitive changes they were experiencing with their age.

I think memory probably getting to the point of the age. (Male, 60-64 years old, Early end-of-study interview)

Older adults with AML identified cancer diagnosis and treatment because they mentioned their changes in cognitive function occurred or became noticeable after the initiation of their cancer treatment.

It got more noticeable when I was in the hospital with the chemo for number of days. There's no question that chemo kind of affected my memory. (Male, 65-69 years old, Early end-of-study interview)

However, some older adults with AML did not think of cancer diagnosis and treatment when experiencing changes in cognition. One of them expressed his doubt.

I don't think that my memory's so much as my enthusiasm or willingness to undertake these things that perhaps I would've liked to have done. So I don't feel that illness or treatment has been impairing my memory. (Male, 85-89 years old, T1 interview)

In addition, one older adult with AML raised other physical/clinical factors, which included other medication, blood cell count, sleep, and fatigue. Specifically, one mentioned that she was given a substantial amount of medication during bone marrow biopsy and could not recall the whole event. The other noticed that he felt "run down" when his Hgb or platelet count

was low; but felt "juiced back up" after infusion. Another older adult with AML found that she had a "gap" in the memory when having difficulty sleeping while she was hospitalized; in comparison, she reported her brain felt "well-rested" when she got a lot of sleep after discharge. Lastly, one claimed his memory was dependent on energy level.

> *My concentration is a matter of being tired, taking more naps, and being sort of unwilling to do the hard work or some harder work. (Male, 85-89 years old, T1 interview)*

Only one older adult with AML perceived psychological factors—emotional distress. He expressed his fear of and worry about the coronavirus disease 2019 (COVID-19) lockdown policy and no COVID-19 vaccine reservation availability. He was also distressed by being diagnosed with cancer, uncertainty about the treatment effect, and his family's worry about his condition.

> *But maybe there is some impact [on memory] because of the medication and just the worry that comes with it. And the worry is not so much about me having that disease. It's about my wife and family that are worried. (Male, 75-79 years old, T2 interview)*

In terms of the subtheme, environmental factor, some older adults with AML received other AML treatments prior to the VEN+HMA/low-dose ara-c and found their difficulty in remembering things and finding words was worse during their in-hospitalization. One further claimed that the cognitive change got better after discharge from the inpatient setting.

> *So it [having difficulty finding words] has gotten a little better because I think what helped was going back to a familiar environment after being so many weeks in the hospital. (Male, 65-69 years old, T1 interview)*

The last subtheme—other factors— contains the codes that were important but difficult to group. Some older adults with AML mentioned that the information and tasks related to AML overwhelmed their brain, mind, and thought process. Specifically, they needed to process huge amounts of information related to their diagnosis and treatment plan; were scheduled five to seven days consecutively for chemotherapy infusion in the clinic for each cycle and periodically regular clinic appointments; and dealt with unexpected appointment changes.

> *I guess I'll attribute it [forgetting things and having difficulty finding words] to taking in all the information, trying to understand everything that I'm going through physically. I've been blessed because I'm not really suffering that much physically, but trying to understand everything that's going on with all the different terminology and what have you. And, like I said, all the different appointments and meetings and discussions, questions, but I think that's, it's just, I'm taking in a lot more information than I did before I was diagnosed with leukemia. (Male, 65-69 years old, T1 interview)*

In addition, some older adults with AML pointed out the shift of their social responsibilities and priorities after their diagnosis could contribute to their cognitive changes. One mentioned being diagnosed of AML actually helped her become more focused and some said this shift could be that their need to focus was not urgent due to unemployment. In addition, some claimed their priorities shifted due to their illness. The need to make themselves available for clinic appointments attributed to the challenges in cognitive function.

> *When you have an illness requires as much time as this illness, just to come to the drive in here, park, walk, all those things, it's a big time thing. So in another life, I never wasted this many hours just to keep myself alive. So I suppose that's a factor that hinges on getting some things done. (Male, 85-89 years old, T1 interview)*

To summarize, older adults with AML identified potential demographic, clinical (cancer diagnosis and treatment), psychological, other (change in life conditions) factors that related to their change in cognitive function across the study follow-up. However, physical (blood cell count, sleep, and fatigue)/clinical (other medication), environmental (inpatient stay), and other (overwhelming information and tasks related to AML) factors were pointed out only at T1 interview.

Common Themes in Caregivers

The four main themes identified in older adults with AML—CRCI experiences, impact of CRCI, CRCI coping strategies, and perceived CRCI related factors—were the same for caregivers (Table 4.4). The following presents the subthemes within the four main themes.

CRCI experience

The theme of CRCI experience included subthemes of ***domains***, ***frequency***, ***ways to notice CRCI***, and ***trajectory of CRCI***. In terms of the domains, caregivers noticed their loved ones experienced memory difficulties. They misplaced things around the houses and forgot the location of the items, had difficulty recalling peoples' names they had been introduced to, or did not remember what happened while they first got sick and got to the emergency room. Additionally, some caregivers pointed out that their loved ones forgot their previous conversation a couple days or even a couple hours later.

I'll say something to him and then a couple hours later, he doesn't remember that I said it, and I'll say I told you that. (Female, Spouse, 60-64 years old, T1 interview)

Several caregivers also mentioned that their loved ones forgot things that were supposed to be done. For example, one caregiver mentioned her husband forgot to clean the dusty stuff in

the house that she had told him to do. Another caregiver mentioned that his father had difficulty keeping track of whether he already took the medication or not.

> *We noted pretty quickly like he couldn't remember if he had taken his pills or not. He had his own system that he used for the pill trays that we ended up having to discard because we couldn't figure it out, and he couldn't remember if he had actually done things, so that was one area. (Male, Children, 45-49 years old, T1 interview)*

Caregivers also observed changes in language and concentration in their loved ones. Some saw their loved ones had difficulty pulling up/recalling the word they were planning to use or used wrong words when talking. In terms of concentration, one caregiver mentioned that her husband was not as focused as they had been that might because they "had other things or situations preoccupied with their lives." Other caregivers mentioned an inability to multitask. They stated that their loved ones "zoomed into" a situation that caught their attention and just ignored other things that were happening around them.

> *I was talking to him about this the other night. We have the kids are over whatever, and we're having a conversation. His phone will ring and he'll just walk out the room, and don't say, excuse me, I've got a call. Or like, whatever comes to his attention at the moment he pays attention to. Not being aware of what's going on around him with other people at the time…So I don't know if that's what. I think that's related to that he didn't use to be like that. (Female, Spouse, 60-64 years old, Early end-of-study interview)*

Lastly, several caregivers also noticed their loved ones struggled to process information. They could not process the information their doctors provided, did not get the point while having conversations with several people, or needed longer time to put their thoughts together.

He's not as quick to respond to questions as he was. He's got to think about it a little bit…It takes some more time to process whatever I'm saying. Not a lot of time; he's still not like he's got dementia or anything like that. (Female, Spouse, 60-64 years old, Early end-of-study interview)

Only two caregivers mentioned the frequency of the difficulty in memory, language, concentration, and processing information in their loved ones was every day. Other caregivers mainly found the problems did not occur on an everyday basis; the frequency could be "every couple of days," "every other day," "every third day," or "once/twice per week."

Yeah, (forgetting things happen) every once in a while or every once in a blue moon. (Female, Spouse, 60-64 years old, T1 interview)

Caregivers noticed changes in cognitive function of their love ones by experiencing or seeing the difficulty when spending time with them. For example, they noticed their loved ones forgot to do things they should have done, needed repetitive confirmation and longer time to process, or experienced struggles they did not used to have.

So minor memory things. We always talk about sometimes on the phone, but now that I'm here and spending more time with her and like I said, I think it has to do with the changing circumstances, her condition that I noticed it more because I'm with her every day now and I can see when she comes in, she's struggling a little bit to hear and she's asking a lot of questions and she's not always processing everything. (Female, Children, 60-64 years old, T1 interview)

Caregivers further identified various trajectories of the change of cognitive function. Several caregivers of older adults with AML that were not newly diagnosed mentioned that their loved ones' cognitive function remained the same. Some caregivers mentioned that they noticed

that their loved ones' cognitive function declined after the start of the chemotherapy. Also, several caregivers pointed out that they noticed that their loved ones' cognitive function decreased when they first got diagnosed and initiated the chemotherapy, but it gradually got better afterwards.

> *With that said, there was clearly a decrease that was occurring for those first, I'd say, two to three weeks after he first landed in the hospital and then he went through his first round of shots and the chemotherapy treatments. However, I would say after that first round where he went on seven days of receiving the shots, within a week or two after that, I would say things rebounded to his sort of pre-leukemia normal that he had and if anything, it actually, I would say, it might even be better now than what he had before even though they had been dialing back his meds a little bit because he is in remission now, which is good. Definitely, to me, he seems like he's at least back to where he was before, possibly even better. (Male, Children, 45-49 years old, T1 interview)*

For the cognitive change from cycle 2 to cycle 4/early end-of-study, one caregiver felt that her husband's cognitive function got better; another caregiver pointed out her husband's cognitive function declined, as he did not respond to question as quickly as before. Most caregivers did not observe any change in their loved ones' cognitive function otherwise.

> *Not really [notice any change in cognitive function] and if it did, it's very subtle and I didn't notice. But I don't think there's much change [in cognitive function]. (Female, Spouse, 60-64 years old, Early end-of-study interview)*

To summarize, caregivers noticed that their loved ones had difficulties in memory, language, concentration, and processing information during the study follow-up. The problems mainly happened every once in a while. Caregivers identified the trajectory of cognitive function

using the categories of increased, declined, and remained stable. Most caregivers claimed their loved ones' cognitive function remained stable when transitioning from T1 to T2/early end-of-study.

Impact of CRCI

Three subthemes were identified, which included ***impact on emotion***, ***disruptions of life***, and ***no impact***. For emotion, caregivers expressed worries about their loved ones' safety and their frustration for trying to help their loved ones. For example, one caregiver expressed his concern and fear when the oncologist allowed his father to drive to clinic appointments because he was not sure whether his father was ready or not. The other caregiver was frustrated because her husband refused to accept help from her or others even when he could no longer do mechanical work. Moreover, not only because of the changes in cognitive function, one caregiver felt overwhelmed by the whole situation.

> *Sometimes I get overwhelmed and I'll just go in the bedroom and cry for a little while and I'll be better. So he doesn't know what happened...because he doesn't deal with that same way than I do. Men are different than women. Women are so much more emotional. (Female, Spouse, 60-64 years old, T1 interview)*

Changes in cognitive function not only impact on caregivers' emotions, but also disrupt their life. One mentioned that it took her and her husband longer time to get things done or do things. Some had more responsibilities, such as managing their loved one's schedule, making notes during clinic visit, figuring out what their loved ones were trying to say or convey in conversation, and providing help any time it was needed.

> *I'm patient because I know that I need to help him with whatever I can and I try to do the best I can, if I have to go a little further, take selling something. I will, I try to, I'm trying*

to help him. Cause I know he's sick and I'm trying to help him. I'm doing the best I can. (Female, Spouse, 65-69 years old, T1 interview)

Moreover, several caregivers expressed the impact on their relationship with their loved ones. For example, one caregiver mentioned her husband forgot and accused her of forgetting to remind him of things even though she had told him. Another caregiver felt that her role changed:

I feel like I'm more of a secretary sometimes than a wife, so that's frustrating sometimes. It's not much different than when I had the seven kids. I was always managing their time and their chores and their this and their that. So it was kind of a natural place for me to fall into, but it's kind of weird doing it with my husband. I feel like I'm mothering him more, but again, as a caregiver, that's what you do. I think it's changed the dynamics of our relationship somewhat but, we just try to laugh more, I think, and not get bogged down with it too much. (Female, Spouse, 60-64 years old, T1 interview)

Although some caregivers identified the impact on emotion and disruption of life, several caregivers claimed CRCI had no impact on them. They stated:

I don't think it impacts my life. I just am alert that this could happen and it could happen with me too, probably. And I, no, I don't think it impacts our lives. (Female, Spouse, 65-69 years old, T2 interview)

To summarize, caregivers identified that their loved ones' CRCI impacted their emotions and disrupted their life over time. No new impacts emerged at any specific time point. Some caregivers identified no impact from CRCI.

CRCI coping strategies

To help their loved ones and themselves cope with changes in cognitive function, caregivers developed ***problem-solving coping strategies*** and ***emotional coping strategies***. For

problem-solving coping strategies, caregivers observed and provided their loved ones with the support and help they needed. For example, one tried keeping their loved one active to keep their loved one's brain going; some managed pillboxes to make sure their loved ones adhered to oral medication and provided verbal reminders to prevent their loved ones from forgetting important things. Some caregivers gave clues or took guesses to figure out what their loved ones were trying to say when they had difficulty pulling out words. Some provided repeated explanations or took notes during clinic visits for their loved ones to help them process information.

> *Yesterday, when I was here, I took note[s] while meeting with the doctor. And so last night she was able to review the notes together and we went through them and then the doctor also gave her the printout. So she actually read through that as well. So the written material really helps her a lot once she's back home and she's got questions, she can go through that. (Female, Children, 60-64 years old, T1 interview)*

In addition to providing support as needed, one caregiver mentioned she served as ears for her mother and helped process everything to make sure her mom understood all requirements for the treatment. Another caregiver took total responsibility for everything.

> *We have to go over details with each other about things. I'm managing all of his appointments. I do the MyChart. I do the questionnaire and communicate with the doctors, and the nurse navigators, and the social worker. So if I make a tweaky mistake, it's hilarious and we get a big kick out of it. Things, as you know, don't always go as smoothly, appointments change at the last minute. (Female, Spouse, 60-64 years old, T1 interview)*

In terms of emotional coping strategies, some caregivers just accepted the changes their loved ones experienced. Caregivers also considered the change in cognitive function of their

loved ones as normal aging process. For example, some caregivers, who were spouses, compared their loved ones' cognitive function with their own cognitive function. Caregivers found that they were also forgetful and might need reminders from their loved ones. One caregiver resided in a retirement home with her husband and thought the changes they experienced were normal.

> *You know all old people, I think, do that. You just can't find the word that you're looking for. I do it too. Maybe he does it a little bit more than I do, but it's just a typical thing that lots of older people do. (Female, Spouse, 80-84 years old, T1 interview)*

Although changes in cognitive function in older adults with AML were observed, caregivers stated the problems were not a major concern or big deal for them. For example, one said it took them longer time to get things done but that it was not big deal since they "have no place to go." Another caregiver mentioned that the change was noticeable but was not as bad as the change of cognition in individuals with Alzheimer disease. Moreover, compared to the diagnosis of AML, the change in cognitive function was not their biggest concern.

> *But I wouldn't say it wasn't like life changing for us and really like existential worry. That wasn't our biggest concern through this whole thing. It was a concern but not the biggest concern. (Male, Children, 45-49 years old, T1 interview)*

Several caregivers also mentioned their hope, positive attitude, or humor toward their loved ones' changes in cognition. For example, they believed it would take time and their loved would get better or change back again. Another caregiver said she and her husband got to spend more time and laughed together at each other to keep a positive vibe.

> *[Changing in memory and forgetting things] Brought a sense of humor into things in a greater way, I think. We laugh at each other more now…So the question is, how has it impacted our lives together? I think it makes it more fun, kind of. We laugh more, but*

also we never did spend a lot of time with each other cause he worked all the time, and I was with the kids and now all of a sudden we're together all the time. You got to laugh, otherwise you cry. (Female, Spouse, 60-64 years old, T1 interview)

To summarize, problem-solving and emotional coping strategies were seen in T1, T2 or early end-of-study interviews. No new coping strategies were identified at certain time point.

Perceived CRCI related factors

Caregivers also identified ***demographic***, ***physical/clinical***, ***psychological***, ***environmental***, and ***other factors*** that they thought might be related to their loved ones' changes in cognitive function. Age was the only demographic factor identified by caregivers. For example, they talked about how their loved ones' memory has been decreasing little by little each year as they aged. Some caregivers mentioned that they themselves were also forgetful; therefore, it could be an aging thing.

Well, he says chemo brain. I say, what is it, old-age brain and just you think of something and then, "Oh, I forgot what I was going to tell you" or something like that. (Female, Spouse, 60-64 years old, T2 interview)

Other possible factors that came up from caregivers were cancer diagnosis and treatment. For example, one caregiver mentioned that she did not realize her husband was that sick when they first came to the emergency room. She recalled that due to the overall weakness from the AML diagnosis, her husband did not remember things that happened during that time. Some caregivers stated that they started noticing cognitive changes after initiating cancer treatment.

Maybe medication is making her a little bit more clouded. She doesn't have all the clarity that she had prior to her treatment and I'm not sure, but it could be that. (Female, Children, 60-64 years old, T1 interview)

Caregivers further pointed out the possibility of other physiological/clinical factors, such as blood cell count, hearing, sleep problems, and fatigue. For example, one caregiver surmised that "there was a possible connection between neutrophil counts and the changes in memory; but was not around his father close enough to have enough datapoints to say that for certain." Several caregivers also brought up the problem of bad hearing. They noted that their loved ones could not hear clearly and questioned if this contributed to their difficulty processing information when in conversation with other people. Moreover, one claimed that memory problems might due to lack of sleep. Some caregivers further mentioned that their loved ones were not thinking when they were tired and it all depended on their energy level.

> *Like this morning, he told me this morning he was tired. So he's not thinking, I've noticed that. When you were asking his questions, he's just tired this morning. (Female, Spouse, 65-69 years old, T2 interview)*

Emotional distress was identified as a psychological factor by caregivers. They mentioned that emotional distress and worries always "crowd out mental space" or were "in the back of their loved ones' minds." With those in mind, their loved ones were unable to process, communicate, and hear other things.

> *She's got some anxiety and some emotional stress that also tuned out some of the things that when people are talking to you, you don't always hear everything because you're still, maybe a little bit of stress or trying a little anxiety when you're in certain circumstances. (Female, Children, 60-64 years old, T1 interview)*

One caregiver also pointed out her husband could not remember what happened when he was in the inpatient setting. Some caregivers noted the change in their life conditions might be one possible factor. For example, their loved ones were so "preoccupied with the situation of

being diagnosis of a terminal illness that they might be thinking about stuff differently from others or were not as engaged in life as they were." Lastly, caregivers also noticed problems with memory and processing information when overwhelming information or tasks were provided to their loved ones. For example, their loved ones could not keep up with the conversation and get the point when more than two persons were having conversation together. They also recalled the difficulty in processing information and memory when their loved ones got huge amount of information regarding AML from health care professionals and tried to make a lot of different decisions they had not made before. Additionally, because the treatment was repetitive and mainly conducted in the outpatient setting, caregivers and their loved ones needed to deal with a "hectic schedule" to coordinate the treatment plan.

> *I would just say in the last two weeks or so we've been having a lot more of a hectic schedule and I think that heightened schedule probably has something to do with it (change in memory and process information). There's more treatment, there's another cycle coming. So we talked about preparing for these cycles coming up because there's a little bit of downtime, but still, there's a lot of appointments in between too. (Female, Children, 60-64 years old, T1 interview)*

To summarize, caregivers identified that age, cancer diagnosis and treatment, fatigue, emotional distress, and overwhelming information and tasks related to AML might be related to their loved ones' change in cognitive function across the study follow-up. However, blood cell count, sleep, in-patient stay, and change in life condition were pointed out only at the T1 interview.

Discussion

This qualitative analysis is the first study exploring CRCI in older adults with AML and their caregivers. The findings summarized their experiences and trajectories of the difficulty in memory, language, attention, and processing information; how these cognitive symptoms impacted their emotions and disrupted their life; the strategies they used to cope with CRCI; and potential factors they thought might contribute to these changes during the first four cycles of VEN+HMA/low-dose ara-c chemotherapy.

Older adults with AML identified the problems in recalling information, finding words to express themselves, and concentrating on things. These aligned with the findings from prior CRCI qualitative studies focusing on adults with breast cancer (Green et al., 2019; Myers, 2012; Tenda et al., 2022; Von Ah et al., 2013a), cervical cancer (Zeng et al., 2017), and prostate cancer (Wu et al., 2013), which also showed a decline or change in long-term or short-term memory, language, and ability to concentrate. During the study interview, we also encountered some scenarios that older adults with AML showed the challenge due to CRCI. For example, when the interviewer tried to probe and confirm the information that was previously mentioned by the older adult with AML, he could not recall what he had said. Moreover, our study found that older adults recognized CRCI when they encountered challenges during daily activities or had it pointed out by their caregivers. Similarly, Tenda et al. (2022) and Wu et al. (2013) reported that adults with breast cancer or prostate cancer became aware of CRCI by comparing their own situation with others' during daily interactions or being told by others. Various trajectories of CRCI were identified in the current study and existing research (Myers, 2012; Tenda et al., 2022; Von Ah et al., 2013a). Specifically, Tenda et al. (2022) found older adults with breast cancer who were treated with hormone therapy mainly reported a decline in their cognitive function

while one participant reported an improvement. Myers (2012) found that adults with breast cancer reported an improvement one to two months after completing chemotherapy; however, Von Ah et al. (2013a) found that there was no change. Different from these cross-sectional qualitative studies (Myers, 2012; Tenda et al., 2022; Von Ah et al., 2013a), our study focused on during chemotherapy and conducted interviews longitudinally at both cycle 2 and cycle 4 of chemotherapy to understand the trajectory of CRCI. In particular, several older adults with AML received intensive chemotherapy previously and did not experience further cognitive changes during VEN+HMA/low-dose ara-c chemotherapy. According to a prior narrative review (Bai & Yu, 2020), cancer survivors who were treated with higher doses of chemotherapy experienced a higher severity of CRCI. VEN+HMA/low-dose ara-c chemotherapy is less intensive and targets older adults or those who cannot tolerate conventional chemotherapy (Mukherjee & Sekeres, 2019). Therefore, it is possible that these older adults with AML did not experience further cognitive decline.

Our study found that CRCI caused emotional distress and disruption of life in older adults with AML who were treated with chemotherapy. Similar to our findings, prior studies also reported the impact of CRCI on the emotions in adults with breast cancer, such as frustration, bothersome, embarrassing (Von Ah et al., 2013a), upset, and discouragement (Tenda et al., 2022). In addition to the impact on emotion, both Tenda et al. (2022) and the current study, with a focus on older adults with cancer, found that CRCI made older adults with cancer less motivated, led them to try to avoid social activities, and further increased caregivers' responsibilities. Different from the findings from Von Ah et al. (2013a), the impact of CRCI on work was not identified as a subtheme in the current study. This might result from the age of the sample and the treatment plan. Specifically, our sample has a mean age of 73.45 years, which is

higher than the retirement age of 65 years. In addition, to receive the VEN+HMA/low-dose ara-c chemotherapy, older adults with AML need to visit the outpatient infusion clinic five to seven days consecutively. They also need regular periodical infusion support between cycles of chemotherapy. Therefore, the participants we interviewed did not continue being employed and tried to keep up with all clinic appointments.

Our study identified several problem-solving and emotional coping strategies used to manage CRCI. The problem-solving strategies identified in this study—such as taking notes or memos, seeking support and validation from family members, making adjustment to their lives, keeping life structured, and cognitive exercises—were also found in other CRCI research (Green et al., 2019; Myers, 2012; Tenda et al., 2022; Von Ah et al., 2013b; Zeng et al., 2017). One of the unique strategies—technology support from voice assistant devices—was brought up by an older adult with AML. Prior studies have included the voiced assistant device for providing clinically appropriate advice (Garg et al., 2018; Sezgin et al., 2020) and serving as a reminder to promote medication adherence (Corbett et al., 2021) that received positive feedback; however, this needs to be further tested. In terms of emotional coping, the religious and spiritual support identified by our study was also discussed in prior breast cancer research (Toledo et al., 2021). Toledo et al. (2021) reported that religion and spiritual beliefs supported adults with breast cancer in coping with symptoms during endocrine therapy. The interviewer also observed a positive attitude when older adults with AML talked about how they cope with CRCI using religious and spiritual support.

Additionally, older adults with AML in the current study did not show major concern toward CRCI. Similar to the findings from Tenda et al. (2022), they considered the changes they experienced as part of the normal aging process and accepted it. This similarity might be the

result of both studies' focus on older adults. Specifically, Tenda et al. (2022) recruited those ages 70 to 85 years, and our study included those who were 60 years and older. Therefore, experiencing difficulty in memory, language, and concentration might not be new to some of older adults with cancer. This also reflects on our findings, which indicated that age was one of the most common perceived related factors of CRCI identified by older adults with AML.

In addition to age, we also identified other possible factors that aligned with other CRCI studies. Aligned with the qualitative findings from Zeng et al. (2017), chemotherapy and other cancer treatment were identified as one of the main perceived risk factors. Also, "getting enough rest" was identified by adults with breast cancer as a way to cope with CRCI (Meyers et al., 2005). Similarly, enough sleep was identified by an older adult with AML as a protective factor in the current study. Furthermore, anxiety, depression, and overwhelming feelings were reported by older adults with AML, which is consistent with prior research in adults with breast cancer (Yang & Hendrix, 2018). In particular, during our recruitment and follow-up period of time, the United States was hit severely by the COVID-19 pandemic—an infectious disease caused by the SARS-CoV-2 virus that can be life-threatening to older adults and people with cancer (Brodin, 2021). People were asked to stay at home, wear masks when going in public, and get vaccinated. Being a high-risk population for serious illness from COVID-19 and the dramatic change from their usual life brought about by lockdowns and restrictions further added to the stress of older adults with AML.

Because cancer treatment is largely shifting from in-patient to out-patient settings, caregivers serve as a vital role in their loved ones' illness journey. According to a qualitative systematic review (Ullgren et al., 2018), caregivers were involved in symptom assessment and management and providing physical and emotional support while being at home. However, to

the best of our knowledge, no study explores caregivers' perspectives on CRCI. Our findings indicated that caregivers also noticed their loved ones' difficulty in memory, finding words, and concentration. In addition, they observed that older adults with AML needed longer times to process information. These findings aligned with prior CRCI research interviewing adults with cancer (Green et al., 2019; Myers, 2012; Tenda et al., 2022; Von Ah et al., 2013a; Wu et al., 2013; Zeng et al., 2017). Our results also found that CRCI impacted caregivers' emotions, changed their relationship with their loved one, and increased their responsibilities. This aligned with prior research indicating that the symptom distress of people with cancer was negatively correlated with caregivers' emotional well-being (Weitzner et al., 2000). Similarly, the same study reported that caregivers of older adults with cancer underwent role change and increased responsibilities (Weitzner et al., 2000). These findings highlight the role of caregivers as symptom assessors and the necessity of supporting caregivers.

Our findings reported that caregivers developed various strategies to support older adults with AML to cope with CRCI. One caregiver mentioned that they tried to keep older adults with AML to stay active to keep their brain active. This strategy was also identified in prior CRCI research (Tenda et al., 2022). Specifically, Tenda et al. (2022) pointed out that older adults with breast cancer tried to stay engaged and active to keep their brain working. The need for caregivers to provide medication management also caught our attention. Similarly, Bender et al. (2014) also reported that CRCI was correlated with medication nonadherence in adults with breast cancer. In addition to subcutaneous infusion, older adults with AML who are treated with VEN+HMA/low-dose ara-c chemotherapy are required to take daily oral medication—VEN. It is crucial for them to adhere to oral medication for their AML treatment plan. In terms of emotional coping strategies, most of caregivers also identified CRCI as normal aging. This might be

because most caregivers recruited in the current study were the spouses of older adults with AML and were also going through the aging process. Because these spouses were also encountering occasional cognitive problems, they were more accepting of CRCI in the older adult with AML. These results highlight the importance of caregivers for older adults with AML and the necessity of incorporating caregivers when developing CRCI interventions.

This qualitative analysis has some limitations. First, a limited number of older adults with AML and caregivers were interviewed in the qualitative component of the study. There were several subthemes mentioned by only one or two participants and that needed to be further explored. Therefore, data saturation was not reached. Secondly, interviews were conducted either while older adults with AML and their caregivers were waiting for infusion or through phone call. Due to the space and time limitation, some interviews were conducted with both older adults with AML and their caregivers present in the same room, which opens the possibility that they may have filtered their responses due to discomfort sharing completely in the presence of a loved one.

There are some major strengths. First, the study addresses the current research gap in CRCI research in older adults with AML by understanding them and their caregivers' perspectives on CRCI. Because ours is one of the first studies to explore caregivers' experiences, our findings provide valuable information for future research and clinical practice for developing CRCI interventions. Secondly, the study conducted interviews longitudinally to explore the trajectory of their CRCI experiences. By doing so, we are able to understand the change of experiences over time. Thirdly, the results were generated with rigor by having two coders conduct the data analysis process and, per study protocol, reach consensus through discussions.

Conclusion

The findings of this study provide an in-depth understanding of the symptom experience, impact, coping strategies, and perceived related factors of CRCI from both older adults with AML and their caregivers. This also informs future research and practice. Using the impact and coping strategies identified by older adults with AML and their caregivers, future researchers will be able to design quantitative correlation studies focusing on the impact of CRCI and CRCI intervention studies. For clinical practice, oncology nurses will be able to provide evidence-based CRCI education, identify CRCI problems early, and provide possible coping strategies to better support older adults with AML and their caregivers to reduce the impact of CRCI on their life.

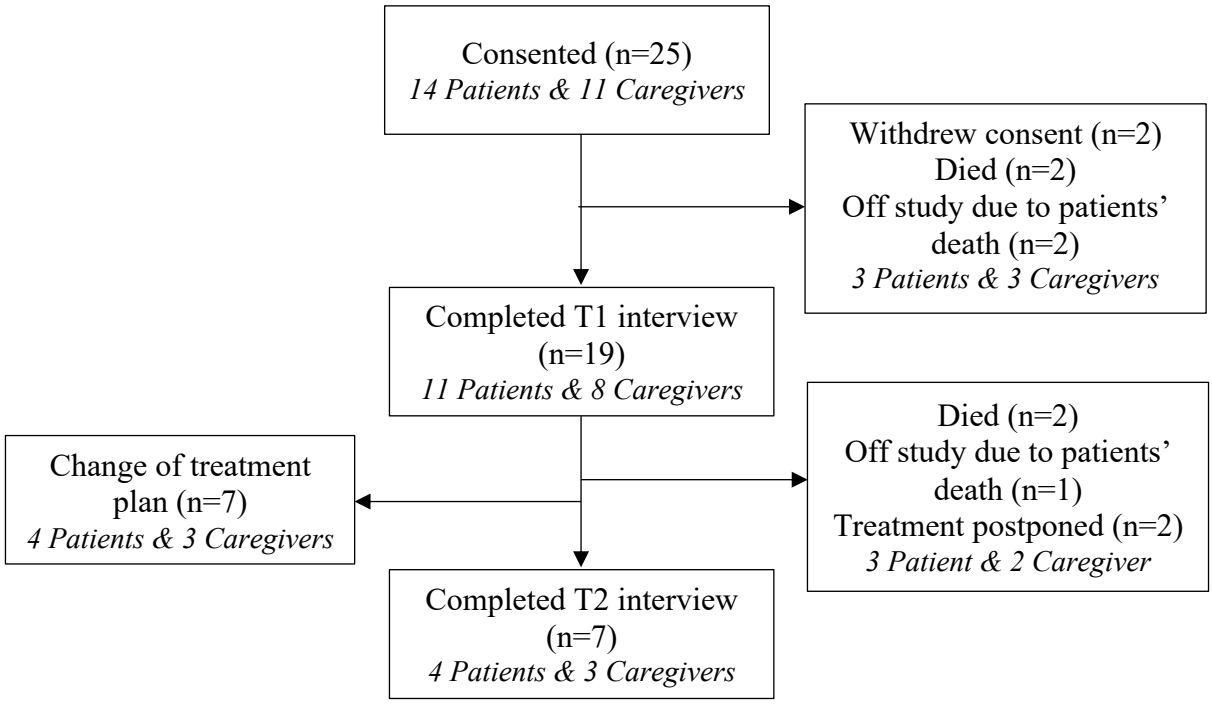

Figure 4.1. **Flowchart of sample recruitment and follow-up**

Table 4.1. **Example semi-structural interview questions for older adults with AML and caregivers**

- Can you tell me about [your/patient's name] [attention, remember things]?
- Can you tell me when you first experienced these changes in [your/patient's name] [pay attention, remember things]?
- Please tell me about any changes in severity of [your/patient's name] [pay attention, remember things] since you first noticed them. For example, did the problem stay the same, become worse over time or improve?
- What kind of factors, if any, have you noticed may contribute to these changes in [your/patient's name] [attention, remember things]?
- Please tell me how you feel about these changes in [your/patient's name] [attention, remember things]? For example, is this troubling or burdening you?

Table 4.2. **Sample characteristics of older adults with AML and their caregivers (n=19)**

Characteristics		Older adults with AML (n=11)		Caregivers (n=8)	
		Mean	SD	Mean	SD
Age		73.45	9.00	62.88	10.40
		n	%	n	%
Gender	Male	8	72.73	1	12.5
	Female	3	27.27	7	87.5
Race	White	10	90.91	7	87.5
	Black or African American	1	9.09	1	12.5
Ethnicity	Non-Hispanic	11	100	8	100
Education level	High school graduate / Graduate equivalency degree	7	63.64	2	25
	College degree	2	18.18	3	37.5
	Advanced degree	1	9.09	3	37.5
	Prefer not to answer	1	9.09	0	0
Annual household income	<$20,000	1	9.09	0	0
	$20,001-40,000	2	18.18	1	12.5
	$40,001-60,000	2	18.18	1	12.5
	$60,001-80,000	3	27.27	2	25
	$80,001-100,000	1	9.09	0	0
	>$100,001	1	9.09	3	37.5
	Prefer not to answer	1	9.09	1	12.5
Marital Status	Single/Never married	0	0	1	12.5
	Married/Partnered	6	54.55	7	87.5
	Divorced	2	18.18	0	0
	Widowed	3	27.27	0	0
Employment (prior to diagnosis)	Yes	6	54.55		
	No	5	45.45		

Table 4.3. **Themes/Subthemes of older adults with AML**

Theme	Subtheme	Code
CRCI experience	Domains	**Memory**
		Forgetting previous conversation
		Forgetting people's names, dates, or events
		Forgetting things that were supposed to be done
		Forgetting the location of the things
		Language
		Having difficulty finding or recalling the right/proper words
		Attention
		Getting distracted easily
		Refocusing life priorities
	Frequency	Every once in a blue moon
		Everyday thing
	Ways to notice CRCI	Pointing out by others
		Patient-perceived cognitive changes
	Trajectory of CRCI	Cognition remains the same
		Cognition declines
		Cognition improves
Impact of CRCI	Emotion	Concern/Worry
		Frustration
	Disruptions of life	Interfering with social activities
		Interfering with daily tasks
		Increased responsibilities for caregivers
	No impact	No impacts on life
CRCI coping strategies	Problem-solving coping strategies	Taking notes/written reminder
		Technical support
		Actively seeking others' help, assistance, or understanding
		Keeping life structured or active
		Cognitive exercises
	No problem-solving coping strategies	No strategies developed
		Pause and think
	Emotional coping strategies	Accepting CRCI as it is
		It is normal aging
		Noticeable but not concerning
		With a sense of humor
		Spiritual support

Theme	Subtheme	Code
Perceived CRCI related factors	Demographic factor	Age
	Physiologic/Clinical factor	Cancer diagnosis
		Cancer treatment
		Other medication
		Blood cell count
		Sleep
		Fatigue
	Psychological factor	Emotional distress related to cancer
		Emotional distress caused by COVID
		Emotional distress related to other issues
	Environmental factor	Inpatient hospital stay
	Other factor	Overwhelming information and tasks
		Changes in life conditions

Table 4.4. **Themes/Subthemes of caregivers**

Theme	Subtheme	Code
CRCI experience	Domains	**Memory**
		Forgetting previous conversation
		Forgetting people's names, dates, or events
		Forgetting things that were supposed to be done
		Forgetting the location of the things
		Language
		Having difficulty finding or recalling the right/proper words
		Attention
		Getting distracted easily
		Refocusing life priorities
		Processing Information
		Having difficulty processing information
	Frequency	Every once in a blue moon
		Everyday thing
	Ways to notice CRCI	Caregiver-perceived cognitive changes
	Trajectory of CRCI	Cognition remains the same
		Cognition declines
		Cognition improves
Impact of CRCI	Emotion	Concern/Worry
		Frustration
	Disruptions of life	Interfering with daily tasks
		Increased responsibilities for caregivers
		Changes in patient-caregiver relationship
	No impact	No impacts on life
CRCI coping strategies	Problem-solving coping strategies	Taking notes/written reminder
		Keeping life structured or active
		Observing needs and providing partial support
		Providing total support
	Emotional coping strategies	Accepting CRCI as it is
		It is normal aging
		Noticeable but not concerning
		With a sense of humor
		Spiritual support
Perceived CRCI related factors	Demographic factor	Age
	Physiologic/Clinical factor	Cancer diagnosis
		Cancer treatment

Theme	Subtheme	Code
		Blood cell count
		Hearing problem
		Sleep
		Fatigue
	Psychological factor	Emotional distress related to cancer
		Emotional distress related to other issues
	Environmental factor	Inpatient hospital stay
	Other factor	Overwhelming information and tasks
		Changes in life conditions

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CHAPTER 5: FINDINGS AND IMPLICATIONS

Introduction

The overarching purpose of this dissertation was to address the current research gap in understanding CRCI's trajectory among older adults with AML who were treated with chemotherapy. The specific aims of the dissertation included: 1) examine the development and trajectory of CRCI severity from initiating chemotherapy to 3 months later in older adults with AML; 2) identify factors (demographic, physical/clinical, and psychological, environmental factors) associated with CRCI in older adults with AML; 3) and describe the CRCI experiences of older adults with AML and their caregivers up to 3 months after initiating chemotherapy. The dissertation consisted of a systematic review (Chapter 2) and quantitative and qualitative analysis of a prospective longitudinal study (Chapter 3 and Chapter 4) of older adults with AML who were treated with VEN+HMA/low-dose ara-c chemotherapy. In this chapter, we provide a summary of the main findings of each chapter, address the strengths and limitation of the dissertation, and end with implications for research and clinical practice.

Findings of Dissertation

First Manuscript (Chapter 2): "Cognitive Function in Adults with Acute Myeloid Leukemia: A Systematic Review"

This manuscript is a systematic review evaluating the current literature on 1) cognitive function during chemotherapy continuum, 2) potential correlates of cognitive function, and 3) cognitive function's predictive relationship on other outcomes. Based on the included 10 quantitative articles, a total of 16%–31.5% and up to 62.2% of adults with AML were identified

as cognitively impaired at the initiation of chemotherapy and after starting chemotherapy, respectively. However, the impaired cognitive domains were found different across studies. In terms of potential correlates, education had a significant positive correlation with cognitive function and cytokines showed mixed findings across studies. Moreover, cohort studies identified a significant prediction between lower cognitive function at diagnosis/initiation of chemotherapy, lower physical performance, and higher mortality. The findings from this manuscript also showed the gaps in current understandings of cognitive function, which included 1) using neuropsychological assessments and subjective patient-reported questionnaire; 2) older adults with AML sample population; and 3) understanding the experience of cognitive function and its impact using a qualitative approach. These gaps further led to manuscript 2 and manuscript 3.

Second Manuscript (Chapter 3): "Cancer-Related Cognitive Impairment and Its Factors in Older Adults with Acute Myeloid Leukemia: A Prospective Longitudinal Study"

This manuscript is a quantitative longitudinal prospective study; the aims are 1) examine the development and trajectory of CRCI severity from cycle 1 to cycle 4 and 2) identify factors associated with CRCI. Medical record review, patient-reported questionnaires, and neuropsychological assessments were used at cycle 1, cycle 2, and cycle 4 of VEN in combination of HMA or low-dose cytarabine chemotherapy. Descriptive analysis, Wilcoxon signed rank test, Fisher-Freeman-Halton Exact Test, and Spearman's Rank Correlation Coefficient were used for data analysis. A total of 14 older adults with AML were recruited. The main findings showed no significant differences in subjective and objective cognitive function between each time point. In addition, no significant differences were identified in cognitive load. The prevalence of subjective cognitive impairment was equal to or more than 50% at T1 (50.0%), T2 (63.64%), and early end-of-study (50.0%), except for T3 (33.33%). Similarly, the

prevalence of objective cognitive impairment was also around half of older adults with AML at T1 (42.86%), T2 (50.0%), and T3 (50.0%). In terms of potential correlates, although results were mixed, variables included symptom burden, insomnia severity, anxiety frequency, sad feeling frequency, nothing can cheer you up frequency, and disease burden. These were negatively correlated with subjective cognitive impairment or cognitive domains (i.e., memory, verbal learning, and executive function). However, our findings were mixed in terms of the relationship between biomarkers and cognitive domains. Specifically, Hgb was positively associated with speeded lexical fluency, processing speed, or executive function at T1 and T2 but was found to be negatively correlated to executive function at early end-of-study.

Third Manuscript (Chapter 4): "Experiences of Cancer-Related Cognitive Impairment in Older Adults with Acute Myeloid Leukemia and their Caregivers: A Qualitative Analysis"

This manuscript is a qualitative analysis of a longitudinal prospective study, the aim of which was to understand older adults with AML and their caregivers' perspectives on experiences of CRCI in older adults with AML. Both older adults with AML and their caregivers were interviewed using semi-structured interview guides at cycle 2 and cycle 4/early end-of-study. Thematic analysis was used to analyze a total of 33 transcripts (19 older adults with AML and 14 caregivers) by two coders. Four main themes: 1) CRCI experiences, 2) impact of CRCI, 3) CRCI coping strategies, and 4) perceived CRCI-related factors were identified in both older adults with AML and their caregivers.

Older adults with AML identified their changes in memory, language, and concentration, but the problems did not occur every day. They noticed these changes by themselves or had them pointed out by others. The severity of the problem varied at the AML diagnosis/initiation of VEN+HMA/low-dose ara-c chemotherapy but remained stable from cycle 2 to cycle 4. Due to CRCI, some older adults with AML felt frustrated or embarrassed, needed longer time to get

things done, tried to avoid social events, or contributed to an increase in their caregivers' responsibilities because of the need to take care them. Therefore, in order to cope with CRCI, different strategies were developed. Some proactive strategies included taking notes, getting support from a smart device or software, keeping life structured, and cognitive exercises. However, some just paused and thought about it when challenges encountered. Emotionally, older adults with AML considered these changes in cognitive function as normal parts of the aging process or accepted the changes. They were not concerned about the problem but handled it with sense of humor or religious support. Finally, older adults with AML identified that age, cancer diagnosis and treatment, sleep, fatigue, blood cell count, inpatient stay, emotional distress, changes in life condition, and overwhelming information and tasks related to AML might relate to their changes in cognitive function.

Caregivers noticed their loved ones experienced difficulty in memory, language, concentration, and processing information that mainly occurred "every once in a blue moon." Specifically, various cognitive function trajectories—increased, declined, and stable—were identified by caregivers. Due to their loved ones' changes in cognitive function, caregivers' emotions were impacted, resulting in feelings such as fear of their loved ones doing things independently, frustration from their loved ones' refusal to accept help, and being overwhelmed with the whole situation. They further experienced increased responsibilities in their caregiving role and a change in their relationship with their loved ones because of being a caregiver and a spouse/child at the same time. Therefore, in order to cope with CRCI, caregivers helped their loved ones by providing either total support or partial support. Specifically, for partial support, caregivers provided written/verbal reminders, figured out the words their loved ones were trying to covey, and managed their loved one's pillbox. Emotionally, they considered the change as a

normal part of the aging process or accepted the problem and did not consider it as major concern. Several also coped with the change using hope, a positive attitude, and humor. Finally, caregivers also identified that age, cancer diagnosis and treatment, sleep, fatigues, hearing problem, blood cell count, inpatient stay, emotional distress, changes in life condition, and overwhelming information and tasks related to AML might relate to their loved ones' changes in cognitive function.

Strengths and Limitations of Dissertation

This dissertation has several strengths. First, the findings of the dissertation add new knowledge about the CRCI phenomenon, an understudied symptom, in older adults with AML and older adults with cancer. Due to the relatively young sample recruited by existing CRCI studies in adults with AML (Meyers et al., 2005; Modzelewski et al., 2011) and lack of CRCI research in older adults with cancer (Loh et al., 2016), our study exclusively focuses on older adults who aged 60 years and older fulfills the current major research gap. Secondly, the findings present both overall cognitive function and its domains by incorporating a patient-reported questionnaire and a battery of neuropsychological assessments to assess CRCI. Compared to existing CRCI studies in adults with AML (Meyers et al., 2005; Modzelewski et al., 2011), our studies provides a more comprehensive understanding of CRCI by including patient-reported outcome measures that show the perceived cognitive changes older adults with AML identified. Thirdly, the study utilizes a longitudinal study design to explore CRCI trajectory from the 1st cycle to 4th cycle of VEN+HMA/low-dose ara-c chemotherapy. VEN+HMA/ low-dose ara-c chemotherapy is a recently approved treatment (Food and Drug Administration, 2018); as a result, little research exists exploring the symptom experience of people with cancer being treated with this regimen. Furthermore, exploring CRCI longitudinally in older adults with

cancer is a research priority in CRCI research focusing on older adults with cancer (Loh et al., 2016). Hence, our study provides valuable information to fill current knowledge gaps.

There are some limitations that are worth noting. First, the sample size of the dissertation is very small. Therefore, the quantitative results are not well-powered and should be interpreted conservatively. Also, some extinct qualitative subthemes we identified should be further explored. Secondly, the dissertation includes a homogeneous sample; therefore, the correlates of CRCI cannot be properly identified and the generalizability of the findings is limited. Thirdly, we encountered barriers such as hearing problems, time constraints, and inflexible schedules during the data collection process. Therefore, the quantitative data of the dissertation has missing values, and the baseline quantitative data were not all from older adults who had never been treated with chemotherapy. Finally, due to a lack of control group data, we used published normative data to calculate RCI to group change of cognitive function into improved, declined, and stable. However, considering the difference of demographic characteristics between the study sample and normative sample, the RCI may not be accurate.

Implications

Implications for Research

The study identifies several areas for future research to target. First, in addition to education level, we suggest that future researchers collect years of education. Doing so will allow researchers to compare their findings with other existing CRCI research. Secondly, we suggest including a healthy control group with sample characteristics similar to the treatment group when conducting CRCI research to allow for calculation of the RCI of neuropsychological assessments from the demographically similar healthy control group to further define cognitive changes in treatment group. Thirdly, we recommend a longer follow-up time frame and

alternative assessments in future research to better under the acute and late onset of CRCI in older adults with AML population and to avoid potential barriers of conducting neuropsychological assessments in older adults with cancer. Fourthly, we suggest recruiting a sufficient sample size with diverse sample characteristics in order to get well-powered findings of trajectory and correlates of CRCI.

Our quantitative and qualitative findings provide a valuable foundation for future quantitative research to 1) identify covariates, which should be included for study design; 2) explore the relationship between CRCI and potential outcomes (such as: caregiver burden, quality of life, or social disconnections); and 3) develop caregiver-included CRCI interventions.

Implications for Practice

The findings show some implications for clinical practice. First, our quantitative findings highlight that cognitive impairment is identified at diagnosis/before the initiation of chemotherapy and the problem persists in older adults with AML. Therefore, clinicians and oncology nurses must provide CRCI education and regularly screen for CRCI. For example, Mayo et al. (2021) provided examples of probing questions that could be used as a way for screening during clinic visits. Secondly, the potential correlates identified in our quantitative findings suggest that clinicians and oncology nurses can identify potential high-risk older adults with AML early in the treatment trajectory and provide necessary rehabilitation referral or support to prevent the CRCI problem from further impacting their quality of life. Thirdly, the qualitative findings present potential CRCI coping strategies that were effective for older adults with AML. This provides clinicians and oncology nurses some suggestions for ways to support older adults with AML who are suffering from CRCI. Finally, the qualitative findings report that CRCI also influences caregivers' lives. This highlights the necessity for clinicians and oncology

nurses to check on how caregivers are doing and provide information they need to better support them while going through the illness journey with their loved ones.

Conclusion

This study examines the trajectory and potential correlates of CRCI in older adults with AML from initiating chemotherapy to the 4th cycle of chemotherapy in older adults with AML. It also provides greater understanding of CRCI experiences from the perspectives of both older adults with AML and their caregivers. The results of this dissertation suggest that up to 75% of older adults with AML experience cognitive impairment after initiating chemotherapy. In addition, disease burden, insomnia, emotional distress, and hemoglobin are potential correlates of CRCI. The qualitative findings of CRCI symptom experience, impact, coping strategies, and perceived risk factors from older adults with AML and their caregivers not only highlight CRCI symptom in this population but also emphasize the importance of having support from caregivers to deal with CRCI.

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APPENDIX 2.1: SEARCHING STRATEGIES IN DATABASES

Database: PubMed (MEDLINE)

Set #		Results
1	"Leukemia, Myeloid, Acute"[Mesh] OR "Leukemia, Myelomonocytic, Acute"[Mesh] OR “Acute Myeloid Leukemia"[tiab] OR "Acute Myeloid Leukemias"[tiab] OR ANLL[tiab] OR "Acute Myeloblastic Leukemia"[tiab] OR "Acute Myeloblastic Leukemias"[tiab] OR "Acute Myelocytic Leukemia"[tiab] OR "Acute Myelocytic Leukemias"[tiab] OR "Acute Nonlymphoblastic Leukemia"[tiab] OR "Acute Nonlymphoblastic Leukemias"[tiab] OR "Acute Nonlymphocytic Leukemia"[tiab] OR "Acute Nonlymphocytic Leukemias"[tiab] OR "Acute Myelogenous Leukemia"[tiab] OR "Acute Myelogenous Leukemias"[tiab] OR "Acute Myeloid Leukemia without Maturation"[tiab] OR "Acute Myeloid Leukemia with Maturation"[tiab] OR "Naegeli-Type Myeloid Leukemia"[tiab] OR "Acute Myelomonocytic Leukemia"[tiab] OR "Acute Myelomonocytic Leukemias"[tiab]	
2	"Antineoplastic Agents"[Mesh] OR "Antineoplastic Agents" [Pharmacological Action] OR "Antineoplastic Combined Chemotherapy Protocols"[Mesh] OR "Chemotherapy, Adjuvant"[Mesh] OR "Consolidation Chemotherapy"[Mesh] OR "Induction Chemotherapy"[Mesh] OR "Maintenance Chemotherapy"[Mesh] OR chemotherapy[tiab] OR chemotherapies[tiab] OR Chemotherapeutic[tiab] OR “antineoplastic drug”[tiab] OR “antineoplastic drugs”[tiab] OR “antineoplastic agent”[tiab] OR “antineoplastic agents”[tiab] OR antineoplastics[tiab] OR “antitumor drug”[tiab] OR “antitumor drugs”[tiab] OR “antitumor agent”[tiab] OR “antitumor agents”[tiab] OR “antitumour drug”[tiab] OR “antitumour drugs”[tiab] OR “antitumour agent”[tiab] OR “antitumour agents”[tiab] OR “anticancer drug”[tiab] OR “anticancer drugs”[tiab] OR “anticancer agent”[tiab] OR “anticancer agents”[tiab]	
3	“Cognition Disorders”[Mesh] OR "Neuropsychology"[Mesh] OR "Neuropsychological Tests"[Mesh] OR "Mental Processes"[Mesh] OR "Brain/drug effects"[Mesh] OR "Attention"[Mesh] OR "Psychomotor Performance"[Mesh] OR cognitive[tiab] OR cognition[tiab] OR neuropsychological[tiab] OR neuropsychology[tiab] OR neurocognitive[tiab] OR neurocognition[tiab] OR neurogenesis[tiab] OR memory[tiab] OR “processing speed”[tiab] OR “information processing”[tiab] OR “executive function”[tiab] OR "Executive Functions"[tiab] OR “executive control”[tiab] OR “executive controls”[tiab] OR learning[tiab] OR psychomotor[tiab] OR	

	chemobrain[tiab] OR chemofog[tiab] OR “chemo brain”[tiab] OR “chemo fog”[tiab]	
4	#1 AND #2 AND #3	202

Database: CINAHL Plus with Full Text

Set #		Results
1	(MH "Leukemia, Myeloid, Acute+") OR (MH "Leukemia, Promyelocytic, Acute") OR (MH "Leukemia, Erythroblastic, Acute") OR TI ("Acute Myeloid Leukemia" OR "Acute Myeloid Leukemias" OR ANLL OR "Acute Myeloblastic Leukemia" OR "Acute Myeloblastic Leukemias" OR "Acute Myelocytic Leukemia" OR "Acute Myelocytic Leukemias" OR "Acute Nonlymphoblastic Leukemia" OR "Acute Nonlymphoblastic Leukemias" OR "Acute Nonlymphocytic Leukemia" OR "Acute Nonlymphocytic Leukemias" OR "Acute Myelogenous Leukemia" OR "Acute Myelogenous Leukemias" OR "Acute Myeloid Leukemia without Maturation" OR "Acute Myeloid Leukemia with Maturation" OR "Naegeli-Type Myeloid Leukemia" OR "Acute Myelomonocytic Leukemia" OR "Acute Myelomonocytic Leukemias") OR AB ("Acute Myeloid Leukemia" OR "Acute Myeloid Leukemias" OR ANLL OR "Acute Myeloblastic Leukemia" OR "Acute Myeloblastic Leukemias" OR "Acute Myelocytic Leukemia" OR "Acute Myelocytic Leukemias" OR "Acute Nonlymphoblastic Leukemia" OR "Acute Nonlymphoblastic Leukemias" OR "Acute Nonlymphocytic Leukemia" OR "Acute Nonlymphocytic Leukemias" OR "Acute Myelogenous Leukemia" OR "Acute Myelogenous Leukemias" OR "Acute Myeloid Leukemia without Maturation" OR "Acute Myeloid Leukemia with Maturation" OR "Naegeli-Type Myeloid Leukemia" OR "Acute Myelomonocytic Leukemia" OR "Acute Myelomonocytic Leukemias")	6,121
2	MH "Antineoplastic Agents+" OR MH "Chemotherapy, Cancer+" OR TI (chemotherapy OR chemotherapies OR Chemotherapeutic OR “antineoplastic drug” OR “antineoplastic drugs” OR “antineoplastic agent” OR “antineoplastic agents” OR antineoplastics OR “antitumor drug” OR “antitumor drugs” OR “antitumor agent” OR “antitumor agents” OR “antitumour drug” OR “antitumour drugs” OR “antitumour agent” OR “antitumour agents” OR “anticancer drug” OR “anticancer drugs” OR “anticancer agent” OR “anticancer agents”) OR AB (chemotherapy OR chemotherapies OR Chemotherapeutic OR “antineoplastic drug” OR	151257

	“antineoplastic drugs” OR “antineoplastic agent” OR “antineoplastic agents” OR antineoplastics OR “antitumor drug” OR “antitumor drugs” OR “antitumor agent” OR “antitumor agents” OR “antitumour drug” OR “antitumour drugs” OR “antitumour agent” OR “antitumour agents” OR “anticancer drug” OR “anticancer drugs” OR “anticancer agent” OR “anticancer agents”)	
3	MH "Cognition disorders+" OR MH "Neuropsychology+" OR MH "Neuropsychological Tests+" OR MH "Mental Processes+" OR MH "Brain+/DE" OR MH "Attention+" OR MH "Psychomotor Performance+" OR TI (cognitive OR cognition OR neuropsychological OR neuropsychology OR neurocognitive OR neurocognition OR neurogenesis OR memory OR “processing speed” OR “information processing” OR “executive function” OR "Executive Functions" OR “executive control” OR “executive controls” OR learning OR psychomotor OR chemobrain OR chemofog OR “chemo brain” OR “chemo fog”) OR AB (cognitive OR cognition OR neuropsychological OR neuropsychology OR neurocognitive OR neurocognition OR neurogenesis OR memory OR “processing speed” OR “information processing” OR “executive function” OR "Executive Functions" OR “executive control” OR “executive controls” OR learning OR psychomotor OR chemobrain OR chemofog OR “chemo brain” OR “chemo fog”	556484
4	#1 AND #2 AND #3	61

Database: Embase

Set #		Results
1	'acute myeloid leukemia'/exp OR 'Acute Myeloid Leukemia':ti,ab OR 'Acute Myeloid Leukemias':ti,ab OR ANLL:ti,ab OR 'Acute Myeloblastic Leukemia':ti,ab OR 'Acute Myeloblastic Leukemias':ti,ab OR 'Acute Myelocytic Leukemia':ti,ab OR 'Acute Myelocytic Leukemias':ti,ab OR 'Acute Nonlymphoblastic Leukemia':ti,ab OR 'Acute Nonlymphoblastic Leukemias':ti,ab OR 'Acute Nonlymphocytic Leukemia':ti,ab OR 'Acute Nonlymphocytic Leukemias':ti,ab OR 'Acute Myelogenous Leukemia':ti,ab OR 'Acute Myelogenous Leukemias':ti,ab OR 'Acute Myeloid Leukemia without Maturation':ti,ab OR 'Acute Myeloid Leukemia with Maturation':ti,ab OR 'Naegeli-Type Myeloid Leukemia':ti,ab OR 'Acute Myelomonocytic Leukemia':ti,ab OR 'Acute Myelomonocytic Leukemias':ti,ab	
2	'antineoplastic agent'/exp OR 'chemotherapy'/exp OR chemotherapy:ti,ab OR chemotherapies:ti,ab OR Chemotherapeutic:ti,ab OR ‘antineoplastic drug’:ti,ab OR ‘antineoplastic drugs’:ti,ab OR ‘antineoplastic agent’:ti,ab OR	

	‘antineoplastic agents’:ti,ab OR antineoplastics:ti,ab OR ‘antitumor drug’:ti,ab OR ‘antitumor drugs’:ti,ab OR ‘antitumor agent’:ti,ab OR ‘antitumor agents’:ti,ab OR ‘antitumour drug’:ti,ab OR ‘antitumour drugs’:ti,ab OR ‘antitumour agent’:ti,ab OR ‘antitumour agents’:ti,ab OR ‘anticancer drug’:ti,ab OR ‘anticancer drugs’:ti,ab OR ‘anticancer agent’:ti,ab OR ‘anticancer agents’:ti,ab	
3	'cognitive defect'/exp OR 'neuropsychology'/exp OR 'neuropsychological test'/exp OR 'mental function assessment'/exp OR 'cognition'/exp OR cognitive:ti,ab OR cognition:ti,ab OR neuropsychological:ti,ab OR neuropsychology:ti,ab OR neurocognitive:ti,ab OR neurocognition:ti,ab OR neurogenesis:ti,ab OR memory:ti,ab OR ‘processing speed’:ti,ab OR ‘information processing’:ti,ab OR ‘executive function’:ti,ab OR ‘Executive Functions’:ti,ab OR ‘executive control’:ti,ab OR ‘executive controls’:ti,ab OR learning:ti,ab OR psychomotor:ti,ab OR chemobrain:ti,ab OR chemofog:ti,ab OR ‘chemo brain’:ti,ab OR ‘chemo fog’:ti,ab	
4	#1 AND #2 AND #3	3326
5	#4 AND ('article'/it)	843

Database: PsycINFO

Set #		Results
1	TI ("Acute Myeloid Leukemia" OR "Acute Myeloid Leukemias" OR ANLL OR "Acute Myeloblastic Leukemia" OR "Acute Myeloblastic Leukemias" OR "Acute Myelocytic Leukemia" OR "Acute Myelocytic Leukemias" OR "Acute Nonlymphoblastic Leukemia" OR "Acute Nonlymphoblastic Leukemias" OR "Acute Nonlymphocytic Leukemia" OR "Acute Nonlymphocytic Leukemias" OR "Acute Myelogenous Leukemia" OR "Acute Myelogenous Leukemias" OR "Acute Myeloid Leukemia without Maturation" OR "Acute Myeloid Leukemia with Maturation" OR "Naegeli-Type Myeloid Leukemia" OR "Acute Myelomonocytic Leukemia" OR "Acute Myelomonocytic Leukemias") OR AB ("Acute Myeloid Leukemia" OR "Acute Myeloid Leukemias" OR ANLL OR "Acute Myeloblastic Leukemia" OR "Acute Myeloblastic Leukemias" OR "Acute Myelocytic Leukemia" OR "Acute Myelocytic Leukemias" OR "Acute Nonlymphoblastic Leukemia" OR "Acute Nonlymphoblastic Leukemias" OR "Acute Nonlymphocytic Leukemia" OR "Acute Nonlymphocytic Leukemias" OR "Acute Myelogenous Leukemia" OR "Acute Myelogenous Leukemias" OR "Acute Myeloid Leukemia without Maturation" OR "Acute Myeloid Leukemia with Maturation" OR "Naegeli-Type Myeloid Leukemia" OR	

	"Acute Myelomonocytic Leukemia" OR "Acute Myelomonocytic Leukemias")
2	DE "Antineoplastic Drugs" OR DE "Chemotherapy" OR TI (chemotherapy OR chemotherapies OR Chemotherapeutic OR “antineoplastic drug” OR “antineoplastic drugs” OR “antineoplastic agent” OR “antineoplastic agents” OR antineoplastics OR “antitumor drug” OR “antitumor drugs” OR “antitumor agent” OR “antitumor agents” OR “antitumour drug” OR “antitumour drugs” OR “antitumour agent” OR “antitumour agents” OR “anticancer drug” OR “anticancer drugs” OR “anticancer agent” OR “anticancer agents”) OR AB (chemotherapy OR chemotherapies OR Chemotherapeutic OR “antineoplastic drug” OR “antineoplastic drugs” OR “antineoplastic agent” OR “antineoplastic agents” OR antineoplastics OR “antitumor drug” OR “antitumor drugs” OR “antitumor agent” OR “antitumor agents” OR “antitumour drug” OR “antitumour drugs” OR “antitumour agent” OR “antitumour agents” OR “anticancer drug” OR “anticancer drugs” OR “anticancer agent” OR “anticancer agents”)
3	DE "Neurocognitive Disorders" OR DE "Consciousness Disorders" OR DE "Delirium" OR DE "Dementia" OR DE "Memory Disorders" OR DE "Cognitive Impairment" OR DE "Neuropsychology" OR DE "Neuropsychological Assessment" OR DE "Halstead Reitan Neuropsychological Battery" OR DE "Luria Nebraska Neuropsychological Battery" OR DE "Mini Mental State Examination" OR DE "Task Switching" OR DE "Wisconsin Card Sorting Test" OR DE "Cognitive Processes" OR DE "Awareness" OR DE "Cognitions" OR DE "Cognitive Reserve" OR DE "Daydreaming" OR DE "Estimation" OR DE "Executive Function" OR DE "Human Channel Capacity" OR DE "Judgment" OR DE "Mentalization" OR DE "Mindfulness" OR DE "Questioning" OR DE "Reality Testing" OR DE "Strategies" OR DE "Accommodation (Cognitive Process)" OR DE "Assimilation (Cognitive Process)" OR DE "Associative Processes" OR DE "Catastrophizing" OR DE "Chunking" OR DE "Classification (Cognitive Process)" OR DE "Cognition" OR DE "Cognitive Appraisal" OR DE "Cognitive Bias" OR DE "Cognitive Discrimination" OR DE "Cognitive Dissonance" OR DE "Cognitive Flexibility" OR DE "Cognitive Generalization" OR DE "Cognitive Maps" OR DE "Cognitive Mediation" OR DE "Cognitive Processing Speed" OR DE "Cognitive Strategies" OR DE "Comprehension" OR DE "Concentration" OR DE "Concept Formation" OR DE "Counterfactual Thinking" OR DE "Decision Making" OR DE "False Beliefs" OR DE "Fantasy" OR DE "Human Information Storage" OR DE "Ideation" OR DE "Imagination" OR DE "Intuition" OR DE "Lexical Access" OR DE "Mental Rotation" OR DE "Metacognition" OR DE

	"Naming" OR DE "Pattern Recognition (Cognitive Process)" OR DE "Problem Solving" OR DE "Rumination (Cognitive Process)" OR DE "Schema" OR DE "Semantic Generalization" OR DE "Social Cognition" OR DE "Thinking" OR DE "Thought Suppression" OR DE "Transposition (Cognition)" OR TI (cognitive OR cognition OR neuropsychological OR neuropsychology OR neurocognitive OR neurocognition OR neurogenesis OR memory OR “processing speed” OR “information processing” OR “executive function” OR "Executive Functions" OR “executive control” OR “executive controls” OR learning OR psychomotor OR chemobrain OR chemofog OR “chemo brain” OR “chemo fog”) OR AB (cognitive OR cognition OR neuropsychological OR neuropsychology OR neurocognitive OR neurocognition OR neurogenesis OR memory OR “processing speed” OR “information processing” OR “executive function” OR "Executive Functions" OR “executive control” OR “executive controls” OR learning OR psychomotor OR chemobrain OR chemofog OR “chemo brain” OR “chemo fog”)	
4	#1 AND #2 AND #3	8

APPENDIX 3.1: NEUROPSYCHOLOGICAL ASSESSMENT PROCEDURE

Name of assessment	Action to perform	
Hopkins Verbal Learning Test - Revised (HVLT-R) Trials 1-3	Reading the standard instruction transcript Reading 12 words, each word one second Trial 1 done Reading the standard instruction transcript Trial 2 done Reading the standard instruction transcript Trial 3 done Borg's 10CR done	
Digit Span	Forward	Reading the standard instruction transcript Reading list of numbers, each digit one second Digit Span forward done Borg's 10CR done
	Backward	Reading the standard instruction transcript Reading list of numbers, each digit one second Digit Span backward done Borg's 10CR done
Delis-Kaplan Executive Function System (D-KEFS) Letter Fluency Test	Reading the standard instruction transcript First letter done (60 seconds) Reading the standard instruction transcript Second letter done (60 seconds) Reading the standard instruction transcript Third letter done (60 seconds) Borg's 10CR done	
Trail Making Test (TMT)-A & B	Reading the standard instruction transcript TMT-A Sample done Borg's 10CR done Reading the standard instruction transcript TMT-A done Borg's 10CR done Reading the standard instruction transcript TMT-B Sample done Borg's 10CR done Reading the standard instruction transcript TMT-B done Borg's 10CR done	
Hopkins Verbal Learning Test -	Waiting for 20-25 minutes Reading the standard instruction transcript	

Revised (HVLT-R)	Trial 4 done
Trial 4	Borg's 10CR done

APPENDIX 4.1: INTERVIEW GUIDE FOR OLDER ADULTS WITH AML

1. Can you tell me about your [attention, remember things]?

   Probe: Tell me more about whether your [attention, remember things] is the same or different since being diagnosed?

      Probe: Can you tell me how did you notice these changes in [attention, remember things]?

2. Can you tell me when you first experienced these changes in [pay attention, remember things]?

   Probes: After your acute leukemia diagnosis? At _____ cycle of chemotherapy?

   Probe: Can you tell me how long did these changes in [pay attention, remember things] last?

3. Please tell me about any changes in severity of [pay attention, remember things] since you first noticed them. For example, did the problem stay the same, become worse over time or improve?

   Probes: Stay the same? Become worse? Improve?

4. What kind of factors, if any, have you noticed may contribute to these changes in [attention, remember things]?

   Probes: Doesn't sleep well? In pain?

5. Please tell me how you feel about these changes in [attention, remember things]? For example, is this troubling or burdening you?

   Probe: As you mentioned these changes in [attention, remember things] are _____ (based on Question 5), how did they impact you and your family's life?

Probe: What kind of techniques or strategies have you used, if any, to help you cope with these changes in [attention, remember things]?

Probes: Take notes/writing memo? Involve caregiver and/or family members?

Probes: Can you tell me more about how these strategies help you cope?

Probes: How have these strategies impacted your daily life?

Is there anything else we have not yet discussed that you would like to share related to what we've been talking about?

APPENDIX 4.2: INTERVIEW GUIDE FOR CAREGIVERS

1. Can you tell me about [patient's name] [attention, remember things]?

   Probe: Tell me more about whether [patient's name] [attention, remember things] is the same or different since being diagnosed?

      Probe: Can you tell me how did you notice these changes in [attention, remember things]?

2. Can you tell me when you first noticed these changes in [patient's name] [pay attention, remember things]?

   Probes: After [patient's name] acute leukemia diagnosis? At _____ cycle of chemotherapy?

   Probe: Can you tell me how long did these changes in [pay attention, remember things] last?

3. Please tell me about any changes in severity of [pay attention, remember things] since you first noticed them. For example, did the problem stay the same, become worse over time or improve?

   Probes: Stay the same? Become worse? Improve?

4. What kind of factors, if any, have you noticed may contribute to these changes in [attention, remember things]?

   Probes: Doesn't sleep well? In pain?

5. Please tell me how you feel about these changes in [pay attention, remember things]? **(cognitive changes experience-distress)** For example, is this troubling or burdening you?

Probe: As you mentioned these changes in [pay attention, remember things] are _____ (based on Question 5), as a caregiver, how did they impact [patient's name's] and your life?

Probe: What kind of techniques or strategies have you used, if any, to help [patient's name] cope with these changes in [attention, remember things]?

Probes: Take notes/writing memo? Involve caregiver and/or family members?

Probes: Can you tell me more about how these strategies help [patient's name] and you cope?

Probes: How have these strategies impacted your daily life?

Is there anything else we have not yet discussed that you would like to mention related to what we've been talking about?

APPENDIX 4.3: CODEBOOK

Codes	Definition
Holistic Coding	
CRCI experiences	Patients' and caregivers' perspectives on patients' cognition (memory, attention, concentration, language) change, the cognition change severity, duration ,and frequency.
CRCI related factors	Patients' and caregivers' perspectives on factors contributing in the change in cognition (memory, attention, concentration, language).
CRCI impact on life	The impact of CRCI on patients and caregivers' life, which may include but not limited to function, daily activities, social connection, and emotion.
CRCI coping strategies	The strategies patients and caregivers used to manage the change in cognition (such as taking notes, making links to memorize, reminder, or talk to Alexa); and patients and caregivers' attitude toward the change in cognition (such as not a big deal, don't use any strategy just let it be...).
Coping strategies on others issues/topics	Patients and caregivers' attitude toward other topics not directly related to CRCI, which may include but not limited to AML diagnosis, treatment...etc.
In-Vivo/Descriptive Coding	
CRCI experiences	
Forgetting previous conversation	Having problem recalling previous conversations with others.
Forgetting people's names, dates, or events	Having problem recalling the name of people being introduced to, the dates, or events.
Forgetting things that supposed to be done	Having problem recalling things that were planning to do or whether the things have been done or not.
Forgetting the location of the things	Having problem recalling things that were placed by patients themselves.
Having difficulty finding or recalling the right/proper words	Having problem coming up with the right/proper words to use when talking to people.
Getting distracted easily	Having problem paying attention and getting distracted easily.
Refocusing life priorities	Changing focuses or things being attended in life.
Having difficulty processing information	Having problem processing information or taking longer time to process information.

Codes	Definition
No cognition problems identified	Identifying that no cognition problems occurred.
Cognition remains the same	Patients or caregivers reported that perceived cognition stayed the same since the AML diagnosis/ treatment.
Cognition declines	Patients or caregivers reported that perceived cognition decreased since the AML diagnosis/ treatment.
Cognition improves	Patients or caregivers reported that perceived cognition got better since the AML diagnosis/ treatment.
Every once in a blue moon	Cognition problems did not occur every day; instead, the problem might happen every now and then.
Everyday thing	Cognition problems occurred every day.
Pointing out by others	Patients or caregivers noticed cognition problems by others telling them.
Patient-perceived cognitive changes ***[patients-specific code]***	Patients noticed cognition changes by experiencing problems in life or during a situation.
Caregiver-perceived cognitive changes ***[caregivers-specific code]***	Caregivers noticed cognition changes by experiencing problems in life or during a situation.
Impact of CRCI	
No impacts on life	Patients or caregivers did not identify any impacts by cognitive changes.
Concern/Worry	Patients or caregivers expressed their concern or worry because of cognitive changes.
Frustration	Patients or caregivers expressed their frustration because of cognitive changes.
Interfering with social activities	Patients or caregivers identified that cognitive changes caused them problems in social activities (ex: talking to others…etc).
Interfering with daily tasks	Patients or caregivers identified that cognitive changes caused them problems in daily tasks, which might include but not limited to performing daily tasks or taking longer time.
Increased responsibilities for caregivers	Patients or caregivers identified that caregivers experienced increased burden or responsibilities due to cognitive changes.
Changes in patients-caregivers relationship quality	Patients or caregivers expressed that cognitive changes caused changes in their relationship between each other.
CRCI coping strategies	

Codes	Definition
No strategies developed	Patients or caregivers did not develop any strategies to manage cognition problems.
Taking notes/written reminder	Patients or caregivers used notes or sticky notes as reminder.
Technical support	Patients or caregivers used technology, such as Alexa, My Chart, as reminder.
Actively seeking others' help, assistance, or understanding	Patients or caregivers looked for help ,assistance, or understanding from others (family members, friends…etc).
Cognitive exercises	Patients or caregivers did some cognitive exercises, such as puzzles or reading, to improve/maintain their cognitive function.
Keeping life structured	Patients or caregivers kept the patients daily activities in a structural way / made routines to cope with cognition changes or actively involved in their daily tasks.
Pause and think ***[patients-specific code]***	Patients took time to work on preventing future problems (ex: making connection to memorize things) or managing existing problems (looking for substituting words when difficulty finding words) caused by changing in cognition.
Observing needs and providing partial supports ***[caregivers-specific code]***	Caregivers observed what is needed and provided partial supports, which may include but not limited to paying more attention to patients, repetitive reminder…etc.
Providing total support ***[caregivers-specific code]***	Caregivers provided total supports on the tasks, which may include but not limited to managing all the appointments, organizing the pills…etc.
Accepting CRCI as it is	Patients or caregivers coped with the changes in cognition by acceptance.
It is normal aging	Patients or caregivers considered the changes in cognition as a normal aging process.
Noticeable but not concerning	Although the changes were noticeable, patients or caregivers did not consider the problem as a concern considering its' impact
With a sense of humor	Patients or caregivers coped with the changes in cognition using positive attitudes.
Spiritual support	Patients or caregivers coped with the changes in cognition using spiritual support, such as religion; positive belief/attitude; hope.

Codes	Definition
CRCI related factors	
Emotional distress related to cancer	Factors identified by patients or caregivers that were distressing emotions related to cancer, which may include but not limited to AML diagnosis, treatment, clinic visits …etc.
Emotional distress caused by COVID	Factors identified by patients or caregivers that were distressing emotions caused by COVID, which may include but not limited to scheduling vaccine, learning online shopping for quarantine…etc.
Emotional distress related to other issues	Factors identified by patients or caregivers that were distressing emotions related to other life issues, which may include but not limited to finances, taking care of spouse, dealing with housing…etc.
Overwhelming information	Factors identified by patients or caregivers that were the feeling of hard to handle or digest the large amount of information related to AML (such as AML diagnosis, treatment side effects, scheduling/appointments…etc) delivered by health care providers.
Changes in life conditions	Factors identified by patients or caregivers that were related to the change in social responsibilities or priorities in life after being diagnosed with AML.
Cancer treatment/diagnosis	Factors identified by patients or caregivers that were related to cancer treatment (such as previous or current chemotherapy, transplant as a treatment option …etc) or cancer diagnosis.
Inpatient hospital stay	Factors identified by patients or caregivers that were related to being admitted to inpatient unit for treatment of AML.
Medication other than cancer treatment	Factors identified by patients or caregivers that were medications, such as sleeping pills, anesthesia medications…etc, but not cancer drugs.
Age	Factor identified by patients or caregivers was age.
Sleep problem	Factor identified by patients or caregivers was difficulty sleeping.
Fatigue	Factor identified by patients or caregivers was fatigue/tiredness.
Hearing	Factor identified by patients or caregivers was difficulty in hearing.
Blood cell counts	Factor identified by patients or caregivers that were blood test results.