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REVIEW

Cancer-related cognitive impairment in survivors of adolescent and young adult non-central nervous system cancer: A scoping review

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Abstract

Objectives: Cancer-related cognitive impairments (CRCI) are common after treatment and can have important impacts on the lives of adolescent and young adult (AYA) cancer survivors—those cancer survivors diagnosed between ages 15 and 39. However, most research focuses on survivors diagnosed under age 15 or over age 39 so we know relatively little about CRCI among AYA survivors of non-central nervous system (CNS) cancers. Here we review the research on CRCI among AYA survivors of non-CNS cancers to determine prevalence, associated factors, and impact on survivors' lives as well as implications for future research.

Methods: In November 2021 we performed a systematic search of the literature in MEDLINE, Web of Science, PsycInfo, CINAHL, EMBASE, and Cochrane Central Register of Controlled Trials to identify peer-reviewed English language articles describing original research with at least one cognitive outcome and conducted with AYA survivors of non-CNS cancer diagnosed as AYAs. We screened 6003 articles and 21 met eligibility criteria. Guided by the PRISMA-ScR Checklist, we extracted study information to meet review objectives.

Results: Most studies employed cross-sectional surveys or interviews, though some employed longitudinal methods, neurocognitive assessments, or brain imaging. From the subset of articles that reported a prevalence we calculated a weighted mean prevalence of 25.75% and weighted median prevalence of 27.8%. The factors associated with CRCI included female gender, higher dose chemotherapy, and comorbidities. CRCI impacted the lives of AYA survivors through impaired role functioning, financial toxicity, and unmet needs.

Conclusions: CRCI is highly prevalent among non-CNS cancer survivors diagnosed as AYAs and impacts quality of life and role functioning. This review suggests a need for further longitudinal, imaging, and mixed methods research and provision of resources to help achieve better quality of life and educational and occupational attainment during what is potentially a decades-long survivorship period. However, although interventions might improve cognition and functioning, the review identified only one pilot study. Digital interventions may be a practical and effective option for this age group, but they have yet to be adequately investigated.

KEYWORDS
adolescent and young adult, cancer, cancer survivors, cognitive dysfunction, cognitive impairment, oncology, psycho-oncology, review

1 | BACKGROUND

In the United States, about 89,500 adolescents and young adults (AYAs)—those between ages 15 and 39[1]—were diagnosed with cancer in 2020[2] and the 5-year survival rate is about 85%.[3] Many survivors suffer from late effects of cancer and its treatment,[4] and cancer-related cognitive impairments (CRCI) can be particularly impactful. CRCI is of concern in AYAs because this is a critical period of brain development and reorganization[5] and cognitive impairments can contribute to lower quality of life over the course of a potentially long period of survivorship.[6] However, although AYA cancer survivors regularly report CRCI after treatment, their needs often go unaddressed.[7] Furthermore, much of the evidence base for managing CRCI in AYA cancer survivors comes from the literature on childhood cancer survivors.[8,9] This review aims to organize the literature on CRCI in AYA survivors of non-central nervous system (CNS) cancers to examine prevalence, associated factors, and impact on survivors' lives as well as implications for future research.

1.1 | Cancer-related cognitive impairment

A growing evidence base[10–13] confirms that cancer and its treatment often have a lasting impact on survivors' memory, attention, executive function, and processing speed[14] and can negatively impact quality of life.[6] Here we briefly introduce definitions and assessments for CRCI.

1.1.1 | Definitions of CRCI

The International Cognition and Cancer Task Force (ICCTF) defines CRCI as scoring 1.5 standard deviations below the mean on two or more neurocognitive assessments or two standard deviations below the mean on one assessment,[15] but this definition isn't universally adopted. Rather than following this definition, studies often use different criteria for CRCI (i.e. 1 or 2 standard deviations below the mean rather than 1.5 standard deviations on one or three assessments rather than two assessments) or use different control or reference groups. Describing how lack of standardization impacts the prevalence of CRCI reported in the literature, Schilder et al.[16] found that prevalence in adult cancer survivors ranged from 1% to over 45% depending on the CRCI criteria and reference group.

1.1.2 | Assessment of CRCI

Cognitive measures also vary widely from study to study. Cognition is assessed using objective neuropsychological batteries that measure performance in specific domains; subjective self-reports, also called patient-reported outcomes (PROs), that measure participants' perceptions of their cognitive capacity; or qualitative methods such as interviews or focus groups. Because the constructs measured by each of these evaluations differ, resulting prevalence estimates are fundamentally different. Evidence suggests that subjective assessment outcomes are strongly correlated to depression, anxiety, or fatigue and only weakly correlated to objective assessment outcomes.[17] Objective assessments usually result in lower CRCI prevalence than subjective assessments.[18]

The ICCTF in 2011 recommended an objective assessment battery consisting of the Hopkins Verbal Learning Test-Revised (HVLT-R), Trail Making Test (TMT), and the Controlled Oral Word Association (COWA).[15] These specific tests were selected to measure learning and memory, processing speed, and executive function because those are the domains mainly affected by cancer and its treatment.

1.2 | Adolescent and young adult cancer survivors

Although the cancer diagnosis rate among AYAs is about eight times the diagnosis rate in children age 14 and under and the risk of late effects is higher,[9] much of the evidence on managing late effects in AYA cancer survivors comes from the literature on childhood cancer survivors.[8,9] However, studies show that AYAs are not just 'big children' and that providers need more reliable evidence to deliver appropriate care to this age group.[9]

The AYA years are a critical period of development, and a cancer diagnosis during this period can impact the entire life course.[19] The frontal lobe and amygdala mature and develop into the 20s and the hippocampus begins to decline in volume after age 30,[20] and each is more vulnerable to stress during those times. Particularly during adolescence, exposure to highly stressful or traumatic events, such as life-threatening illness, can induce changes in the brain and be a predisposing factor for developing major depressive disorder and anxiety-related disorders.[20,21] Cancer and its treatment can also disrupt important developmental milestones of adolescence and early adulthood, including those related to cognition, and change educational and career trajectories.[14] Compounding these impacts, AYAs often do not have the social or material support more readily available to those who are older or younger.[22] These factors make it important to understand the nature of CRCI and its impacts on those specifically diagnosed with cancer as AYAs.

1.2.1 | CRCI in other age groups

Reported prevalence of CRCI ranges from 6% to 68% in childhood survivors[11] and from 1% to 75% in adult survivors.[16,23] The majority

of research into identifying specific CRCI symptoms has been conducted with older breast cancer survivors[10,13,14,23] and shows that CRCI may present as worse scores on neuropsychological assessments of specific cognitive domains such as attention, processing speed, executive function, memory, and verbal fluency as well as subjective outcomes such as difficulty multi-tasking, 'tip-of-the-tongue' phenomena, and cognitive fatigue. Most evidence on CRCI in childhood cancer survivors is from survivors of CNS cancer, those receiving CNS-directed treatments such as cranial radiation therapy,[13] or survivors of acute lymphoblastic leukemia treated with modern chemotherapy protocols.[24] Although CRCI occurs in survivors of childhood and AYA non-CNS cancers, little is known about how it presents within specific cognitive domains, brain structures, and brain activity. Thus, one purpose of this review is to collate the evidence for CRCI in AYA survivors of non-CNS cancers.

1.2.2 | CRCI among different cancers and treatments

CRCI is observed in 6%–68% of childhood survivors[11] and 1–75% of adult survivors.[16,23] CRCI associated with cancers and treatments, like cranial radiation, that directly affect the CNS, are suspected to be at least partly organic in origin, most likely due to a direct effect on brain tissue.[13] Non-CNS cancers also cause CRCI through various mechanisms. For example, research suggests that cancer affects cognition even prior to diagnosis,[13] while some suggests that cognitive changes might be due to post-traumatic stress from the cancer diagnosis.[25,26] Although colloquial references such as 'chemo-brain' or 'chemo-fog' imply that chemotherapy is primarily responsible for CRCI,[13,14] empirical evidence supports associations between CRCI and radiation or surgical resection as well.[13] While differences in cancer type and treatment, demographics, and assessments of cognition make comparisons difficult, recent systematic reviews have attempted to disentangle these effects. Torrente et al.[10] reports that domain-specific impairments vary based on cancer and treatment type. For example, breast cancer patients exhibit impairments in attention, memory, information processing, and executive function, but only colorectal cancer survivors exhibit decreases in verbal memory. Neural imaging studies identify changes in brain structure (i.e. white matter microstructure and cerebral networks) as well as changes in brain activity assessed while performing cognitive tasks.[10] The affected neural areas, such as the frontal cortex, are mainly important for executive function and memory. Chan et al.[27] shows that colorectal survivors report subjective impairment regardless of treatment but data suggests that severity is higher among those receiving chemotherapy.

1.3 | Objectives

This review aims to answer the following research questions concerning AYA survivors of non-CNS cancers:

(1) What is the prevalence of CRCI?
(2) What are the factors associated with CRCI?
(3) What are the impacts of CRCI?

2 | METHOD

2.1 | Data sources and search strategies

We completed a systematic search in November 2021 for relevant articles indexed in Pubmed, Web of Science, PsycINFO, Cumulative Index of Nursing and Allied Health Literature (CINAHL), Excerpta Medica dataBASE (EMBASE), and the Cochrane Central Register of Controlled Trials (CENTRAL). The following key search terms were used: 'adolescent', 'young adult', 'AYA', 'cancer', 'neoplasm', 'cognition', 'cognitive impairment', 'impairment', 'CRCI', 'memory', 'concentration', 'chemo brain', 'chemo fog', 'late effects', and 'unmet needs.' We also reviewed references of review articles and screened articles for additional literature.

2.2 | Inclusion criteria

Inclusion criteria were:

(1) Full-text article in a peer-reviewed venue,
(2) published in the English language,
(3) published from January 2011 through November 2021,
(4) presented original research including only post-treatment non-CNS cancer survivors diagnosed between ages 15 and 39 or stratified outcomes by age, and
(5) included at least one outcome addressing cognition.

To incorporate the range of research, we included both qualitative and quantitative research studies. We excluded studies that included survivors of CNS cancers or survivors who received CNS-directed treatments, such as cranial radiation, in an attempt to remove possible organic bases for CRCI because these survivors have a much higher rate of CRCI than survivors of non-CNS cancers.[13]

2.3 | Procedure

Employing PRISMA-ScR scoping review methods,[28] our search yielded 6003 articles. We used Covidence software[29] to remove 1832 duplicates and then screened 4171 abstracts. Two team members independently screened each abstract and conflicts were reconciled through consensus with one author (LMV) being the final arbiter. We then screened 322 full-text articles in the same manner, selecting 21 articles for synthesis. The PRISMA flow diagram for the screening process is in Figure 1.

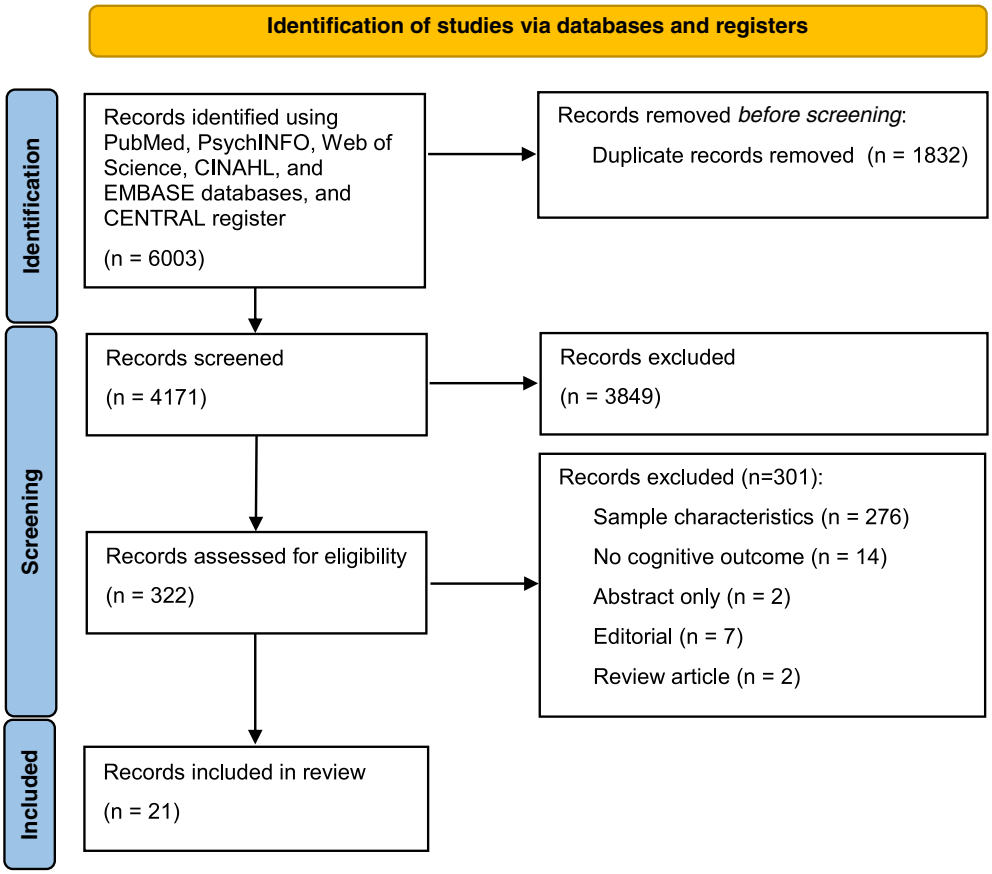

FIGURE 1 PRISMA flow diagram for identification of studies via databases and registers

2.4 | Extraction and charting of results

We extracted study methods, participant characteristics, study measures, CRCI findings, and results concerning prevalence, associated factors, or impacts of CRCI. This information was independently verified by a research assistant and articles were organized by study method. Two authors (LMV and SM) independently formed themes around factors associated with CRCI and impact of CRCI and harmonized those themes through discussion. Two authors (LMV and AP) appraised study quality following the Mixed Methods Appraisal Tool (MMAT) Version 2018,[30] a validated checklist for appraising quality in reviews that include qualitative, quantitative, and mixed methods. Percentage of criteria met is reported, with 100% indicating the highest quality.

3 | RESULTS

Evidence from the 21 included articles was organized by study method (quantitative or qualitative methods further divided into cross-sectional or longitudinal studies) with study and participant details, measures used, cognitive outcomes reported, and quality appraisal listed in Appendix 1.

3.1 | Research methods

Fifteen studies used quantitative methods and six used qualitative methods. Of the quantitative studies, eleven were cross-sectional and four were longitudinal. All six of the qualitative studies were cross-sectional. Articles reported a wide range of data collection methods including surveys, interviews, objective and subjective cognitive assessments, focus groups, and brain imaging with several studies employing more than one method. Figure 2 shows data collection methods grouped by quantitative and qualitative methods plus cross-sectional and longitudinal study designs.

3.1.1 | Cognitive measures

All 15 quantitative studies used PROs, and one quantitative cross-sectional study and one quantitative longitudinal study used objective assessments. The wide range of objective and subjective assessments used hindered comparison between studies. These include validated cognitive assessments such as the ICCTF's recommended HVLT, TMT, and COWA, subjective assessments such as the Short Form Health Survey (SF-36), and general quality of life instruments such as the EORTC QLQ–C30. Several quantitative studies also used

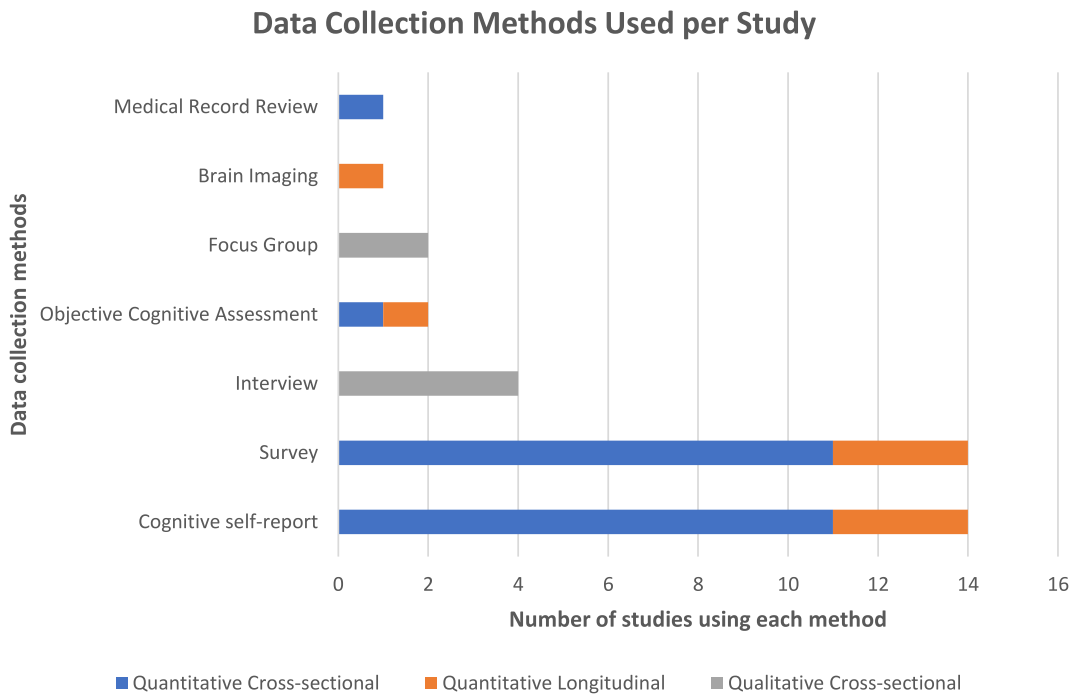

FIGURE 2 Data collection methods used

investigator-developed instruments to gain information on self-reported cognitive function, late effects, long-term follow-up care, needs, and other outcomes and factors associated with CRCI. Qualitative studies did not specifically assess cognition, instead allowing cognitive concerns to emerge in interview or focus group content.

3.2 | Prevalence of CRCI in AYAs

We used the subset of nine articles reporting prevalence of at least one cognitive outcome to calculate mean and median prevalence weighted by number of participants (Table 1). For articles reporting more than one prevalence outcome we used the mean. We used weighted calculations to reflect the number of participants in each study and prevent outsized influence of studies with small sample sizes. We included quantitative and qualitative studies and prevalences based on PROs. We calculated an overall weighted mean prevalence of 25.75% and overall weighted median prevalence of 27.8%.

3.3 | Factors associated with CRCI in AYAs

Quantitative studies reported factors associated with CRCI in AYAs such as treatment type, cancer type, age, gender, and comorbidities.

3.3.1 | Cancer type and treatment

Husson et al.[34] found that CRCI was associated with prior incidence of leukemia, Hodgkin's lymphoma, or a cancer with a lower survival rate; Prasad et al.[39] found that survivors of lymphoma and sarcoma were at lower risk of CRCI than survivors of leukemia; and Nowe et al.[37] found that breast and gynecological cancer survivors reported higher CRCI than testicular cancer survivors. However, Smith et al.[41] found no association between cancer type and CRCI.

CRCI was associated with chemotherapy across all cancer types, although different cancers exhibited different risk levels,[32] and was also associated with prescription of tranquilizers.[40]

3.3.2 | Age

Studies took different approaches to examining the relationship between age and self-reported CRCI. Some studies compared AYA survivors with adult survivors[32,48] while others compared subgroups within the AYA cohort.[33,41] Some compared based on age at diagnosis[32,33] while others made comparisons based on age at participation.[41,48] Both older age[33,48] and younger age[32,41] were associated with CRCI. Of note, Drabbe et al.'s results for higher CRCI in younger AYAs held after correcting for time since diagnosis, comorbidities, and treatment.[32]

3.3.3 | Gender

All studies comparing outcomes by gender reported a higher rate of self-reported CRCI among females.[33,34,37,42,44] Female AYA lymphoma survivors exhibited significantly more CRCI than males,[33] and females scored significantly higher on the negative Impact of Cancer

TABLE 1 Prevalence of Cancer-related cognitive impairments (CRCI) reported per article and weighted mean and median across articles

Article	Gender and age	N	Reported prevalence
Quantitative—self-report			
Brock et al.[42]	• 74.7% female, 25.3% male	502 survivors	18%, baseline
	• age at diagnosis = 18–39 years		16%, 12 months
	• time post-diagnosis at enrollment = 0–4 years		
Prasad et al.[39]	• 50.4% female, 49.6% male	1054 survivors	13.9% impaired task efficiency
	• age at diagnosis = 15–21 years		21.6% impaired memory
Tan et al.[44]	• 46.2% female, 53.8% male;	91 survivors	22.5%, 1 month
	• age at diagnosis = 15–39 years		25.7%, 6 months
	• mean age at enrollment = 28.4 years (6.7SD)		20.7%, 12 months
Dewar et al.[31]	• 81.6% female, 18.4% male	2646 survivors	27.8%
	• age at diagnosis = 15–39 years		
	• age at enrollment = 25–75+ years		
	• time post-diagnosis at enrollment = 10 or more years		
Mellblom et al.[36]	• 72.9% female, 27.1% male	1294 survivors	27.9%
	• age at diagnosis = 19–39 years (mean = 33)		
	• mean age at enrollment = 49 years		
	• mean time post-diagnosis at enrollment = 15 years		
Parsons et al.[43]	• 35.6% female 64.4% male	388 survivors	30% problems 'paying attention'
	• age at diagnosis = 15–39 years		53% problems 'forgetting'
	• time post-diagnosis at enrollment = 15–35 months		28% trouble 'keeping up'
Rey et al.[40]	• 100% female	222 survivors	37.4%, 10 months
	• age at diagnosis = 18–40 years		36.5%, 16 months
			42.3%, 28 months
Qualitative—self-report			
Magrath et al.[50]	• 50% female, 50% male	8 survivors	100%
	• age at diagnosis = 16–19 years		
	• age at enrollment = 18–27 years		
D'Agostino et al.[47]	• 60% female, 40% male	5 survivors	100%
	• age at enrollment = 18–35 years (mean = 25.6 (4.1SD))		
Calculated Prevalence			
Weighted Prevalence			**Mean: 25.75%**
			Median: 27.8%

Note: For articles reporting more than one prevalence, calculations use the mean per article.

summary scale and cognitive function subscale than males across all cancer types.[34] Other studies also report higher CRCI associated with being female.[37,42,44]

3.3.4 | Comorbidities

CRCI was associated with several comorbid conditions, most frequently fatigue and mental illness.[31,33,34,38,40,44] Husson et al.[33,34] found that self-reported CRCI was associated with having physical fatigue or having two or more comorbid health conditions, such as diabetes or asthma. Similarly, Nowe et al.[37] reported an association between self-reported CRCI and comorbidities. Several articles reported that CRCI and physical fatigue were comorbid and some suggest that they may be tightly coupled.[33,34,38,44] All of these studies examined self-reported CRCI except for Nugent et al.[38] which employed an objective cognitive assessment.

3.3.5 | Other factors

In addition to finding that self-reported CRCI was associated with being female and fatigue, depression, and/or anxiety, Tan et al.[44] found that CRCI was associated with smoking and Indian ethnicity. Magrath et al.[50] found that cognitive fatigue was also closely entwined with and often indistinguishable from what their study called 'chemobrain.' Rey et al.[40] found that, particularly among younger women, self-reported CRCI was associated with having lower educational attainment, being unemployed, and being a non-native language speaker. A small pilot of a 12-week physical activity intervention for CRCI that measured outcomes using objective assessment and brain imaging, post-intervention, found that participants exhibited no change in cognitive performance, but brain imaging identified significant increases in some neural activity.[45]

3.4 | Impacts of CRCI on AYA cancer survivors

3.4.1 | Lived experience and characterization of cognitive function

The survivor voice in the qualitative studies gave powerful context for the results of the quantitative studies. Possibly due to a perceived lack of preparation for CRCI in survivorship,[52] survivors felt 'overwhelmed' and 'surprised' by the impact of CRCI.[46] They indicated a sense of loss,[49] experienced difficulty adjusting to changes,[51] reported 'forgetting' or difficulty 'keeping up',[43] and often found that CRCI was more difficult to handle than other symptoms because it was 'invisible'.[53] Participants were frustrated with concentration problems, with one saying they were now 'a different person entirely'.[50] Survivors expressed a mismatch between expectations of what their cognitive abilities would be and the often poorer reality that they experienced later.[54]

3.4.2 | Role functioning

CRCI was commonly associated with difficulties in role functioning.[38,39,41,46–49] Survivors reported worse concentration, memory, and attention[35,36,41,43,46,49] and were concerned about the impacts of these deficits on employment and education.[38,42,43,46,49] CRCI was the strongest predictor of reduced work ability[42] and it was associated with unemployment.[33,34,40]

Yet, a substantial proportion of AYA cancer survivors with CRCI did return to work or school. Over 72% of those either working or in school full-time prior to diagnosis returned to work or school although 30% still endorsed problems with 'paying attention' and 28% reported trouble 'keeping up with work or studies.'[43] However, only 34% of those working or in school part-time prior to diagnosis had returned to that level.[43] CRCI impeded study and the completion of coursework[50] and was associated with financial toxicity.[37]

3.4.3 | Quality of life

Lower quality of life was attributed to CRCI.[33,40,48] Lymphoma survivors had significantly worse scores in the cognitive domain of a health-related quality of life measure than age- and gender-matched controls,[33] and survivors with CRCI expressed that their lives had completely changed and that they struggled to cope.[48,50]

3.4.4 | Unmet information and support needs

Survivors often expressed unmet needs around CRCI.[35,47,51] AYA cancer survivors expressed disappointment in the lack of resources and support they received and specifically wanted better access to cognitive assessment and rehabilitation.[47] Dewar et al.[31] recommended that more services to mitigate cognitive issues become a standard part of AYA survivorship care.

4 | DISCUSSION

4.1 | Prevalence and measures of CRCI in AYA cancer survivors

We calculated a 25.75% weighted mean prevalence and 27.8% weighted median prevalence but these estimates are somewhat low compared to other published estimates around 35% for CRCI in survivors of non-CNS cancer.[10,13] Several sampling factors might influence the other published estimates. First is the inclusion of older participants who may also be experiencing cognitive decline due to aging.[53] Second is the inclusion of patients in active treatment who often exhibit higher decline than survivors.[13] Third is the inclusion of survivors of CNS cancers and CNS-directed therapies who often exhibit a higher rate of CRCI.[13]

Results also depend on the assessment used, the diagnoses and treatments included in the sample, and the sampling method,[16] further complicating direct comparisons between studies. However, many AYA survivors clearly consider themselves impaired in comparison to their pre-diagnosis cognitive capabilities, and AYA cancer survivors report higher levels of CRCI in all studies comparing prevalence between survivors and controls.[31,39] Survivors often perceive themselves to have CRCI although objective cognitive assessments show function within normal ranges, a phenomenon that may occur due to the decline being too subtle for objective assessments to detect, particularly if prior functioning was above the normal range (see Costa and Fardell[17] for a more in-depth discussion of this topic). Furthermore, unlike many people experiencing decline due to aging or disease, AYAs are usually able to offer insight into their functioning and reliably report their experiences. Although many current objective measures are unable to detect subtle decline,[55] problems they do not detect are no less impactful or worrisome to those experiencing them.[56]

Objective and subjective assessments also measure different constructs: objective assessments measure performance while subjective assessments measure experience. Overall, objectively measured impairment is less prevalent than subjectively measured impairment.[18] For example, Nugent et al.[38] report no significant difference between survivors and controls on objective measures, but report small and medium effect sizes and significantly more subjective memory problems among survivors.

4.2 | Factors associated with CRCI in AYA cancer survivors

Although some studies perpetuated the connotation that chemotherapy primarily causes CRCI, using phrases like 'chemo brain'[51] and 'chemo-fog',[49] this review indicates that chemotherapy is only one factor associated with CRCI and such language may promote the problematic bias attributing CRCI only to chemotherapy. Studies found associations between CRCI and leukemia,[34,39] Hodgkin's lymphoma,[34] breast and gynecological cancers,[37] and cancers with a lower survival rate[34]; female gender[33,34,37,42,44]; physical fatigue[33,34,38,44]; and anxiety and/or depression.[31,33,34,38,40,44]

Studies examining treatment type did find a relationship between chemotherapy and CRCI in AYA survivors,[32] but it was unclear whether a specific chemotherapy regimen or agent was responsible. However, research has shown other treatments to be associated with CRCI[13] and future studies should further explore this idea.

4.3 | Impacts of CRCI on AYA cancer survivors

Although some survivors obtain help with CRCI, most say that their needs are not adequately met. That lack of support can complicate resumption of education and career and contribute to financial toxicity. Several authors recognized this shortcoming and recommended more assistance be offered to AYA survivors.[31,40,47,51]

4.4 | Implications for future AYA CRCI research

This review surfaced areas for improving research on CRCI in AYA survivors, particularly the inclusion of more:

1. consistent cognitive measures,
2. longitudinal studies,
3. well-characterized participant and control samples,
4. consistent stratification by age,
5. mixed methods studies, and
6. consistent, standard, objective terminology.

The first four items were discussed by the ICCTF in 2011,[15] indicating a remaining gap in bringing consistency to studying cognition in cancer survivorship.

4.4.1 | Cognitive measures

The studies in this review used many different published scales, cognitive batteries, and investigator-generated scales and surveys, but a standard battery that includes both an accurate, easy-to-administer objective assessment and a validated self-report instrument might give researchers and clinicians the tools they need to understand the severity and nature of CRCI in AYA patients, allow comparison between studies, and provide feedback to patients. To help rectify this inconsistency, the ICCTF recommended objective assessment using a core battery along with supplemental tests,[15] while the Cancer Neuroscience Initiative PROs Working Group recommended subjective assessment using the PROs Management Information System (PROMIS) Cognitive Function Short Form 8a.[56] However, final selection of appropriate assessments must be based on careful definition of study goals.

4.4.2 | Longitudinal studies

Only four of the 21 articles in this review reported results of longitudinal studies. Although cross-sectional studies offer important insights, a relative lack of longitudinal studies hampers our ability to characterize the trajectory of cognitive issues in AYA cancer survivors over time.

4.4.3 | Participant samples and control groups

Many samples were characterized in terms of treatment regimen, cancer type, gender, age at diagnosis, time since end of active treatment, and comorbidities. Fewer were characterized in terms of other risk factors known to be associated with CRCI such as comorbidities, post-traumatic stress disorder, fatigue, childhood trauma, and stress.[9,21] Without measuring these factors, we are unable to account for as many of the elements known to co-occur with CRCI as possible. To further establish correlations between factors, studies should include comparison to appropriate control groups and published normative data.

4.4.4 | Age specification and stratification

Studies often include AYAs in their samples but do not adequately specify age, stratify by age, or analyze age groups separately, although we know that different age groups have different outcomes.[9] Consistent specification of age at diagnosis, age at study, time since diagnosis, and time since end of active treatment is helpful for understanding and comparing findings. Stratification or grouping by NCI-defined age groups is important for identifying differences attributable in part to developmental differences between those age groups.

4.4.5 | Mixed methods

Mixed methods allow the investigation of both quantitative relationships as well as the qualitative context in which they reside. Both data types are needed to characterize the CRCI experience and develop interventions that address challenges AYA survivors with CRCI face at home, school, and the workplace.

4.4.6 | Consistent terminology

Articles use inconsistent and often non-standard or subjective terminology to refer to CRCI. Some articles discuss only cognitive domains such as attention, concentration, thinking, or memory; others use synonyms such as 'cognitive fatigue' or 'cognitive concerns;' while others use colloquial terms such as 'chemo-fog'[49] and 'chemo brain'.[51] A lack of consistent, precise terminology makes it difficult to readily identify all articles investigating CRCI.

4.5 | Research implications

Based on the review of research on CRCI in survivors of AYA cancer, we have several recommendations for future research.

4.5.1 | Intervention research

Trials of interventions with other age groups show promising results[10,12,13] but interventions targeted to helping AYA survivors overcome CRCI are critical. As demonstrated with childhood cancer survivors,[24] changes to treatment protocols may improve cognitive outcomes. Although a very small pilot study, Wurz et al.[45] gave encouraging results for AYA survivors using a physical activity intervention and this review also shows that mental health and smoking may be targets for intervention. Furthermore, AYAs expressed a need for better cognitive health resources during survivorship,[47,51] and authors advised that CRCI complaints deserve greater consideration than they are currently afforded[40] and that better cognitive care should become a standard part of AYA survivorship care.[31]

4.5.2 | Cognitive neuroscience research

One study used brain activity as an outcome,[45] illustrating the utility of imaging and other cognitive neuroscience research. Studies using brain monitoring and imaging methods could identify changes in the brains of cancer survivors before, during, and after treatments or interventions to elucidate the relationship of those changes with function.

4.5.3 | Leveraging widespread mobile technology use

The inconvenience and logistical challenges associated with research participation are particularly burdensome for underserved groups who are often underrepresented in research—including those who are non-white, young, single, low-income, or unemployed.[57] Effective use of technology can help lower these barriers, enabling people to participate who might otherwise be unable. Mobile health technologies are especially attractive for reaching younger people since 96% of those ages 18–29 in the US own a smartphone, and they are the only means of Internet access for many younger, lower-income, and non-white Americans.[58] Beyond research, technology is also a scalable means of implementing assessments and delivering interventions.[13,59]

4.5.4 | Study limitations

Due to the variability in CRCI definitions and measures, as well as the diversity of cancer types and treatments across studies, our prevalence calculations may be inaccurate, and estimates of CRCI prevalence in different AYA survivor populations need further research. Inconsistency in terminology around cognitive impairment may have also impeded our ability to identify all publications assessing CRCI in AYA cancer survivors.

5 | CONCLUSION

CRCI is common after cancer treatment ends and can have long-term consequences for survivors, particularly for AYA cancer survivors pursuing an education or beginning a career. To advance the goal of developing interventions for mitigating CRCI in AYAs, this review collated the original research on cognitive symptoms, identified gaps, and specified priorities for future research. Factors positively associated with CRCI were female gender, higher dose chemotherapy, and comorbidities. Impacts of CRCI are impaired role functioning, low quality of life, and unmet needs. Additional longitudinal and intervention studies, particularly those leveraging digital health technologies, are necessary to develop evidence-based interventions for AYA survivors of non-CNS cancers with CRCI.

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CONFLICT OF INTEREST

No conflict of interest has been declared by the authors.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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