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Pretreatment cancer-related cognitive impairment in older patients

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ABSTRACT

Introduction. Cognitive impairment is common in older adults and may be worsened by cancer and its treatment. While cancer-related cognitive impairment (CRCI) during and after therapy is well documented, less is known about cognitive deficits present before treatment begins.

The objective herein, was to identify factors independently associated with pretreatment CRCI in older adults with cancer, using data from **a** geriatric oncology service in **a** tertiary hospital in Lima, Peru.

Material and methods. This observational case-control study analyzed data from Comprehensive Geriatric Assessments (CGA) conducted in patients aged ≥ 60 years prior to initiating chemotherapy or surgery. Cognitive function was assessed using the Mini-Mental State Examination (MMSE), with CRCI defined as an MMSE score < 24. Multivariate logistic regression was used to identify independent predictors of CRCI.

Results. A total of 189 patients were included (58 with CRCI, 131 without), with a mean age of 75.1 years; 45% were women. The overall prevalence of CRCI was 30.7%. In univariate analysis, CRCI was associated with older age, fewer years of education, malnutrition, depression, higher comorbidity burden, functional dependence, lower handgrip strength, and sarcopenia in women (all $p < 0.05$). In multivariate analysis, three variables remained significantly associated with CRCI years in education (adjusted OR = 0.75; 95% CI 0.67–0.84; $p < 0.001$), handgrip strength (adjusted OR = 0.90; 95% CI 0.83–0.98; $p = 0.015$), and presence of depression (adjusted OR = 3.32; 95% CI 1.20–9.17; $p = 0.020$).

Conclusions. Nearly one in three older adults with cancer presented with cognitive impairment before treatment. Higher educational attainment and greater handgrip strength were associated with lower odds of CRCI, while depression significantly increased the risk. These findings highlight the need for early cognitive screening and comprehensive interventions targeting modifiable factors in geriatric oncology care.

Keywords: cancer, cognition, elderly, cognitive decline, aging

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Introduction

According to GLOBOCAN, in 2022 there were over 12 million new cancer cases among individuals aged 60 years or older worldwide, with 7.6% occurring in Latin America and the Caribbean [1]. It is estimated that this region is home to approximately 4 million cancer survivors — a number expected to increase in the coming years [2]. This trend is largely attributable to advances in cancer detection and treatment, which have significantly improved survival rates. As a result, maintaining the quality of life for older adults living with cancer has become a growing concern. A key aspect of this involves preventing or managing complications and adverse effects of cancer and its treatments, one of which is cancer-related cognitive impairment (CRCI).

Cancer-related cognitive impairment refers to cognitive decline that occurs in individuals with cancer and can affect domains such as working memory, attention, executive functioning, orientation, language comprehension, and processing speed [3]. A recent operational definition describes CRCI as a temporary or persistent,

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subjective or objective change in higher cognitive processes associated with cancer or its treatments [4].

Various risk factors have been associated with CRCI. These include treatment-related effects such as chemotherapy (commonly referred to as "chemo brain") [3], antihormonal therapy, and cranial radiation. Other contributing factors include genetic predisposition (e.g., *APOE*, *COMT*, *BDNF* polymorphisms), older age, comorbidities, and psychological or social factors such as depression, anxiety, fatigue, sleep disturbances, post-traumatic stress disorder, loneliness, caregiver burden, and low socioeconomic status [5].

Although CRCI often emerges during or after cancer treatment, it can also be present before treatment begins. Studies suggest that approximately 30% of patients exhibit CRCI prior to starting therapy, over 75% during treatment, and about 35% months or even years after completing treatment [6]. Despite this, relatively few studies have examined CRCI in the pretreatment phase, and virtually none have been conducted in South American populations.

Given the aging population and rising cancer incidence in Latin America, research into pretreatment CRCI is urgently needed. Understanding its prevalence and associated risk factors could guide early interventions to preserve cognitive function and improve quality of life in older cancer patients.

The objective of this study was to identify risk factors associated with pretreatment CRCI in older Peruvian patients with cancer.

Material and methods

Study design and participants

This was a retrospective, observational, case-control study based on data extracted from Comprehensive geriatric assessments (CGA) conducted at a tertiary hospital in Lima, Peru. The study included patients aged 60 years and older with a histologically confirmed diagnosis of cancer, evaluated prior to the initiation of chemotherapy or surgical treatment. Patients were categorized as cases if they exhibited cognitive impairment, defined as a mini-mental state examination (MMSE) score of less than 24 [7]. Those with MMSE scores of 24 or higher were classified as controls.

The CGAs were performed between January 2023 and February 2025. A non-probability convenience sampling method was applied. The sample size was calculated assuming a control group proportion of 0.05, an odds ratio of 6, a 95% confidence level, and a statistical power of 80%, resulting in a minimum required sample of 50 cases and 50 controls.

Eligibility criteria

Inclusion criteria for both cases and controls were as follows: patients aged 60 years or older, either hospitalized or treated as outpatients; a confirmed diagnosis of cancer; a CGA requested by the oncology department; and a CGA performed prior to any cancer-specific treatment. Exclusion criteria included illiteracy or conditions preventing reliable MMSE administration, such as significant visual or hearing impairments; hand disorders that interfered with grip strength testing (e.g., rheumatoid arthritis); and the presence of central nervous system tumors or brain metastases.

Comprehensive geriatric assessment

The CGA was conducted by geriatricians and included evaluations of functional status, nutrition, cognition, mood, social context, and comorbidities. Functional status was assessed using the Katz Index of Basic Activities of Daily Living (BADL) [8]. Nutritional status was evaluated using the Mini Nutritional Assessment–Short Form (MNA-SF) [9]. Depression was identified through a documented clinical diagnosis, current use of antidepressant medication, or a semi-structured interview based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) [10]. Comorbidity burden was assessed using the Cumulative Illness Rating Scale for Geriatrics (CIRS-G) [11], excluding cancer-related conditions in accordance with the instrument guidelines. Additional variables collected included age, sex, body mass index (BMI), years of education, and type of cancer.

Cognitive assessment

Cognitive function was measured using the Spanish version of the MMSE. A score of less than 24 was used to define cognitive impairment [7]. The MMSE was selected based on recommendations from the International Cancer and Cognition Task Force (ICCTF), which supports its use for assessing domains commonly affected in cancer patients [12, 13]. This instrument has been previously validated and applied in similar clinical settings [14].

Handgrip strength measurement

Handgrip strength (HGS) was assessed using a Jamar hand dynamometer in accordance with the Southampton protocol [15]. Two alternating measurements were taken for each hand. The highest score from each hand was recorded, and the greater of the two was used in the

analysis. Probable sarcopenia was identified according to the revised European Working Group on Sarcopenia in Older People (EWGSOP2) criteria, defined as HGS < 27 kg for men and < 16 kg for women [16].

Statistical analysis

Descriptive statistics were used to summarize demographic and clinical characteristics. Continuous variables were reported as means with standard deviations (SD) or medians with ranges, depending on the distribution, while categorical variables were expressed as frequencies and percentages. Comparative analyses between cases (MMSE < 24) and controls (MMSE ≥ 24) were performed using the Student t-test or Mann–Whitney U test for continuous variables, and the chi-square test for categorical variables. Odds ratios (OR) with 95% confidence intervals (CI) were calculated to assess associations between CRCI and potential risk factors in univariate analysis.

To identify independent predictors of CRCI, a multivariate logistic regression model was constructed using the enter method, including age, sex, years of education, handgrip strength, nutritional status (MNA-SF), comorbidity burden (CIRS-G), functional dependence (Katz), and presence of depression. Adjusted odds ratios (aOR) with 95% confidence intervals were reported. Model performance was assessed using the chi-square test for model fit, Nagelkerke R^2, and classification accuracy. A p-value < 0.05 was considered statistically significant. All analyses were performed using IBM SPSS Statistics version 28.0.

Ethical considerations

This study was approved by the Research Ethics Committee of Almenara Hospital in Lima, Peru. All data were anonymized, and measures were taken to ensure confidentiality and compliance with ethical standards.

Results

A total of 189 older adult patients with cancer were included in the study, comprising 58 cases with cognitive impairment and 131 controls without impairment. The overall mean age of participants was 75.1 years, with 55% male and 45% female. The prevalence of CRCI prior to treatment was 30.7%.

Regarding physical and clinical characteristics, probable sarcopenia was observed in 63.4% of men and 45.8% of women. The prevalence of malnutrition, defined as a MNA-SF score of < 8, was 38.1%, while depression was present in 14.8% of the sample. The mean CIRS-G total score was 5.8. These characteristics are detailed in Table 1.

The most frequently diagnosed cancers were colorectal (n = 49, 25.9%), followed by stomach (n = 22, 11.6%), lung (n = 20, 10.6%), pancreas (n = 16, 8.5%), liver (n = 16, 8.5%), and biliary tract (n = 8, 4.2%). Less common tumors included those of the kidneys (n = 7, 3.7%), skin (n = 7, 3.7%), prostate (n = 6, 3.2%), non-Hodgkin lymphoma (n = 6, 3.2%), head and neck (n = 6, 3.2%), and breast (n = 5, 2.7%). Other tumour

Table 1. Characteristics of the study population (n = 189)

Variable	Value
Age [years], mean (SD)	75.1 (7.7)
Sex, n (%)	
Male	104 (55.0)
Female	85 (45.0)
HGS [kg], mean (SD)	20.3 (7.2)
Probable sarcopenia, n (%)	
Male (HGS < 27 kg)	66 (63.4)
Female (HGS < 16 kg)	39 (45.8)
Body mass index, mean (SD)	24.5 (4.3)
Years of education, mean (SD)	10.7 (3.9)
Malnutrition (MNA-SF < 8), n (%)	72 (38.1)
Comorbidities, n (%)	
Depression (DSM-IV)	28 (14.8)
Hypertension	33 (17.5)
Type 2 diabetes mellitus	23 (12.2)
CIRS-G total score, mean (SD)	5.8 (3.1)
Functional impairment (Katz < 6/6), n (%)	55 (29.1)
Primary tumour type, n (%)	
Colorectal	49 (25.9)
Gastric	22 (11.6)
Lung	20 (10.6)
Pancreas	16 (8.5)
Liver	16 (8.5)
Bile ducts	8 (4.2)
Kidneys	7 (3.7)
Skin	7 (3.7)
Prostate	6 (3.2)
Non-Hodgkin lymphoma	6 (3.2)
Head and neck	6 (3.2)
Breast	5 (2.7)
Other	13 (6.9)
Presence of metastasis, n (%)	30 (15.9)

ADL — Activities of daily living; CIRS-G — Cumulative Illness Rating Scale for Geriatrics; DSM-IV — Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; HGS — handgrip strength; MNA-SF — Mini Nutritional Assessment–Short Form; SD — standard deviation

Table 2. Risk factors associated with cancer-related cognitive impairment (CRCI) prior to cancer treatment in older adults

Variable	Controls (MMSE ≥ 24) n = 131	Cases (MMSE < 24) n = 58	p-value	OR (95% CI)
Age [years], mean (SD)	73.8 (7.4)	78.0 (7.7)	0.0005	–
Sex, n (%)				
Male	73 (55.7)	31 (53.5)	0.772	–
Female	58 (44.3)	27 (46.6)	0.772	–
Handgrip strength (kg), mean (SD)	21.5 (6.9)	17.4 (7.0)	0.0002	–
Probable sarcopenia, n (%)				
Male (HGS < 27 kg)	42 (57.5)	24 (77.4)	0.058	2.50 (0.96–6.62)
Female (HGS < 16 kg)	20 (34.5)	19 (70.4)	0.003	4.51 (1.68–12.12)
Body mass index, mean (SD)	24.8 (4.2)	23.9 (4.4)	0.167	–
Years of education, mean (SD)	11.9 (3.7)	8.2 (3.2)	< 0.0001	–
Malnutrition (MNA-SF < 8), n (%)	43 (32.8)	29 (50.0)	0.026	2.05 (1.10–3.85)
Comorbidities, n (%)				
Depression (DSM-IV criteria)	14 (10.7)	14 (24.1)	0.017	–
Hypertension	24 (18.3)	9 (15.6)	0.640	0.82 (0.35–1.89)
Type 2 diabetes mellitus	17 (13.0)	6 (10.3)	0.610	0.77 (0.29–2.08)
CIRS-G total score, mean (SD)	5.3 (2.9)	6.8 (3.3)	0.002	–
Functional impairment (Katz ADL < 6/6), n (%)	25 (19.1)	30 (51.7)	< 0.0001	4.54 (2.31–8.92)

ADL — Activities of daily living; CI — confidence interval; CIRS-G — Cumulative Illness Rating Scale for Geriatrics; DSM-IV — Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; HGS — handgrip strength; MNA-SF — Mini Nutritional Assessment–Short Form; MMSE — Mini-Mental State Examination; OR — odds ratio; SD — standard deviation

types accounted for 13 cases (6.9%). A total of 30 patients (15.9%) presented with metastatic disease at the time of evaluation (Tab. 1).

When comparing cases and controls, no statistically significant differences were found in the prevalence of type 2 diabetes mellitus or arterial hypertension. However, patients with CRCI were significantly older (mean age 78.0 *vs.* 73.8 years; p = 0.0005) and had fewer years of formal education (mean 8.2 *vs.* 11.9 years; p < 0.0001). Cancer-related cognitive impairment cases also had higher rates of malnutrition (50% *vs.* 32.8%; p = 0.026) and depression (24.1% *vs.* 10.7%; p = 0.017), along with a higher mean CIRS-G total score (6.8 *vs.* 5.3; p = 0.002). Functional impairment, as measured by a Katz Index score of < 6/6, was significantly more frequent among CRCI cases (51.7% *vs.* 19.1%; p < 0.0001).

In addition, cases demonstrated significantly lower handgrip strength (mean 17.4 kg *vs.* 21.5 kg; p = 0.0002). Among female participants, sarcopenia was notably more common in those with CRCI compared to controls (70.4% *vs.* 34.5%; p = 0.003). These associations are summarized in Table 2.

In a multivariate logistic regression model that included age, sex, years of education, handgrip strength, nutritional status, comorbidity burden, functional status, and depression, three variables remained significantly associated with CRCI. Higher years of education (OR = 0.75; 95% CI 0.67–0.84; p < 0.001) and greater handgrip strength (adjusted OR = 0.90; 95% CI 0.83–0.98; p = 0.015) were independently associated with lower odds of CRCI, while the presence of depression was associated with increased odds (adjusted OR = 3.32; 95% CI 1.20––9.17; p = 0.020). The overall model was statistically significant (Chi-square = 71.35, df = 8, p < 0.001), with a Nagelkerke R^2 of 0.444 and an overall classification accuracy of 80.4%.

Table 3. Multivariate logistic regression for predictors of pretreatment cancer-related cognitive impairment (CRCI)

Variable	Adjusted OR (95% CI)	p-value
Age [years]	1.02 (0.96–1.08)	0.526
Female sex	0.42 (0.14–1.24)	0.114
Years of education	0.75 (0.67–0.84)	< 0.001
Handgrip strength [kg]	0.90 (0.83–0.98)	0.015
Malnutrition (MNA-SF)	0.98 (0.84–1.13)	0.758
Functional dependence (Katz Index < 6/6)	0.72 (0.49–1.07)	0.102
Comorbidity burden (CIRS-G)	1.12 (0.98–1.28)	0.112
Depression (DSM-IV criteria)	3.32 (1.20–9.17)	0.020

CI — confidence interval; CIRS-G — Cumulative Illness Rating Scale for Geriatrics; DSM-IV — Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; MNA-SF — Mini Nutritional Assessment–Short Form; OR — odds ratio

Discussion

This study aimed to examine the characteristics of CRCI prior to the initiation of cancer treatment in older adults. A CRCI prevalence of 30.7% was found, and several significant risk factors were identified, including older age, fewer years of education, malnutrition, depression, greater comorbidity burden, functional dependence in basic activities of daily living, and sarcopenia (particularly among women). Notably, malnutrition, depression, and sarcopenia are potentially preventable and modifiable, which underscores the importance of early detection and intervention.

Although multiple studies have investigated cognitive impairment before cancer treatment, only three have specifically focused on patients with a mean age of 60 years or older. These studies reported a CRCI prevalence ranging from 35% to 40% in patients with hematologic malignancies and pancreatic cancer [17––19]. However, those studies used cognitive screening tools different from the MMSE, such as the Hopkins Verbal Learning Test, Clock-in-the-Box, and the Five-Word Delayed Recall Test, making direct comparison difficult.

The observed association between CRCI and factors such as malnutrition, sarcopenia, and depression are consistent with findings from previous research in older adult populations. Two recent meta-analyses demonstrated a significant link between malnutrition and cognitive impairment in older adults [20, 21]. Similarly, a meta-analysis by Yang et al., [22] which included nine studies, concluded that sarcopenia is a significant risk factor for cognitive decline in aging populations. These findings suggest that older adults with cancer may be particularly vulnerable to CRCI due to overlapping biological and clinical mechanisms.

Cancer itself may exacerbate risk factors for sarcopenia — such as anorexia, reduced physical activity, and systemic inflammation — which are also implicated in cognitive decline. Several pathophysiological mechanisms have been proposed to explain CRCI, including the release of inflammatory cytokines (e.g., interleukin-1β, interleukin-2, interleukn-6, tumor necrosis factor-alpha, interferons), tumour-derived extracellular vesicles, infiltration of immune cells into the brain, and disruption of the blood–brain barrier [22]. These cancer-related biological processes may accelerate cognitive aging or trigger neurodegeneration.

Depression is another well-established contributor to cognitive impairment in older adults [23]. In patients with cancer, depression is more prevalent and may amplify the risk of CRCI. This reinforces the importance of addressing mental health as part of comprehensive oncogeriatric care. The most recent Lancet Commission on dementia prevention emphasizes the role of modifiable factors such as nutrition, physical fitness, and mental health in preventing or delaying cognitive decline [24].

In the present multivariate analysis, which adjusted for clinical and demographic confounders, three factors remained significantly associated with CRCI years of education (protective), handgrip strength (protective), and presence of depression (risk factor). These findings support the hypothesis that reduced cognitive reserve (reflected by lower educational attainment), poorer physical performance, and mental health disorders are independent contributors to cognitive vulnerability in older adults with cancer. While malnutrition, comorbidity burden, and functional dependence were associated with CRCI in univariate analysis, their effects were attenuated in the multivariate model, suggesting overlap or mediation through other factors. These results underscore the value of incorporating brief assessments of cognitive reserve, muscle strength, and mental health into routine oncogeriatric evaluations to better stratify risk and guide early intervention.

This study has several limitations. First, the analysis included patients with various cancer types and did not stratify findings by tumour site, which may influence CRCI prevalence and associated risk profiles. Future research should investigate CRCI in specific cancer types. Second, cognitive function was assessed using the MMSE, a general screening tool that may not detect subtle domain-specific impairments. Comprehensive neuropsychological testing would be needed to

characterize the specific cognitive domains affected. Furthermore, recent research has shown variability in CRCI prevalence depending on the cognitive instrument used; comparisons between the MMSE and other tools such as the Montreal Cognitive Assessment (MoCA) have revealed discrepancies in sensitivity and specificity [25].

Conclusions

In conclusion, nearly one-third of older adults with cancer in the current cohort exhibited cognitive impairment prior to treatment. Significant risk factors for CRCI included malnutrition, depression, comorbidities, and sarcopenia — all of which are potentially modifiable. Future studies should focus on early detection, domain-specific cognitive evaluation, and targeted interventions, particularly in populations at higher risk, such as older people in low- and middle-income countries.

Article information and declarations

Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restriction

Ethics statement

This study was approved by the Research Ethics Committee of Almenara Hospital in Lima, Peru. The necessary strategies were implemented to maintain the privacy of patient information.

Author contributions

T.J.O.: concept and design, drafting of the manuscript, critical revision of the manuscript for important intellectual content; E.C.-M.: acquisition, analysis, interpretation of the data, critical revision of the manuscript for important intellectual content; R.R.-O.: drafting of the manuscript, supervision, critical revision of the manuscript for important intellectual content.

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Conflict of interest

Authors declare no conflict of interest related to this study.

Supplementary material

None.

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