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# Pre-treatment cognitive impairment in patients with NSCLC: Prevalence and psychosocial factors

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ABSTRACT

*Background:* Cancer-related cognitive impairment (CRCI) is increasingly recognized in patients with non-central nervous system malignancies, including non-small cell lung cancer (NSCLC), although evidence on pre-treatment cognitive functioning and associated psychosocial factors remains limited. This exploratory study investigated baseline cognitive functioning in NSCLC patients before oncological treatment and examined the role of cognitive reserve, emotional distress, sleep quality, and subjective cognitive complaints.

*Methods:* Fifty NSCLC patients underwent comprehensive neuropsychological and psychological assessment before treatment initiation. Cognitive functioning was evaluated through standardized tests assessing global cognition, executive functions, memory, attention/processing speed, and language. Cognitive impairment was classified according to International Cognition and Cancer Task Force criteria. Psychological measures included subjective cognitive complaints, depressive symptoms, anxiety, sleep quality, cognitive reserve, and quality of life. Associations with a Composite Cognitive Score (CCS) and domain-specific scores were examined using univariable linear regression analyses.

*Results:* Eighteen patients (36%) met criteria for objective cognitive impairment at baseline. Higher cognitive reserve was associated with better global cognitive performance and stronger attention/processing speed and executive functioning. Conversely, depressive symptoms, anxiety, and poorer sleep quality were associated with lower CCS and worse performance across several domains, particularly global cognition, memory, and attention/processing speed. Subjective cognitive complaints showed partial concordance with objective cognitive performance.

*Conclusions:* Cognitive impairment may already be present in a substantial proportion of NSCLC patients before treatment initiation. Early cognitive and psychosocial assessment may help identify patients at higher risk for CRCI and guide supportive interventions. These findings support early multidisciplinary screening strategies targeting vulnerable patients before treatment.

## 1. Introduction

Patients diagnosed with non-central nervous system (non-CNS) cancers often experience cognitive difficulties, commonly referred to as cancer-related cognitive impairment (CRCI) (Joly et al., 2015; Ta et al., 2012) with significant consequences on quality of life (QoL), social and emotional well-being (Wefel et al., 2011, 2015). Literature reports short-term and working memory, attention, executive functions and/or processing speed as the cognitive domains most affected by this impairment, particularly following chemotherapy (Deprez et al., 2018). For years, CRCI has been thought to be mainly associated with chemotherapy treatment, given chemotherapy's potential to alter brain

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metabolism and cellular function through direct cytotoxic damage to nerve cells; however, more recent literature also reports other oncological treatments (e.g., immunotherapies, endocrine therapies, and cancer surgery) playing a crucial role in the development of patients' cognitive difficulties (Lange et al., 2019). In line with this, neuroimaging evidence and structural MRI studies in breast cancer research indicate that chemotherapy is associated with reduced gray matter volume and density, as well as white matter microstructural alterations compared with healthy controls (Di Iulio et al., 2019; Conti et al., 2025). Radiotherapy and proton therapy have also been shown to induce anatomical, morphological, and metabolic damage in brain tissue, including atrophy affecting both gray and white matter and various brain substructures, including the hippocampus and hippocampal gyrus (Witzmann et al., 2021). These alterations in temporal and parietal regions may also offer an anatomic-functional framework to explain why impairments predominantly emerge in attention, memory, and working memory domains (Cabeza et al., 2008). Because of key disease-related factors such as greater incidence, age at onset, life expectancy, disease progression, and treatment modalities, CRCI has been predominantly studied in breast cancer patients. However, in recent years, research on cancer-related cognitive impairment has expanded to include patients with small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), where cognitive deficits are common, clinically significant, and has been shown to arise regardless of tumor treatment (Simó et al., 2015). Importantly, CRCI is increasingly recognized as a multifactorial condition that may emerge both before and after the initiation of cancer treatment (Ta et al., 2012). In this context, cognitive impairment detected prior to treatment may reflect cancer- and host-related mechanisms rather than treatment-induced neurotoxicity (Simó et al., 2015). Moreover, according to a meta-analysis by Ye and colleagues (2024) in patients with SCLC, a large proportion of patients (approximately 60–90%) develop cognitive impairments within 1–5 months after completing chemotherapy. In contrast, in patients with NSCLC, cognitive deficits have been observed even prior to chemotherapy initiation, particularly in verbal memory, with further deterioration following treatment and only partial recovery over the course of follow-up (Ye et al., 2024). Nonetheless, the mechanism and the onset underlying cognitive impairment in lung cancer patients remain poorly understood. In a cross-sectional study by Bartels and colleagues (2021) authors investigate a potential role of neuronal autoantibodies in cognitive impairment in lung cancer patients. Specifically, neuronal autoantibodies produced mainly in response to SCLC, can cross-react with neuronal proteins, potentially triggering neuroinflammation and synaptic dysfunction, which together may contribute to cognitive impairment in lung cancer patients (Bartels et al., 2021). In addition, several psychological factors seem to play a significant role in the onset of CRCI in lung cancer patients: in a study by Pang and colleagues (2023) authors find that high levels of distress correlate with poorer memory performance and lower quality of life (QoL) (Pang et al., 2023). Literature also points to sleep alterations, anxiety, fatigue and lack of physical exercise as other risk factors for the development of cognitive impairment (Ye et al., 2024). Moreover, studies have shown that a crucial role is played by cognitive reserve, which acts as a protective factor against cognitive impairment by enabling the brain to better cope with age-related changes and neuropathology (Stern and Barulli, 2019). Cognitive reserve reflects the cumulative effect of life experiences such as education, occupational complexity, and engagement in cognitively stimulating activities, which contribute to more efficient or flexible use of neural networks. As a result, individuals with higher cognitive reserve are often able to maintain cognitive functioning for longer, even in the presence of brain changes or damage (Stern and Barulli, 2019).

Given these recent findings and the paucity of the scientific literature, the aim of the present work is to further explore cognitive impairment in lung cancer patients with NSCLC. The primary endpoint will be the presence of cognitive impairment prior to the initiation of cancer treatment (i.e. chemotherapy, surgery or radiotherapy) assessed through a comprehensive neuropsychological evaluation. In addition, this study will assess the impact of various potential risk factors on the cognitive profile of lung cancer patients, including psychological symptoms (anxiety, depression, and sleep disorders), and cognitive reserve.

## 2. Methods

### 2.1. Participants

A total of 50 lung cancer patients were recruited for this study between January 2024 and November 2025.

Eligibility criteria included patients aged 18 years or older, with a confirmed diagnosis of NSCLC (stages I–IV), who were fluent in both oral and written Italian. Patients who were candidates for lung surgery or those who would undergo adjuvant therapy (e.g., chemotherapy or immunotherapy) were included. Exclusion criteria consisted of patients with brain metastases, a history of lung cancer, concurrent neurological or psychiatric disorders, prior brain radiotherapy, or those over the age of 75. The study received ethical approval from the European Institute of Oncology (IEO) (UID4401), and written informed consent was obtained from all participants before data collection.

### 2.2. Study procedure

This monocentric study was conducted by the Applied Research Division for Cognitive and Psychological Science of the European Institute of Oncology (IEO) in collaboration with the Thoracic Surgery Division. Patient selection was performed by the medical team during multidisciplinary meetings, based on predefined inclusion and exclusion criteria. Eligible patients were then approached by a neuropsychologist with previous experience in research, who provided eligible patients with comprehensive information about the study. Details and objectives of the study were clearly explained, and patients were invited to participate by signing a written informed consent form. Participation in the study was fully voluntary and no monetary compensation was offered to participants. After obtaining a signed informed consent, a specialized neuropsychologist carried out a thorough neuropsychological and psychological evaluation. The assessments took place in a designated setting within the hospital, specifically equipped for cognitive testing, ensuring a controlled and standardized environment. All methodologies and procedures described in the study protocol adhered to relevant guidelines and regulations. Relevant clinical factors of patients, such as age, education level, concurrent medications, and smoking habits, were recorded on the case report forms. Neuropsychological and psychosocial assessments were conducted at baseline, prior to the initiation of any type of cancer treatment.

### 2.3. Material

A specialized neuropsychologist administered a comprehensive cognitive and psychological assessment to each patient. Specifically, tests were conducted to evaluate overall cognitive functioning, executive functions, learning, short-term and long-term memory, working memory, interference, inhibition and attention. The complete neuropsychological assessment lasted approximately one and a half hours and included both neuropsychological tests and self-report psychological questionnaires, which were completed by the patients on-site during the same session.

#### 2.3.1. Neuropsychological assessment

All neuropsychological tests used to assess various cognitive domains in lung cancer patients are listed below, for a detailed description of each test and its specific purpose within the assessment protocol.

First, to assess global cognitive functioning, two different screening tests were administered: the Mini-Mental State Examination (MMSE)

and the Montreal Cognitive Assessment (MoCA). MMSE is a widely used, brief screening tool (5–10 min) designed to identify cognitive deterioration. It involves 11 tasks that assess various cognitive domains such as orientation, memory, attention, the ability to respond to verbal and written commands, and ability to copy a given figure. Raw scores were corrected using normative data from Measso and collaborators (1993) («(PDF) The Mini-Mental State Examination, Normative). MoCA is a 10-minute cognitive screening tool that targets mild cognitive impairment. It evaluates eight cognitive domains: short-term and delayed verbal memory, visuospatial abilities, executive functions, attention, concentration, working memory, language, and orientation to time and place. The raw score was corrected using the normative data from Santangelo and collaborators (2015) (Santangelo et al., 2015). To evaluate executive functions, the Frontal Assessment Battery (FAB) was administered. This 10-minute screening tool includes six subtests that assess cognitive abilities linked to the frontal lobes: conceptualization, mental flexibility, motor programming, sensitivity to interference, inhibitory control, and environmental autonomy. The raw score was corrected based on normative data from Aiello and colleagues (2022) (Aiello et al., 2022). In addition to the FAB, other tests were employed to explore specific executive functions. More specifically, the Stroop Color and Word Test (SCWT) was used to evaluate selective and sustained attention as well as interference and inhibitory control. The test consists of three pages with respectively colored words, colored circles, and incongruent colored words; patients are required to firstly read words and then to read colors aloud as quickly and as accurately as possible. The raw score was corrected using data from Brugnolo and others (2016) (Brugnolo et al., 2016).

The Phonemic Verbal Fluency (PVF) task was used to assess lexical access and executive functioning, particularly strategic retrieval, cognitive flexibility, and inhibitory control. Patients are asked to generate as many words as possible starting with a specific given letter within 60 s. The raw score was corrected using normative data from Costa and colleagues (2014) (Costa et al., 2014).

Memory was assessed through several tests. The Ray Auditory Verbal Learning Test (RAVL) was used to evaluate verbal learning and memory. Patients listen to a list of 15 words and are asked to repeat them aloud, as many as they remember, independently of the order in which they were presented: this process is repeated over five trials, to promote learning abilities. After a 15-minute delay, the patient is asked to recall all of the words they can remember from the list, independently of the order in which they were presented. This test provides both immediate and delayed memory scores. The raw score was corrected using data from Carlesimo and collaborators (1996) (Carlesimo et al., 1996). The Digit Span Test (forward and backward) evaluates verbal short-term memory. Patients are presented with sequences of digits and asked to repeat them in the same order they were presented (forward) or in reverse order they were presented (backward). Similarly, the Corsi Block-tapping Test assesses visuospatial short-term memory by having patients reproduce sequences of blocks in the same order they were presented. In both tests normative data from Monaco and colleagues (2013) (Monaco et al., 2013) was used to correct raw scores. Attention was evaluated using the Trail Making Test (TMT), which consists of two parts. In part A, patients are presented with numbers from 1 to 25, scattered randomly across a paper sheet and are required to connect the numbered circles in ascending order as quickly as possible. In part B, patients are presented with numbers from 1 to 13 and letters from A to N, and must connect them by alternating between numbers to letters in ascending order (1-A 2-B, etc). The test assesses visual exploration, selective attention and visuomotor processing speed (Part A), as well as increased executive demands, particularly alternating attention and cognitive flexibility under higher cognitive load (Part B). Raw scores were corrected using normative data from Siciliano and collaborators (2019) (Siciliano et al., 2019).

Cognitive impairment is classified following the International Cognition and Cancer Task Force (ICCTF) recommendations (Wefel et al., 2011) which advocate for a standardized, multi-test approach rather than relying solely on a single cognitive screening tool.

Patients are classified as cognitively impaired if they meet one of the following criteria:

- Two or more test scores $\leq -1.5$ SDs from the normative mean, or
- One test score $\leq -2.0$ SDs from the normative mean.

All raw scores obtained from the neuropsychological tests were demographically adjusted prior to statistical analysis, using the corresponding healthy Italian normative control group provided for each cognitive test as the reference cohort.Specifically, in order to assess cognitive performance as a continuous measure across different tests and domains, t-scores are obtained for each neuropsychological test using the mean and SD of the normative data for the healthy Italian population. Finally, a Composite Cognitive Score (CCS) was computed as the mean of all standardized cognitive test scores, providing a global index of cognitive performance (Bartels et al., 2021).

Neuropsychological tests were grouped into five broader cognitive domains based on the primary construct each instrument was designed to assess, as commonly done in the literature on cognitive assessment in oncology and consistent with ICCTF recommendations (Wefel et al., 2011; Capetti et al., 2026a). Domain-specific composite scores were calculated by averaging the individual test scores after harmonizing score direction, when necessary, so that higher values consistently reflected better performance.

Global cognitive functioning included the screening measures of MoCA and MMSE; executive functions included the FAB, Stroop Color and Word Test, and TMT-B; memory comprised the RAVLT, Digit Span Test, and Corsi Block-Tapping Test; attention/processing speed included TMT-A and the SDMT. Finally, PVF was classified within a separate language domain, as it requires lexical retrieval and language-mediated output, although it also heavily relies on executive processes such as strategic retrieval, cognitive flexibility, and inhibitory control.

#### 2.3.2. *Psychological assessment*

In addition to the neuropsychological assessments, a psychological evaluation was also conducted, investigating several key domains. The following psychological assessments were administered. The Functional Assessment of Cancer Therapy-Cognition (FACT-COG) was administered to assess subjective cognitive deficits in cancer patients (Bonomi et al., 1996; Joly et al., 2015). This self-report questionnaire consists of 37 items divided into four subscales: perceived cognitive impairments (PCI), impact of perceived cognitive impairments on quality of life (QOL), comments from others (OTHER), and perceived cognitive abilities (PCA).

The Cognitive Reserve Index questionnaire (CRIq) is a standardized tool used to assess an individual's cognitive reserve, that is, the brain's ability to cope with age-related changes or pathology through pre-existing cognitive resources (Nucci et al., 2012). It is composed of three main sections: Education, which evaluates years and level of formal and informal education; Working Activity, which considers the type, duration, and cognitive demand of occupational experiences; and Leisure Time, which examines engagement in cognitively stimulating activities during free time (e.g., reading, social activities, hobbies).

Each section contributes to a total index score that reflects the individual's overall cognitive reserve. The CRIq is widely used in research to explore how life experiences influence resilience against cognitive decline and neurological disorders.

To evaluate depressive and anxious symptoms, two self-report questionnaires were used: the Depression Inventory-II (BDI-II) and the State-Trait Anxiety Inventory-Y form (STAI-Y), respectively. The BDI-II (Beck et al., 1961; Ghisi et al., 2026) comprises 21 items assessing the presence and severity of depressive symptoms, while the STAI-Y («Manual for the State-Trait Anxiety Inventory Form Y1 – Y2, 2026; Ilardi et al., 2021) includes 40 items, 20 assessing trait anxiety and 20

assessing state anxiety.

The Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989) was used to investigate sleep quality and disturbances in sleep patterns. This self-report questionnaire consists of 19 items that generate seven component scores: sleep latency, sleep duration, subjective sleep quality, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The raw score was corrected using the normative data from Curcio and collaborators (2013) (Curcio et al., 2013).

The EORTC-Core Quality of Life Questionnaire (EORTC-QoL-C30) (Aaronson et al., 1993; Pilz et al., 2022; Marzorati et al., 2019) was also administered. It is an internationally recognized 30-item tool used to assess the QoL in cancer patients.

### 2.4. Statistical analysis

Continuous variables were summarized as medians and ranges, while categorical variables were presented as counts and percentages.

The proportion of patients with cognitive impairment prior to the initiation of cancer treatment was reported as a proportion with 95% confidence intervals (CI).

Univariable linear regression models were used to evaluate the association between patients' sociodemographic and clinical characteristics, as well as self-report questionnaires, and the CCS.

Additional univariable linear regression models were performed to evaluate the associations between self-report questionnaires and the five cognitive domains (global functioning, memory, attention and information processing speed, executive function, and language).

All reported p-values were two-sided, with a p-value $< 0.05$ considered statistically significant.

All statistical analyses were conducted using SAS software, version 9.4 (SAS Institute, Cary, NC, USA).

**Table 1**
Patients' characteristics.

| Variable | Level | Overall (N = 50) |
|---|---|---|
| **Age (years), median (min-max)** | | 65 (28–73) |
| **Sex, N (%)** | Female | 24 (48) |
| | Male | 26 (52) |
| **Marital status, N (%)** | Single | 5 (10) |
| | Married | 37 (74) |
| | Cohabiting | 1 (2) |
| | Divorced | 5 (10) |
| | Widowed | 2 (4) |
| **Years of education, median (min-max)** | | 13 (5–18) |
| **Caregiver, N (%)** | No | 3 (6) |
| | Yes | 47 (94) |
| **Previous cancer, N (%)** | No | 35 (70) |
| | Yes | 15 (30) |
| **Diabetes, N (%)** | No | 45 (90) |
| | Yes | 5 (10) |
| **Obesity, N (%)** | No | 47 (94) |
| | Yes | 3 (6) |
| **Hypertension, N (%)** | No | 26 (52) |
| | Yes | 24 (48) |
| **Thyroid disorder (hypo/hyperthyroidism), N (%)** | No | 46 (92) |
| | Yes | 4 (8) |
| **Current smoker, N (%)** | No | 36 (72) |
| | Yes | 14 (28) |
| **Former smoker, N (%)** | No | 12 (24) |
| | Yes | 38 (76) |
| **Number of years smoking, median (min-max)** | | 27 (0–57) |
| **Cognitive difficulties, N (%)** | No | 41 (82) |
| | Yes | 9 (18) |

## 3. Results

### 3.1. Participant Characteristics

Patient demographics and clinical features are summarized in Table 1. Fifty patients with lung cancer were included in the study, with a median age of 65 years (range 28–73). The sample was balanced by sex, with 24 females (48%) and 26 males (52%). Most patients were married or cohabiting (76%), while 24% were single, divorced, or widowed. Median education was 13 years (range 5–18), indicating an overall medium-high educational level. Almost all patients had an identified caregiver (94%), and 30% of patients had a pre-existing diagnosis of non-lung cancer. Regarding comorbidities, 10% had diabetes, 6% obesity, 48% hypertension, and 8% a thyroid disorder. The majority were former smokers (76%), 14 patients (28%) were current smokers, and the median duration of smoking was 27 years (range 0–57). At baseline, 18% of patients reported subjective cognitive difficulties. Further details on cognitive and psychological measures at baseline are provided in Supplementary Table 1.

### 3.2. Primary outcome and modelling approach

At baseline, 18 of 50 patients (36%; 95% CI: 23–49%) met the predefined criteria for cognitive impairment (CI 2 < 1.5 SD). This proportion indicates that more than one-third of patients already exhibited objective cognitive deficits before or at the very beginning of oncological treatment. Among patients classified as cognitively impaired according to ICCTF criteria, memory was the most frequently affected domain (50.0%), followed by language and global cognitive functioning (both 22.2%), executive functions (16.7%), and attention (11.1%). As some patients exhibited impairment in more than one cognitive domain, these percentages are not mutually exclusive.

### 3.3. Associations between clinical/psychosocial characteristics and Composite Cognitive Score

Univariable linear regression models showed no significant associations between Composite Cognitive Score (CCS) and most sociodemographic or clinical variables, including age (+5 years: $\beta = 0.07$, $p = 0.23$), sex (male vs. female: $\beta = 0.28$, $p = 0.14$), marital status (married/cohabiting vs. others: $\beta = -0.10$, $p = 0.65$), caregiver (yes vs no: $\beta = 0.40$, $p = 0.33$), previous cancer ($\beta = -0.28$, $p = 0.18$), diabetes ($\beta = -0.52$, $p = 0.11$), obesity ($\beta = -0.13$, $p = 0.76$), hypertension ($\beta = 0.30$, $p = 0.12$), thyroid disorder ($\beta = 0.22$, $p = 0.54$), current smoker ($\beta = 0.01$, $p = 0.95$) and former smoker ($\beta = -0.08$, $p = 0.74$). In contrast, higher cognitive reserve (CRIq Total) was significantly associated with better cognitive performance (+5 unit: $\beta = 0.09$, $p = 0.002$). Subjective cognitive functioning was positively associated with CCS for three out of the four subscales FACT-COG: PCI (+5 unit: $\beta = 0.13$, $p = 0.018$), QOL (+1 unit: $\beta = 0.16$, $p = 0.001$), OTH (+1 unit: $\beta = 0.12$, $p = 0.021$), whereas FACT-COG PCA did not reach statistical significance (+1 unit: $\beta = 0.02$, $p = 0.13$). Higher depressive symptoms (+1 unit of BDI-II: $\beta = -0.05$, $p < 0.001$), higher state and trait anxiety (+5 unit of STAI-Y State: $\beta = -0.10$, $p = 0.016$; +5 unit of STAI-Y Trait: $\beta = -0.12$, $p = 0.005$), and poorer sleep quality (+1 unit of PSQI: $\beta = -0.06$, $p = 0.020$) were all significantly associated with lower CCS, while global QoL (+1 unit of EORTC-QoL-C30: $\beta = 0.09$, $p = 0.25$) was not significantly associated with CCS. Table 2 reported results of linear regression models, whereas Fig. 1 graphically shows the significant association between CCS and clinical and psychosocial variables.

### 3.4. Associations between psychological variables and cognitive domains

Analyses by cognitive domains confirmed and refined the pattern observed for CCS (Table 3). Higher cognitive reserve (+5 unit of CRIq Total) was significantly associated with better performance in global

**Table 2**
Univariable linear regression models evaluating the association of patients' sociodemographic and clinical characteristics and self-report questionnaires with Composite cognitive score (CCS) (N = 50).

| Variable | Level | β (SE) | P-value |
|---|---|---|---|
| **Age** | +5 years | 0.07 (0.06) | 0.23 |
| **Sex** | Female | Ref. | - |
| | Male | 0.28 (0.19) | 0.14 |
| **Marital status** | Single/Divorced/ Widowed | Ref. | - |
| | Married/Cohabiting | −0.10 (0.23) | 0.65 |
| **Caregiver** | No | Ref. | - |
| | Yes | 0.40 (0.40) | 0.33 |
| **Previous cancer** | No | Ref. | - |
| | Yes | −0.28 (0.21) | 0.18 |
| **Diabetes** | No | Ref. | - |
| | Yes | −0.52 (0.31) | 0.11 |
| **Obesity** | No | Ref. | - |
| | Yes | −0.13 (0.41) | 0.76 |
| **Hypertension** | No | Ref. | - |
| | Yes | 0.30 (0.19) | 0.12 |
| **Thyroid disorder (hypo/ hyperthyroidism)** | No | Ref. | - |
| | Yes | 0.22 (0.35) | 0.54 |
| **Current smoker** | No | Ref. | - |
| | Yes | 0.01 (0.22) | 0.95 |
| **Former smoker** | No | Ref. | - |
| | Yes | −0.08 (0.23) | 0.74 |
| **CRP** | +5 mg/L | −0.01 (0.01) | 0.46 |
| **CRIq - Total** | +5 | 0.09 (0.03) | 0.002 |
| **FACT-COG - PCI** | +5 | 0.13 (0.05) | 0.018 |
| **FACT-COG - QOL** | +1 | 0.16 (0.05) | 0.001 |
| **FACT-COG - OTH** | +1 | 0.12 (0.05) | 0.021 |
| **FACT-COG - PCA** | +1 | 0.02 (0.01) | 0.13 |
| **BDI-II** | +1 | −0.05 (0.01) | < 0.001 |
| **STAI-Y - State anxiety** | +5 | −0.10 (0.04) | 0.016 |
| **STAI-Y - Trait anxiety** | +5 | −0.12 (0.04) | 0.005 |
| **EORTC-QoL-C30** | +1 | 0.09 (0.08) | 0.25 |
| **PSQI** | +1 | −0.06 (0.03) | 0.020 |

functioning (β = 0.13, p = 0.003), attention and information processing speed (β = 0.08, p = 0.004), and executive function (β = 0.11, p = 0.003), but not significantly with memory (β = 0.04, p = 0.23) or language (β = 0.04, p = 0.31). Depressive symptoms showed robust negative associations across domains: BDI-II (+1 unit) was inversely associated with global functioning (β = −0.08, p < 0.001), memory (β = −0.03, p = 0.048), attention/IPS (β = −0.05, p < 0.001), and executive function (β = −0.05, p < 0.001), with a borderline effect on language (β = −0.03, p = 0.064). State anxiety (+5 unit of STAI-Y State) was negatively associated with global functioning (β = −0.15, p = 0.010), memory (β = −0.10, p = 0.035), and attention/IPS (β = −0.09, p = 0.016), while associations with executive function (β = −0.08, p = 0.12) and language (β = −0.09, p = 0.12) were not significant. Trait anxiety (+5 unit of STAI-Y Trait) showed similar patterns, with significant inverse associations with global functioning (β = −0.20, p = 0.003), memory (β = −0.14, p = 0.007), and attention/IPS (β = −0.13, p = 0.003), and non-significant associations with executive function (β = −0.10, p = 0.085) and language (β = −0.09, p = 0.13). Poor sleep quality was significantly associated with lower global functioning (+1 unit of PSQI: β = −0.11, p = 0.007) and worse memory (β = −0.07, p = 0.040), showed a non-significant trend for attention/IPS (β = −0.05, p = 0.098), and no significant associations with executive function (β = −0.06, p = 0.11) or language (β = −0.02, p = 0.62).

## 4. Discussion

The present study aimed to evaluate cognitive functioning in patients with NSCLC prior to treatment initiation, while also examining the contribution of psychosocial variables to global cognitive performance.

Notably, 36% of participants met ICCTF criteria for objective cognitive impairment at baseline. This relatively high prevalence suggests that cognitive deficits may already be present before exposure to chemotherapy, radiotherapy, or immunotherapy, pointing to a potential role of disease-related mechanisms in shaping cognitive functioning. These findings support the notion that CRCI may already be detectable at diagnosis, before the initiation of anticancer treatments, representing a pre-treatment manifestation of CRCI rather than a treatment-associated effect. A key strength of the present study is the assessment of patients prior to treatment initiation, allowing cognitive functioning to be characterized independently of treatment-related effects and providing unique insight into cognitive vulnerability associated with the disease itself. This finding is consistent with emerging evidence documenting pre-treatment cognitive impairment in NSCLC populations (Simó et al., 2015). Several biological mechanisms may underlie this phenomenon, including cancer-related systemic inflammation, neuronal autoantibodies, and paraneoplastic processes (Bartels et al., 2021). Furthermore, lung cancer patients may be particularly vulnerable to cognitive dysfunction due to immune-mediated mechanisms. Bartels and collaborators (2021) reported the presence of neuronal autoantibodies in more than one-third of lung cancer patients, with autoantibody positivity being associated with an increased likelihood of cognitive impairment. Although these mechanisms were not directly investigated in the present study, these findings suggest that neuronal autoantibodies may contribute to cancer-related cognitive impairment and support the hypothesis that disease-related neurobiological processes may affect cognitive functioning even before the initiation of anticancer treatments. Many oncological diseases are characterized by a chronic inflammatory state including elevated levels of pro-inflammatory cytokines such as interleukin−6 (IL-6), tumor necrosis factor-alpha (TNF-α), interleukin−1β (IL-1β), and vascular endothelial growth factor (VEGF) (Mujinya et al., 2025). These pro-inflammatory cytokines can influence brain functioning either by crossing the blood–brain barrier or via signaling pathways involving circumventricular organs, ultimately promoting neuroinflammation and synaptic alterations (Olson and Marks, 2019). Such processes may therefore contribute to the cognitive, affective, and fatigue-related symptoms observed in oncological patients, even in the absence of direct central nervous system involvement or treatment-related neurotoxicity.

Converging evidence from neuroimaging studies further supports the presence of brain alterations in patients with non-CNS tumors. Reductions in cortical thickness and surface area, particularly in frontal and temporal regions, including the parahippocampal area, as well as decreased white matter volume in frontal, parietal, and limbic regions, have been reported in untreated oncological populations (Lange et al., 2019; Olson and Marks, 2019; Conti et al., 2025). These structural differences may underlie impairments in attention, memory, and executive functioning observed in the population investigated by the present work.

Beyond biological mechanisms, our findings highlight the role of

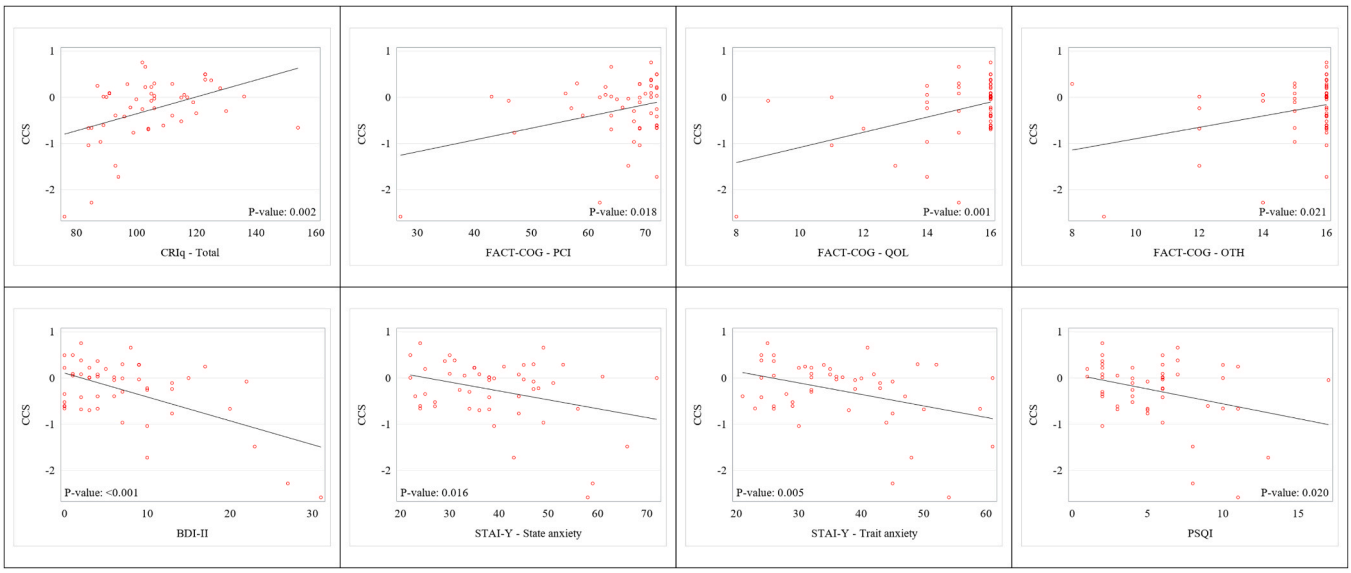


**Fig. 1.** Association of self-report questionnaires with Composite cognitive score (CCS) (N = 50).

**Table 3**
Univariable linear regression models evaluating the association of self-report questionnaires with Global functioning, Memory, Attention and IPS, Executive function and Language (N = 50).

| Variable | Unit | Global functioning | | Memory | | Attention and IPS | | Executive function | | Language | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | β (SE) | P-value | β (SE) | P-value | β (SE) | P-value | β (SE) | P-value | β (SE) | P-value |
| **CRIq - Total** | +5 | 0.13 (0.04) | 0.003 | 0.04 (0.04) | 0.23 | 0.08 (0.03) | 0.004 | 0.11 (0.04) | 0.003 | 0.04 (0.04) | 0.31 |
| **BDI-II** | +1 | −0.08 (0.02) | < 0.001 | −0.03 (0.02) | 0.048 | −0.05 (0.01) | < 0.001 | −0.05 (0.02) | < 0.001 | −0.03 (0.02) | 0.064 |
| **STAI-Y - State anxiety** | +5 | −0.15 (0.06) | 0.010 | −0.10 (0.05) | 0.035 | −0.09 (0.04) | 0.016 | −0.08 (0.05) | 0.12 | −0.09 (0.05) | 0.12 |
| **STAI-Y - Trait anxiety** | +5 | −0.20 (0.06) | 0.003 | −0.14 (0.05) | 0.007 | −0.13 (0.04) | 0.003 | −0.10 (0.06) | 0.085 | −0.09 (0.06) | 0.13 |
| **PSQI** | +1 | −0.11 (0.04) | 0.007 | −0.07 (0.03) | 0.040 | −0.05 (0.03) | 0.098 | −0.06 (0.04) | 0.11 | −0.02 (0.04) | 0.62 |

cognitive reserve and psychosocial factors in explaining interindividual variability in cognitive performance. Higher CRIq scores were positively associated with global cognitive functioning and most cognitive domains, supporting the hypothesis that cognitive reserve may act as a protective factor against cognitive decline (Stern, 2012). In the context of CRCI, individuals with greater reserve, often linked to higher educational attainment, occupational complexity and engagement in cognitively stimulating activities, may be better equipped to cope with disease- and treatment-related challenges (Lange et al., 2019; Országhová et al., 2021). Our results extend this framework to NSCLC patients, suggesting that cognitive reserve may also play a relevant role in non-CNS cancers such as NSCLC.

In contrast, psychological distress and sleep disturbances were consistently associated with poorer cognitive performances. Higher levels of depressive symptomatology and anxiety, as well as reduced sleep quality, were found to be linked to lower global cognitive scores and deficits across multiple domains. These findings are aligned with prior literature pointing to how mood disturbances and sleep impairment can negatively affect attention, memory, and executive functioning (Semkovska et al., 2019; Wardle-Pinkston et al., 2019; Fortier-Brochu et al., 2012). In oncological settings, these factors may exacerbate cognitive vulnerability through mechanisms such as reduced cognitive resources, attentional bias, neurobiological stress responses, and disrupted circadian regulation (Lange et al., 2019; Janelsins et al., 2014). Importantly, psychological distress and sleep disturbances represent potentially modifiable contributors to cognitive vulnerability, highlighting the clinical relevance of their early identification and management in patients with NSCLC (Janelsins et al., 2014).

Another relevant finding concerns the relationship between subjective and objective cognitive functioning. Indeed, three of the four FACT-COG subscales were positively associated with global cognitive performance, suggesting that patients reporting better perceived cognition also tended to perform better on neuropsychological measures. Although discrepancies between subjective complaints and objective performance have been frequently reported in the literature (Hutchinson et al., 2012), our findings indicate that subjective cognitive perceptions may, at least in part, reflect actual cognitive functioning in this population. As such, self-reported cognitive difficulties may represent a useful clinical indicator for identifying patients who could benefit from further cognitive assessment or supportive interventions.

Taken together, these findings support an underlying multifactorial model of cognitive impairment in NSCLC patients. While biological processes such as systemic inflammation and cancer-related neurobiological changes most likely contribute to cognitive alterations, psychosocial factors, including cognitive reserve, emotional distress, and sleep quality, also play a significant role in shaping cognitive outcomes. Integrating these dimensions into clinical assessment may therefore provide a more comprehensive understanding of cognitive vulnerability in lung cancer patients and inform the development of targeted supportive interventions.

## 5. Limitations

This work comes with some limitations. First and foremost, although it is a preliminary, exploratory study, the limited sample size might have impacted the statistical analysis and made it difficult for these results to possibly be generalized to the general population. For this reason, we performed further analysis per cognitive domain, with in mind the objective to guide future research and analysis on a larger sample.

Furthermore, our sample presented with a few comorbidities, such as

diabetes (10%), obesity (6%), hypertension (48%), and thyroid disorder (8%). Even though we controlled for these comorbidities in our analysis and found no association between these variables and CCS, any medications these patients were on for their specific comorbidity might have influenced our results. Given the negative impact that some medications seem to have on cognition (Hafez et al., 2023), how little is known on the onset and mechanisms of CRCI in oncological patients (Ferrari et al., 2024), and the high percentage of comorbidities within this population (Wenkstetten-Holub et al., 2021), it's possible that patients' coexisting conditions may have influenced our results. Moreover, given the participants' diagnosis of NSCLC, these preliminary results can not ensure reliability and generalizability for SCLC patients.

## 6. Clinical implications and future research

From a clinical perspective, these findings have several potential implications. First, the protective role of cognitive reserve suggests that interventions aimed at promoting cognitive engagement and cognitive stimulation may be beneficial for patients at risk of CRCI. Secondly, the strong association between psychological distress and cognitive performance highlights the importance of routine screening for depression and anxiety in oncological care. Addressing emotional distress through psychological or psychosocial interventions may indirectly improve cognitive functioning and overall QoL (Bognár et al., 2024). Finally, given the association between sleep quality and cognition, sleep assessment and management should be considered an integral component of supportive cancer care. In this context, a personalized medicine approach that integrates patient-specific risk profiles may be particularly valuable (Pravettoni and Gorini, 2011), including the potential use of non-invasive brain stimulation techniques, which have shown promising effects on cognitive functioning as well as on anxiety and depressive symptoms (Luisi et al., 2025; Capetti et al., 2024). These approaches may complement established interventions such as cognitive rehabilitation in patients with non-CNS cancers (Capetti et al., 2026b).

Furthermore, the availability of a pre-treatment cognitive baseline provides an important reference point for future longitudinal studies. Repeated assessments across the treatment trajectory may help clarify the evolution of cognitive functioning over time, distinguish disease-related from treatment-related cognitive changes, and identify factors associated with resilience or vulnerability to CRCI. In addition, although further longitudinal studies are needed, cognitive reserve may represent a promising stratification variable in oncology settings. Routine assessment of cognitive reserve could contribute to the early identification of patients who are potentially more vulnerable to cognitive impairment and may benefit from targeted cognitive monitoring and supportive interventions. In this context, cognitive stimulation and rehabilitation programs may help mitigate the impact of cognitive difficulties on daily functioning and QoL.

Future research with larger samples is needed to clarify the temporal dynamics of CRCI and to better understand the mechanisms underlying cognitive changes in lung cancer patients. Further research should also investigate whether interventions targeting modifiable factors such as psychological distress or sleep disturbances may mitigate cognitive impairment in this population.

In future perspectives, it would be valuable to address whether different norming approaches for determining patients' cognitive status might be explored in future studies. While the 1.5–2-SD-based approach remains the method recommended by international guidelines, regression-based norming approaches relying on non-parametric estimation of cut-offs (e.g., the Equivalent Score method) may offer advantages in controlling for demographic confounders and overcoming issues related to the non-normality of cognitive test score distributions in the general population. Since the publication of these guidelines, a substantially larger amount of data has been collected in the oncological population, which may enable the development of novel classification methodologies for cognitive impairment specifically tailored to cancer patients.

## 7. Conclusion

This exploratory study contributes to the growing literature on cognitive functioning in non-CNS cancer populations and provides preliminary evidence that cognitive reserve and psychosocial factors may play a meaningful role in cognitive outcomes among patients with NSCLC. These findings may inform future research aimed at identifying risk and protective factors for CRCI and support the development of targeted supportive interventions for lung cancer patients.

## CRediT authorship contribution statement

**Serena Sdinami:** Writing – review & editing, Writing – original draft. **Lorenzo Conti:** Writing – review & editing, Writing – original draft, Resources, Project administration, Methodology, Conceptualization. **Jenny Luisi:** Writing – review & editing, Writing – original draft, Methodology. **Gabriella Pravettoni:** Supervision. **Benedetta Capetti:** Writing – review & editing, Writing – original draft, Resources, Project administration, Methodology, Conceptualization. **Matteo Chiari:** Writing – original draft, Investigation, Conceptualization. **Monica Casiraghi:** Supervision, Conceptualization. **Samuele Frassoni:** Writing – original draft, Methodology, Formal analysis, Data curation. **Vincenzo Bagnardi:** Supervision, Methodology, Formal analysis, Data curation. **Chiara Marzorati:** Writing – review & editing, Supervision. **Roberto Grasso:** Writing – review & editing, Supervision, Funding acquisition.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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