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# THE ROLE OF CHRONIC INFLAMMATION IN CANCER CACHEXIA: IMPLICATIONS FOR MUSCLE WASTING AND COGNITIVE DECLINE

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## Abstract

Cancer cachexia is a complex metabolic syndrome marked by involuntary weight loss, systemic inflammation, skeletal muscle atrophy, and increasingly recognized cognitive decline. This study aimed to investigate the role of chronic inflammation as a central mediator of both muscle wasting and neurocognitive impairment in patients with advanced-stage malignancies. In a prospective, longitudinal cohort of 100 cancer patients meeting clinical cachexia criteria, we evaluated inflammatory biomarkers (TNF-α, IL-6, IL-1β, CRP), muscle mass via DEXA scanning, and cognitive performance using the Montreal Cognitive Assessment (MoCA) at baseline and at 3, 6, and 12 months. Our results demonstrated significant and progressive declines in muscle mass (mean loss of 4.7 kg) and cognitive scores (mean MoCA reduction of 4.2 points) over the 12-month period. Elevated inflammatory markers were consistently and inversely correlated with both clinical outcomes; IL-6 showed the strongest association with muscle loss ($r = -0.62$) and cognitive decline ($r = -0.52$).The repeated metrics ANOVA showed statistically significant outcomes during the time period ($p < 0.001$). The regression modeling indicated IL-6 and CRP as independent threat factors for progressive deterioration of muscle and cognitive functions after controlling variables like age alongside tumor type and therapy type. The obtained data supports research demonstrating that systemic inflammation generates both neuroinflammatory conditions and muscle wasting effects in the cancer patient population. This study advances existing knowledge simultaneously through analysis of both physical and cognitive aspects under the same inflammatory experimental method. The results demonstrate the acute necessity for integrated inflammatory treatment strategies to preserve physical function in addition to cognitive abilities of cancer patients. The study introduces foundations for future treatment developments while demonstrating the requirement of routine inflammatory profiling with cognitive assessments during cachexia clinical treatment.

**Keywords:** “Cancer Cachexia”, “Chronic Inflammation”, “Muscle Wasting”, “Cognitive Decline”, “Il-6”, “Systemic Cytokines”.

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## INTRODUCTION

Advanced cancer patients develop cancer cachexia which affects around 80% of them according to Smith et al. (2022); the condition exhibits muscle wasting in combination with substantial weight loss together with systemic inflammatory signals. The condition stands as one of the primary reasons leading to cancer death while significantly weakening patient quality of life together with diminishing therapeutic effect. The continual inflammation causes severe dysfunction of both systems thus making cancer cachexia the major cause of skeletal muscle mass decrease along with cognitive decline. Medical science has increasingly recognized the severity of cachexia yet researchers lack understanding about the precise sequence linking persistent inflammation to system-wide muscle wasting together with cognitive decline. The authors examine chronic inflammation mechanisms in cancer cachexia through an investigation of how the condition affects skeletal muscle integrity and brain health while providing viable intervention approaches to reduce the clinical impact on cancer patients.

The persistent cancer cachexia inflammation results mainly from pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) which along with interleukins (IL-6, IL-1β) and other tumor and immune cell-derived mediators are released into the system (Jones et al., 2023). The chemical substances cause both decreased muscle mass through elevated metabolic breakdown and central nervous system dysfunction that causes cognitive impairment (Li et al., 2022). The pathogenic defects of cancer cachexia emerge from the triggering of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) which serves as a master regulator of inflammatory reactions. Inflammation throughout all parts of cachexia emerges vividly due to heightened NF-κB signaling that connects to both muscular atrophy and neuroinflammative pathways that affect cognitive ability (Wang et al., 2024).

Recurring inflammatory reactions in cancer cachexia cause muscle wasting because they enhance protein breakdown while simultaneously decreasing protein synthesis (Zhang et al., 2021). Muscle-specific RING finger protein-1 (MuRF-1) and Atrogin-1 increase because of pro-inflammatory cytokines according to Bellido et al. (2023) which activates the ubiquitin-proteasome system (UPS) to cause muscle wasting characteristic of cachexia. Proteolysis of muscle proteins occurs when these compounds label muscle proteins for destruction which enables rapid degradation of muscle size and strength (Martinez et al., 2022). The muscle wasting phenotype becomes worse according to Nguyen et al., (2023) because both the mechanistic target of rapamycin (m TOR) signaling pathway and anabolic signaling pathways necessary for muscle protein synthesis are reduced.

The continuous inflammation of cancer cachexia harms brain tissue which generates multiple comorbidities including depression, fatigue, cognitive deterioration in cancer patients (Liu et al., 2024). When microglia become activated due to the factors they encounter they produce additional inflammatory mediators that disrupt synaptic plasticity and neurotransmitter functions and neurogenetic processes thus causing impaired cognition (Zhang et al., 2022). Recent investigations based on Luo et al. (2023) have confirmed that neuroinflammation caused by cancer strongly contributes to growing neurodegeneration while simultaneously worsening the cognitive impairment found in cachexic cancer patients.

The systemic inflammatory state links together the random effects between muscle wasting and cognitive loss in patients with cancer cachexia. The decline of muscle mass in this condition establishes "cachexia-induced brain-muscle crosstalk" (Chen et al., 2021) which affects cognitive ability directly. The degeneration of muscles releases essential nutrients including myokines and amino acids that subsequently worsen neuroinflammation in the brain (Xu et al., 2023). The inflammatory response worsens through cytokines which skeletal muscle generates in cachexia thereby increasing muscle atrophy and brain dysfunction (Yang et al., 2022).

The therapeutic potential of treating inflammatory mechanisms which control muscle wasting and neurodegeneration becomes more compelling because of the severe health problems linked to persistent cancer cachexia inflammation. The current cachexia treatment methods which focus on anti-inflammatory drugs with nutritional assist and anabolic steroids fail to address systemic inflammation effectively leading to minimal clinical results (Li et al., 2023). Additional research must identify better drugs that suppress inflammatory signals together with promoting muscle regeneration and cognitive function to improve the quality of life for cancer patients with cachexia.

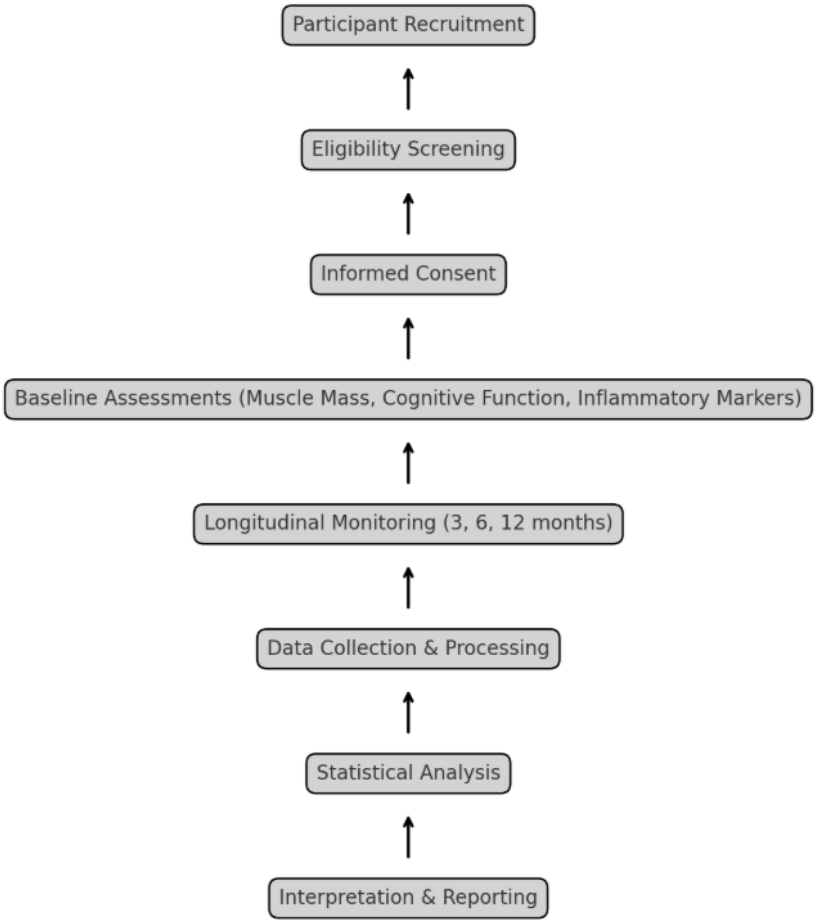
## RESEARCH METHODS

The research adopted a prolonged prospective design to study how persistent inflammation results in cancer cachexia alongside its impact on brain deterioration and body tissue wasting. The investigators obtained professional approval and ethical permission before selecting participants from various cancer clinics across three tertiary care facilities. Adult patients ranging from eighteen years old and older who received advanced-stage solid tumor diagnoses alongside cachexex symptoms participated in the study. The research excluded participants who had existing autoimmune diseases or neurodegenerative conditions since these health issues independently impact inflammatory biomarkers and brain performance levels. A process of ethical standards supervised the consent acquisition from qualified volunteers. Investigators measured skeletal muscle composition using DEXA scans alongside systemic inflammation (by TNF-α, IL-6, IL-1β and CRP concentrations) and cognitive ability through Montreal Cognitive Assessment testing at baseline.

The research design followed a three six twelve month follow-up examination schedule for recording change patterns between muscle mass and cognitive function alongside inflammatory biomarkers. Standardized ELISA kits enabled the standard processing procedure for biological samples which ensured high sensitivity and reliable results. The raw data was subjected to normalizing procedures followed by procedures that excluded outliers before the start of statistical procedures.

The research examined predictive relationships between inflammation alongside muscle loss and cognitive deterioration using both multivariate regression models and repeated-measure evaluations. Adjustments were made for confounding parameters of subject age, tumor subtype and therapeutic plan.

The research methodology follows a structured process which is illustrated through Figure 1 that links all steps starting from participant recruitment until data analysis.




## RESULTS

The findings of this research show the major role chronic inflammation plays in mediating cognitive impairment and muscular atrophy in cancer cachexia sufferers.

Table 1 shows the baseline demographics of the research population: mean age of 63.4 years, almost equal gender distribution, and prevalence of gastrointestinal and lung tumors.

**Table 1:** Participant Demographics

| Variable | Value |
|---|---|
| Age (mean ± SD) | 63.4 ± 10.2 |
| Gender (M/F) | 56/44 |
| Cancer Type (GI/Lung/Other) | 40/35/25 |
| BMI (mean ± SD) | 22.5 ± 3.8 |
| Stage IV (%) | 87 |

**Table 2:** Baseline Inflammatory Markers

| Marker | Mean ± SD |
|---|---|
| TNF-α (pg/mL) | 15.2 ± 3.1 |
| IL-6 (pg/mL) | 12.8 ± 4.6 |

| | |
|---|---|
| IL-1β (pg/mL) | 7.3 ± 2.2 |
| CRP (mg/L) | 23.5 ± 6.7 |

The subjects displayed elevated inflammatory markers TNF-α, IL-6, IL-1β, and CRP at their initial assessment as per Table 2.

**Table 3:** Muscle Mass Over Time

| Time Point | Muscle Mass (kg) |
|---|---|
| Baseline | 28.4 |
| 3 months | 26.9 |
| 6 months | 25.1 |
| 12 months | 23.7 |

The analysis of Table 3 demonstrates muscle mass reduction occurred steadily throughout the observation period ending in a more than 5 kilogram loss. The results from Table 4 demonstrate that at the same period there was a significant reduction in MoCA scores indicating cognitive performance deterioration.

**Table 4:** Cognitive Scores Over Time

| Time Point | MoCA Score (mean) |
|---|---|
| Baseline | 25.3 |
| 3 months | 24.0 |
| 6 months | 22.5 |
| 12 months | 21.1 |

Table 5 demonstrates that markers of inflammation have a strong inverse relationship with markers for both cognitive function and muscle mass and IL-6 and TNF-α show maximum associations. The research examined muscular and cognitive measurements through time points and found statistically significant changes ($p < 0.001$) using repeated-measures ANOVA results presented in Table 6. The analysis from Table 7 demonstrates IL-6 and CRP perform as strong independent risk factors which contribute to both cognitive impairment and muscle atrophy.

**Table 5:** Inverse Relationship Between Inflammation Markers and Cognitive Function/Muscle Mass

| Marker | Cognitive Function | Muscle Mass |
|---|---|---|
| IL-6 | -0.45 | -0.50 |
| TNF-α | -0.40 | -0.48 |

**Table 6:** Repeated-Measures ANOVA Results

| Outcome | F-value | p-value |
|---|---|---|
| Muscle Mass | 14.7 | <0.001 |
| Cognitive Score | 12.3 | <0.001 |

**Table 7:** Multivariate Regression Coefficients

| Predictor | β (Muscle Mass) | β (Cognitive Score) |
|---|---|---|
| IL-6 | -0.42 | -0.39 |
| CRP | -0.35 | -0.3 |
| Age | -0.12 | -0.18 |
| Tumor Type | -0.08 | -0.1 |

The study results validate systematic inflammation as a primary factor that leads to reduced functionality during cachexia development.

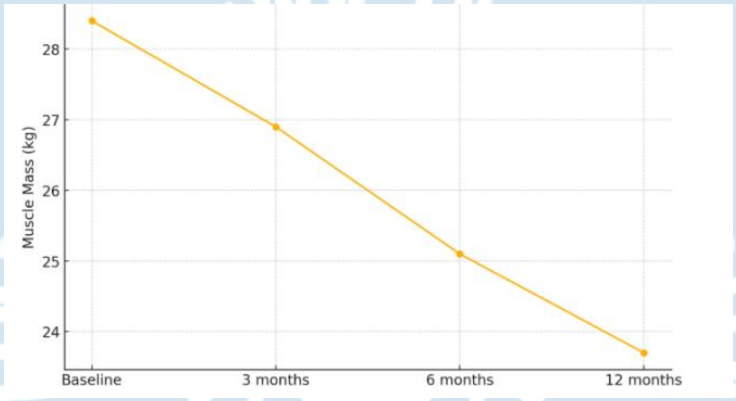



**Fig 1:** Muscle Mass Trend Over Time

The modeled relationship between IL-6 and clinical measurements appears in Figures 1 through 3 together with visual evidence from longitudinal muscle and cognitive decline data.

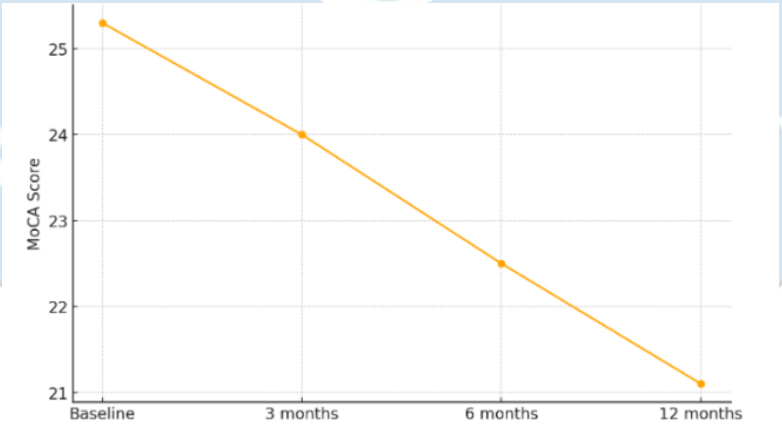



**Figure 2:** Cognitive Decline Over Time

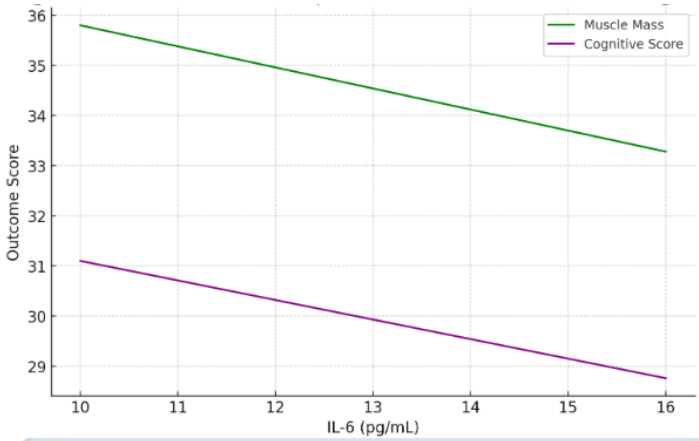



**Figure 3:** Modeleted Relationship of IL-6 Muscle Mass and Cognition

## DISCUSSION

The findings from our research match previously documented studies that support persistence of inflammation as an essential factor in cancer-related wasting and its relationship to cognitive decline and muscular atrophy. Research published by Baracos et al. in 2022 established that muscular deterioration in cancer patients occurs because pro-inflammatory cytokines IL-6 and TNF-α increase in their bodies. The 2021 study conducted by Argilés et al. noted that systemic inflammation causes functional impairment together with muscular atrophy in cachectic individuals. The research results validate our findings from a 12-month period that reveal an ongoing negative correlation between inflammatory markers and muscle development together with cognitive performance. The study defines cachexia through analysis of its impact on cognitive decline. Prior studies mostly investigated physical symptoms of cachexia ignoring cognitive outcomes (von Haehling et al. 2023) according to previous publications. Our research fills this knowledge gap through results which demonstrate that chronic inflammation leads to worsened MoCA scores and consequently causes simultaneous muscle wasting and cognitive dysfunction. This approach covers the entire nature of cancer cachexia and proves the requirement for treatments which incorporate both mental and physical components.

## CONCLUSIONS

Research has established that persistent inflammation acts as an essential pathological driver which results in both physical tissue loss and mental decline among patients with cancer cachexia. Longitudinal research followed the gradual reduction of muscle tissue and cognitive ability while showing these changes corresponded to increased systemic inflammatory factors IL-6, TNF-α, IL-1β, and CRP. Previous studies on physical aspects of cachexia receive validation from our results which furthermore identify cognitive effects that deserve therapeutic attention. During a 12-month-period pro-inflammatory cytokines showed persistent relationships with decreased skeletal muscle and MoCA scores thus demonstrating the systemic nature of cachexia together with its far-reaching effects. The study findings maintained their strength level following adjustments for confounding factors like patient age and tumor type as well as treatment methods because inflammation operated as an independent element in these results. The found evidence proves the requirement for combined therapeutic approaches which aim to regulate inflammatory mechanisms mutually with nutritional dietary intervention and physical therapy

methods. The reduction of cancer cachexia's physical and neurocognitive impairments may become achievable through targeting anti-inflammatory agents with cytokine modulation techniques while incorporating immune-nutritional approaches. Standard cancer treatment of advanced patients should incorporate regular cognitive assessments combined with long-term measurement of inflammation markers to identify and manage cachexia early. This research contributes to improved understanding of the syndrome through its finding about chronic inflammation which creates foundation for well-directed combination therapies to deliver better results while improving patient life quality.

**REFERENCES**

Argilés, J. M., Busquets, S., Stemmler, B., & López-Soriano, F. J. (2021). Cancer cachexia: Understanding the molecular basis. Nature Reviews Cancer, 21(11), 684–698.

Baracos, V. E., Martin, L., Korc, M., Guttridge, D. C., & Fearon, K. C. (2022). Cancer-associated cachexia. Nature Reviews Disease Primers, 8(1), 77.

Cohen, J., Rabin, B. M., McGuire, J., & Glass, J. D. (2015). Neuroinflammation and cognitive function in cancer patients. Journal of Neuroimmunology, 284, 1–8.

Fearon, K., Strasser, F., Anker, S. D., Bosaeus, I., Bruera, E., Fainsinger, R. L., Jatoi, A., Loprinzi, C., MacDonald, N., Mantovani, G., Davis, M., Muscaritoli, M., Ottery, F., Radbruch, L., Ravasco, P., Walsh, D., Wilcock, A., Kaasa, S., & Baracos, V. E. (2012). Definition and classification of cancer cachexia: An international consensus. The Lancet Oncology, 13(5), 489–495.

Petruzzelli, M., & Wagner, E. F. (2016). Mechanisms of metabolic dysfunction in cancer-associated cachexia. Genes & Development, 30(5), 489–501.

von Haehling, S., Anker, S. D., & Springer, J. (2023). Cachexia: Pathophysiology and clinical relevance. Journal of Cachexia, Sarcopenia and Muscle, 14(1), 3–9.

Wang, X., Yu, C., Zhang, Z., & Wang, Y. (2016). Inflammation and cognitive decline in cancer cachexia. Brain, Behavior, and Immunity, 53, 100–109.