Exploring the association between pro-inflammatory mediators and sarcopenia in cancer patients through different diagnostic tools: a narrative review

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Background and Objective: Sarcopenia, characterized by the progressive loss of skeletal muscle mass (MM) and muscle function, is a common and debilitating condition in cancer patients, significantly impacting their quality of life, treatment outcomes, and overall survival. The pathophysiology of sarcopenia is multifactorial, involving metabolic, hormonal, and inflammatory changes. Recent research highlights the role of chronic inflammation in the development and progression of sarcopenia, with pro-inflammatory cytokines being key mediators of muscle catabolism. The primary objective of this study was to assess the role of pro-inflammatory cytokines in identifying sarcopenia among cancer patients. As a secondary objective, we aim to investigate whether the methods used for assessing sarcopenia, both imaging and functional, align with established guidelines.

Methods: A search of the Web of Science was conducted for English-language articles published since 2005, with the following terms: "Cancer" AND "Sarcopenia" AND "Pro-inflammatory cytokine*" OR "Interleukin*". Inclusion criteria included peer-reviewed controlled trials, observational studies, case reports, and case series. To avoid redundancy, articles with results which were included in systematic reviews, narrative reviews, or scoping reviews were excluded from this review.

Key Content and Findings: The analysis of 10 selected papers, including 1,138 cancer patients, revealed a lack of assessment of muscle strength (MS) and muscle functional performance in most of the studies on sarcopenia, contradicting the comprehensive nature of sarcopenia that includes MM, MS, and muscle functionality. There is no standardization of pro-inflammatory mediators for sarcopenia identification.

Conclusions: Future research should focus on establishing cutoff points for inflammatory mediators and identifying which cytokines are linked to sarcopenia. Given the complexity of sarcopenia in different cancers, new projects should investigate whether cytokine expression depends on the tumor type. Moreover, considering that the majority of the study population comprised elderly individuals with primary sarcopenia, it is crucial to discern the extent to which the findings are influenced by age versus cancer-related factors.

Keywords: Cancer; pro-inflammatory cytokines; interleukins; sarcopenia

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Introduction

Background

Globally, cancer incidence has been on the rise due to factors such as aging populations, lifestyle changes, and improved diagnostic techniques (1). According to Global Cancer Observatory (GLOBOCAN) 2020 data, there were an estimated 19.3 million new cancer cases and 10 million cancer-related deaths worldwide in 2020 (2). This increase underscores the need for continued research and effective public health strategies to manage and prevent cancer.

Cancer patients face an increased risk of muscle loss through two distinct mechanisms: cachexia, characterized by the cytokine-driven breakdown of muscle and fat tissues, and sarcopenia, which is the age-related decline in muscle mass (MM) due to changes in muscle synthesis signaling pathways (3). Cancer and sarcopenia are closely interconnected, as cancer can aggravate muscle wasting and weakness, thereby contributing to sarcopenia. Cancer-related sarcopenia arises from a combination of factors, including systemic inflammation, nutritional deficiencies, and the direct impact of tumor metabolism. This muscle wasting not only reduces the quality of life for cancer patients but also negatively affects treatment outcomes and survival rates. Effective management of sarcopenia in cancer patients is crucial for improving overall prognosis and enhancing the effectiveness of cancer therapies (4-6).

Sarcopenia

According to the European consensus on sarcopenia [European Working Group on Sarcopenia in Older People (EWGSOP)], sarcopenia is defined as the loss of muscle strength (MS), MM, and muscle functional performance (7). Since 2016, it has been considered a disease (ICD-10M62.84) by the World Health Organization (WHO) (8). Sarcopenia can primarily, result from inflammageing, a systemic inflammation associated with aging, which arises from dysfunctions in the neuroendocrine and immune systems. Secondary sarcopenia is due to diseases such as cancer and other inflammatory diseases that affect muscle function (9).

For the diagnosis of sarcopenia, the EWGSOP proposes the use of an algorithm consisting of four stages: identification of sarcopenia risk using the SARC-F (Strength, Assistance in walking, Rise from a chair, Climb stairs, and Falls), a simple questionnaire that is self-reported, accessible, and quick to apply (10). Once the risk of sarcopenia has been detected, the EWGSOP proposes the assessment of MS, by measuring handgrip strength (HGS) or the sitting and standing test (SST) (7). People with reduced MS ("probable sarcopenia") are then referred for measurement of MM and/or muscle quality (MQ) to confirm the diagnosis (7).

The recommendation is to perform dual energy X-ray absorptiometry (DXA), computed tomography (CT), and magnetic resonance imaging (MRI) for scientific studies and, in clinical practice, the use of DXA and bioelectrical bioimpedance analysis (BIA). BIA is a popular method for assessing body composition due to its portability, noninvasiveness, and cost-effectiveness. It does not involve significant ionizing radiation, is low-cost, and measures body composition and hydration status by analyzing resistance and reactance, making it suitable for diverse settings and medical conditions (11). DXA has been frequently used in scientific research due to its good correlation with gold-standard instruments (CT and MRI), being more accessible and presenting less exposure to irradiation. Functional capacity assessment, as proposed by the EWGSOP, is indicated to detect the severity of sarcopenia. The recommended functional tests are the gait speed assessment, Short Physical Performance Battery (SPPB), Timed Up and Go test, and 400-meter walk test (7).

Pro-inflammatory cytokines

Sarcopenia is closely linked to inflammatory cytokines. These cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1beta (IL-1β), play a significant role in the development and progression of sarcopenia by promoting chronic inflammation. Elevated levels of inflammatory cytokines can lead to muscle protein degradation and impair muscle regeneration, exacerbating muscle wasting. This

inflammatory response is often observed in aging, chronic diseases, and cancer, contributing to the onset and severity of sarcopenia. The systemic immune-inflammation index (SII) has been correlated to a variety of disorders and a recent systematic reviewer and meta-analysis investigated the relationship between SII and sarcopenia and show high SII level increased the risk of sarcopenia (12,13).

Cytokines comprise a diverse group of low molecular weight proteins produced by macrophages, lymphocytes, endothelial cells, muscle cells, fibroblasts, and adipocytes when stimulated by physiological and/or pathological agents. Cytokines, including interleukins, are key regulators of immune responses and play pivotal roles in cancer development and progression (14). Interleukins are induced by an aggressive agent, inflammatory process, and/or diseases, serving as a means of communication for innate and adaptive immune cells, as well as non-immune cells and tissues. Consequently, interleukins play a critical role in the development, progression, and control of cancer. They can create an environment conducive to cancer growth, while also being essential for a productive immune response against the tumor (14).

These interleukin properties can be leveraged to enhance immunotherapies for improved efficacy and reduced side effects. Pro-inflammatory interleukins, particularly relevant in cancer development and progression, are described in the literature (14) and are also implicated in muscle catabolism leading to sarcopenia (15). Elevated levels of inflammatory interleukins are associated with sarcopenia (16), and exercise has been shown to reduce these mediator levels, indicating an anti-inflammatory effect of exercise (17).

In cancer patients, secondary sarcopenia due to the disease and/or treatment adverse effects often leads to a sedentary lifestyle, further compromising MS and MM. While several interleukins are reported to increase in cancer patients, their direct association with sarcopenia remains inconclusive in the current literature.

Rationale and knowledge gap

Sarcopenia is a common and debilitating condition in cancer patients, significantly impacting their quality of life, treatment outcomes, and overall survival (4,7,18). This narrative review aims to enhance the understanding of pro-inflammatory mediators associated with sarcopenia and the diagnostic tools used to identify sarcopenia in patients with various types of cancer.

Objectives

The primary objective of this study was to evaluate which pro-inflammatory cytokines are used in identifying sarcopenia among cancer patients. Specifically, we aim to (I) associate the findings of inflammatory cytokines with sarcopenia, (II) evaluate the methods used to identify sarcopenia, such as MM (measured by DXA, CT, or BIA scans) and MS (assessed by grip strength) and (III) assess if the literature followed the guidelines of the 2019 European Sarcopenia Consensus for sarcopenia identification. We present this article in accordance with the Narrative Review reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-24-128/rc).

Methods

A series of searches on the Web of Sciences were conducted to identify relevant articles on pro-inflammatory cytokines associated with sarcopenia in cancer patients. The search utilized the keywords: “Cancer” AND “Sarcopenia” AND “Pro-inflammatory cytokine*” OR “Interleukin*”. Initial screening of the search results was based on titles and abstracts to determine their relevance to the theme (*Table 1*).

The selection was further refined to include articles that investigated, discussed, or presented findings related to sarcopenia pro-inflammatory cytokines measure in cancer patients, focusing on (I) type of cytokine, (II) tumor type, and (III) methods of sarcopenia identification. This narrative review prioritized peer-reviewed controlled trials, observational studies, case reports, and case series. To avoid redundancy, articles with results which were included in systematic reviews, narrative reviews, or scoping reviews were excluded from this review.

Study eligibility was independently determined by two investigators (J.A.B.C. and A.V.C.) based on the manuscript titles and abstracts using Rayyann®. Subsequently, two other investigators (A.P.D.L. and L.S.M.P.) on the study team conducted a full-text review. For data extraction, a standardized data abstraction form was developed, involving a primary reviewer (L.S.M.P.) who completed the form and a secondary reviewer (A.P.D.L.) who checked for accuracy and completeness. Any conflicts were resolved by the four reviewers through an iterative process and discussion to reach a consensus. The data captured on the abstraction forms included the first author, title, year of publication, study type, type of cancer, pro-inflammatory cytokine evaluated, method of assessment of sarcopenia, number

Table 1 The search strategy summary

Items	Specification
Date of search	30 April 2024
Databases searched	Web of Science
Search terms used	"Cancer" AND "Sarcopenia" AND "Pro-inflammatory cytokine*" OR "Interleukin*"
Timeframe	01 January 2005 to 30 April 2024
Inclusion and exclusion criteria	Inclusion: English, original articles Exclusion: review articles
Selection process	Selection: two independent reviewers (J.A.B.C. and A.V.C.). Full-text review for final eligibility: A.P.D.L. and L.S.M.P.

of participants, primary and secondary endpoints, and statistical outcome.

Key findings

The review incorporated ten articles, including nine prospective studies, encompassing 1,138 cancer patients (*Figure 1*). The most common cancers examined were colorectal (four studies), mixed tumors (two studies), and pancreatic, non-small cell lung cancer (NSCLC), hepatocarcinoma, and clear-cell renal carcinoma, each represented by one study (Table S1).

This review reveals that cancer-related sarcopenia is prevalent across various cancer types, at all stages, persisting both before and after tumor resection, and is often associated with poorer patient outcomes. Notably, despite the high incidence of breast cancer (2), none of the studies reviewed investigated interleukins related to sarcopenia in breast cancer patients.

Most participants were elderly, with a mean age above 65 years, a group often affected by primary sarcopenia due to inflammageing, defined as an age-related increase in the levels of pro-inflammatory markers in blood and tissues (19). Inflammaging is assessed by measuring pro-inflammatory cytokines in the blood. Aging is associated with immune dysregulation (immunosenescence), the most evident characteristics of which are elevated levels of pro-inflammatory cytokines in the blood. The pro-inflammatory state is measured and characterized by high circulating levels of pro-inflammatory markers, including IL-1, IL-6, IL-8, IL-13, IL-18, C-reactive protein (CRP), interferon alpha (IFNα) and interferon beta (IFNβ), transforming growth factor beta (TGFβ), tumor necrosis factor (TNF) and its soluble receptors (members of the TNF receptor superfamily 1A and 1B), and serum amyloid (20). This primary sarcopenia, resulting from neuroendocrine and immunological system dysregulation, leads to increased inflammatory interleukins (21). Consequently, patients in these studies likely experienced both primary sarcopenia and secondary cancer-induced sarcopenia, exacerbating inflammatory interleukin levels.

Cytokines and cancer-related sarcopenia

The review highlights the crucial role of interleukins and other cytokines in cancer-related sarcopenia. Among the studies reviewed, IL-6 and TNF-α were the most frequently investigated cytokines, showing a strong association with sarcopenia across various cancer types. For example, Dalbeni *et al.* and Kays *et al.* identified IL-6 as a potential diagnostic marker for sarcopenia in advanced cirrhotic hepatocellular carcinoma (HCC) and clear cell renal cell carcinoma (ccRCC), respectively (22,23). Lipshitz *et al.* and Scheede-Bergdahl *et al.* found that TNF-α was significantly associated with sarcopenia, although trends with IL-6 and IL-8 were also noted (24,25). Tenuta *et al.* reported elevated levels of IL-6 (P=0.004) and TGF-α (P=0.042) in sarcopenic patients with NSCLC compared to non-sarcopenic patients (26). Among the patients studied, 40% were sarcopenic, and this group exhibited an eightfold higher risk of disease progression compared to non-sarcopenic patients. Hou *et al.* highlighted IL-8 as significantly associated with sarcopenia and an independent predictor of survival in pancreatic cancer patients (27). Additionally, Hu *et al.* found high levels of IL-23 in sarcopenic colorectal cancer (CRC) patients, correlating with poor prognosis (28).

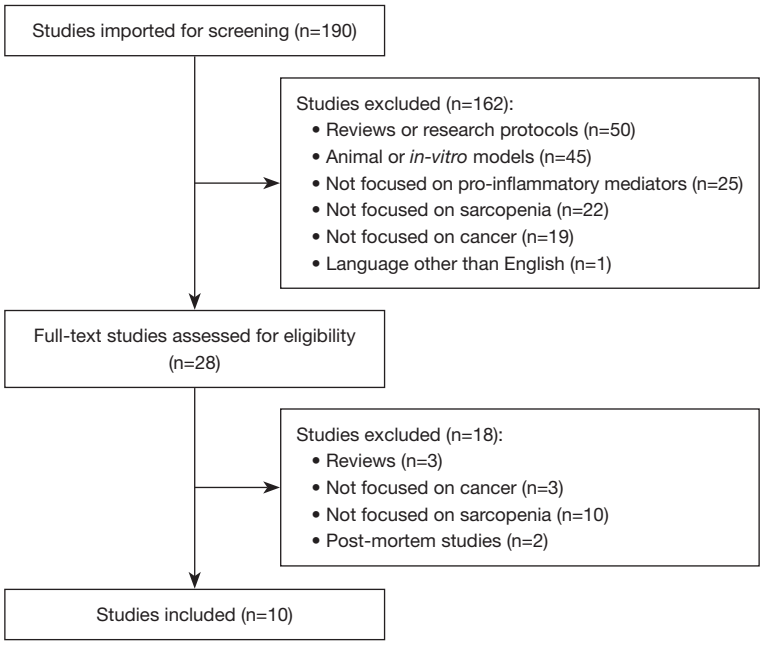

Figure 1 Study selection flowchart.

In contrast, other studies, including those by Aro *et al.* and He *et al.*, which assessed various cytokines, did not find a significant association between serum cytokine levels and sarcopenia (29,30). Aro *et al.* (29) reported that sarcopenia and/or myosteatosis (fat infiltration into skeletal muscle) were linked to an elevated neutrophil-to-lymphocyte ratio (NLR), though no connection with Glasgow Prognostic Scores (31) was observed. Reisinger *et al.* found that skeletal MM did not predict plasma concentrations of CRP and IL-6 but noted a significant association between low skeletal MM and elevated plasma calprotectin concentrations, a marker of neutrophil activation (32). He *et al.* observed that low muscle quantity was associated with a higher NLR and a negative relationship with interferon-gamma induced protein 10 (IP-10) levels. IP-10, which plays a significant role in inflammatory and immune responses. However, the study did not find any association between muscle quantity and the local inflammatory environment of the tumors in the patient cohort (30).

Imagining methods of sarcopenia diagnoses

The studies reviewed primarily utilized radiographic methods such as CT and DXA to assess sarcopenia. CT imaging, particularly at the level of the lumbar vertebrae and specific muscles such as the psoas and abdominals, was the most common method used, as seen in studies by Dalbeni *et al.*, Kays *et al.*, Hou *et al.*, Hu *et al.*, Aro *et al.*, He *et al.*, and Reisinger *et al.*, where sarcopenia prevalence and its association with inflammatory markers were analyzed (22,23,27-30,32). CT scans allowed for precise measurement of MM, although they did not always include MS assessments, which is a limitation noted in several studies. In contrast, DXA, as used by Scheede-Bergdahl *et al.* and Tenuta *et al.*, provided a strong correlation with gold-standard instruments like CT and MRI while also considering MS, thereby offering a more comprehensive evaluation of sarcopenia (25,26). The review underscores the importance of these imaging techniques in diagnosing sarcopenia, although it also highlights the need for a more holistic approach that includes both MM and function.

Functional methods of sarcopenia diagnosis

In addition to radiographic measurements, the review emphasizes the importance of functional assessments in diagnosing sarcopenia. The European consensus on sarcopenia recommends evaluating MS, muscle quantity, and physical performance, however, few studies in the review incorporated. For instance, Scheede-Bergdahl *et al.* used HGS alongside DXA to assess sarcopenia, adding robustness to their study by including a functional

measure (25). Lipshitz *et al.* also employed BIA and hand dynamometry to evaluate MS and sarcopenia, finding significant associations between interleukins and reduced HGS (24). The review highlights the argument against relying solely on MM measurements, as MS and functionality are crucial components of sarcopenia diagnosis. The inclusion of the muscle quality index (MQI) in diagnostic algorithms is suggested as it accounts for muscle performance, offering a more accurate reflection of sarcopenia's impact on physical function. Cawthon *et al.* [2020] highlighted the significance of HGS and slow gait, showing their independent association with higher risks of mobility limitations, falls, hip fractures, and mortality, whereas MM measurements (using DXA) did not significantly correlate with these outcomes (33).

Conclusions

The findings suggest that cytokines, particularly IL-6, IL-8, and TNF-α, play a crucial role in the inflammatory processes leading to sarcopenia in cancer patients.

The review also revealed that most studies did not assess MS and functional performance, which are integral components of sarcopenia, extending beyond the loss of MM. The variability in how sarcopenia was measured—whether through BIA, DXA, or CT/MRI—emphasizes the need for future research to establish standardized cutoff points for inflammatory mediators and to explore the relationship between cytokine expression and different cancer types.

Additionally, since most study participants were elderly with primary sarcopenia, it is crucial to differentiate the effects of age from those of cancer in these findings.

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Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-24-128/rc

Peer Review File: Available at https://atm.amegroups.com/article/view/10.21037/atm-24-128/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-24-128/coif). A.P.D.L. serves as an unpaid editorial board member of *Annals of Translational Medicine* from June 2024 to May 2026. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary

Table S1 Summary of included studies

References	Year	Country/region	N	Age (years)	Gender	Tumor type	Tumor stage	Cytokines	Assessment of sarcopenia
Scheede-Bergdahl *et al.* (25)	2012	Canada	83	Mean ± SD: 61.8±12.9	56.6% male; 43.4% female	Mixed	III–IV	IL-1β, IL-6, IL-8, and TNF-α	DXA
Reisinger *et al.* (32)	2016	The Netherlands	87	Mean ± SD: 65.6±11.9	64% male; 36% female	CRC	I–IV	IL-6	CT scan
He *et al.* (30)	2018	China	125	Median (range): 59 (19–87)	61.1% male; 39.9% female	CRC	I–III	CRC: IL-1α, IL-1β, IL-1RA, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-13, IL-15, IL-17, IL-12 P40, IL-12 P70, EGF, IFNα-2, IFNγ, IP-10, MCP-1, MCP-3, MIP-1α, MIP-1β, TNF-α, TNFβ, VEGF, FGF-2, TGF-α, FIT-3L, fractalkine, GRO, MDC, sCD40L, and sIL-2Rα	CT scan
Hou *et al.* (27)	2018	Taiwan	110	Median (range): 66 (37–85)	61.6% male; 38.4% female	Pancreatic	I–IV	IL-1β, IL-6, IL-8, and TNF-α	CT scan
Kays *et al.* (23)	2020	USA	217	Mean ± SD: 59.65±12.46	Not specified	CCRCC	I–IV	IL-6	CT scan
Hu *et al.* (28)	2021	Taiwan	114	Mean ± SD: 63.2±12.8	60% male; 40% female	CRC	I–IV	IL-23	CT scan
Tenuta *et al.* (26)	2021	Italy	47	Median (IQR): 67 (61–74)	57.4% male; 42.6% female	NSCLC	IV	IL-6, TNF-α and TGF-α	DXA
Aro *et al.* (29)	2022	Finland	222	≥70 (57.2%); <70 (42.8%)	52.7% male; 47.3% female	CRC	I–IV	IL-1R1, IL-4, IL-6, IL-7, CXCL8, IL-9, IL-12 P70, IFNγ, CXCL10, CCL2, CCL4, CCL11, and PDGF-BB	CT scan
Dalbeni *et al.* (22)	2023	Italy	93	Mean ± SD: 70±15	83.8% male; 16.2% female	HCC	I–IV	IL-6	CT scan
Lipshitz *et al.* (24)	2023	South Africa	40	Mean ± SD: 64.03±12.63	65% male; 35% female	Mixed tumors	IV	IL-6, IL-8 and TNF-α	BIA, HGS

Total number of patients: 1,138. SD, standard deviation; IL-1β, interleukin-1beta; IL-6, interleukin-6; IL-8, interleukin-8; TNF-α, tumor necrosis factor-alpha; DXA, dual-energy X-ray absorptiometry; CRC, colorectal cancer; CT, computed tomography; IL-1α, interleukin-1alpha; IL-1RA, interleukin-1 receptor antagonist; IL-2, interleukin-2; IL-3, interleukin-3; IL-4, interleukin-4; IL-5, interleukin-5; IL-7, interleukin-7; IL-9, interleukin-9; IL-10, interleukin-10; IL-13, interleukin-13; IL-15, interleukin-15; IL-17, interleukin-17; IL-12 P40, interleukin-12 p40; IL-12 P70, interleukin-12 p70; EGF, epidermal growth factor; IFNα-2, interferon alpha-2; IFNγ, interferon gamma; IP-10, interferon-gamma induced protein 10; MCP-1, monocyte chemoattractant protein-1; MCP-3, monocyte chemoattractant protein-3; MIP-1α, macrophage inflammatory protein-1alpha; MIP-1β, macrophage inflammatory protein-1beta; TNFβ, tumor necrosis factor beta; VEGF, vascular endothelial growth factor; FGF-2, fibroblast growth factor-2; TGF-α, tumor growth factor alpha; FIT-3L, FMS-like tyrosine kinase 3 ligand; GRO, growth-related oncogene; MDC, macrophage-derived chemokine; sCD40L, soluble CD40 ligand; sIL-2Rα, soluble interleukin-2 receptor alpha; CCRCC, clear cell renal carcinoma; IL-23, interleukin-23; IQR, interquartile range; NSCLC, non-small cell lung cancer; IL-1R1, interleukin 1 receptor type I; CXCL8, C-X-C motif chemokine ligand 8; CXCL10, C-X-C motif chemokine ligand 10; CCL2, chemokine ligand 2; CCL4, chemokine ligand 4; CCL11, chemokine ligand 11; PDGF-BB, platelet-derived growth factor subunit B; HCC, hepatocellular carcinoma; BIA, bioimpedance analysis; HGS, hand grip strength.

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