Peer Review File

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Reviewer A

I enjoyed reading this article and commend the authors for exploring the different facets underlying sarcopenia and the deficiencies seen in cancer sarcopenia literature. Overall the manuscript was written well. Below see my comments per section.

Introduction:
Comment 1: Line 42; perhaps mention that cancer cachexia when describing how can can "exacerbate muscle wasting and weakness". As cachexia is a separate entity from sarcopenia.
Reply 1: We include a new sentence according to the study of Meza-Valderrama et al.
Changes in the text: 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 due to changes in muscle synthesis signaling pathways (Meza-Valderrama, D.et al.).

Comment 2: Line 53; is inflammaging a typo? I am unfamiliar with this term. Perhaps you meant inflammation
Reply 2: It is a typo. The correct term is "inflammaging" or "inflammageing." This concept was first introduced in 2000 by Prof. Franceschi and represented a significant, if not revolutionary, advancement in our understanding of immune changes in response to lifelong stress (Fulop et al., 2023). Since then, the concept of inflammaging/inflammageing has become a cornerstone in the study of immunosenescence and geroscience, being recognized as a key factor contributing to age-related diseases. (*Reference: Fulop, T., Larbi, A., Pawelec, G., Khalil, A., Cohen, A. A., Hirokawa, K., Witkowski, J. M., & Franceschi, C. (2023). Immunology of Aging: The Birth of Inflammaging. Clinical Reviews in Allergy & Immunology, 64(2), 109-122. https://doi.org/10.1007/s12016-021-08899-6).*
Changes in the text: Please see comment 3.

Comment 3: Line 53-55 is a run on sentence and hard to follow; consider shortening by stating "sarcopenia can be primary due to systemic inflammation associated with aging, even in the absence of disease, due to dysfunction of the neuroendocrine and immune systems."
Reply 3: The sentence was rewritten as suggested.
Changes in the text: Sarcopenia can primarily due to inflammageing, a systemic inflammation associated with aging, which arises from dysfunctions in the neuroendocrine and immune systems.

Comment 4: Line 72, remove "characterize by the loss of muscle and function". You have already defined sarcopenia thus this is redundant.
Reply 4: We agree with the reviewer.

Changes in the text: The sentence was excluded as suggested.

Comment 5: Line 103, again remove the definition of sarcopenia "characterized by the progressive loss of skeletal muscle mass..). this has already been stated.
Reply 5: We agree with the reviewer.
Changes in the text: The definition of sarcopenia was excluded as suggested.

Comment 6: Line 105, consider adding Prado et al reference (Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. Lancet Oncol. 2008;9:629–635.) to this as this was one of the first studies to associated sarcopenia and cancer outcomes with radiographic analysis.
Reply 6: Thank you for the comment.
Changes in the text: The reference was added to the manuscript.

METHODS:
Comment 7: I am somewhat concerned by the limited number of articles (N=10) found. I would expect much more containing the keywords utilized. Does the web of sciences incorporate pubmed, google scholar, etc?
Reply 7: When selecting a database for our review, we evaluated both PubMed and Web of Science. From PubMed, we retrieved 93 papers, and from Web of Science, we obtained 190 papers. Notably, over 90% of the papers were similar across both databases, leading us to choose Web of Science for its comprehensive coverage. Google Scholar was not considered as a primary option because, unlike the more structured databases, it relies on web crawlers to search across a vast array of internet sites without a well-defined background database. This can result in less consistent and less focused search results.
Changes in the text: None.

Comment 8: what time frame was considered for inclusion?
Reply 8: 01 January 2005 to 30 April 2024.
Changes in the text: This data was added to Table 1.

Discussion
Comment 9: First, I do not think it is necessary to write a new paragraph for every single article reviewed. That is what your table (table 2) is for. I felt this cause this section of the manuscript to be cumbersome to read. Next, I am not sure why you subdivided the discussion based on method of measuring sarcopenia. Your main objective is to describe relationship between sarcopenia and inflammatory cytokines. I believe all together you could write a discussion where each paragraph has a theme (cytokines reviewed, radiographic of measuring sarcopenia, functional assessments of sarcopenia).
Reply 9: We agree with the reviewer.
Changes in the text: We rewrite the Discussion section with the 4 main themes suggested.

Comment 10: Line 154; consider changing intriguingly to interestingly

Comment 10: The discussion section was rewritten.
Changes in the text: The term was excluded.

Comment 11: Line 158; consider changing inflammaging as above
Reply 11: The discussion section was rewritten.
Changes in the text: Please see comment 2.

Comment 12: Line 167, consider definiting myosteatosis when used for first time
Reply 12: The discussion section was rewritten.
Changes in the text: The term was excluded.

Comment 13:Line 189; consider using “muscle quantity” as SMI is a newly used term. I would be easier to say muscle quantity than to describe what SMI means (radiographically calculated and adjusted by patients height).
Reply 13: The discussion section was rewritten.
Changes in the text: The term was excluded.

Comment 14: Line191-203; listing all these cytokines is not necessary. Consider just saying in one sentence the authors that the authors evaluated X number of cytokines in patients with metastatic CRC….
Reply 14: The discussion section was rewritten.
Changes in the text: The list of cytokines was excluded as suggested.

Comment 15: Line 204; again consider saying low muscle quantity instead of SMI
Reply 15: The discussion section was rewritten.
Changes in the text: The term was excluded.

Comment 16: Line 237; here you mention cachexia for the first time. As state in the introduction I feel it is important to mention cachexia there.
Reply 16: We included cachexia in in introduction section.
Changes in the text: Please see comment 1.

Conclusion:
Comment 17: I would briefly comment on the variability of how sarcopenia was measured (BIA, DEXA, CT/MRI).
Reply 17: The change was made.
Changes in the text: The conclusion section was rewritten.

Comment 18:Line 296; “given this context, studies on sarcopenia in patients with various types of cancer remain inconclusive”. I would consider rewording or removing this sentence. This is an overreach as several studies time and time again (prado et al, martin et al, etc) have demonstrated the poor association of sarcopenia with outcomes. I would not say its inconclusive.
Reply 18: We agree with the author.
Changes in the text: The sentence was excluded.

Reviewer B

Comment 1: The aim of this research was to examine the relationship between circulating cytokines and sarcopenia-related characteristics in cancer patients. The selection process involved utilizing Web of Science to search for specific keywords such as "cancer", "sarcopenia", “interleukin*” and "cytokine*”. Out of an initial pool of 190 papers, the authors narrowed down their review to 10 relevant studies. The variability in study participants, assessment methods, and study design poses a challenge in the investigation of sarcopenia. The diverse cancer types, tumor stages, and various techniques like CT imaging, DXA, BIA, and HGS used to measure muscle mass contribute to the complexity of comparing findings across studies. Additionally, the writing format is very poor. Several information duplications can be find in the introduction paragraphs. The main content of the document consists of brief summaries of the 10 studies, failing to establish significant connections between them.

Although, the topic discussed in this review holds significant relevance and deserves to be acknowledged. The authors identified a notable gap in knowledge regarding the involvement of inflammation in cancer-related sarcopenia and cachexia. The suggestion for future research to accurately diagnose sarcopenia by incorporating both muscle mass and muscle strength measurements is crucial for a comprehensive understanding of this condition.

Major points:
Comment 1: The assessment of only 10 papers discussing the prominent themes of inflammation, sarcopenia, and cancer does not lead to any clear conclusion.
Reply 1: Although the number of eligible manuscripts was limited to only 10 papers, the manuscript offers insights into the complex relationship between inflammation, sarcopenia, and cancer. It critically synthesizes existing research, identifies gaps in the literature, and proposes directions for future investigation. Our review revealed a notable scarcity of studies focusing on pro-inflammatory cytokines and cancer-related sarcopenia in human models. Most of the existing literature consists of research protocols, studies on animal models, or investigations of sarcopenia that are not specific to cancer.
Changes in the text: None

Comment 2: The wide range of studies on different types and stages of cancer, along with the diverse approaches to evaluating sarcopenia, makes it difficult to reach firm conclusions.
Reply 2: We appreciate the reviewer's feedback. However, as noted in response to comment 2, narrowing the focus to a specific tumor type, stage, or sarcopenia diagnostic method would significantly reduce the number of eligible articles for analysis. We believe that our results underscore the need for further research in this area and highlight the importance of broadening the scope of future studies to address these gaps in the literature.
Changes in the text: None.

Comment 3: The writing style necessitates significant enhancement, with the removal of

redundant information and the verification of data accuracy. The main body of the text should not merely consist of isolated descriptions of each paper, but rather establish connections between the various studies, which is crucial for a review study.
Reply 3: We agree with the reviewer.
Changes in the text: The discussion section has been revised to more clearly establish connections among the included studies.

Minor points:
Comment 4: Line 102. This paragraph is repetitive. Several parts in the text are recurrently defining sarcopenia (Abstract and Introduction). Please avoid repetitions.
Reply 4: We agree with the reviewer.
Changes in the text: We reviewed the manuscript, and the repetitions have been removed.

Comment 5: Line 107. The topic of chronic inflammation is already mentioned in Introduction.
Reply 5: We agree with the reviewer.
Changes in the text: We reviewed the manuscript, and the repetitions have been removed.

Comment 6: Line 110. Repetition. In p.4 the topic is already introduced.
Reply 6: We agree with the reviewer.
Changes in the text: We reviewed the manuscript, and the repetitions have been removed.

Comment 7: Line 114. A definition and explanation of the method is missing. Move this technique to paragraph Sarcopenia 1.2. where the other techniques are explained.
Reply 7: We agree with the reviewer.
Changes in the text: The following sentence was added to 1.2: 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 (Mandalá et al., 2023).

Comment 8: Line 116. Again repetitive.
Reply 8: We agree with the reviewer.
Changes in the text: We reviewed the manuscript, and the repetitions have been removed.

Comment 9: Line 163. Limited description of various nature studies with minimal interconnection among them. Please rewrite.
Reply 9: As suggested by Reviewer 1, we rewrote the discussion, focusing on four main topics: cytokines reviewed, radiographic methods for measuring sarcopenia, and functional assessments of sarcopenia.
Changes in the text: The Discussion section was rewritten.

Comment 10: Line 167. Which inflammatory marker? neutrophil–lymphocyte ratio (NLR), please specify?
Reply 10: Yes, it was NLR.

Changes in the text: The Discussion section was rewritten and the following sentence included: However, Aro et al. reported that sarcopenia and/or myosteatosis (the infiltration of fat into skeletal muscle) were associated with an elevated neutrophil-to-lymphocyte ratio (NLR), although a connection with Glasgow Prognostic Scores (McMillan DC, 2013) was not observed in their study.

Comment 11: Line 168. “Glasgow prognostic scores” Please include citation: McMillan, D.C. The systemic inflammation-based glasgow prognostic score: A decade of experience in patients with cancer. Cancer Treat. Rev. 2013, 39, 534–540.
Reply 11: The reference was added accordingly.
Changes in the text: Please see comment 10/

Comment 12: Line 185. What is the significance of these findings? What role does Calprotectin play?
Reply 12: Calprotectin is a specific marker of neutrophil activation.
Changes in the text: The Discussion section was rewritten and the following sentence was included: Finally, Reisinger et al. found that skeletal muscle mass did not predict plasma concentrations of C-reactive protein (CRP) and IL-6. However, low skeletal muscle mass was significantly associated with elevated plasma calprotectin concentrations, a specific marker of neutrophil activation.

Comment 13: Lines 191-203. Avoid include just a list of non-significant information listing names and highlight just the relevant information.
Reply 13: We agree with the reviewer.
Changes in the text: The Discussion section was rewritten and the list of cytokines was excluded.

Comment 14: Line 204. Founded in the local tumor but not in skeletal muscle?
Reply 14: We apologize for the misunderstanding. The sentence has been revised for clarity.
Changes in the text: The following sentence was added in the Discussion section: However, the study did not find any association between muscle quantity and the local inflammatory environment of the tumors in the patient cohort.

Comment 15: Line 205. IP-10 I guess the authors mean IL-10, usually defined as anti-inflammatory. Please put it in context.
Reply 15: IP-10 means interferon-gamma-induced protein 10.
Changes in the text: The following sentence was added in the Discussion section: 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.

Comment 16: Line 215. Is there any relationship between IL-23 and sarcopenia?
Reply 16: Yes. It was better described in the Discussion section.
Changes in the text: The following sentence was added: Additionally, Hu et al. found high levels of IL-23 in sarcopenic colorectal cancer (CRC) patients, correlating with poor prognosis.

Comment 17: Line 241. How the authors distinguish between cachexia and sarcopenia in the patients? This is not reported in the quoted paper.
Reply 17: As shown in Figure 1, the abstracts of all 190 papers were reviewed. Papers that assessed cachexia rather than sarcopenia were excluded. Figure 1 indicates that the 22 papers excluded for "not reporting sarcopenia" were related to cachexia. Additionally, we have included a sentence in the introduction to better distinguish between cachexia and sarcopenia.
Changes in the text: In the Introduction section (1.1), the following sentence was added: 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 due to changes in muscle synthesis signaling pathways (Meza-Valderrama, D.et al.).

Comment 18: Line 246. High, but significant or not significant?
Reply 18: High and significant.
Changes in the text: Please see 3.1: Tenuta et al. reported elevated levels of IL-6 ($p=0.004$) and TGF-α (0.042) in sarcopenic patients with non-small cell lung cancer (NSCLC) compared to non-sarcopenic patients.

Comment 19: Line 248. measured how?
Reply 19: We add the required information in the manuscript.
Changes in the text: The text was added in 3: 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), IFNα and IFNβ , transforming growth factor-β (TGFβ), tumor necrosis factor (TNF) and its soluble receptors (members of the TNF receptor superfamily 1A and 1B), and serum amyloid (Ferrucci L, Fabbri E. Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty. Nat Rev Cardiol. 2018 Sep;15(9):505-522. doi: 10.1038/s41569-018-0064-2. PMID: 30065258; PMCID: PMC6146930).

Comment 20: Line 253. None of the papers that were reviewed made use of this index for assessing sarcopenia. Is there any research available that has employed this method to measure inflammation markers? If not, the rationale for its mention remains unclear.
Reply 20: The European Sarcopenia Consensus (Cruz-Jentoft, A. J. et al . (2019). Sarcopenia: revised European consensus on definition and diagnosis. Age and Ageing, 48(1), 16-31)determined the criteria for assessing sarcopenia. This consensus is followed by numerous authors in their publications. The association between pro-inflammatory cytokines and sarcopenia has been described in several studies (WangJ et at 2024; Bano et al 2017; Ferrucci et al 2018): . Nonetheless, the association between pro-inflammatory mediators and sarcopenia in cancer patients using different diagnostic tools still needs to be further researched and this was the objective of the present study
Changes in the text: None.

Comment 21: Line 273. The content in this paragraph duplicates the information already presented in both the Introduction and Materials and Methods sections.
Reply 21: We agree with the reviewer.
Changes in the text: The duplicated information has been removed.