We wish to thank all four reviewers for their careful reading of our manuscript and their punctual observations and comments, which have led to a revision greatly improving clarity and quality of our submission. Here are point-by-point responses with reference to the revised manuscript:

Response to Reviewer #1

We thank the Reviewer for these insightful comments.

1. IL-6 is a cytokine that is classified as a myokine, meaning it is produced and released by muscle cells. It is secreted in response to muscle contraction during physical activity. IL-6 is also associated with muscle hypertrophy and repair. It helps regulate muscle growth and can counteract muscle wasting conditions, such as sarcopenia, by promoting muscle regeneration on adaptation to exercise, whereas a pro-inflammatory cytokines IL-6 is involved in the body's immune response. The authors should discuss about IL-6 in more details.

   We have expanded the discussion of IL-6 to clearly distinguish its dual role. The revised manuscript now differentiates between acute, exercise-induced IL-6 acting as a myokine with adaptive (as in the case of infection or flares of autoimmune diseases) and regenerative effects, and chronic low-grade IL-6 elevation characteristic of inflammaging, produced by many different cell types, which is associated with catabolic signaling and muscle dysfunction.

2. In page 3, line 143, which source of IL-10 is the author referring to?

   We have clarified that IL-10 is primarily derived from regulatory T cells and monocyte/macrophage lineages, with a minor contribution from skeletal muscle, and we have specified this explicitly in the revised text.

3. Are the authors trying to say that the spread of inflammatory changes from the peripheral level to the central nervous system is involved in the onset of sarcopenia?

   We do not claim a direct causal spread from peripheral inflammation to the central nervous system. The revised manuscript now clearly states that the involvement of the CNS is supported by associative and longitudinal evidence, consistent with a shared inflammatory milieu rather than a proven causal pathway. The inflammaging concept embraces all aspects, functions and organs which are impaired by aging.

Response to Reviewer #2

(1) According to this paper, the viewpoint of skeletal Muscle Function Deficit (SMFD) appears to be similar to that of frailty. What is better about SMFD, compared to the Fried's frailty score or frailty index score.
We have added a dedicated paragraph clarifying that SMFD differs conceptually and operationally from frailty. While frailty is a global clinical syndrome, SMFD is a muscle-specific, continuous, and mechanistically grounded construct that captures early neuromuscular vulnerability and precedes the clinical expression of frailty.

(2) This paper is very similar to their recent paper (Ref. number 16; MedRxiv 2025:2025.10.06.25337404. 241 https://doi.org/10.1101/2025.10.06.25337404.) The originality and novelty of this article should be more clearly indicated in comparison with their recent paper (Ref. 16).
We now explicitly state that the MedRxiv paper focused on the operational definition and validation of the SMFD score, whereas the present Viewpoint develops the broader biological, neuromuscular, and inflammatory framework underlying SMFD. The aims and scope of the two papers are now clearly differentiated.

(3) What is the most important impact of this study?
The most important impact of this work is the proposal of SMFD as a function-based, biological framework that integrates muscle quality, power, and neuromuscular integrity, providing a potential bridge between mechanistic biology and clinical risk stratification.

(4) Comments regarding "limitations of this study" and/or "new directions" are necessary in the discussion.
A new section has been added to explicitly address study limitations and outline future research directions, including external validation and interventional studies.

(5) In Line 76, "(Figure 1)" is indicated. However, I cannot find this figure.

Figure 1 has now been added, we apologize for the mistake.

Response to Reviewer #3

We thank the Reviewer for the constructive suggestions.

1. Line 39: In "The aging process induces a progressive muscle decline, traditionally defined as sarcopenia [1]", please clarify more on muscle. What aspect of muscle is declined?

   We have clarified which aspects of muscle decline are involved (mass, strength, power, quality, and neuromuscular control).

2. Line 41-42: In "Muscle mass loss leads to a decrease in quality of life, affecting overall well-being and self-sufficiency [2].", not only "Muscle mass loss" that decreases quality of life. Muscle function also decreases quality of life, affecting overall well-being and self-sufficiency. Please complete this sentence.

   The role of muscle function, in addition to mass, in determining quality of life has been explicitly stated.

3. Line 65-67: In "The delay in sarcopenia identification may also explain the proliferation of definitions such as sarcopenic obesity [11], dynapenia [12], powerpenia [7], and myosteatosis [13]", please explain more on four of these terms.

   Brief explanations and references of dynapenia, powerpenia, sarcopenic obesity, and myosteatosis have been added.

4. Please add more information which are city and country of Chianti area.

   The Chianti area is now specified as Tuscany, Italy.

5. Line 76: Figure 1 is absent.

   Figure 1 has been added, we apologize for missing inclusion.

6. This article may provide more helpful information by adding more detail of the InCHIANTI-study including number and characteristics of participants, methods, and weak point (if available).

   We insert a Supplementary Figure outlining the InCHIANTI-Study design, which can be found in the reference cited.

Response to Reviewer #4

We appreciate the Reviewer's thoughtful and detailed critique.

1. While the manuscript proposes Skeletal Muscle Function Deficit (SMFD) as an integrative umbrella concept encompassing sarcopenia, dynapenia, powerpenia, and myosteatosis, it does not sufficiently clarify the substantive conceptual or mechanistic advances beyond existing multidimensional definitions. At present, SMFD appears largely as a re-labelling or consolidation of existing constructs rather than a clearly novel paradigm.
   We have strengthened the manuscript by explicitly delineating how SMFD advances beyond existing multidimensional definitions, emphasizing its function-centered, mechanistic, and preclinical nature rather than a simple consolidation of terms.
2. The manuscript repeatedly characterizes inflammaging as the "main driver" or "orchestrating factor" of SMFD. However, the majority of cited evidence is observational and associative in nature. Strong causal language is therefore not fully supported by the available data, and the distinction between correlation and causation should be made more explicit.
   We agree with this comment, therefore we have revised the text to avoid overstated causal claims, consistently distinguishing association from causation and aligning our language with the observational nature of the evidence.
3. The proposed neuro-muscular inflammaging axis is conceptually appealing, yet the mechanistic links between central nervous system changes, peripheral nerve dysfunction, and muscle impairment remain largely inferential.
   We now explicitly frame this axis as a biologically plausible, hypothesis-driven model supported by converging evidence, while acknowledging that direct mechanistic proof remains to be established.

Comments from the editorial Office:

1. We notice that you may have cited your own or your co-authors' 15 published papers and the self-citation rate is higher than 20%. We kindly suggest that you reduce the self-citations or increase some other citations. You can find detailed markers in the attachment. Thanks for your cooperation.

   We had kept the references to the possible minimum, but since our self citation is unavoidable, we decided to expand the number of references for several points of the manuscript. We hope this will be an acceptable reduction.

2. We noticed that the backmatter section of your manuscript is incomplete. We would appreciate it if you could make the necessary revisions based on our comments in the attachment.

   We completed all matters indicated in the backmatter section. Thank you for pointing this out to us.

SIGNED: Roberto Paganelli, M.D. – corresponding author (for all co-authors).