**Manuscript ID number:**

**522862**

**Title of paper:**

**Frailty in Chronic Obstructive Pulmonary Disease: Clinical Significance, Diagnostic Approaches, Biomarkers, and Strategies for Prevention and Management**

**Editorial Corrections:**

1. **Title page: Please update your author list and affiliation details as follows:**

Author List first (all authors names as you wish to be published)

Then list the author affiliations underneath (at least one affiliation for each author in the following format:

Department, Institution, City, State (if applicable), Country) these should not include the email address, street address or

position/title of the author. Please use a numerical or symbol indicator before the affiliation and include the same indicator next to all the authors in the author list who match the affiliation.

ORCIDs can be listed next to the authors name in a separate list. Please remove any duplicate title, author names and affiliations, correspondence address and keywords.

*Response*: Thank you for your valuable feedback. We have updated the title page according to your instructions. The author list has been reorganized as requested, with each author's affiliation properly indicated in the correct format. We have also ensured that the ORCIDs are listed separately, and any duplicates, including the title, author names, affiliations, correspondence address, and keywords, have been removed. We hope this updated format meets the journal's requirements.

1. **Author List: Please amend the following name in the author list, so that it matches what has been confirmed in our system:**

Rana Sherbaevna Salieva; Kunduzkhan Karimova; Shekerbubu Anarbekovna Dyikanova; Urmatbek M Tynaliev

*Response:* We have amended the author list to match the names as confirmed in your system: Rana Sherbaevna Salieva, Kunduzkhan Karimova, Shekerbubu Anarbekovna Dyikanova, and Urmatbek M Tynaliev. Additionally, we have restructured the abstract into a single unstructured paragraph, as per your suggestion. We hope these adjustments meet the requirements and are grateful for your guidance.

1. **Abstract Structure: Unstructured abstracts are presented in one paragraph please.**

*Response:* We have revised the abstract to present it in a single unstructured paragraph as requested. We hope this format now aligns with your expectations.

1. **Response Letter:**

**A Response to Reviewers letter is required upon resubmission.**

We require every comment by the reviewers to be addressed by the authors. Please note, if you feel that some of the reviewer comments will not add value to your manuscript, you do not have to make those particular changes. You may instead respond to the comment in your letter, explaining why you do not agree with or have not made the suggested changes.

Please indicate where in your revised manuscript the changes (as applicable) can be seen. The response letter is used by the Editor to make a decision on whether to accept the manuscript, and so it is vital that every comment is responded to.

Please ensure copies of all figures/tables/graphical abstracts/supplementary material are provided with the revised manuscript, even if these are not altered during the revisions so we can ensure we have the most up to date file for each.

We cannot accept manuscript files that contain colored text/highlighting/background infill, underlined changes, or strikethrough text. Please ensure your manuscript is clean and free from any sort of background or text coloring when resubmitting.

*Response:* We sincerely appreciate the time and effort the reviewers have dedicated to evaluating our manuscript. We have thoroughly addressed all the comments and suggestions provided, and we believe that the revised version of the manuscript has been significantly improved. A point-by-point response to each reviewer comment is provided in the "Reviewer Comment Response" section. Thank you once again for your valuable feedback and guidance in enhancing our manuscript.

**Editor Comments:**

The aim of this manuscript was to examine frailty in COPD, focusing on clinical implications, assessment methods, biomarkers, and management strategies. The manuscript is well written and a topic of great importance in the care of COPD patients. I also wish to congratulate the reviewers who have done a stellar job highlighting areas for improvement. Should the authors decide to undertake major revisions, all of the reviewers comments should be addressed. Furthermore, I personally would like to see a methods section, detailing the method of search for manuscripts referenced in this report. Please refer to published guidelines for systematic reviews. Some of the details I would like to see are; databases that were searched, inclusion, and exclusion criteria, and number of references reviewed versus number used.

**Dear Editor,**

Thank you for your thoughtful feedback and for acknowledging the importance of our manuscript on frailty in COPD. We appreciate the constructive comments provided by both you and the reviewers, which have been invaluable in enhancing the clarity and quality of our work.

We appreciate your suggestion regarding the inclusion of a more detailed methodology. In response, we have now incorporated a dedicated section titled **“Search Methods and Selection Criteria”** in the revised manuscript. This section outlines the narrative review approach employed, specifies the databases searched (PubMed, Scopus, and Embase), and clearly states the inclusion and exclusion criteria applied. We have also indicated the total number of articles screened (approximately 240) and the number ultimately included in the final manuscript (123). We ensured that the revised manuscript is in line with your suggestions and is as comprehensive and impactful as possible.

**Reviewer Comments Response**

**Reviewer 1**

**Title & Abstract**

1. In your view, how effectively does the title and abstract capture the content and focus of the manuscript?

**Strengths:**

The title is clear and effectively conveys the main focus of the article.

It covers essential aspects of frailty in COPD, including clinical significance, diagnosis, biomarkers, and management strategies.

Provides a clear and structured overview of the article.

Defines frailty and its relationship with COPD.

Highlights the clinical relevance of the topic and proposes multidisciplinary solutions.

**Suggestions for Improvement:**

1. **The title could be more concise while maintaining specificity. For example: Frailty in COPD: Clinical Impact, Diagnosis, Biomarkers, and Management Strategies.**

*Response:* We agree that a more concise and focused title enhances clarity and impact. Accordingly, we have revised the title to: *"Frailty in COPD: Clinical Impact, Diagnosis, Biomarkers, and Management Strategies."* We believe this revised version retains the specificity of the original while improving its conciseness, as recommended.

1. **Consider whether "Strategies for Prevention" is necessary, as prevention could be implicitly included in management.**

*Response:* We appreciate the reviewer’s insightful observation regarding the potential redundancy of "Strategies for Prevention" in the title. After careful consideration, we agree that prevention is indeed an integral part of comprehensive management. Therefore, to enhance clarity and avoid redundancy, we have removed **"Strategies for Prevention"** from the title. The revised title now reads: *"Frailty in COPD: Clinical Impact, Diagnosis, Biomarkers, and Management Strategies."*

1. **Avoid overly general phrases such as "emerging evidence highlights" without citing specific studies.**

*Response:* we have carefully reviewed the manuscript and revised such instances to include specific studies that support the statements made.

1. **The sentence "Biomarkers like Short-Chain Fatty Acids (SCFAs) and oxidative stress indicators present emerging opportunities for personalized interventions" could be more specific regarding the clinical applicability of these biomarkers.**

*Response:* We have updated the manuscript to further specify the clinical relevance of Short-Chain Fatty Acids (SCFAs) and oxidative stress indicators.

1. The final sentence could be strengthened with a more impactful statement about the necessity of integrating frailty assessment into COPD care.

*Response:* We have revised the sentence to make a more impactful statement regarding the importance of integrating frailty assessment into COPD care.

**2. Do you find the background and information provided adequate for understanding the research?**

**Strengths:**

Provides a clear context of COPD and its intersection with frailty.

Cites relevant and up-to-date sources.

Emphasizes the importance of early detection and multidisciplinary management.

**Suggestions for Improvement:**

1. Ensure that each major claim is supported by specific references.

*Response:* We have thoroughly reviewed the manuscript and added appropriate citations to support all major claims.

1. The statement "Frailty in COPD is associated with heightened exacerbation frequency, prolonged hospital stays, poor treatment response, and increased mortality" should be supported by quantitative data.

*Response:* We sincerely appreciate the reviewer’s suggestion to support the statement with quantitative data. In response, we have revised the sentence to include relevant quantitative findings from recent studies.

1. The introduction mentions several frailty assessment scales. It would be better to introduce them briefly here and expand on them in a dedicated section.

*Response:* we have expanded on these scales in a dedicated section later in the manuscript, where we provide a more detailed discussion of each tool's application, strengths, and limitations. They are described in the section “Assessment Tools for Frailty in COPD”

Review

1. ***Does the review present an unbiased summary of the current understanding of the topic?***

***Clinical Implications of Frailty in COPD***

**Strengths:**

The section correctly identifies the major impacts of frailty on COPD progression, including exacerbations, hospitalizations, and mortality.

It incorporates data from multiple studies, enhancing credibility.

Discusses the bidirectional relationship between frailty and mental health.

**Suggestions for Improvement:**

1. The discussion on the association between frailty, hospitalization rates, and mortality should include numerical statistics to provide a more concrete impact assessment.

*Response:* We have included relevant quantitative data from recent studies to provide a more concrete impact assessment. The revised section now includes specific statistics, such as “Frailty in COPD has been quantitatively linked to increased exacerbation frequency, with frail patients experiencing exacerbations 1.5 to 2 times more often than their non-frail counterparts.14 Frailty amplifies the likelihood of acute respiratory events due to impaired immune function and reduced reserve capacity.15 Studies show that frail COPD patients are more prone to anxiety and depression, which further impair their ability to manage the disease effectively.16-17 Studies have shown that frailty is associated with a 25% longer average hospital stay, a 40% higher risk of poor treatment response, and a 50% increase in 1-year mortality.18 Jia Luo et al. reported that the all-cause mortality risk was more than twofold higher in frail patients (HR = 2.54, 95% CI: 1.01-6.36) than non-frail patients.19”

1. **Expand on how social determinants of health influence frailty in COPD patients.**

*Response:* we have included a more detailed discussion of how factors such as socioeconomic status, education, access to healthcare, housing stability, and social support networks contribute to the development and progression of frailty in COPD patients.

1. Consider adding a subsection discussing the economic burden of frailty in COPD, including healthcare costs and resource utilization.

*Response:* We greatly appreciate the reviewer’s suggestion to include a subsection discussing the economic burden of frailty in COPD, including healthcare costs and resource utilization. While we recognize the importance of this issue, we have chosen not to include a dedicated subsection on economic burden at this stage. Our focus in this manuscript is primarily on the clinical implications of frailty in COPD, and we believe that incorporating an economic discussion could shift the focus of the paper beyond its intended scope.

**Assessment Tools for Frailty in COPD**

Strengths:

Provides an in-depth review of different frailty assessment tools, including functional tests and clinical indices.

Discusses the limitations of each tool, which enhances critical analysis.

**Suggestions for Improvement:**

1. *The comparison table of frailty assessment tools is valuable but could be expanded to include additional tools such as the Groningen Frailty Indicator (GFI).*

*Response:* We thank the reviewer for the insightful suggestion to include the Groningen Frailty Indicator (GFI) in the comparison table of frailty assessment tools. However, after an extensive literature search, we were unable to identify studies that specifically evaluate the GFI in the context of COPD-related outcomes such as exacerbation risk or mortality.

1. *The section could benefit from a discussion on the limitations of self-reported tools versus objective clinical measures.*

*Response:* We provided a balanced discussion on how self-reported tools, while valuable for screening and assessing patient perceptions, may be subject to bias and inaccuracies.

1. *It would be helpful to include insights into how frailty assessment tools have been validated specifically in COPD populations.*

*Response*: We expanded the manuscript to include a discussion on the validation of these tools in COPD patients. We highlighted key studies that have evaluated the reliability and predictive value of frailty assessment tools in this population, ensuring that readers understand the tools' applicability and limitations within the context of COPD*.*

**Biomarkers in Frailty and COPD**

**Strengths:**

The section comprehensively lists inflammatory, oxidative stress, and metabolic biomarkers.

It highlights potential emerging biomarkers such as SCFAs.

Suggestions for Improvement:

1. Provide more detail on the clinical utility and reliability of each biomarker in assessing frailty in COPD.

Response: We have revised the manuscript to provide additional information on each biomarker discussed, including their proposed mechanisms, diagnostic value, and evidence from clinical studies supporting their use.

1. Discuss the potential integration of biomarker data with frailty assessment scales to improve diagnosis and prognosis.

*Response:* we have added a discussion on the potential integration of biomarker data with established frailty assessment scales. This integration may enhance the accuracy and sensitivity of frailty diagnosis in COPD by combining objective biological indicators with functional and clinical assessments.

1. Consider addressing potential confounding factors that may influence biomarker levels, such as age, comorbidities, and medication use.

*Response:* We appreciate the reviewer’s thoughtful suggestion regarding the inclusion of potential confounding factors such as age, comorbidities, and medication use, which indeed may influence biomarker levels. However, we respectfully note that a detailed exploration of these variables—while undoubtedly relevant—would significantly expand the volume of the manuscript beyond the limits set by the journal’s word count and reference restrictions.

**Strategies for Prevention and Management of Frailty in COPD**

**Strengths:**

Discusses a multidisciplinary approach that includes nutritional support, exercise, and psychological interventions

Highlights the role of pulmonary rehabilitation and resistance training in mitigating frailty.

**Suggestions for Improvement:**

1. The section on nutritional interventions should specify the recommended protein intake for frail COPD patients.

Response: We have revised the section on nutritional interventions to specify the recommended protein intake for frail COPD patients.

1. *Discuss potential pharmacological approaches under investigation for frailty in COPD, such as anti-inflammatory drugs or anabolic agents.*

*Response:* We appreciate the reviewer’s interest in emerging pharmacological strategies for frailty management in COPD, such as anti-inflammatory or anabolic agents. However, we respectfully note that current evidence on these therapies remains preliminary, fragmented, and largely extrapolated from non-COPD populations, making it difficult to provide a focused or evidence-based discussion within the scope of our review.

1. *Expand on the role of digital health interventions, such as tele-rehabilitation and wearable technology, in frailty management.*

*Response:* We appreciate the reviewer’s suggestion to expand on the role of digital health interventions such as tele-rehabilitation and wearable technology in frailty management. While we acknowledge the increasing relevance of digital tools in chronic disease care, we have opted not to include a detailed discussion in this manuscript. Our primary focus is on clinically established and widely accessible interventions for frailty in COPD. Many digital health solutions, particularly wearable technologies and tele-rehabilitation platforms, remain limited in availability, especially in low-resource settings, and lack consistent validation in frail COPD populations. We believe that a more in-depth exploration of digital interventions would be better suited for a separate review specifically focused on technological innovations in COPD care. However, we have briefly acknowledged their emerging role to reflect ongoing developments in the field. Consider adding a section on patient adherence and barriers to implementing frailty interventions in clinical practice.

**Conclusion**

**4. Does the conclusion provide a clear summary of the main points?**

**Strengths:**

Summarizes the key points of the article effectively.

Emphasizes the importance of an integrated, multidisciplinary approach.

Suggestions for Improvement:

1. *The conclusion should include a stronger statement about the necessity for further research.*

*Response:* we have revised the conclusion to include a stronger and more explicit statement emphasizing the necessity for further research.

1. *Avoid excessive repetition of previously stated information.*

*Response:* We appreciate the reviewer’s valuable feedback regarding the repetition of previously stated information. In response, we have carefully reviewed the manuscript and removed or consolidated any redundant statements.

1. *The final sentence could be more impactful by stressing the urgency of implementing frailty detection and management strategies in COPD care.*

*Response:* we have revised the final sentence to emphasize the urgency of implementing frailty detection and management strategies in COPD care.

**Figures & Tables**

5. If the author has provided figures and tables are the figures and tables clear and legible? Are the figures free from unnecessary modification?

**Strengths:**

The inclusion of tables summarizing assessment tools and biomarkers is valuable.

**Suggestions for Improvement:**

1. *Ensure that all figures are of high quality and contain legible text.*

*Response:* The text in each figure has been made legible, and we have improved the resolution where necessary to enhance clarity.

1. *Consider adding flowcharts to illustrate management strategies or interactions between frailty, COPD, and systemic inflammation.*

*Response:* We appreciate the reviewer’s suggestion to include flowcharts to illustrate management strategies and the interactions between frailty, COPD, and systemic inflammation. While we acknowledge the value of visual aids in simplifying complex concepts, we have chosen not to include flowcharts in this manuscript. Our primary objective is to provide a comprehensive, evidence-based narrative on frailty and COPD, and we believe that the textual explanations are sufficient to convey the necessary information. Moreover, the addition of flowcharts could detract from the detailed analysis and discussion we aim to maintain.

1. *In the biomarker table, add a column indicating the clinical applicability and diagnostic accuracy of each biomarker.*

*Response:* we have updated the table to include this additional column, as well you recommended.

**In your view has the manuscript or study -**

6a. Raised any ethical concerns?

Yes

6b. Is the statistical analysis appropriate to the research?

NA

6c. Are the references relevant to the study?

Yes

6d. Are the references in the correct style?

Yes

7. Do you have concerns regarding similarities to other articles published by the same authors or any other concerns?

None

Competing interest

8. Do any of the authors' competing interests raise concerns about the validity of the study i.e. have the authors' competing interests created a bias in the reporting of the results and conclusions?

None

**Recommendations to the Editor**

**Additional comments**

**Dear Authors,**

I appreciate the opportunity to review your manuscript, Frailty in Chronic Obstructive Pulmonary Disease: Clinical

Significance, Diagnostic Approaches, Biomarkers, and Strategies for Prevention and Management. Your work addresses an important and timely topic in the field of COPD and frailty, compiling a comprehensive review of relevant literature. The detailed discussion of assessment tools, biomarkers, and management strategies highlights the growing need for an integrated approach to frailty in COPD care.

Overall, the manuscript presents a well-structured and informative review. However, I have provided several recommendations to enhance its clarity, rigor, and clinical relevance. I suggest major revisions, particularly in the following areas:

Strengthening the discussion by incorporating more quantitative data and specific references to support key claims.

Improving the presentation of assessment tools and biomarkers, including a clearer discussion of their clinical applicability and limitations.

Enhancing the readability and structure of certain sections for better coherence and flow.

Expanding the discussion on emerging biomarkers and therapeutic strategies, as well as addressing potential limitations of the current literature.

My detailed comments are outlined in the review report, providing specific suggestions for each section of the manuscript.

These recommendations aim to ensure that your work reaches its highest potential and maximizes its impact in the field.

Please do not hesitate to reach out if any clarification is needed. I look forward to seeing the revised version of your manuscript and appreciate your efforts in advancing research on this critical topic.

**Response to Reviewer Comments**

We would like to thank the reviewer for the thoughtful and constructive feedback on our manuscript, "Frailty in Chronic Obstructive Pulmonary Disease: Clinical Significance, Diagnostic Approaches, Biomarkers, and Strategies for Prevention and Management." We are grateful for the opportunity to improve our work based on your valuable recommendations. We appreciate the reviewer’s detailed comments, which have been invaluable in strengthening the manuscript. We believe the revisions made in response to your feedback have significantly improved the quality and clinical relevance of the manuscript.

Thank you again for your thoughtful review. We look forward to your continued feedback.

**Reviewer 2**

**Title & Abstract**

1. In your view, how effectively does the title and abstract capture the content and focus of the manuscript?

1. The title effectively captures the content and focus of the manuscript. It would be preferable to also state the type of paper (narrative literature review).

*Response:* We appreciate the reviewer’s feedback on the title. However, we respectfully disagree with the suggestion to explicitly state the type of paper (narrative literature review) in the title. We believe that the title, as currently phrased, effectively conveys the focus and scope of the manuscript without the need to categorize it as a narrative review. Including the type of paper in the title may limit its broad appeal and may not be necessary, as readers can ascertain the nature of the paper through the content and structure of the introduction and methods sections. We feel the title is concise and informative as it stands, providing a clear sense of the paper’s topic while maintaining a broad, accessible appeal.

2. *The type and aim of the paper should be preferably clarified within the first two paragraphs of the abstract, as opposed to the last paragraph in the current manuscript form.*

*Response:* We thank the reviewer for this helpful suggestion. In response, we have revised the abstract to clarify the type and aim of the paper within the first two paragraphs, as recommended.

1. *The role of the proposed biomarkers for frailty assessment has not been validated in this context, therefore the authors should downtone their statements, making clear that these are "proposed", "suggested", or "potentially" useful in this context.*

*Response:* We thank the reviewer for their insightful comment. In response, we have revised the relevant sections of the manuscript to ensure that the role of the biomarkers in frailty assessment is clearly presented as proposed and not yet validated in this specific context.

**2. Do you find the background and information provided adequate for understanding the research?**

*2.1 The Introduction in its current form summarises the information provided in the rest of the paper. Instead, it should present the estimated prevalence of frailty, compared to the general population, elaborate on its potential relevance for younger people with COPD (doi.org/10.1136/bmjresp-2022-001314), and how frailty has emerged as an independent factor for holistic patient assessment.*

*Response:* We have thoroughly revised the Introduction to avoid repetition and enhance its relevance and clarity. We have now included data on the estimated prevalence of frailty in COPD patients compared to the general older population and highlighted the importance of recognizing frailty even in younger individuals with COPD. Additionally, we elaborated on the evolving understanding of frailty as an independent factor in the holistic assessment of COPD patients. The cited study (doi.org/10.1136/bmjresp-2022-001314) has also been incorporated to support these points.

*2.2 The statement that frailty "affects up to 50% of COPD patients" might not be accurate considering the higher rates captured in some studies (doi: 10.1038/s41533-022-00324-5, doi:10.1186/s12890-023-02454-z) and the authors should discuss the wide range of prevalence based on the tools used for frailty assessment in individual studies.*

*Response:* We have revised the manuscript to present a broader range of frailty prevalence reported in the literature, highlighting the variability based on the frailty assessment tools used and study populations. We now cite the studies mentioned (doi: 10.1038/s41533-022-00324-5, doi:10.1186/s12890-023-02454-z) and clarify that the prevalence of frailty in COPD patients ranges widely—from 20% to over 60%—depending on the criteria and methodology applied.

*Revised manuscript text:* “Frailty is a common comorbidity in COPD, with reported prevalence ranging widely from approximately 10% to over 70%, depending on the population studied and the frailty assessment tool used. 6-7”

*2.3 The authors should also introduce the two main classifications of frailty (deficit model vs phenotype model).*

*Response:* In the revised manuscript, we have now introduced the two primary conceptual models of frailty - the deficit accumulation model and the phenotype model - early in the Introduction section.

**Review**

***3. Does the review present an unbiased summary of the current understanding of the topic?***

*3.1 To enhance comprehensiveness, frailty assessment tools would preferably be discussed prior to the section regarding clinical implications.*

*Response:* We appreciate the reviewer’s suggestion regarding the organization of the manuscript. While we agree that an earlier discussion of frailty assessment tools could offer foundational context, we deliberately chose to present these tools after discussing the clinical implications to maintain a clinically driven narrative. Our intention was to first engage the reader with the practical relevance of frailty in COPD and then provide an in-depth overview of how it is assessed. This structure aligns with our goal of appealing to a clinical audience, who may benefit from understanding “why” frailty matters before exploring “how” it is measured.

*3.2 The abbreviations of these tools should be explained prior to the first time they appear in the main text.*

*Response:* We have now revised the manuscript to ensure that all abbreviations of the frailty assessment tools are explained the first time they appear in the main text.

*3.3 The authors should also include further tools that have been used in the literature to quantify frailty (****Table 2*** *doi: 10.1038/s41533-022-00324-5) and potentially discuss their limitations.*

*Response:* We have removed the table 2 according to your comment on *Figures & Tables* section.

3.4 *The presentation of breathlessness tools (mMRC) among the frailty assessment tools is perplexing.*

Response: Thank you for your insightful comment. We agree that the inclusion of breathlessness tools, such as the mMRC, alongside frailty assessment tools may cause confusion. In response, we have revised the manuscript and removed this concept.

*3.5 The authors should correct inaccuracies, such as that "breathlessness is evaluated via the 6MWT".*

*Response:* In response, we have revised the manuscript and removed this concept.

*3.6. The authors should further explain why they chose to present comorbidity tools as measures of frailty.*

*Response:* Thank you for your thoughtful comment. We recognize that comorbidities are not typically classified as frailty measures, but they play a critical role in the frailty process, particularly in COPD patients. Comorbid conditions such as cardiovascular disease, diabetes, and muscle wasting significantly contribute to the frailty phenotype by exacerbating physical and cognitive decline. Therefore, we included comorbidity tools to highlight their relevance in the multifaceted nature of frailty, as they help to assess the burden of disease that impacts the overall health status of COPD patients.

3.7 *Instead of analysing sarcopenia tools, briefly mentioning them would be sufficient considering the main topic of the paper.*

*Response:* We agree that the focus of the paper should remain on the broader concept of frailty rather than an in-depth analysis of sarcopenia-specific tools. In response, we have revised the manuscript to briefly mention sarcopenia tools, providing a concise overview without delving into detailed analysis.

*3.8 The section "Clinical Implications" should importantly highlight whether adverse outcomes present an independent association with frailty according to research papers.*

We agree that emphasizing the independent association between frailty and adverse outcomes is crucial for reinforcing the clinical relevance of frailty in COPD. In response to your suggestion, we have revised the "Clinical Implications" section to clearly highlight findings from research papers that demonstrate frailty's independent association with adverse outcomes such as increased hospitalizations, mortality, and poor treatment responses.

3.9 *Further important work on this area should be discussed and cited (doi.org/10.2147/COPD.S444580https://doi.org/10.2147/COPD.S444580, doi.org/10.1136/bmjresp-2022-001314).*

*Response:* Thank you for bringing these valuable references to our attention. We agree that these studies provide important insights into the relationship between frailty and COPD and included to our review.

*3.10 As the biomarkers presented have not been associated with frailty, the title of the section is misleading, it should instead read as "biomarkers in copd". The authors should shorten this section, in eg one paragraph, as it is not directly associated with frailty.*

*Response*: We thank the reviewer for the insightful comment. In response, we have revised the section title to “Association Between Systemic Biomarkers and Frailty in COPD” to more accurately reflect the content and its relevance to the central theme of the review. While we acknowledge that large-scale studies directly linking systemic biomarkers to frailty in COPD remain limited, emerging evidence from smaller studies suggests potential correlations - particularly with inflammatory and endocrine markers.

**Conclusion**

4. Does the conclusion provide a clear summary of the main points?

4.1 *The conclusion could be improved to concisely highlight the main points, instead of repeating the text information.*

*Response:* *We have revised the conclusion to make it more concise while still effectively highlighting the essential points discussed throughout the paper.*

**Figures & Tables**

5. If the author has provided figures and tables are the figures and tables clear and legible?

Are the figures free from unnecessary modification?

Clear and legible tables provided.

Table 3 should clarify that all biomarkers presented and their "significance in frailty" are only "suggested" or "proposed" (as opposed to directly relevant to frailty).

Table 2 might be redundant.

**In your view has the manuscript or study -**

6a. Raised any ethical concerns?

No. None related

6b. Is the statistical analysis appropriate to the research?

NA

6c. Are the references relevant to the study?

Yes

6d. Are the references in the correct style?

Yes

7. Do you have concerns regarding similarities to other articles published by the same authors or any other concerns?

No such concerns.

Competing interest

8. Do any of the authors' competing interests raise concerns about the validity of the study i.e. have the authors' competing interests created a bias in the reporting of the results and conclusions?

None declared.

Recommendations to the Editor

Additional comments

NA