

Peer Review File

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Reviewer A

Comment 1: My main concerns with this manuscript are that the authors aim to discuss something that is somewhat obvious to readers in the field, but I do not think they are able to provide enough novel or substantive recommendations on how care should be modified to make this an interesting article.

Reply: Thank you for a detailed review of our manuscript. We aimed to summarize the key concepts of frailty, sarcopenia and the interaction of cognitive-physical function. The interplay of cognitive-physical function is an emerging concept that is important to highlight in the ILD population. In order to highlight the key recommendations, we have added a clinical implications section on how the content of this review may impact clinical care.

Comment 2: Introduction could be significantly strengthened -- there are areas that are repetitive, so would work on tightening the writing to avoid redundancy.

Reply: Thank you for this comment. We have reviewed our introduction section and have shortened it to ensure there is no redundancy.

Comment 3: The authors mention that frailty is common and associated with worse outcomes, but it is not clear that they propose specific interventions to address this.

Reply: The best interventions to address frailty among older healthy adults have not yet been fully defined, and the diversity of interventions and outcome measures makes this process challenging¹). Thus, interventions for ILD patients with frailty are yet to be fully established; however, we discuss several strategies to combat frailty through pulmonary rehabilitation and increasing physical activity.

References:

- 1) Macdonald SH, Travers J, Shé ÉN, Bailey J, Romero-Ortuno R, Keyes M, O'Shea D, Cooney MT. Primary care interventions to address physical frailty among community-dwelling adults aged 60 years or older: A meta-analysis. PLoS One. 2020 Feb 7;15(2):e0228821. doi: 10.1371/journal.pone.0228821. PMID: 32032375; PMCID: PMC7006935.

Comment 4: In the section on skeletal muscle: Some of this section seems repetitive. I also think that more distinction should be drawn between this and frailty -- should the section be renamed specifically sarcopenia?

Reply: Thank you for your comment. In accordance with the reviewer's comment, section 2.3 was deleted to avoid redundancy, and included into section 2.1. And, we emphasized this further and highlight that frailty encompasses other elements beyond skeletal muscle and physical function such as psycho-social function.

We added the above sentence in the 2.1. Limb muscle dysfunction and its associated risk factors.

(P 13, Line 270-273)

Original:

“Increased fatigue has an important impact on ADL and physical activity levels, independent of age and disease severity.”

Revised:

“Increased fatigue has an important impact on ADL and physical activity levels, independent of age and disease severity, and frailty encompasses other elements beyond skeletal muscle and physical function such as psycho-social function.”

Comment 5: Does exercise actually mitigate/improve sarcopenia or weakness? Oddly, reading this, I was still left with lack of clarity on the data supporting this.

Reply: Thank you for highlighting this important matter.

Several previous reports have shown that exercise, including resistance training, can improve sarcopenia in healthy older adults with sarcopenia. Exercise programs have the potential to support muscle function in older people with sarcopenia (149,150). Strength training has been shown to improve peripheral muscle strength in ILD patients. In accordance with the reviewer's comment, we added the above sentence in the 4.1 Whole body exercise section. (P 24, Line 508-513)

" Several previous reports have shown that exercise including resistance training actually improve sarcopenia in healthy older adults who have sarcopenia. Exercise programs have the potential to support muscle function in older people with sarcopenia (149, 150). The evidence for peripheral muscle strength improvement in ILD has only been investigated in several studies, but there have been notable improvements in quadriceps strength with pulmonary rehabilitation (151, 152). "

References:

149) Chen N, He X, Feng Y, et al: Effects of resistance training in healthy older people with sarcopenia: a systematic review and meta-analysis of randomized controlled trials. Eur Rev Aging Phys Act 2021; 18(1):23

150) Papadopoulou SK, Papadimitriou K, Voulgaridou G, et al: Exercise and Nutrition Impact on Osteoporosis and Sarcopenia-The Incidence of Osteosarcopenia: A Narrative Review. Nutrients 2021; 13(12)

151) Naz I, Ozalevli S, Ozkan S, et al: Efficacy of a Structured Exercise Program for Improving Functional Capacity and Quality of Life in Patients With Stage 3 and 4 Sarcoidosis: A RANDOMIZED CONTROLLED TRIAL. J Cardiopulm Rehabil Prev 2018; 38(2):124-130

152) Perez-Bogerd S, Wuyts W, Barbier V, et al: Short and long-term effects of pulmonary rehabilitation in interstitial lung diseases: a randomised controlled trial. Respir Res 2018; 19(1):182

Comment 6: How is section 2.3 different/distinct from preceding sarcopenia discussion?

Reply: Thank you for your comment. In accordance with the reviewer's comment, section 2.3 was deleted, and incorporated into section 2.1.

(P 12, Line 257-261, P 13, Line 262-265)

Original:

“Moreover, ILDs other than IPF are treated with systemic corticosteroids and immunosuppressive therapies (66, 67), which may contribute to skeletal muscle dysfunction.”

Revised:

“Moreover, ILDs other than IPF are treated with systemic corticosteroids and immunosuppressive therapies (63, 64), that can contribute to skeletal muscle dysfunction through various side effects. This is considered to occur due to increased muscle proteolysis and decreased protein synthesis (65, 66). which contributes to muscle atrophy, decreased muscle fiber size and corresponding skeletal muscle weakness (67-69). This can be increasingly exacerbated by long-term corticosteroid treatment in ILD patients (56). Corticosteroid treatment has been associated with skeletal muscle weakness, even in those

with mild dyspnea (70) highlighting the importance of early intervention in ILD through exercise and physical activity to counter skeletal muscle dysfunction.”

References:

- 56) Hanada M, Sakamoto N, Ishimatsu Y, et al: Effect of long-term treatment with corticosteroids on skeletal muscle strength, functional exercise capacity and health status in patients with interstitial lung disease. *Respirology* 2016; 21(6):1088-1093
- 63) Kim R, Meyer KC: Therapies for interstitial lung disease: past, present and future. *Ther Adv Respir Dis* 2008; 2(5):319-338
- 64) Vacchi C, Sebastiani M, Cassone G, et al: Therapeutic Options for the Treatment of Interstitial Lung Disease Related to Connective Tissue Diseases. A Narrative Review. *J Clin Med* 2020; 9(2)
- 65) Schakman O, Gilson H, Thissen JP: Mechanisms of glucocorticoid-induced myopathy. *J Endocrinol* 2008; 197(1):1-10
- 66) Schakman O, Kalista S, Barbé C, et al: Glucocorticoid-induced skeletal muscle atrophy. *Int J Biochem Cell Biol* 2013; 45(10):2163-2172
- 67) Dekhuijzen PN, Decramer M: Steroid-induced myopathy and its significance to respiratory disease: a known disease rediscovered. *Eur Respir J* 1992; 5(8):997-1003
- 68) Fournier M, Huang ZS, Li H, et al: Insulin-like growth factor I prevents corticosteroid-induced diaphragm muscle atrophy in emphysematous hamsters. *Am J Physiol Regul Integr Comp Physiol* 2003; 285(1):R34-43
- 69) Gupta A, Gupta Y: Glucocorticoid-induced myopathy: Pathophysiology, diagnosis, and treatment. *Indian J Endocrinol Metab* 2013; 17(5):913-916
- 70) Hanada M, Ishimatsu Y, Sakamoto N, et al: Corticosteroids are associated with reduced skeletal muscle function in interstitial lung disease patients with mild dyspnea. *Respir Med* 2020; 174:106184

Comment 7: There is repeated use of the word "furthermore," which is distracting.

Reply: Thank you for pointing this out. In accordance with the reviewer's comment, we decreased use of the word "furthermore," throughout the manuscript.

Comment 8: In the section on cognition, the authors discuss dual tasking, but when reading it, the direct connection to ILD was not so clear.

Reply: Thank you for your comments. We are not able to provide evidence of dual tasking in ILD patients because we are not aware of publications of this paradigm in this group of patients. However, the dual tasking experimental paradigm has been used extensively in older adults, other diseases, and to a lesser extent in patients with COPD. An Ovid Medline search provided 137 reviews on dual tasking, 1,972 articles that describe dual tasking in older adults and 7 papers in COPD patients. The dual task paradigm can detect whether simultaneous cognitive and physical tasks result in decrements in one or both activities. It appears to be a more sensitive indication of cognitive interference or exceeding cognitive capacity during physical tasks than screening tools such as the Mini mental state examination (MMSE). Due to the extensive application of dual tasking in older adults and more recent use in COPD patients, we believe that it might be a very useful tool to examine and provide insight into cognitive interference with motor control during physical activities.

Comment 9: Exercise training: in section 4.2, the term "IMT" was used without preceding definition.

Reply: Thank-you for noting this issue. In accordance with the reviewer's comment, we have revised this term to define the abbreviation at its first mention - inspiratory muscle training (IMT)

(P 25, Line 535-537)

Original:

“Evidence that IMT can improve dyspnea and mitigate functional aspects associated with ILD progression is limited by the paucity of well-designed studies.”

Revised:

“Evidence that inspiratory muscle training (IMT) can improve dyspnea and mitigate functional aspects associated with ILD progression is limited by the paucity of well-designed studies.”

Comment 10: Overall: the authors cite things but don't delve into the specifics of what this all means for ILD patients and what the real world implications / quality improvement lessons might be from this.

Reply: Thank you for this comment. We have added a clinical implications section to highlight the real-world implications from the review article.

Reviewer B

Comment: This narrative review summarizes key literature regarding rehabilitation for patients with ILD. The presentation of existing evidences is comprehensive, clear, succinct and organized. The author has also weaved in insights very applicable to routine clinical practice for this group of very vulnerable patients.

Importantly, the manuscript also points towards key areas lacking consensus within the scientific community e.g. sarcopenia definition and measurement, as well as future domains of research, especially the potential impact of integration of motor learning, dual tasking, and improving automaticity in rehabilitation.

In my humble opinion, the manuscript will serve as a very useful resource for clinicians interested in this field.

Reply: Thank you for your comments. We appreciate your review.

Reviewer C

Major comments

Comment 1: Introduction, line 75 "idiopathic" ILD

ILD of unknown cause has official term of IIP, so the author should use this name.

Reply: Thank you for highlighting this important matter. In accordance with the reviewer's comment, we changed the following sentence in the Introduction section.

(P 5, Line 89-90)

Original:

“It can also arise from unknown causes, known as "idiopathic" ILD.”

Revised:

“They can also arise from unknown causes, known as idiopathic interstitial pneumonias.”

Comment 2: Introduction, line 76 Often, ILD is a progressive, refractory lung disease.

Since the disease term, ILD includes reversible diseases such as COP, it should be noted that ILD with pulmonary fibrosis is treated and progressive.

Moreover, the author should note that IPF is the subtype with gravest prognosis among ILDs.

Reply: Thank you for your comment. In accordance with the reviewer's comment, we changed the following sentence in the Introduction section.

(P 5, Line 91-93)

Original:

"Often, ILD is a progressive, refractory lung disease. Its progression may take several clinical forms: rapid deterioration after diagnosis, acute respiratory decline due to exacerbation followed by a period of stability, or stability for a number of years."

Revised:

" The clinical course of the different interstitial lung diseases ranges from completely reversible to self-limiting to progressive and can be fatal despite optimal management. "

Comment 3: Result, section 4 (4. Exercise Training in Pulmonary Rehabilitation in ILD)

The mention of the evidence for pulmonary rehabilitation for ILD patients is insufficient. As the author referred in the present study, please clarify the results of the RCT, prospective, and retrospective studies of pulmonary rehabilitation for ILD, and discuss to what extent the effectiveness of pulmonary rehabilitation has been proven.

Reply: Thank you for highlighting this important matter and agree that this section could be further strengthened. The benefits of pulmonary rehabilitation were recently illustrated in a Cochrane review. In accordance with the reviewer's comment, we added the following paragraph in the 4.1 Whole body exercise section.

(P 23, Line 496-501, P 24, Line 502-504)

"Recently, the effect of pulmonary rehabilitation in ILD has been comprehensively reported in an updated Cochrane Review (142). This review summarized evidence from 21 studies, of which data from sixteen studies were synthesized in meta-analyses (356 participants undertook pulmonary rehabilitation and 319 were control participants). Improvements in functional exercise capacity, dyspnea and HRQL were significant. In particular, the 6MWD was a sensitive outcome and exceeded its clinical minimum important difference with a mean improvement of 40 meters 95% CI (33 to 47) in 585 ILD participants. Holland AE et al. (55) emphasized that this updated Cochrane Review reported benefits of pulmonary rehabilitation that persisted as long as 6 to 12 months."

References:

142) Dowman L, Hill CJ, Holland AE. Pulmonary rehabilitation for interstitial lung disease. Cochrane Database Syst Rev. 2014 Oct 6;(10):CD006322. doi:

10.1002/14651858.CD006322.pub3. Update in: Cochrane Database Syst Rev. 2021 Feb 1;2:CD006322. PMID: 25284270.

55) Holland AE. Physiotherapy management of interstitial lung disease. J Physiother. 2022 Jul;68(3):158-164. doi: 10.1016/j.jphys.2022.06.006. Epub 2022 Jun 23. PMID: 35753970.

Comment 4: The author stated that pulmonary rehabilitation has proved to improve long-term outcome of ILD patients on line 443. However, I consider that the evidence for this treatment appears to be mostly short-term outcome, with only a few reports of long-term outcome.

Reply: Certainly, short-term outcomes have been demonstrated, but there is limited scientific evidence regarding long-term effects of pulmonary rehabilitation in ILD. In accordance with the reviewer's comment, we changed the following sentence in the Introduction section.

(P 23, Line 492-496)

Original:

“It is an important therapeutic strategy because of its demonstrated, improved long-term outcomes for ILD patients irrespective of age”

Revised:

“It is an important therapeutic strategy because of its demonstrated, improved short-term outcomes for ILD patients irrespective of age, however, sustained benefits are less certain (145). Most studies report durations of 8 to 12 weeks but a couple of studies followed patients for 26 or 48 weeks (145).”

References:

145) Yohannes AM, Casaburi R, Dryden S, et al: The effectiveness of pulmonary rehabilitation on chronic obstructive pulmonary disease patients with concurrent presence of comorbid depression and anxiety. *Respir Med* 2022; 197:106850

Comment 5: Moreover, please discuss the effectiveness of pulmonary rehabilitation for dementia and depression that the authors have discuss in this review.

Reply: In accordance with the reviewer's comment, we added the below sentence in 4.3 Potential future directions in pulmonary rehabilitation section.

(P 27, Line 569-575)

" Generally, pulmonary rehabilitation improves comorbid depression and anxiety in chronic respiratory patients (145). However, the effectiveness of pulmonary rehabilitation for dementia has not been explicitly investigated. Moreover, often times clinical manifestations often associated with dementia are exclusion criteria (i.e. the ability to attend sessions on a regular basis). Although pulmonary rehabilitation has the potential to improve cognition or diminish cognitive interference, its impact on dementia remains unclear."

Reference:

145) Yohannes AM, Casaburi R, Dryden S, Hanania NA. The effectiveness of pulmonary rehabilitation on chronic obstructive pulmonary disease patients with concurrent presence of comorbid depression and anxiety. *Respir Med*. 2022 Jun;197:106850. doi: 10.1016/j.rmed.2022.106850. Epub 2022 Apr 9. PMID: 35427843.

Minor comments

Comment 6: Result, section 2 (Skeletal muscle limitations in ILD)

The order of subnumbers after 2 is incorrect.

Reply: Thank you for pointing out this issue. In accordance with the reviewer's comment, we have revised the order of numbering for the subsections.

Reviewer D

Comment: A warm thank you to the authors for conducting a comprehensive review on an area that needs research attention. I note with interest, in particular, the section on cognitive impairment in patients with ILD, its pathogenesis and impact on dyspnea.

Reply: Thank you for your comment. We appreciate your review.