**Author’s response to reviews**

**Title:** Prognostic value of cardiopulmonary exercise testing in patients with systemic sclerosis

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**Author’s response to reviews:**

Prof. Harrison W. Farber

In this revision Ewert et al have responded to the questions and suggestions raised by the Reviewers and Editors during the initial review. The authors have responded to these issues appropriately and have improved the manuscript - especially with the changing of the control group. That said, there are a few remaining points to clarify.

1) The authors have now compared to SSc-ILD patients to SSc-no-ILD patients. The authors should give further detail on how the parameters (CT/PFTs) were chosen o separate the two groups.

Answer:

“Thank you for this comment. The definition of limited or extended ILD is important for major aspects of our study, and we have tried to clarify this in the 3rd paragraph of the ‘Study design and participants’ section.

In preparing our study, we had discussed among the participating centers the slight variation in the published definitions of significant interstitial lung disease. These were, in detail:
Mukerjee D et al. [Ann Rheum Dis 2003;62:1088–92], who referred to MacDonald SLS et al. [Radiology 2001;221:600–605]. These studies defined ILD by grade 3 to 4 pulmonary fibrosis detected by HR-CT and by TLC <70 %predicted. However, MacDonald et al. excluded collagenoses in their study and this definition is therefore not strictly applicable.

Condliffe R et al. [Am J Respir Crit Care Med 2009;179:151–57] and similarly Chung L et al. [Chest 2010;138:1383–94] categorized collagenoses as “PH group 3“ if HR-CT showed moderate to severe fibrosis and FVC resp. TLC were <60 %predicted.

Goh NS et al. [Am J Respir Crit Care Med 2008;177:1248–54] and Launay D et al. [Chest 2011;140:1016-24] defined a limited pulmonary manifestation (ILD) if <20% of the parenchyma in HR-CT were involved and / or the FVC resp. TLC was ≥70 %.

The ACR/EULAR definition of SSc [van den Hoogen F et al. Arthritis Rheum 2013] reads in their table 2 “ILD: Pulmonary fibrosis on HRCT or chest radiograph, most pronounced in the basilar portions of the lungs”. Therefore, the participating centers of our study consented to apply the definition proposed by Goh NS et al. [16]. We have explained these criteria now more clearly and added the ACR/EULAR definition as a reference [15].

The paragraph now reads:

“Pulmonary manifestation was assessed by HR-CT and pulmonary function testing as defined by the American College of Rheumatology/European League Against Rheumatism criteria [15]. Parenchyma involvement <20% was considered to represent a limited manifestation. Extensive manifestation was defined as ≥20% parenchyma involvement. Patients with an uncertain extent of manifestation according to HR-CT were classified as extensive manifestation if forced vital capacity (FVC; as percentage of predicted [%predicted]) was <70% of normal [16].”

In the results section, paragraph “Subgroup with interstitial lung disease” a new sentence was added: “All 195 patients with interpretable HR-CT were included in the subgroup analysis of pulmonary manifestation; of these, 191 patients had a complete pulmonary function test.”

2) The comparisons in the subgroups with RHC are somewhat confusing. Although most clinical parameters and hemodynamics were worse in the RHC group (as would be expected), the CPET parameters were worse in the non-RHC group. Since the authors note that the centers used the CPET as a predictor of need for RHC, this disparity would suggest that the centers did not use the CPET appropriately in all cases or the CPET is not sensitive enough to be used for this purpose. Nor was there a difference in CPET metrics re prognosis. This does temper, to some degree, the prognostic value of CPET and the premise of the manuscript.

Answer:

“We are sorry for the confusing mistake that occurred when the new paragraph on RHC was added in revision 1. We erroneously switched the VE/VCO2-slope values for the RHC and non-RHC groups in the manuscript. The right numbers were always presented in supplementary table S1. These correctly show worse values for the RHC group in nearly all parameters: Maximum power (in Watts), Maximum power (%predicted) ,VO2@AT (% of peakVO2 predicted), peakVO2 (mL·min⁻¹), peakVO2
We have corrected this in the paragraph “Subgroup with right heart catheterization” and added the values of peakVO2 because this is the most commonly used parameter. The last sentence of this paragraph now reads:

“Most CPET parameters in the RHC group were worse compared with the non-RHC group (e.g. VE/VCO2-slope, 35 [IQR, 29–47] vs 29 (IQR, 26–33); peakVO2, 1087 (IQR, 824–1380) vs 1270 (IQR, 1097–1292) mL∙min⁻¹; both p<0.001; see supplementary table S1).”

By thoroughly checking table S1, we also discovered a missing unit for petCO2@AT and added “mmHg” in this line. Otherwise, supplementary table S1 is unchanged.

3) There are several places were grammar could be changed to improve flow and readability:
e.g. Right heart catheterization was performed according to the guidelines…
e.g. rather than "had more often a RHC" - more frequently underwent RHC

Answer:

“We have changed the relevant sentences in the tw paragraphs “Subgroup with right heart catheterization “ in the Methods and Results, and in the paragraph “Subgroup with interstitial lung disease”. In addition, we re-wrote the last sentence of the discussion (“Moreover, CPET can differentiate between…”) to avoid the repetition of “allow” in two sentences.

To improve flow and readability of the final version of the manuscript and the response letter, we again asked Dr Paul Overton (Beacon Medical Communications Ltd, Brighton, UK) for assistance, funded by the University of Greifswald.

Additional changes:

• The paragraph “funding” was deleted, because the funding was related to the control group.

• The supplemental tables are numbered in the order of mentioning, i.e. the numbers S1 and S3 have been exchanged.

Prof. Reda Girgis
the authors have made appropriate revisions.

Specific Comments:

1. In discussion , starting on line 34 of page 18, the sentence reading: "These improved parameters contrast with the fact that only one study actually proved a better survival in patients treated with the new immunosuppressive agents [53]" this study did not and no study that I am aware of suggests improved survival. Please delete or re-word this.
Answer:

“We are grateful for this correction, and agree that our interpretation of the cited study was incorrect. This study, by Prof. Volkmann et al., explains that “Both SLS I and II demonstrated that treatment with immunosuppression led to short-term improvements in surrogate measures of SSc-ILD outcomes…” (our italics). Because we have already cited the SLS studies [47], the previous reference [53] was deleted. The sentence now reads:

“These therapies have been shown to improve parameters of pulmonary function that are related to prognosis, such as DLCO, DLCO/FVC and TLC [45, 50, 51], but to date no study has actually demonstrated improved survival in patients treated with immunosuppressive agents.”

2. Next paragraph has RHK, instead of RHC

Answer:

“Thank you for the correction, we have changed our German abbreviation to ‘RHC’.”