Author’s response to reviews

Title: EFFECTIVENESS OF PULMONARY REHABILITATION IN PATIENTS WITH INTERSTITIAL LUNG DISEASE OF DIFFERENT ETIOLOGY: A MULTICENTER PROSPECTIVE STUDY

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Author’s response to reviews:

Dear Editors and Reviewers,

thank you for the thoughtful and constructive review of our paper. We have carefully read your comments and suggestions, and we have modified the manuscript accordingly.

Please find enclosed a point-by-point response.
While we hope that you will find the revised version of the manuscript acceptable for publication as an original article in “BMC Pulmonary Medicine”, we will be happy to respond to further outstanding comments and questions, should they occur.

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Reviewer 1, Nathan Sandbo

We thank the reviewer for the precise and thorough reviewing process of our work. While we have appreciated all of his comments, we still believe that our manuscript could help clinicians in reinforcing the knowledge on the effects of pulmonary rehabilitation when delivered to ILD patients.

Major comments

Comments to the Author

In this manuscript by Tonelli and colleagues, the authors undertook a prospective cohort study to examine the efficacy of pulmonary rehabilitation in patients with interstitial lung disease and seek to determine how specific ILD diagnoses and severity of disease is associated with response to this therapy. This was a multicenter (two centers) study, however, the cohort size was relatively small (41 patients). Most patients had IPF (63%). The authors' primary findings were that in the majority of patients with ILD participation in pulmonary rehab was associated with a positive response in 6MW distance. Secondly, they found that a low baseline 6MW distance was associated with greater improvement in 6MWD by the end of pulmonary rehabilitation. The authors did not identify any association of greater or lesser treatment response with specific ILD entities.

Overall, the authors rightly identified some of the questions that remain in the field vis-à-vis patient selection for participation in pulmonary rehabilitation; namely does illness severity or specific ILD diagnosis impact response to this therapy. However, it appears that their study was underpowered to answer these questions. It is unclear if the authors performed power calculations to try to estimate how many patients need to be included to see a difference in the stated endpoints.
More importantly, the authors have rightly cited several studies in their introduction that establish the efficacy of PR in IPF and a mixed population of ILDs. Additionally, Collard et al showed that low 6MW distances were associated with larger improvements on 6MW test. Thus, this study largely confirms the findings of previous studies, which of course, does have value. However, there is no additional conclusions provided from this study design that moves the field forward.

In summary, it does not appear that the study was sufficiently powered to meet its objectives, nor are there sufficiently new and impactful conclusions from this study to justify its publication in BMC Pulmonary Medicine at this time.

Answer to reviewer’s comments.

We thank the reviewer for his thoughtful review of our manuscript. As we stated in the introduction section (page 2, line 15) our study was designed with two different aims: the main objective was “to confirm the positive impact of rehabilitation in a population of patients with ILDs of different etiology” while the second was “to further investigate whether baseline exercise capacity, disease severity or ILD etiology might differently affect clinical outcomes following a standard PR course”. With reference to the major outcome we agree with the reviewer that several studies establish the efficacy of PR in IPF and a mixed population of ILDs. Nonetheless, the ultimate guidelines on diagnosis and management of Idiopathic Pulmonary Fibrosis (IPF) (Raghu G et al., Am J Respir Crit Care Med 2011) still provide a weak recommendation for PR in IPF, claiming for more evidence on the real achievable gain. For this reason we believe that a further confirm on the beneficial effects of pulmonary rehabilitation on functional performance and symptoms in patients with ILD might reinforce its clinical value and stress for a careful consideration in the whole management of these dramatic diseases. Having said that, we thank the reviewer for his comment as he gave us the chance to clarify the explorative nature of our study, that is even truer for the second objectives. As it was correctly mentioned we did not perform a sample size computation to estimate how many patients were needed to see a difference in the stated endpoints. Thus we have calculated the power expected by our study group for the primary outcome (changes from baseline in 6MWDT [meters] and SGRQ [total score]) indicating the minimum difference the sample is able to appreciate (a difference ≥3% from baseline for major outcomes). We have added this sentence to the statistical section: “The statistical power expected for the present study population was calculated with reference to the primary outcomes and the minimum difference appreciable by our sample was assessed at ≥3% of baseline values for major outcomes” (see also replay to comment 1 by reviewer #2). Furthermore a subsequent trial, whose sample size has been computed on the base of these assumptions, is ongoing. We have finally stated the need for a further study with stronger statistical design in the discussion section.

Minor comments

Comment 1

On page 3, line 6 - awkward sentence structure, please rephrase.
Answer to reviewer’s comment 1

We thank the reviewer for this comment. We rephrase the sentence as follows: “Consequently, as ILD progresses, the patient’s daily activities decline early following symptoms. This reduction in everyday performance begins even before that ventilatory limitation with functional impairment occurs”.

Reviewer 2, Fabiano di Marco

Tonelli R et al carried out a prospective study aimed at confirming the efficacy of rehabilitation in a population of patients with ILDs and investigating whether baseline exercise capacity, disease severity or ILD etiology might affect outcomes. The study is interesting, since the role of PR in ILD is still controversial, and patients' selection can be crucial; in general the paper is well done.

We thank the reviewer for the accurate and careful reviewing process of our manuscript. We appreciate all of his suggestions and we have tried to modify the manuscript accordingly.

Major comments

Comment 1

A "sample size" computation analysis is required. If, as I suspect, the number was not decided before the study, I suggest to include a comment in the "statistical analysis" chapter where to include the power expected by this number for the primary outcome of the study (i.e. the minimum difference this sample is able to appreciate).

Answer to reviewer’s comment 1

We thank the reviewer for this thoughtful comment that gave us the chance to clarify the explorative nature of our study. As he has correctly mentioned we did not perform a sample size computation to estimate how many patients were needed to see a difference in the specified endpoints. We have appreciated his suggestion to complete the statistical section with the calculation of the power expected by the analysis of our sample. In particular we have added the sentence: “The statistical power expected for the present study population was calculated with reference to the primary outcomes and the minimum difference appreciable by our sample was assessed at ≥3% of baseline values for major outcomes”. Moreover we have specified in the Discussion section the explorative nature of our study stating that “First of all this was a preliminary trial whose explorative nature resulted in the lack of a sample size computation analysis. A subsequent study with a sample size computed on the basis of the evidence provided by the present study is needed”.

Comment 2
Background: "In particular, the impaired level of gas exchange seems to be the major cause leading to exercise intolerance in these patients". Indeed, sometimes patients with ILD are limited by ventilation (I would add a comment on this).

Answer to reviewer’s comment 2

We accept the reviewer comment. We have modified the manuscript and we have added the following sentence: “Furthermore ILD patients experience greater physical and social limitations once ventilatory constraint has established, reducing their functional reserves”.

Comment 3

In table 1 I suggest to add information about smoking history, type of LTOT (during effort vs. continuous), PaO2, PaCO2 (if available), the diagnosis (not only IPF or not IPF).

Answer to reviewer’s comment 3

We thank the reviewer for his comment. We have modified table 1 and we have added the information as requested. Non IPF diagnoses were added in the text: “Among patients with ILD other than IPF, 8 had pulmonary fibrosis associated to connective tissue disease, 4 had chronic hypersensitivity pneumonitis, 2 had sarcoidosis and 1 had asbestos-related ILD”.

Comment 4

Table 2. The P values are relative to the changes as absolute or relative values?

Answer to reviewer’s comment 4

We accept the reviewer comment that gave us the opportunity to specify, in the caption of Table 2, that: “p value are referred to relative changes”.

Comment 5

I’m not sure Figure 1 is relevant for the reader.

Answer to reviewer’s comment 5

We thank the reviewer for his comment. Nonetheless we believe that a schematic algorithm of the study procedures might help the reader to better understand how the trial was conducted. Just in case, this could be considered as a supplement material to deliver online only (body document will be then modified accordingly).

Comment 6
Since endurance time is so far considered one of the most sensitive outcomes for exercise capacity, I suggest to add a new figure for the analysis of the correlation between changes in ET and FCV, DLCO, etc.

Answer to reviewer’s comment 6

We thank the reviewer for this comment. We have added a new figure (Figure 5) for the analysis of the correlation between changes in endurance time and etiology, baseline FCV, DLCO, GAP, power achieved during endurance test and distance covered at 6MWDT. We have also added coherent sentences in the text referring to this comparison: Abstract – “with the functional improvement at the 6MWDT (meters), at the incremental and endurance cyclo-ergometry (endurance time) and the HRQoL were assessed”. Main document, Statistical analyses—“Changes from baseline in 6MWDT (meters) and in Endurance Time (minutes) and SGRQ (total score) following PR were considered as indicators of improvement in functional capacity and HRQoL respectively (3,27)”. Results – “endurance time at cycle ergometer (Figure 5, panel F)” and “see also in Figure 3,4 and 5 panels A to E”. Caption of Figure 5 – “Figure 5. Correlation between baseline FVC (2A), DLCO (2B), GAP index (2C), ILD etiology (2D), power developed at endurance test (ET) (2E), distance covered at 6MWDT and change in Endurance Time after PR”.

Minor comments

Comment 1

Abstract: "with the functional improvement of and HRQoL were assessed" please, check this sentence.

Answer to reviewer’s comment 1

We thank the reviewer for this comment. We have checked the sentence and emended the manuscript accordingly.

Comment 2

I suggest to merge descriptive analysis and patients' stratification in a single "statistical analysis" chapter.

Answer to reviewer’s comment 2

We thank the reviewer for this comment. We have modified the manuscript accordingly.

Comment 3

The number of decimals for the different units should be wisely decided (e.g. two decimal for 6MWT distance are evidently not required, such as for watts, age, % of FEV1 and FVC, etc)
Answer to reviewer’s comment 3

We thank the reviewer for this comment. We have emended the manuscript accordingly.

Comment 4

Discussion "In our opinion, multiple aspects deserve attention and discussion." I think this sentence is redundant.

Answer to reviewer’s comment 4

We thank the reviewer for this comment. We believe that this sentence could give a more fluent connection between the introduction part of the discussion and the major points examined thereafter. We have thus modified the sentence to “Multiple aspects deserve discussion”.

Reviewer 3, Maroula Vasilopoulou

The research article by Tonelli et al. aimed to confirm the efficacy of rehabilitation in a population of patients with ILDs and to investigate whether baseline exercise capacity, disease severity or ILD etiology might affect outcomes. The manuscript is well written. Please find my major and minor considerations that need to be attended by the authors as indicated below.

We gratefully thank the reviewer for the precise, thoughtful and accurate review of our work. We have really appreciated all of her comments and we tried to improve the manuscript following her specific indication.

Specific major points

Comment 1

Introduction

A general comment is that authors provide an adequate introduction section. However, authors should emphasized at the introduction session about the type of pulmonary rehabilitation in these patients. Which are the evidence? Which is the gap? Interval, continuous and/or muscle training, comment on that.

Answer to reviewer’s comment 1

We thank the reviewer for this comment. We have modified the introduction trying to emphasize the type of pulmonary rehabilitation delivered to ILD patients reported to date in literature. In particular, we have added the following sentence: “consisting of tailored and supervised training on aerobic and resistance exercises, breathing techniques and education sessions focused on self-management of symptoms and physical activity promotion”. The current evidence is that people with ILD experience important exercise intolerance and a large symptom burden and that PR
programs including exercise training have beneficial effect on exercise capacity, symptoms and quality of life. We believe that the gap might be identified in two major points that we have tried to investigate. We have stated these concepts in the final part of the introduction section to clearly formulate the rationale for our study: “In summary 1) despite the beneficial effect of PR in ILD patients has been supported by a growing body of evidence, the ultimate IPF guidelines still provide a weak recommendation for PR and 2) the impact of disease severity and ILD etiology on PR outcomes remains not well understood”.

Comment 2

Line 6: which symptoms? Why the symptoms affects patients? Please comment on that.

Answer to reviewer’s comment 2

We thank the reviewer for her comment. We have specified the symptoms affecting ILD patients as disease progresses trying to link them with the reduction of functional performance. In particular we have added the following sentence: “Consequently, as ILD progresses, the patient’s daily activities decline early following symptoms (shortness of breath, tiredness, muscle fatigue). This reduction in everyday performance begins even before that ventilatory limitation with functional impairment occurs (3). Furthermore ILD patients experience greater physical and social limitations once ventilatory constraint has established, reducing their functional reserves”. We conclude that “due to the progressive exercise limitation, individual’s health-related quality of life (HRQoL) is markedly affected”.

Comment 3

Add Figure 1 at this session.

Answer to reviewer’s comment 3

We thank the reviewer for her suggestion that we have accepted. We have added Figure 1 to the Methods section.

Comment 4

Why you did not have a control group? Age-matched controls? Please clarify (this is a very important issue).

Answer to reviewer’s comment 4

We thank the reviewer for this comment. We agree that the lack of an age-matched control group should be indicated as a major limitation of our study. We have added this concept in the discussion section: “In addition, the lack of a control group could limit the likely significance of our findings, while …”.

Comment 5
FEV1 to be FEV1.

Answer to reviewer’s comment 5

We thank the reviewer for this comment. We have modified the manuscript accordingly.

Comment 6

Lines 29-34: Incremental exercise testing (1-min increments of 10 W) to a symptom-limited maximum was performed on an electronically braked ergometer for lower limbs pre-post PR. The patients were familiarized with the apparatus days prior to the test; they were encouraged to keep exercising for as long as possible while pedaling at 50 to 60 rpm and were instructed to maintain work levels until they reached a symptom-limit. An additional endurance cycle-ergometer test was performed at the 80% of peak load reached at the incremental test.

I am confused, you did an incremental and a constant test? If yes where is the results from the constant test? Please comment on that.

Answer to reviewer’s comment 6

We thank the reviewer for this comment and we are very sorry for this cut-and-paste mistake. Indeed, the sentence “An additional endurance cycle-ergometer test was performed at the 80% of peak load reached at the incremental test” was wrongly reported. We have thus removed this sentence from the revised manuscript.

Comment 7

SaO2, page 5: to be SaO2, but also you took from patient’s arterial oxygen saturation? Blood gases? Better to change that with SpO2?

Answer to reviewer’s comment 7

We thank the reviewer for this comment. We have emended the manuscript accordingly. We have added the blood gases values at baseline in Table 1.

Comment 8

Line 27, page 5, add reference (The educational topics included medication and oxygen use, nutrition, panic control and relaxation techniques, as well as psychosocial support and issues of palliation and/or end-of-life related to the disease progression).

Answer to reviewer’s comment 8

We thank the reviewer for this comment. We have added the appropriate reference in the new version. (ref #6, namely Nici L, Donner C, Wouters E, et al. American Thoracic
Comment 9

You must provide details about your pulmonary rehabilitation program (days/week of PR/intensity/type of exercise/muscle training/repetitions/leisure walking exercise at hospital/at home?). These may affect the explanation of your results. In my opinion this session need to be written again with more details, because your first aim is the confirmation of the efficacy of rehabilitation program in ILD patients.

Answer to reviewer’s comment 9

We thank the reviewer for this important comment. We agreed on the need for more details regarding our PR program. We have added the following sentences to better detail it: “The two centers involved provided a standardized similar and shared PR course as recommended (6,26). PR program consisted of: 6-hour/week individually exercise training with endurance training for upper and lower limbs, 2 session of breathing techniques lasting 30 minutes for four to five times per week and 3 sessions of group education per week. Exercise training consist of aerobic (treadmill, stationary bikes) and resistance training (light weights, resistance bands) and included supervised cycle and supported arm ergometry, and leisure walking. Breathing training consisted of breathing techniques (controlled and diaphragmatic breathing), pacing and energy conservation. Supplemental oxygen was delivered to maintain normal level of oxygen saturation. PR was tailored on the patient’s functional status and performance”.

Comment 10

STATISTICAL ANALYSES

You did power analysis? Based on which outcome? Please comment on that, although you mentioned to your limitation section about the limited size.

Answer to reviewer’s comment 10

We thank the reviewer for this thoughtful comment. Actually, we did not perform a sample size computation to estimate how many patients were needed to see a difference in the specified endpoints. We have completed the statistical section with the calculation of the power expected by the analysis of our sample. In particular we have added the sentence: “The statistical power expected for the present study population was calculated with reference to the primary outcomes and the minimum difference appreciable by our sample was assessed at ≥3% of baseline values for major outcomes”. (see also replay to comment 1 by reviewer #2). Moreover, we have specified in the Discussion section the explorative nature of our study stating that “First of all this was a preliminary trial whose explorative nature resulted in the lack of a sample size computation analysis. A subsequent study with a sample size computed on the basis of the evidence provided by the present study is needed”.

Comment 11

Results

Table 1 needs more information (for example SpO2, FEV1 and FVC in L, blood gases (only baseline measurements?), drug therapy, and comorbidities). Why the values are different in the results section and table 1 about GAP index?

Answer to reviewer’s comment 11

We thank the reviewer for this comment. We have implemented Table 1 with the available information and corrected the inconsistencies among GAP indices values.

Comment 12

FEV1 to be FEV1

Answer to reviewer’s comment 12

We thank the reviewer for this comment. We have modified the manuscript accordingly.

Comment 13

O2 to be O2

Answer to reviewer’s comment 13

We thank the reviewer for this comment. We have modified the manuscript accordingly.

Comment 14

There is a small amount of female patient, you consider this point at your analysis? Comment on that.

Answer to reviewer’s comment 14

We thank the reviewer for this interesting comment. We did not consider this point in our analysis as we have ascribed it to the predominance of IPF patients in the study population.

Comment 15

Table 2 Why the values are different in the results section and table 2? (6MWDT, endurance power developed during incremental). The data from the constant test?

Answer to reviewer’s comment 15
We thank the reviewer for this comment. We have corrected the Table 2 and the results section emending inconsistent data. With reference to the constant test see Answer to reviewer’s comment 7.

Comment 16

Figures 2 and 3, are not in high resolution, so it is very difficult to read (needs to be clearer).

Answer to reviewer’s comment 16

We thank the reviewer for this comment. We have re-designed the Figures in high resolution.

Comment 17

The discussion section is well written and authors have adequately discussed all currently published studies but in my opinion this session is too big.

What you mean about submaximal exercise capacity? What about the type of exercise during PR program? Please comment on that.

Answer to reviewer’s comment 17

We thank the reviewer for her comment that gave us the chance to explain that with "a submaximal exercise capacity" we intended the effort achieve during 6MWDT while with “exercise capacity at peak intensity” we meant the maximum effort produced during endurance test. With reference to the type of exercise during PR we have indicated them in details in the Methods section. With reference to the Discussion session we agree that it might seem too long. Notwithstanding we believe that such a detailed session could be appropriate to discuss all the possible considerations derivable from the results and the several limitations of our explorative study.

Minor points

Comment 1

Title

I proposed: Effectiveness of Pulmonary Rehabilitation in patients with Interstitial Lung Disease: a multicenter prospective study. Please provide a more concise title. Comment on my proposal.

Answer to reviewer’s comment 1

We thank the reviewer for this comment. We agree with the need for a more concise title. Thus, we were glad to accept the Reviewer’s suggestion and we have changed the title into “Effectiveness of Pulmonary Rehabilitation in patients with Interstitial Lung Disease of Different Etiology: a multicenter prospective study”.

Comment 2

Abstract

A general comment is that this section is adequately written. However authors should:

1. Re-phrase the sentence “Uncertainty still remains on how disease severity and/or etiology might impact on benefits” to be more understandable.

Answer to reviewer’s comment 2

We thank the reviewer for this comment. We have re-phrased the sentence in order to make it more understandable: “It is still unclear whether disease severity and/or etiology might impact on the reported benefits”.

Comment 3

2. Replace Materials and Methods with Methods only.

Answer to reviewer’s comment 3

We thank the reviewer for this comment. We have modified the manuscript accordingly.

Comment 4

3. Provide some keywords representing the main content of the article.

Answer to reviewer’s comment 4

We thank the reviewer for this comment. We have modified added some keywords: “Pulmonary Rehabilitation”, “Interstitial Lung Diseases”, “Endurance Test”, “Endurance Time”, “Functional Performance”.

Comment 5

References

Please update GOLD reference.

Answer to reviewer’s comment 5

We thank the reviewer for this comment. We have updated the indicated reference.

Reviewer 4, Heleen Demeyer
Based on 41 patients enrolled in a PR program, in 2 centers, the authors confirm the effectiveness of a PR program in ILD patients. The authors did not find a difference in effectiveness of the program between IPF (n=26) and non-IPF patients. Exercise capacity at baseline was negatively correlated with the gains in 6MWT and SGRQ.

I read with interest this manuscript, confirming the short-term effectiveness of a PR program in ILD patients. The authors did not provide a sample size calculation. The sample size seems small to make firm conclusions about the effectiveness of PR depending on the ILD etiology. In addition, the authors describe that patients followed either an in- or an outpatient PR program. It is not clear whether this difference is linked with the center of inclusion or whether both centers included patients in an in-and outpatient PR program. The authors do not compare patients (1) in the 2 centers and (2) the in-and outpatient program. This information is important, both for baseline characteristics and effectiveness of the PR program, to exclude these (center and program) as a possible confounder of the results.

We really thank the reviewer for the accurate and detailed review of our manuscript. We have gratefully appreciated all of her comments and we tried to improve the manuscript following her specific indication.

Major comments

Comment 1

A limitation of the present study is the lack of a control group. Because the results show that a low baseline is related to a greater improvement, this could be interpreted as a regression to the mean effect. The lack of a control group should be included as a limitation in the manuscript.

Answer to reviewer’s comment 1

We thank the reviewer for this suggestion with which we absolutely agree. We believe that the lack of control group should be indicated as a major limitation of our study. We have added this concept in the discussion section: “In addition, the lack of a control group could limit the likely significance of our findings, while…”.

Comment 2

30 patients were inpatient, 11 patients followed an outpatient rehabilitation program. Did the duration of the program and effectiveness differ between the in and outpatient program? I have the same question concerning the center of inclusion. These 2 variables should be tested as confounders of the associations. Please provide data comparing the in- and outpatient rehabilitation program (baseline characteristics (including % of IPF patients) and intervention effects).

Answer to reviewer’s comment 2
We thank the reviewer for this comment that we have much appreciated. We have performed a supplemental statistical analysis to investigate whether the duration of the program and effectiveness differ between the in- and out-patient program and center of inclusion. We found that in- and out-patients enrolled in both centers were comparable for all the assessed baseline characteristics. Moreover, we have shown that neither the setting (of PR) nor the center resulted in different effectiveness on all the measured outcomes. Therefore, we have modified the manuscript body text in order to clearly state these findings. In particular we have added the following sentences: Results – “Among patients who completed the program the number of rehabilitation sessions performed ranged from 26 to 32 and did not differ between in and outpatients” and “Baseline features were comparable with no statistically significant difference between patients enrolled in the two centers and involved in the in- and outpatient program (see Table 1)” and “being not influenced by PR setting and center of enrollment (see Figure 2)”;

Discussion – “delivered as in and outpatient setting”. Captions and legends – “Figure 2. Effect of PR setting and center of enrollment on PR effectiveness expressed in terms of relative change from baseline. Cycle dyspnea and leg fatigue were assessed at isotime. * Center A = Don Gnocchi” Institute, Firenze, Italy. ** Center B = Villa Pineta” Rehabilitation Hospital in Pavullo n/F, Modena, Italy”.

Just in case, this added part could be considered as a supplement material to deliver online only.

Comment 3

Did the authors perform a sample size calculation? The study is based on a rather small sample, with several different ILD etiologies and 2 different PR programs (in and outpatient). Therefore, the sample size could be a limitation.

Answer to reviewer’s comment 3

We thank the reviewer for her thoughtful comment. Actually we did not perform a sample size computation to estimate how many patients were needed to see a difference in the specified endpoints. We have completed the statistical section with the calculation of the power expected by the analysis of our sample. In particular we have added the sentence: “The statistical power expected for the present study population was calculated with reference to the primary outcomes and the minimum difference appreciable by our sample was assessed at ≥3% of baseline values for major outcomes” (see also reply to comment 1 by reviewer #2). Moreover, we have specified in the Discussion section the explorative nature of our study stating that “First of all this was a preliminary trial whose explorative nature resulted in the lack of a sample size computation analysis. A subsequent study with a sample size computed on the basis of the evidence provided by the present study is needed”.

Comment 4

The authors have chosen the change in 6MWD following PR as an indicator of improvement in functional capacity. Are the results similar when using endurance time, perhaps a more sensitive outcome after PR?
Answer to reviewer’s comment 4

We thank the reviewer for this interesting consideration with which we agree. We have conducted a supplemental analysis on this outcome. We have added a new figure (Figure 5) for the analysis of the correlation between changes in endurance time and etiology, baseline FCV, DLCO, GAP, power achieved during endurance test and distance covered at 6MWDT. We have also added the following sentences in the text referring to this comparison.

Abstract – “with the functional improvement at the 6MWDT (meters), at the incremental and endurance cyclo-ergometry (endurance time) and the HRQoL were assessed”.

Main document, Statistical analyses – “Changes from baseline in 6MWDT (meters) and in Endurance Time (minutes) and SGRQ (total score) following PR were considered as indicators of improvement in functional capacity and HRQoL respectively (3,27)” Results – “endurance time at cycle ergometer (Figure 5, panel F)” and “see also in Figure 3,4 and 5 panels A to E”. Caption of Figure 5 – “Figure 5. Correlation between baseline FVC (2A), DLCO (2B), GAP index (2C), ILD etiology (2D), power developed at endurance test (ET) (2E), distance covered at 6MWDT and change in Endurance Time after PR”.

Comment 5

Why did the authors use in the analyses the % change of baseline and not the absolute change in exercise capacity and health status?

Answer to reviewer’s comment 5

We thank the reviewer for this comment. We have chosen the relative change because, despite the study population showed an average mild to moderate impairment of respiratory and exercise capacity, it seemed more appropriate to refer the changes obtained following PR to the each peculiar baseline values.

Comment 6

Please include the % of patients achieving the MID in 6MWD and SGRQ. Does this differ between IPF/non IPF? Baseline characteristics?

Answer to reviewer’s comment 6

We thank the reviewer for this comment. We have added the information requested in the Results section: “The minimal clinically important difference (MCID) in 6MWD and SGRQ was achieved by 75.6% and 80.3% of patients respectively. Nor IPF diagnosis neither other baseline features influenced the achievement of the MCID in the major outcomes”.

Comment 7
It would be interesting to include tertiles of baseline characteristics and report the absolute change in 6MWD / SGRQ / endurance time per tertile. This would be interesting to add to the correlations.

Answer to reviewer’s comment 7

We thank the reviewer for this comment. It would be undoubtfully interesting to report the absolute change in 6MWD / SGRQ / endurance time per tertile. Unfortunately the limited sample size does not allow an appropriate analysis for tertiles. We will consider this suggestion for the further trials.

Minor comments

Comment 1

The duration and frequency of the PR program is missing. The authors indicate that the PR program had at least 24 sessions. Please include duration, frequency and range (min-max) of attended sessions.

Answer to reviewer’s comment 1

We thank the reviewer for this comment that gave us the chance to indicate duration, frequency and range (min-max) of attended rehabilitation sessions. We have added the following sentences: Methods – “and was conducted 6 days a week, once daily the first week and twice daily thereafter. Each rehabilitation session lasted at least 3 hours”. Results – “One subject with hypersensitivity pneumonitis (non IPF) dropped out as he developed bacterial pneumonia in hospital, once he had completed 20 rehabilitation sessions. Among patients who completed the program the number of rehabilitation sessions performed ranged from 26 to 32”.

Comment 2

Was dyspnea measured every minute during the endurance test? This information is lacking in the methods. In the introduction the authors describe that a reduction in dyspnea would be a main aim of PR. It would be interesting to give more details about iso-time dyspnea in the results (comparison IPF - non-IPF, relation with baseline characteristics).

Answer to reviewer’s comment 2

We thank the reviewer for this comment. We completed the method section as indicated: “The perceptions of dyspnea and limb efforts were determined at the beginning and at the end of 6MWD and every 2 minutes during cycle-ergometry using the modified Borg scale”. We agree with the reviewer that more information about correlation between iso-time dyspnea and etiology or baseline characteristics would have been interesting. In the methods section we stated that: “Changes from baseline in 6MWDT (meters) and in Endurance Time (minutes) and SGRQ (total score) following PR were considered as indicators of improvement in functional capacity (3,27)
and HRQoL respectively”. As these were the pre-specified outcomes of this explorative study, we did not consider reduction in iso-time dyspnea for our comparison. We will take in great consideration the reviewer’s comment in a further study with a sample size calculation made on this outcome.

Comment 3

When comparing IPF and non IPF, nevertheless described in the statistical analyses as a ttest, this seems analyzed using a correlation.

Answer to reviewer’s comment 3

We thank the reviewer for this comment. We corrected the manuscript coherently. See statistical analysis section.

Comment 4

Was the effectiveness different in patients receiving oxygen therapy?

Answer to reviewer’s comment 4

We thank the reviewer for this comment. We agree with the reviewer that it would be interesting to know whether oxygen therapy would have influenced PR effectiveness. Unfortunately the reduced number of patient on O2 therapy and the different way of delivering (continuous VS on effort) did not allow a reliable analysis. We will take in great consideration the reviewer’s comment in a further study.

Comment 5

Were the correlations different in IPF and non-IPF patients? It would be interesting to indicate in the plots the IPF and non-IPF patients.

Answer to reviewer’s comment 5

We particularly appreciate the reviewer for this comment. We agree with the reviewer that it would be of great interest to know whether the correlations would differ in IPF and non-IPF patients. This is an explorative study and the distinction between IPF and non-IPF has been used to assess if etiology would have influenced the effects of PR on major outcomes. Notwithstanding the comparison between correlations with baseline features based on etiology will be the main outcome of a new well-designed study, specifically powered for this analysis.

Comment 6

Please include in the description of the statistics that the results will be described as mean and SD
Answer to reviewer’s comment 6

We thank the reviewer for this comment. We have modified the manuscript accordingly.

Comment 7

Please be consistent in reporting data (SD missing / SD between brackets / ±SD).

Answer to reviewer’s comment 7

We thank the reviewer for this comment. We have modified the manuscript coherently.

Comment 8

P6 line 21, please include the unit of FVC

Answer to reviewer’s comment 8

We thank the reviewer for this comment. We have modified the manuscript as indicated.

Comment 9

In the discussion the authors describe that the better LF parameters and exercise capacity at baseline could explain the greater improvements as compared to a previously published meta-analysis. The results of the present paper show that LF at baseline is not a predictor of success. Isn't this contradictory to your results?

Answer to reviewer’s comment 9

We thank the reviewer for this comment. In our work we stated that: “The observed major benefits might be due to the peculiar baseline features of the study population, constituted of ILD patients with mild to moderate impairment of respiratory function and a measurable exercise capacity (although substantially reduced as expected) even at peak intensity. The permissive level of lung function derangement let almost all the patients to complete the rehabilitation program (only 1 patient left the study protocol for the onset of infectious pneumonia), with increased exercise tolerance both at submaximal and maximal performance”. We have postulated that “less deranged lung in interstitial diseases may provide greater chance to successfully undertake and complete rehabilitation training, issuing its positive results over a limited baseline functional capacity”. At the same time we have showed “how ILD patients of different nature and severity could equally gain benefits from PR without any significant difference in terms of improvement”. We do not think that these assumptions are contradictory because what we have demonstrated was that amongst patients with mild to moderate impairment of respiratory function and a measurable exercise capacity, the different level of lung derangement does not influence the benefits of pulmonary rehabilitation. In other words, if lung function and exercise capacity were preserved enough to permit the completion of PR program, the benefits achieved would not be influenced by their baseline differential values.
Comment 10

Discussion: what do the authors mean with "a measurable exercise capacity even at peak intensity"?

Answer to reviewer’s comment 10

We thank the reviewer for this question that gave us the chance to explain that with "a measurable exercise capacity even at peak intensity" we intended the maximum effort produced during endurance test. In other words we meant that, at baseline, our population presented a preserved average level of exercise capacity, both at submaximal (6MWDT) and maximal (Endurance Test) level. This could have contributed to the high rate of PR completion.

Comment 11

Discussion: what do the authors mean with "a permissive level of lung function" and "peculiar baseline features"?

Answer to reviewer’s comment 11

We thank the reviewer for this question. With "a permissive level of lung function" and "peculiar baseline features" we intended a mild to moderate derangement of FVC and DLCO and a preserved average level of exercise capacity. These might have contributed to the high rate of PR completion.

Comment 12

Tables and figures: please provide more information in the captions.

Answer to reviewer’s comment 12

We thank the reviewer for this comment. We improved the caption of tables and figures. In particular we have added: “Statistical significant is indicated by p value while correlation is indicated by the Pearson’s correlation coefficient r” to all figures captions. We have added to Table one’s caption: “Baseline features of study population. * Center A = Don Gnocchi Institute, Firenze, Italy. ** Center B = Villa Pineta” Rehabilitation Hospital in Pavullo n/F, Modena, Italy”. We added to Table two’s caption: “Outcome measures with absolute and relative change following PR” and “p value are referred to relative changes”.