RANDOMIZED CONTROL TRIAL ON EFFICACY OF HOME BASED GUIDED PULMONARY REHABILITATION PROGRAM IN INTERSTITIAL LUNG DISEASE PATIENTS

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CERTIFICATE

This is to certify that the thesis titled **"Randomized Control Trial on Efficacy of Home Based Guided Pulmonary Rehabilitation Program in Interstitial Lung Disease Patients"** is the bona fide work of **Dr. Rishabh Kochar** carried out under our guidance and supervision in Department of Pulmonary Medicine, All India Institute of Medical Sciences, Jodhpur.

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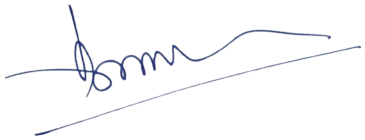
DR. MAHENDRA KUMAR GARG Professor and Head Department of General Medicine All India Institute of Medical Sciences, Jodhpur	
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"No duty is more urgent than that of returning thanks"

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Dr. Rishabh Kochar

CONTENTS

LIST OF ABBREVIATIONS

6- MWD	6- Minute Walk Distance
ATS	American Thoracic Society
BMI	Body mass index
COPD	Chronic Obstructive Pulmonary Disease
CRDQ	Chronic respiratory disease questionnaire
CTD-ILD	Connective Tissue Disease Related Interstitial Lung Disease
DLCO	Diffusing capacity of the lungs for carbon monoxide
DPLD	Diffuse Parenchymal Lung Disease
ERS	European Respiratory Society
FITT	Frequency, Intensity, Time and Type
FVC	Forced Vital Capacity
GAD-7	Generalized Anxiety Disorder Assessment
HADS	Hospital Anxiety and Depression Scale
HP	Hypersensitivity Pneumonitis
HRQoL	Health Related Quality of Life
IIP	Idiopathic Interstitial Pneumonia
ILD	Interstitial Lung Disease
IPF	Idiopathic Pulmonary Fibrosis
IQR	Interquartile range
K-BILD	King's Brief ILD Questionnaire
mMRC	Modified Medical Research Council dyspnea score
NSIP	Non-specific Interstitial Pneumonia
OP	Organizing Pneumonia
PHQ-9	Patient Health Questionnaire
PR	Pulmonary Rehabilitation
QoL	Quality of Life
REE	Resting Energy Expenditure
SD	Standard Deviation
SGRQ	St. George's Respiratory Questionnaire
SpO2	Oxyhemoglobin saturation by pulse oximetry
TEE	Total Energy Expenditure
VAPA	Virtual Physiotherapist Agent

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SUMMARY

Background: Interstitial lung diseases include a wide array of maladies affecting the pulmonary interstitium and leading to inflammation and destruction of lung parenchyma. The most common ILDs have a tendency to cause lung fibrosis and rapid decline in lung volume and diffusion capacity which leads to decrease in effort tolerance causing reduced activity and deconditioning which further worsens the exertional capacity setting up a vicious cycle. Trials of rehabilitation in ILD patients have shown favorable outcome but most have been hospital based which are associated with high costs and not sustainable in the long term. In this study we aimed to assess efficacy and problems associated with home based rehabilitation program.

Objective: Assess the change in ILD patients' exercise capacity, health -related quality of life, mental health, FVC and DLCO after home-based rehabilitation program, and find deterrents and factors responsible to non-adherence to rehabilitation program

Methods: We enrolled 57 patients with diverse types of ILDs in the study irrespective of severity. After baseline measurements, the patients were randomized to a control group (n=27) which received usual care along with psychiatric consultation, when deemed necessary, and the intervention group (n=30) which underwent multi-pronged rehabilitation for 12 weeks including exercise, education, nutrition advice, and psychiatric consultation. At the end of 12 weeks we assessed the differences between the two groups in multiple predetermined parameters. Simultaneously, a record was made of the patients who dropped out from the study, and reasons for the same were determined.

Results: Home-based rehabilitation program was effective in stabilizing the lung function (Mean FVC increase by 130ml) and exercise capacity (mean 6-MWD increase by 16m) while improving the quality of life and mental well-being in patients who completed the program. The difference from the control group or magnitude of

change from the baseline was not statistically significant as seen in other institution based programs. There is also a high prevalence of anxiety (23%) and depression (28%) in patients with ILD which negatively impacts the motivation to exercise and quality of life.

The study suffered from significant drop-outs from the rehabilitation group (40%) where the main problems identified were severe dyspnea on exercise, poorer exercise capacity and lung function at baseline, financial constraints in buying devices for supplemental oxygen therapy, and lack of motivation due to anxiety and depression.

C**onclusions:** Home-based rehabilitation program can slow the decline of lung function and exercise capacity, but not as significantly when compared to a hospital-based rehabilitation program. Significant dyspnea on exercise, poor financial status and inadequate means to supplement oxygen during exercise are major deterrents in adherence to rehabilitation. Patients with more severe disease, uncontrolled depression and anxiety, and limited exercise capacity are poor candidates for home-based rehabilitation program.

INTRODUCTION

The term interstitial lung disease (ILD) encompasses a large group of > 200 parenchymal pulmonary disorders majority of which are classified as rare (1). ILDs have a variable natural history and course depending on environmental factors, patient factors, and the treatment modality used. Some ILDs run a benign course with years of remission, and even complete reversal of disease on appropriate management, like respiratory bronchiolitis ILD on smoking cessation (2), non-fibrotic hypersensitivity pneumonitis (HP) on antigen avoidance (3) and some drug-induced ILDs. Others, like idiopathic pulmonary fibrosis (IPF), fibrotic hypersensitivity pneumonitis, and fibrotic non-specific interstitial pneumonia (NSIP), are usually relentlessly progressive. They are associated with gradually increasing fibrosis, falling lung volumes, and deterioration of lung function even after adequate therapy (4). Different fibrosing ILDs have a variable pattern of inflammation and fibrosis as well as a varying rate of progression eventually resulting in irreversible parenchymal fibrosis causing ventilatory constraint, impaired gas exchange, and abnormal lung mechanics leading to dyspnea and limitation in exercise capacity. Consequently, as ILD progresses, the patient's daily activities decrease rapidly due to shortness of breath, tiredness, and muscle fatigue. In the advanced stages, physical and social limitations are significant and health-related quality of life (HRQoL) is markedly affected (5). Limited activity and poor QoL lead to anxiety and depression in addition to the symptoms (6).

Duchemann et al.. estimated the crude prevalence of ILD at 97.9 per 100000 per year and an incidence of 19.4 per 100000 per year in France (7). Other studies worldwide estimate the incidence of ILD between 1 to 70.1 cases per 100,000 populations and the prevalence of ILDs between 6.27 and 97.9 per 100,000. The exact prevalence and distribution of ILDs in India remain unknown, but Dhooria et al.. attempted to estimate the same. Their study estimated that the crude annual incidence of ILDs (all subtypes combined, per 100,000 populations) was 10.1–20.2 and prevalence between 49.0–98.1 per 100,000. This puts the cumulative national burden of ILDs at 0.45–0.89 million. Sarcoidosis, connective tissue disease-related ILD (CTD-ILDs), and hypersensitivity pneumonitis were reported as the commonest ILDs in India, and all have a progressive fibrosing subtype (8). Such massive number of patients poses a significant challenge to the health system regarding the cost and availability of

resources and carries a significant financial burden. Patients with ILD tend to receive frequent hospitalization and rapid decline in pulmonary function, and many end up needing long-term oxygen support, further increasing the restriction on physical activity.

Universal guidelines for the medical management of different types of ILD are challenging to develop because of the variable pathogenesis and heterogeneity of disorders making up this disease spectrum. In addition, there is also a lack of effective treatment strategies to halt and reverse the disease process. Although pharmacotherapy with anti-fibrotics, corticosteroids, and cytotoxic drugs can slow the progression of the disease, it does not reduce the already-established fibrosis. It is often inadequate in improving patients' health-related quality of life (HRQoL). Pharmacotherapy alone does not suffice for extra-pulmonary complications such as weakness, effort limitation, and depression and additional measures are needed to restore the patients' lives to as normal as possible (9). Proper management of ILD thus includes treatment directed toward the underlying lung disease and measures to improve exercise tolerance, functional capacity, psychological well-being, nutrition care, and, consequently, the quality of life. These measures are encompassed under the umbrella term of pulmonary rehabilitation (PR).

Pulmonary rehabilitation (PR) has been defined in the 2013 ATS/ ERS consensus statement as: "*Pulmonary rehabilitation is a comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies which include, but are not limited to, exercise training, education and behavior change, designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence to health-enhancing behaviors."* (10) A thorough PR program has many arms and requires a multidisciplinary team for appropriate strategy and delivery. The components of an ideal rehabilitation program are:

- Exercise training
- Breathing techniques
- Energy saving techniques

- Disease education
- Counseling and psychological support
- Nutritional Advice

Although pulmonary rehabilitation (PR) has been studied extensively in Chronic Obstructive Pulmonary Disease (COPD) and has proven beneficial beyond doubt (11), the utility and benefits of PR in ILD patients are supported by weak recommendations due to low quality of evidence and variable disease phenotype (12). Despite inadequate evidence, PR is recommended as a part of standard care across all ILD phenotypes- except during acute exacerbation. Though more and more studies are being done worldwide, the data on PR in ILD patients in India is minimal. Though some home-based rehabilitation studies have been done in COPD patients (13), most studies on rehabilitation in ILD patients have been institution based. This makes the rehabilitation program dependent on hospitals, needing special equipment and machines. These add to the cost of pharmacotherapy and transportation and are a negative motivation for rehabilitation.

Lacunae in current knowledge

Randomized controlled trials on the effect of PR in ILD patients have been few, and most were conducted in an institutional set-up needing patients to visit the hospital for the rehabilitation program. Also, these studies have relied heavily on machines such as cycle ergometers and treadmills with the need for constant supervision (14–16). To our knowledge, only two trials have been done on home-based PR in ILD patients (12). One focused on walking training (17), while the other used video call and smart devices (18). These problems make rehabilitation very costly and inconvenient for the patient. Traditional rehabilitation practices also burden hospitals and increase healthcare service utilization, necessitating more staff and equipment. Studies documenting the efficacy of a holistic home-based PR approach and its economics are lacking. Since there are very few studies on home-based PR in ILD patients, we are unaware of the possible constraints and barriers to the same. Also, very few studies have evaluated the impact of PR on anxiety and depression in ILD patients. To date, no studies have examined or validated the use of the Patient Health Questionnaire (PHQ-9) and Generalized Anxiety Disorder (GAD-7).

The goal of this study is to assess the effect of home-based, machine-independent rehabilitation practices on patients' short- and long-term health. This will add to existing practices so that the patients in their homes can safely and effectively carry out the rehabilitation program. The study also aims to develop a program with minimal additional costs and less dependence on frequent hospital visits for pulmonary rehabilitation.

REVIEW OF LITERATURE

The ILDs or diffuse parenchymal lung disease (DPLD) are a heterogeneous group of disorders with variable natural history ranging from complete remission in some cases to rapid loss of lung function and death within a few years in others. There are more than 200 types of ILDs with both known and unknown etiology, each with its own natural history. The recent ATS/ ERS guidelines divide this heterogeneous group of diseases into four major subclasses- a) DPLD of known causes, b) Idiopathic interstitial pneumonias or IIPs, c) granulomatous DPLD, d) Other forms of DPLD including rare diseases (19). The most common ILD worldwide comprises IPF, CTD-ILD, sarcoidosis, and hypersensitivity pneumonitis, with some regional differences in prevalence. (20)

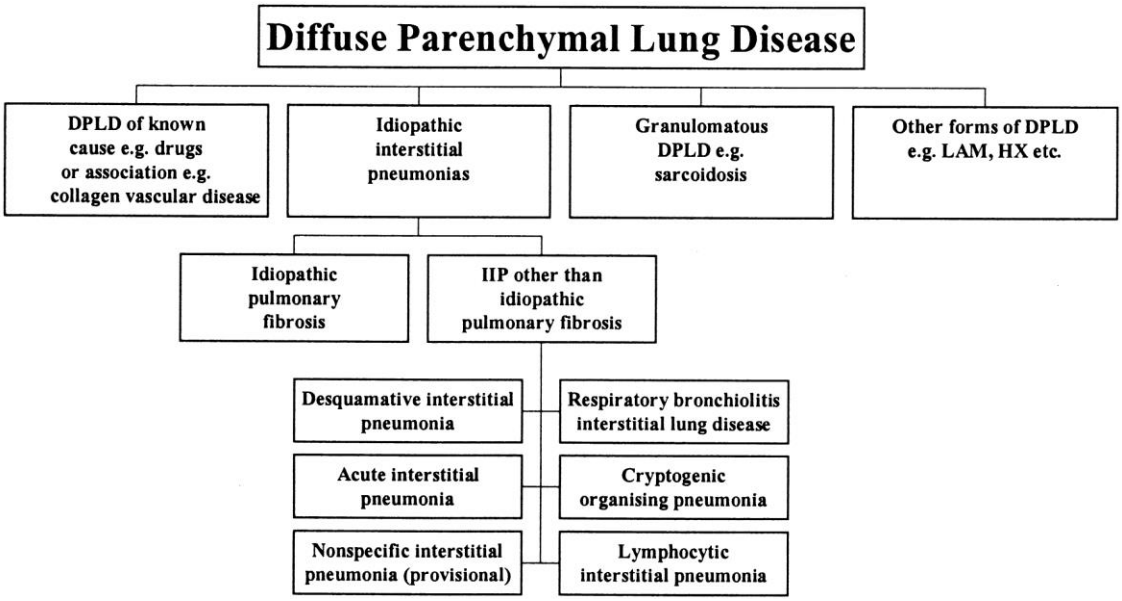


Figure 1- Revised ATS/ ERS classification of DPLD (19)

The most common ILDs affecting the Indian population are sarcoidosis, hypersensitivity pneumonitis, IPF, and CTD-ILDs (8). IPF, by its very nature, is progressively fibrosing, while the other three have a variable course, but all have a progressive fibrosing sub-phenotype. These progressive fibrosing ILDs are characterized by increasing fibrosis, a decline in lung function, worsening quality of life, and early mortality (4). In India, these fibrotic subtypes comprise more than 75%

of all ILD cases and are part of a group where PR, in addition to usual care, can be effective in improving the functional status and HRQoL. Though PR is recommended for all ILD types, most studies on PR in ILD have been done in these subtypes only. (12)

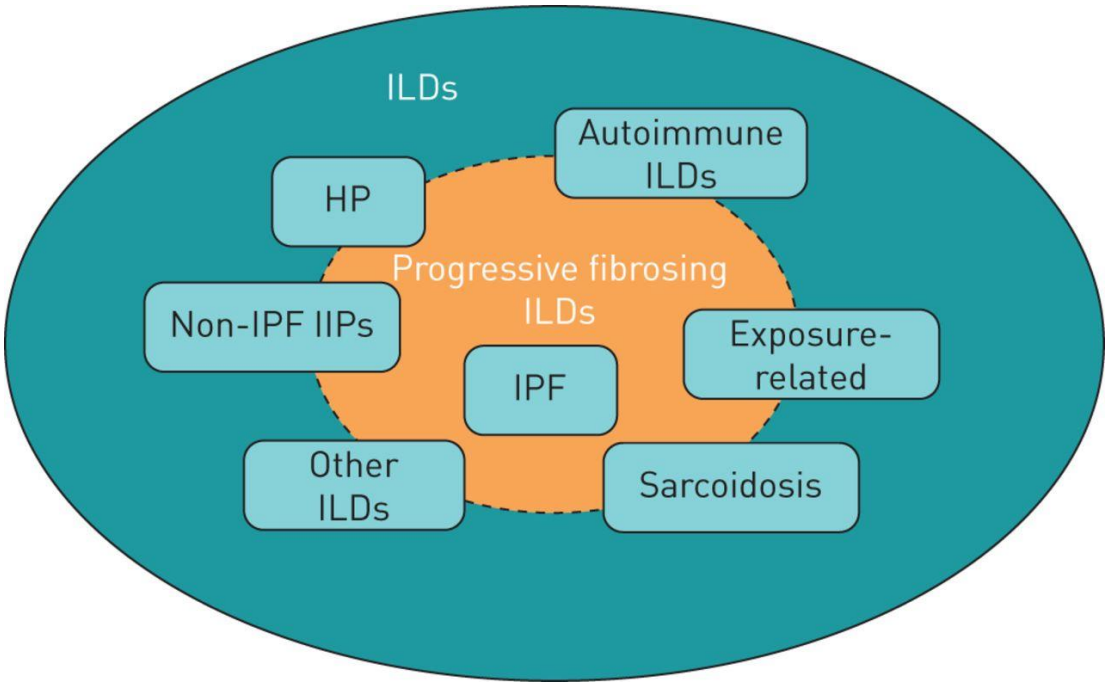


Figure 2- Major ILDs with a progressive fibrosing phenotypes (4)

The benefit of PR in patients with COPD has been established for more than 20 years now. It is considered an essential part of the treatment of COPD patients and is as important as medical therapy (11). A study on home-based rehabilitation for COPD patients using minimal resources and cost-effective methods by AE Holland et al.. compared hospital-based rehabilitation to home-based rehabilitation in COPD patients finding that home-based intervention was non-inferior to a hospital-based PR program, and the same was achievable at a lesser cost to the patients and lesser health care utilization. The study also found that there were lesser drop-outs in the home-based PR (n=7) compared to the hospital-based program (n=44) for an almost similar number of initial recruits (13).

Despite a significant role in patients with COPD, the role of rehabilitation in patients with ILD is still under evaluation, and only a few high-quality studies have been done. As for home-based rehabilitation program, only two randomized controlled trials on the efficacy of home-based PR in ILD patients have been found in the published literature. One of these trials by Wewel et al. randomized 99 ILD patients to a training group (n=49) with scheduled daily walking- twice daily walking for 15 minutes and a control group (n=50) with no scheduled walking. They found that the 6-minute walking distance remained stable over six months in the training group, but it decreased in the control group. There was also an increase in exercise capacity measured by ergospirometry in the training group at six months, whereas it declined in the control group. There were no changes in dyspnea scores or QoL scores at six months. (17)

The second randomized trial on home-based PR in ILD patients by Heras et al. was done in stable IPF patients. 29 patients were randomized to the usual care group (n=14) and tele-rehabilitation (n=15) group, respectively. The tele-rehabilitation group underwent rehabilitation with video and chat consultations with a physiotherapist and workout sessions with a virtual physiotherapist agent (VAPA) for three months. The study found that differences in 6-MWD between groups after three months of PR program was +39.5m in the rehabilitation group with a p=0.03. Adherence to the program was 63%, with high patient satisfaction. Despite improvement in 6-MWD, differences between groups in exercise activity measured by pedometry, QoL scores, and pulmonary function test were not significant. (18)

In their study done in 2005, Holland et al. randomized 57 subjects to receive hospital-based PR or medical care without rehabilitation. The program completion rate was 80%, and no adverse events were observed during the rehabilitation. In the group that received rehabilitation, 6- Minute Walk Distance (6-MWD) increased following training (mean increase of 35m compared to controls). The patient who underwent rehabilitation also had a reduction in modified medical research council dyspnea score (mMRC) by 0.7 points along with improvements in dyspnea and fatigue. The benefit from rehabilitation was lost after one year of completion of the program (16).

Bihiyga Salhi and colleagues did a prospective, nonrandomized, non-controlled study in 31 patients with established restrictive lung disease with a 24-week outpatient

multidisciplinary rehabilitation program compared to the commonly done 8-12 weeks rehabilitation program. The primary outcome was an improvement of 6-MWD at the end of 12 weeks. The data revealed that the improvement in 6-MWD was significant at 12 weeks (from 390 ±140m to 445±142m). After 24 weeks of training, the 6-MWD score improved even further to 463±146m highlighting the fact that sustained improvement can be obtained with longer training durations (21).

Promising data have emerged from a recently done randomized control trial to assess the efficacy of 6 month long PR program on short and long-term outcomes by Bogerd et al.. The study included 60 patients of ILD (multiple subtypes) who were randomly assigned to a control group receiving standard care without the intervention and a study group that, in addition to standard care, received six months of pulmonary rehabilitation on an outpatient basis. Although the study was for six months duration, a significant improvement was already there after three months of PR in exercise tolerance, total scores of health status, activity score, dyspnea score, emotion, and mastery. The study showed a mean improvement of 72 meters in 6-MWD. The benefits of PR were maintained for one year (9).

Benoit Wallaert et al. did a study on home-based rehabilitation of ILD patients to assess its feasibility and long-term outcomes on the patients. One hundred twelve patients were evaluated and provided with an eight-week rehabilitation program with once-weekly retraining and psychological support. The patients were then followed for 12 months to find the long-term benefit of PR. The completion rate of the eight-week outpatient program was 90%, and patients who completed the study had better baseline FVC and DLCO values than those who did not. At the end of 8 weeks, the patients had a better quality of life, better exercise capacity, and improved anxiety control. At the end of 12 months, the benefit of the improved exercise capacity and anxiety control was still above the baseline values. This study establishes the long-term benefits of PR. The data from this study also suggests that home-based pulmonary rehabilitation protocols are not only feasible but also effective (22).
In the Indian scenario, a retrospective observational study was done by Prabhudesai et al.. The study included patients with restrictive lung diseases, including various types of ILDs. The study enrolled 100 patients, and 21 were lost to follow-up. The eight-

week rehabilitation program showed a mean improvement of 61.8 meters in 6- Minute Walk Distance (23).

Depression and anxiety are also very common in patients with ILD. The prevalence of depression and anxiety in ILD patients ranges from 14%-49% and 21%-60%, respectively, depending on the scale used for assessment and the patient population (6). Though a lot of interventions target physical well-being and QoL indices, hardly any studies have been done with a focus on depression or anxiety as a primary outcome measure of effectiveness PR. The most commonly used anxiety and depression scales in ILD patients are the Hospital Anxiety and Depression Scale (HADS), Center for Epidemiologic Studies Depression scale, Beck depression inventory and Beck anxiety inventory, Geriatric Depression Scale, and the Wakefield Self-assessment of Depression Inventory. None of these screening tools have been validated in ILD patients. To date, there are no studies that examined or validated the use of the Patient Health Questionnaire (PHQ-9) and Generalized Anxiety Disorder (GAD-7).

A study by Deniz et al. aimed to evaluate the difference in gains with PR in different types and severity of ILDs. The study found that eight weeks of PR program lead to significant improvement in exercise capacity and QoL. As a measure of secondary outcome, they found statistically significant improvement in anxiety and depression scores following PR. (24)

A Cochrane review (2021) on pulmonary rehabilitation for ILD came up with following conclusions as discussed (12):

1. There was no reported complication due to PR programs and these appear to be safe in ILD patients
2. PR results in improvements in functional exercise capacity and health-related quality of life.
3. PR can improve maximum exercise capacity- participants of PR program had better walking distance than those who did not undergo PR.
4. People with all types of ILD should be included in pulmonary rehabilitation programs

By reviewing existing literature, we can safely conclude that pulmonary rehabilitation programs are both feasible and effective. Home-based PR is also better in terms of cost-effectiveness and compliance rates of the patients, as has been shown in trials in COPD patients, though data are lacking on the efficacy of home-based PR in ILD patients. Also, there are no guidelines on an optimum exercise training method for people with ILD, and a detailed stepwise rehabilitation program for ILD patients does not exist with each study using their own strategy for PR. Theoretically, home-based programs also lead to lesser utilization of healthcare resources and manpower utilization.

Although there is a benefit of PR in ILD patients, the strength of evidence on home-based rehabilitation is low because there are not a lot of randomized control trials on it. The benefit of PR in ILD has not been evaluated in the Indian context, and no RCT has been done in India till now. Also, many studies have evaluated the impact of rehabilitation on QoL and dyspnea scores along with exertion capacity, but no study has directly addressed the impact of PR on depression and anxiety in ILD patients.

Table 1- Summary of major trials on hospital based pulmonary rehabilitation in ILD patients

Trial	Subjects	Intervention	Outcome
Short term improvement in exercise capacity and symptoms following exercise training in interstitial lung disease. AE Holland et al.. 2008 (16)	57 subjects with ILD (37 IPF) Study, n=30 Control, n = 27	Study group- 8 weeks of supervised exercise training Control group- weekly telephone support	- 80% completion rate for exercise program. - Mean increase in 6-MWD in study group- 35m - Reduction in mMRC score- by 0.7 points - Improvement in dyspnea and fatigue on CRDQ
Physical activity and quality of life improvements of patients with idiopathic pulmonary fibrosis completing a pulmonary rehabilitation program. IA Gaunaurd et al..2014(25)	21 subjects with IPF Study, n= 11 Control, n= 10	Study group- 3 month rehabilitation program- 90 min twice weekly exercise sessions- 24 total sessions Control group- usual level of activities	- Study group had higher levels of physical activity throughout the program- measured by metabolic equivalent of task minutes - Study group had improved SGRQ symptom scores whereas it worsened in controls
The evidence of benefits of exercise training in interstitial lung disease: a randomized controlled trial LM Dowman et al..2017 (26)	142 subjects- IPF=61, asbestosis=22, CTD-ILD= 23, Others=36 Study, n = 74 Control, n= 68	Study group- 8 weeks supervised exercise training Control group- usual care	- Study group had higher 6-MWD (mean=25m) and better QoL scores after PR - Lower baseline 6-MWD and worse symptoms were associated with greater benefits - Benefits from PR are lost by 6 months

Trial	Subjects	Intervention	Outcome
Short-Term Effects of Comprehensive Pulmonary Rehabilitation and its Maintenance in Patients with Idiopathic Pulmonary Fibrosis: A Randomized Controlled Trial I Jarosch et al.. 2020 (27)	54 subjects with IPF Study, n= 36 Control, n= 18	Study group- 3 weeks of comprehensive in-patient PR done 5-6 days per week Control group- usual care	- 6-MWD improved significantly immediately after 3 weeks of PR (mean difference of 61m between two groups) - Higher baseline FVC and anxiety symptoms were associated with more short term 6-MWD improvement - CRDQ scores improved in PR group - Benefits were not sustained at 3 months after PR
Long-term effects of pulmonary rehabilitation on daily life physical activity of patients with stage IV sarcoidosis: A randomized controlled trial B Wallaert et al.. 2020. (28)	38 subjects with stage 4 sarcoidosis Study, n= 20 Control, n= 18	Study group- 2 months supervised PR program Control group- counseling	- No inter-group difference at 12 months in physical activity score. (difference in time spent in activities above 2.5 metabolic equivalents) - PR increased exercise tolerance at 6 and 12 months and decreased dyspnea score at 6 months

Trial	Subjects	Intervention	Outcome
Survival rates after a rehabilitation program in patients with interstitial lung disease V Barbier et al.. 2014 (29)	60 subjects Study, n=unknown Control, n=unknown	Study group- 6 months of PR Control group- usual care Survival recorded for 2 years	- No difference in survival at 2 years between both groups

Table 2- Summary of trials on home based pulmonary rehabilitation in ILD patients

Trial	Subjects	Intervention	Outcome
Home-based walking training in patients with interstital lung diseases A. R. Wewel et al., 2005 (17)	99 subjects with ILD Study, n= 49 Control, n= 50	Study group- scheduled twice daily walking for 15 mins Control group- no scheduled walking	- 6-MWD remained stable in study group at 6 months whereas it declined in the control group - Exercise capacity improved in study group but declined in control group - No difference in QoL or dyspnea scores between 2 groups after 6 months
Tele-rehabilitation program in idiopathic pulmonary fibrosis De Las Heras et al., 2021 (18) Home based rehabilitation	29 subjects with IPF Study, n= 15 Control, n= 14	Study group- 3 months of tele-rehabilitation using video/ chat consultation with physiotherapist and virtual physiotherapy agent(VAPA) Control group-usual care without rehabilitation	- 63% adherence to PR - Patient in tele-rehabilitation group had sustained the baseline 6-MWD at the end of 3 months whereas it fell in the control group - No difference in the two groups in QoL and lung function parameters.

AIMS AND OBJECTIVES:

Primary:

1. Assess the change in exercise capacity of ILD patients with the home based rehabilitation program
2. Assess the impact of rehabilitation program on patient's dyspnea score, health -related quality of life and psychological impact on the patient.

Secondary:

1. Identify the change in FVC and DLCO of the patients undergoing rehabilitation
2. Find deterrents and factors responsible to non-adherence to rehabilitation program

MATERIALS AND METHODS

Study setting – Department of Pulmonary Medicine at All India Institute of Medical Sciences, Jodhpur, Rajasthan.

Study design – Prospective, Non-blinded, Randomized Control Trial

Study participants – All patients with ILD irrespective of subtype, with controlled disease activity (no deterioration of lung function in last 3 months) and no history of recent (<3 month) exacerbation or hospitalization.

Study duration – Patients were recruited during 20 month period from December 2020 to August 2022.
Recruited patients were followed up for 12 weeks after inclusion

Inclusion criteria:

- Patients with clinically diagnosed ILD- irrespective of subtype

Exclusion criteria:

- Patient with recent hospitalization/ exacerbation (<3 months)
- Hemodynamically unstable patient with cardio-pulmonary failure
- Patient who have any contraindications to exercise/ exertion
- Bed bound/ moribund patient
- Pre-existing psychiatric illness (before ILD onset), dementia, orthopedic disability, severe arthritis leading to difficult engagement in exercise
- Severe exercise-induced hypoxemia not correctable with oxygen supplementation (SpO2< 85%)
- Lack of motivation, non-adherence or patient's unwilling to give consent
- Active smoking

Sampling and sample size: The study was a randomized controlled trial. Based on a previous study by AE Holland et al. (16) a minimal 6-MWD benefit of 38 ± 43 m might be expected after 3 months. To expect a similar change of 40±43 meters, a

sample size of 21 patients in each arm was needed to show a statistically significant difference at the 0.05 p-level with 90% power. Taking for possibility of 20% dropouts during the study, the total number in each arm goes to 25, total n=50. Following recruitment, patients were randomized based on a random number table.

$$n1=\frac{(\sigma_1^2+\sigma_2^2/K)(z_{1-\alpha/2}+z_{1-\beta})^2}{\Delta^2}$$

$\Delta = |\mu 2-\mu 1|$ = absolute difference between two means

$\sigma 1$, $\sigma 2$ = variance of mean #1 and #2

n1 = sample size for group #1**= 21**

n2 = sample size for group #2 **=21**

α = probability of type I error

β = probability of type II error

z = critical Z value for a given α or β

k = ratio of sample size for group #2 to group #1

Against an initial target of fifty patients, 57 total patients were recruited in the study. These fifty seven patients were randomized to rehabilitation group (n=30) and usual care group (n=27)

Methodology:

- Data was collected using a predesigned, structured pro forma.
- Patients were selected – consecutively from OPD and the details of the study were explained. Consenting patients were randomized via random number table to either rehabilitation or control group. All patients were give basic education about the need for healthy lifestyle and their disease and its nature.
    - The control group was given standard care, disease education, advice to exercise and psychological support with no additional maneuvers.
    - The rehabilitation group will be provided with Holistic PR with a multipronged approach- including both exercise and non-exercise rehabilitation.
- Baseline characteristics were noted for all included patients- height, weight, demographic parameters, spirometry data, DLCO, 6-MWD and quality of life.

- King's Brief ILD questionnaire (K-BILD) was used to record health related quality of life data in the patients
- MMRC scale was used to assess breathlessness.
- Patient Health Questionnaire (PHQ-9) and General Anxiety Disorder-7 (GAD-7) questionnaires were used for initial screening of the patients and to assess pre and post intervention depression and anxiety scores.

Rehabilitation group - first visit after randomization included-

- Psychological assessment for any problems being faced by the patient and necessary advise or intervention for same was initiated based on risk assessment scores
- Guided and supervised exercise training was done on day 1 to determine the patients' threshold and decide on further exercise plan
- Nutrition advise relevant to patients' condition
- Education about disease and proper use of medications
- Patients were followed up weekly and guided at their homes via calls and messages.

Control group- patients in this group after randomization were given advice regarding disease, exercise and proper use of medication and to continue their routine activities without any active intervention. Patients with high GAD-7/ PHQ-9 scores were referred to psychiatrist for evaluation and management.

After randomization and during the entire study period (12 weeks)

- Patients in rehabilitation group were followed telephonically for adherence to program, problems incurred, and for modification in exercise regime.
- Patients were re-evaluated in hospital at Week-6 of the study with a physical visit. Assessment of problems with PR, reinforcement for exercise, retraining, re-education was done along with increment of exercise protocol in those who were able to tolerate the previously prescribed regimen.
- At the end of study duration (week-12) all patient data was collected in a manner similar to the initial protocol at the time of recruitment and was recorded for comparison.

Drop-Outs- Drop out from the study was defined as any of the following.

1. Patient withdrew consent after initial enrollment
2. Patient did not follow up/ answer calls after initial enrollment
3. Patient in intervention group refused to continue rehabilitation program due to any reason
4. Patient developed acute worsening of symptoms (as judged by the trial team), exacerbation of ILD or hospitalization due to any reason after randomization.
5. Patient who needed major treatment change after randomization (initiation or discontinuation of nintedanib/ pirfenidone during the trial was not considered as major change)

Rehabilitation program

Exercise rehabilitation was based on FITT (Frequency, Intensity, Time, and Type) principle and assessment of patients' disease severity. Gradual increase in exercise duration and intensity was done based on patient's initial evaluation and tolerance to the initial exercise prescription.

- The patients in intervention arm were started on gradually incremental exercise protocol. The adherence, and tolerance to PR regimen was discussed telephonically and increments, if needed, were conveyed to the patient on weekly basis
- Initial protocol included low level, interval endurance exercise for 10-30 minutes daily depending on patient's abilities.
    - The level and duration of exercises were increased thereafter
    - Those who could not tolerate the initial prescription or increase after 3-6 weeks were asked to continue low intensity exercises.
    - The patients who could complete the initial regimen were shifted from interval to continuous exercise protocol over 3-6 weeks depending on individual capacity.
    - Those who tolerated continuous exercise were shifted to high intensity interval/ continuous training and if not, the low intensity exercise was continued
    - Patients who needed oxygen support either at rest or during exertion were prescribed the same wherever necessary during exercise.

The exercise protocol included

- **Endurance training-** activities such as walking, stair climbing, running
- **Resistance training-** for improving muscle function by using gravity (squatting), fixed weights, use of resistance bands. Functional activities and activities of daily living
- **Flexibility training-** to include simple stretching and movement exercises to be done on a daily basis.

Non- exercise arms -

1. **Breathing control and breathing exercises**- in addition to exercise protocol, patients will be taught breathing exercises and breath control techniques using diaphragmatic breathing, mindful breathing techniques and incentive spirometry.

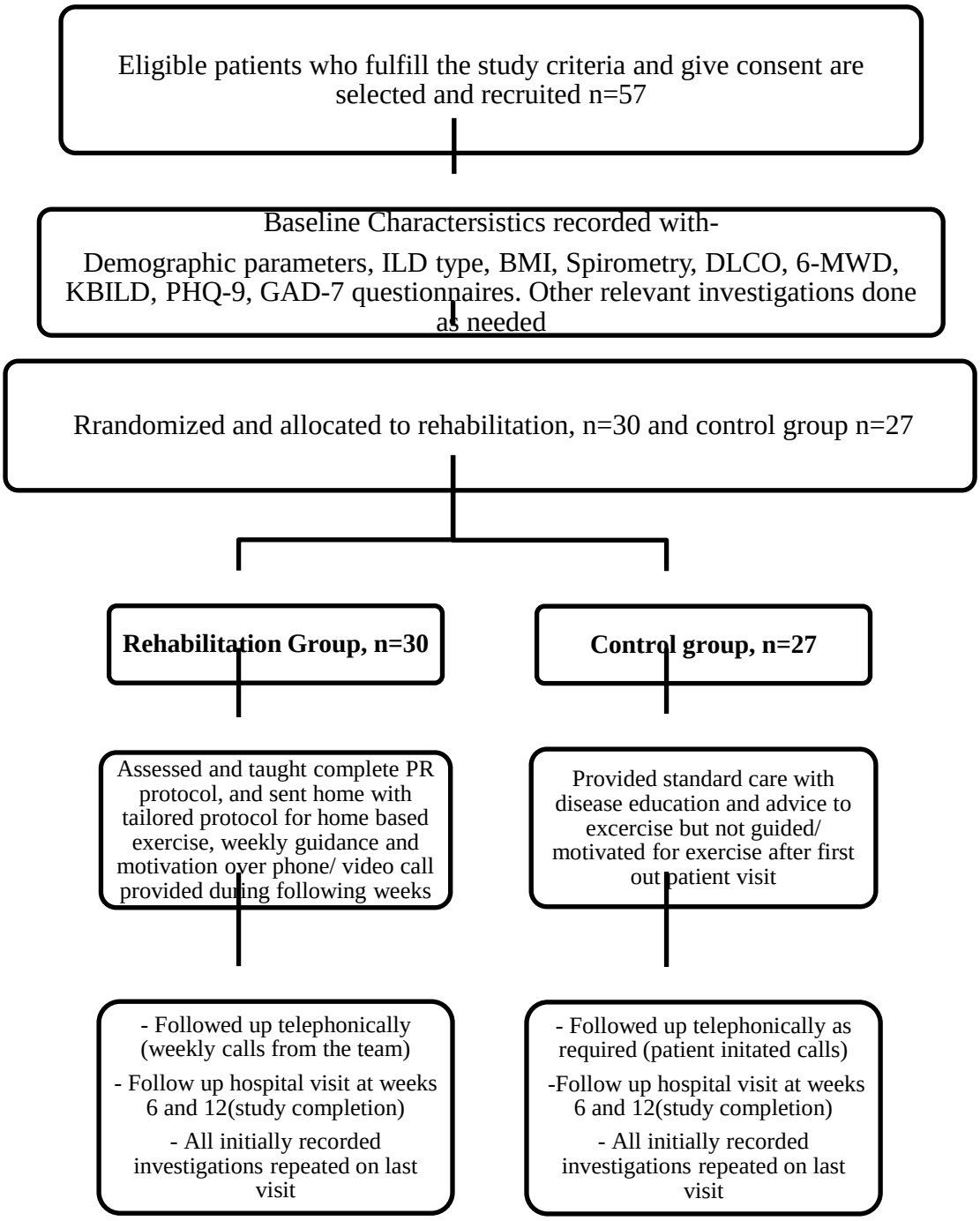
2. **Psychological evaluation and rehabilitation-** at the initial visit all the patient underwent a psychological assessment and interview regarding their problems and expectations
    a. Based on interview the necessary protocol- supportive sessions, coping skills and/ or therapeutic intervention were initiated based on patients' problems
    b. For depression and anxiety symptoms- the initial and end of study assessment of the patients was done with the help of Patient Health Questionnaire (PHQ-9) and General Anxiety Disorder-7 (GAD-7) questionnaires (30,31). Score of ≥10 on PHQ-9 and score ≥10 on GAD-7 questionnaire at the baseline was used as threshold for referral to psychiatrist for further assessment and management.

       Patients were initiated on behavioral therapy, counseling, pharmacotherapy or a combination of these at the discretion of the treating doctor. The status of patients' randomization was not communicated to the psychiatrist in order to maintain similar degree of treatment and prevent any preferential treatment.
    c. Quality of Life assessment was done with the help of King's Brief ILD questionnaire (K-BILD) (32)
3. **Education-** all patients were educated regarding disease activity, progression, medication use, symptom management and anxiety control. After an initial session in hospital, further follow up was telephonically.
4. **Nutrition support-** at the time of recruitment, resting energy expenditure (REE) and total energy expenditure (TEE) was determined along with Body mass index (BMI). Based on these data patients in the rehabilitation group were given specific nutritional advice for maintaining appropriate nutritional status and to fill up for any deficiencies.

The monitoring of the patients and compliance verification at home was done by phone calls and video conferencing wherever feasible.

Patients in both rehabilitation group and control group were re-evaluated at weeks 6 and 12 after inclusion in the study for changes in baseline characteristics. Assessment at week 6 included 6-MWD along with reinforcement, re-training, and re-education and exercise increments.

Figure 3- Study Plan



Statistical analysis

Statistical analysis was done using python and Microsoft Excel. Categorical variables are expressed as frequencies and percentages. The baseline characteristics between the two groups were compared using paired and unpaired t-tests. Differences in the values for each subject before and after treatment were evaluated using the paired and unpaired t-test.

Changes in study outcomes over time (6-MWD, K-BILD scores, PHQ-9 and GAD-7 scores) were assessed using student-T test.

The differences between continuous variables were analyzed using the Mann-Whitney test and the differences between categorical variables were analyzed using the chi square test. P-values less than 0.05 were considered statistically significant.

Ethical considerations

The study was done after the approvals by the institutional research committee and institutional ethics committee.

Studies on pulmonary rehabilitation have already shown that it does not pose any risk to the patients. A written informed consent was taken from all eligible participants. Patient and their attendants were fully informed about the study and its utility and that enrolment in this study posed no substantial risk to the participants. They were also explained that they were free to withdraw their consent at any point of time during the study without having any consequences on their treatment and follow-up in the institute.

Except rehabilitation program, participants were not exposed to any additional procedures for the sole purpose of the study

RESULTS

Overall group characteristics: 57 patients were included in the study which was more than the calculated sample size of 50 patients. The mean age of the entire group was 56 years. Of the 57 patients, 27 patients were male and 30 were females.

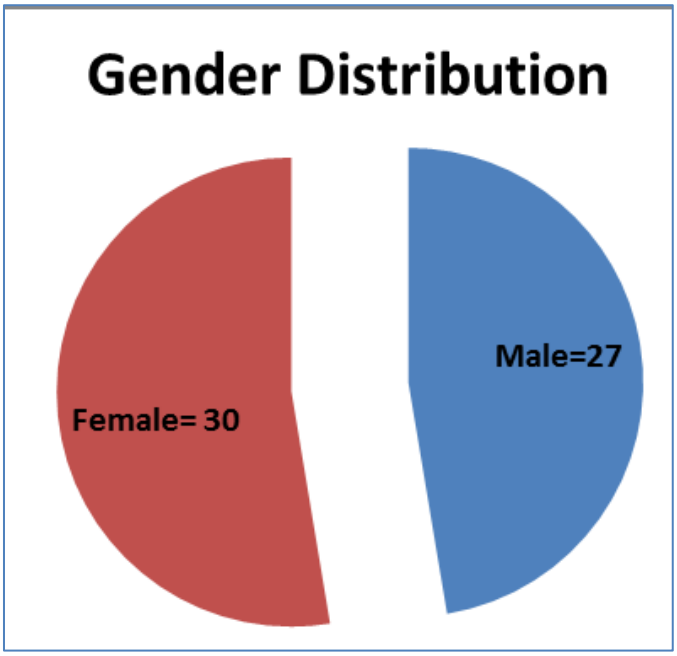


Figure 4- Gender distribution of the overall study population

Type of ILDs- Patients with various types of ILD was included in the study and their overall distribution is described in following text. Most patients had hypersensitivity pneumonitis (n=17), followed by NSIP (n=13) and IPF (n=11). There were 8 patients with organizing pneumonia (OP) - all had CTD related ILD, 3 patients with sarcoidosis and 2 each with mixed pattern (HP/NSIP overlap) and undifferentiated ILD where the final diagnosis could not be reached even after a multi-disciplinary discussion. One patient with post-Covid-19 diffuse parenchymal involvement was also recruited in the study.

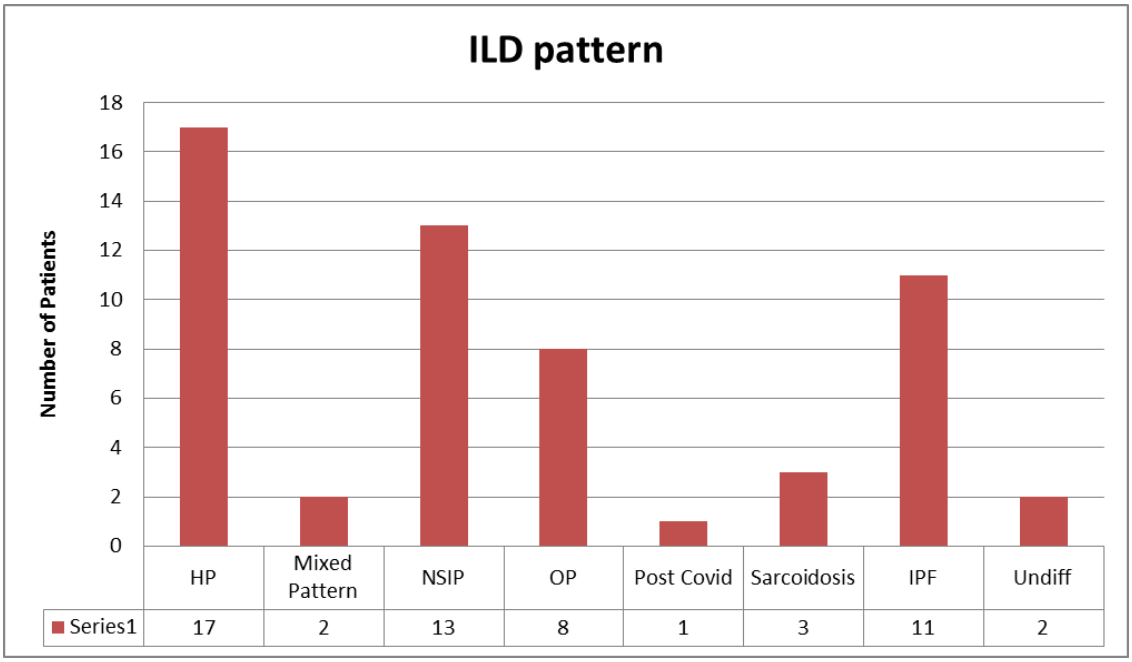


Figure 5- Distribution of ILD types in overall study population

Legends- HP=hypersensitivity pneumonitis, NSIP= non-specific interstitial pneumonia, OP= organizing pneumonia, IPF= idiopathic pulmonary fibrosis, undiff-undifferentiated ILD

Baseline comparison between intervention and control arm.

After initial recruitment, patients were randomized into the control group and the trial group.

The baseline characteristics of the two groups are compared in following table.

Variable	**Intervention arm**		**Control Arm**			**p value**
Gender	Male	16	Male	11		0.34
	Female	14	Female	16		
	Mean	**SD**	**Mean**	**SD**	**95% CI**	**p value**
Age	55.8 years	11.8	55.8 years	12.6	-6.4439 to 6.5550	0.9864
BMI	24.6 kg/m^2	5.37	25.8 kg/m^2	5.04	-1.6410 to 3.9099	0.4162

Table 3- Baseline comparison of gender, age and BMI between intervention and control group

Of 57 patients recruited in the study, 27 patients were randomized to the control arm and 30 patients were randomized to the intervention group. Mean age was 55.8± 11.8 and 55.8± 12 in the intervention arm and control arms. The BMI of both groups was also comparable- 24.67 ±5.5 in the intervention arm and 25.81 ±5.04 in the control arm. Though BMI was slightly higher in the control arm the difference was not statistically significant (p=0.41).

The gender distribution of both the groups was slightly skewed with more males in intervention arm (n=16 versus n=11 in control arm) but the difference between the two groups was not statistically significant (p=0.34).

Distribution by ILD types between control and intervention group

As discussed previously, the study had a heterogeneous composition of patients with multiple types of ILD. The most common ILD was hypersensitivity pneumonitis followed by NSIP and IPF. The patients were randomly assigned to the control and intervention arm. Control arm had more patients with HP (n=13) compared to the intervention arm (n=4) whereas the intervention arm had more patients with IPF, NSIP and OP. Despite randomization, there was a statistically significant difference in overall distribution of ILD types between both groups mainly due to inclusion of more subjects with HP in the control arm (p-value- 0.027).

GROUP	HP n=17	Mixed pattern n=2	NSIP n= 13	OP n=8	Post-Covid n=1	Sarcoid n=3	IPF n=11	Undifferentiated n= 2	Total n=57
Control arm	13	1	4	3	0	2	4	0	27
Trial arm	4	1	9	5	1	1	7	2	30

Table 4- Distribution by ILD type between intervention and control group

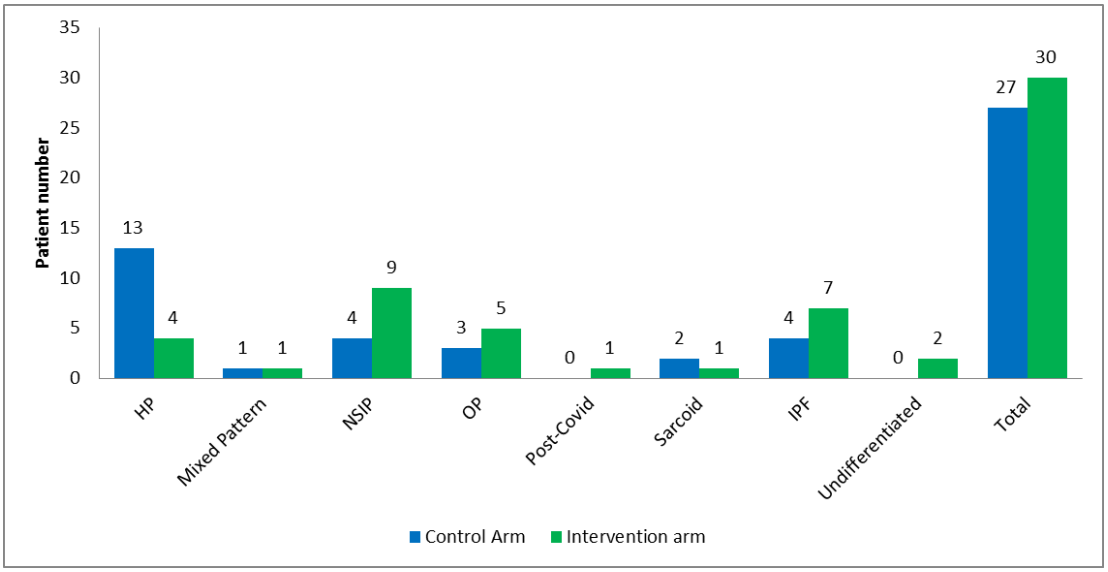


Figure 6- Distribution by ILD type between intervention and control group

Differences at baseline in duration of illness, resting oxy-hemoglobin saturation (SpO2, by pulse oximetry), mMRC dyspnea score and long term oxygen use between control and intervention arms

The control and intervention arms were not adequately matched with regards to base line SpO2, and long term oxygen use. More patients in the intervention arm were on long term oxygen therapy (LTOT) – seven compared to only one in the control arm (p=0.347) and consequently baseline room air SpO2 in the patients was also significantly different, 92.07% (intervention) versus 96.67% (controls, p =0.008). This lead to a skewed distribution of patients with worse baseline dyspnea score in the intervention arm but the difference was not statistically significant.

Contrary to above, the median total duration of illness was more in the control group (53.74 months) as compared to intervention arm (36.16 months) but the difference was not statistically significant.

Variable					95% CI	p value
	Intervention arm		Control arm			
Duration of ilness (months)	36.16	33.68	53.74	41.35	-2.3653 to 37.5134	0.0829
mMRC Dyspnea score (median, IQR)	3 (1-3)		2(1-2)		1	0.0519
On LTOT (n)	7(23.33%)		1(3.7%)			0.0347
SpO2 (room air)	92.07%	6.52%	96.67%	1.593	2.016 to 7.184	0.0008

Table 5- Baseline differences in duration of illness, dyspnea score, and SpO2

Baseline differences in Lung Function tests and 6-MWD

The mean FVC and DLCO% in the intervention arm was 1.39 liters and 32.8% while the values in control arm were 1.62 litres and 37.2% respectively. Although the values in control arm were slightly higher for both FVC and DLCO, the difference was not statistically significant. The 6-MWD (mean ± SD) of the intervention and control arms was 221.3±177.5 meters and 286±105.3 meters, respectively, and the difference was not statistically significant.

Two patients, one in each group, were unable to perform the spirometry, DLCO and 6-MWD tests and their data was not included in the baseline comparison.

Variable	Mean	SD	Mean	SD	95% CI	p value
	Intervention Arm		Control Arm			
FVC	1.39	0.77	1.62	0.70	-0.17 to 0.62	0.2567
FEV1	1.19	0.64	1.39	0.63	-0.13 to 0.55	0.2220
F1V1/ FVC (%)	83.22	18.07	85.94	7.34	-4.75 to 10.20	0.4688
DLCO (corr %)	32.8%	24.58	37.2%	18.8	-7.25 to 16.19	0.4479
6-MWD (meters)	221.3	177.5	286.8	105.4	-13.09 to 144.13	0.1005

Table 6- Baseline differences in Lung Function tests and 6-MWD

Baseline difference in quality of life, anxiety and depression scores

We used King's brief ILD questionnaire (K-BILD) for quality of life assessment, patient health questionnaire (PHQ-9) for depression screening and generalized anxiety disorder assessment (GAD-7) to screen for anxiety. Following table shows the baseline comparison between groups-

Variable	Mean	SD	Mean	SD	95% CI	p value
	Intervention Arm		Control Arm			
K-BILD	62.3	21.1	58.5	14.4	-13.5 to 5.8	0.4317
PHQ-9	7.7	7.1	6.5	5.1	-4.5 to 2.0	0.4564
GAD-7	5.3	6.1	6.0	5.7	-2.4 to 3.8	0.6401

Table 7- Baseline difference in quality of life, anxiety and depression scores

The intervention arm had higher scores on K-BILD (better quality of life), and PHQ-9 questionnaire; whereas the control arm had higher score in GAD-7 but none of these differences reached statistical significance.

After initial screening of entire study population (n=57), sixteen (28%) patients with PHQ-9 score ≥10 and thirteen (22.8%) patients with GAD-7 score of ≥10 were deemed to be at high risk of depression and anxiety respectively. These patients were referred to specialist psychiatrist for evaluation and management irrespective of the trial group that they were randomized to. The intervention group had six patients with GAD-7 ≥10 and eleven patients with PHQ-9 ≥10 whereas the control group had seven patients with GAD-7 ≥ 10 and five patients with PHQ-9 ≥10

12 week follow-up

After randomization patients were followed up for 12 weeks. The trial group underwent holistic rehabilitation whereas the control group received usual care and education. All patients with clinically significant PHQ-9 and GAD-7 scores were referred for psychiatric evaluation irrespective of the group they were enrolled in. Seventeen patients dropped out from the study in the follow-up period due to various reasons discussed later. From 17 subjects who dropped out, 12 patients were in the rehabilitation group and 5 patients were in the control group. Due to significant number of dropouts, the final data was evaluated by per-protocol analysis only. Following table shows the key summary of the observed results:

Variable	Intervention group, n=18		Control group, n=21				
	Mean	SD	Mean	SD	Difference	95% CI	P value
MMRC(median, IQR)	1.5(1-2)		2(1-2)				0.79
6-MWD (meters)	318.6	149.4	306.8	98.3	-11.8	-92.7 to 69.2	0.7704
DLCO (%)	36.7	26.4	40.7	16.8	4.0	-9.9 to 18.0	0.5606
FVC (liters)	1.72	0.87	1.66	0.66	-0.06	-0.54 to 0.43	0.8092
K-BILD	64.8	28.8	61.3	12.2	-3.6	-17.2 to 10.2	0.6065
PHQ-9	3.7	3.7	4.6	3.2	0.9	-1.3 to 3.2	0.4068
GAD-7	2.6	2.8	3.2	3.1	0.5	-1.3 to 2.6	0.4880

Table 8- Inter-group difference at the end of 12 weeks

All the patients who completed 12 weeks of rehabilitation had lesser dyspnea scores, lesser anxiety and depression scores and better FVC compared to the control group. Also, the patients who had completed 12 weeks of rehabilitation had higher mean 6-MWD compared to the control arm and scored better on the QoL domain as assessed by the K-BILD questionnaire. The control group had a higher DLCO as compared to

the intervention arm. Despite an overall improvement across almost all domains, none of these differences reached a statistical significance.

Comparison of changes in different parameters between week-0 and week-12: On comparing changes in both groups to their baseline characteristics, following changes were seen-

Variable	Intervention group, n=18		Control group, n=22				
	Mean	SD	Mean	SD	Difference	95% CI	P value
6-MWD (meters)	16.3	29.1	9.0	22.5	7.3	-17.4 to 64.8	0.3734
DLCO (absolute change in DLCO %)	-0.06	6.72	-0.36	13.52	0.30	-6.8 to 7.4	0.9303
FVC (liters)	0.13	0.40	0.05	0.13	0.08	-0.27 to 0.10	0.364
K-BILD	1.8	8.8	4.1	5.7	- 2.3	-2.3 to 7.0	0.3125
PHQ-9	-2.9	4.0	-1.9	3.3	-1.0	-1.4 to 3.3	0.4042
GAD 7	-0.7	2.3	-2.3	5.3	1.6	-0.2 to 5.3	0.0662

Table 9- Magnitude of change from baseline parameters in intervention and control groups

When comparing the changes from baseline to 12 weeks, after excluding the drop-outs, the data showed an improvement across all domains in both the groups barring DLCO which decreased on 12 week follow-up. The rehabilitation group showed more improvement in the domains of physical activity (change in 6-MWD more by 7.3mts), FVC (increase more by 80ml in rehabilitation group) and depression scores whereas the control group showed better quality of life score, higher decrease in anxiety scores. Both the groups showed an overall improvement at 12 weeks across most domains. Despite this, there is neither a statistically significant inter-group difference nor a significant change from baseline in both the groups.

Figures

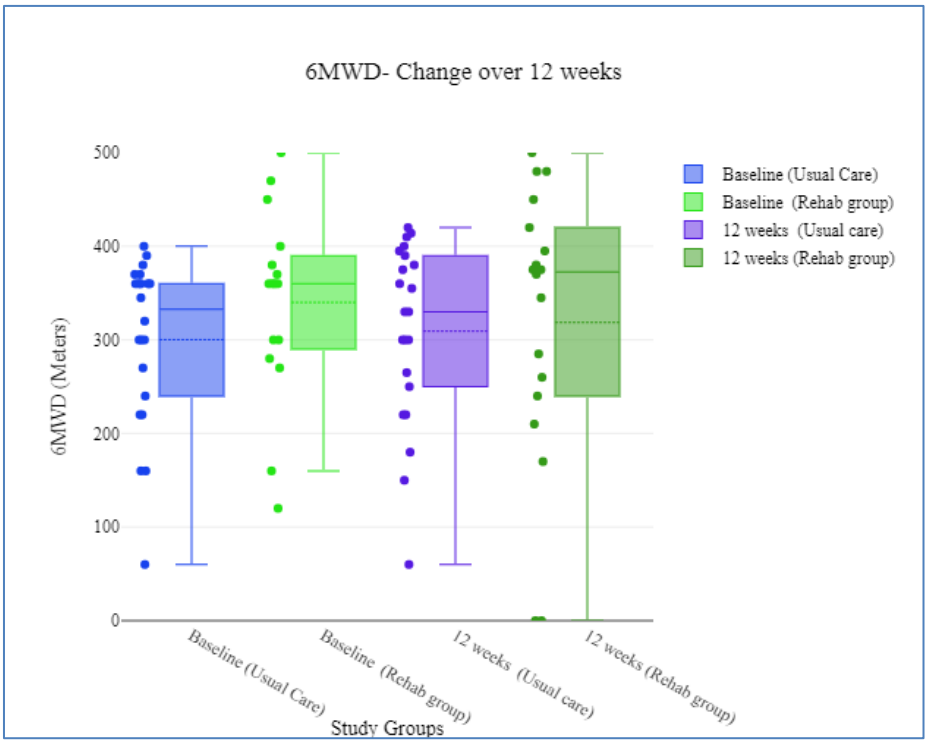


Figure 7- Box and whisker plot showing change in 6-MWD in both groups over 12 weeks

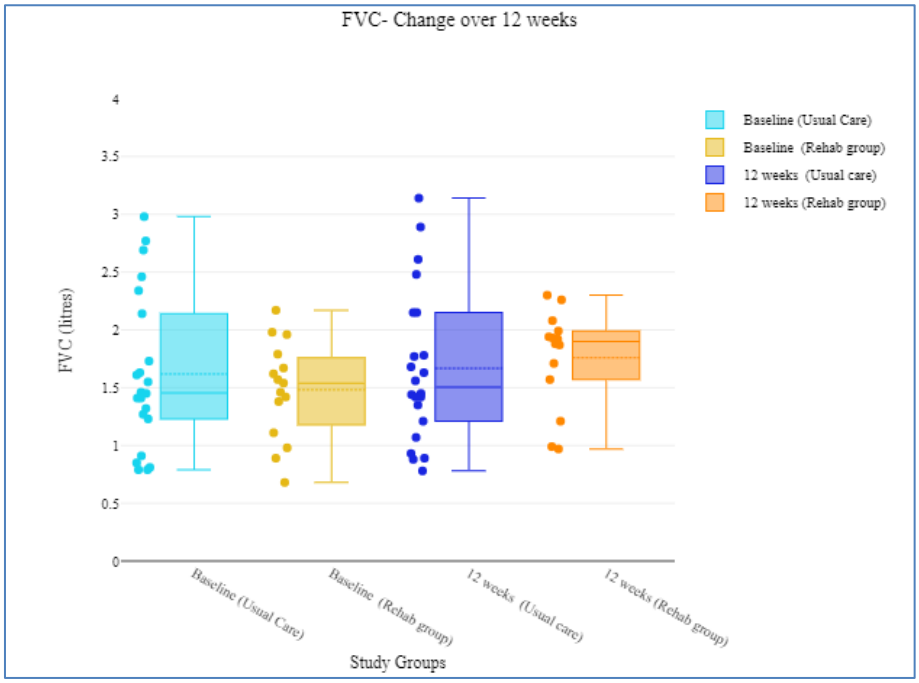


Figure 8- Box and whisker plot showing change in FVC in both groups over 12 weeks

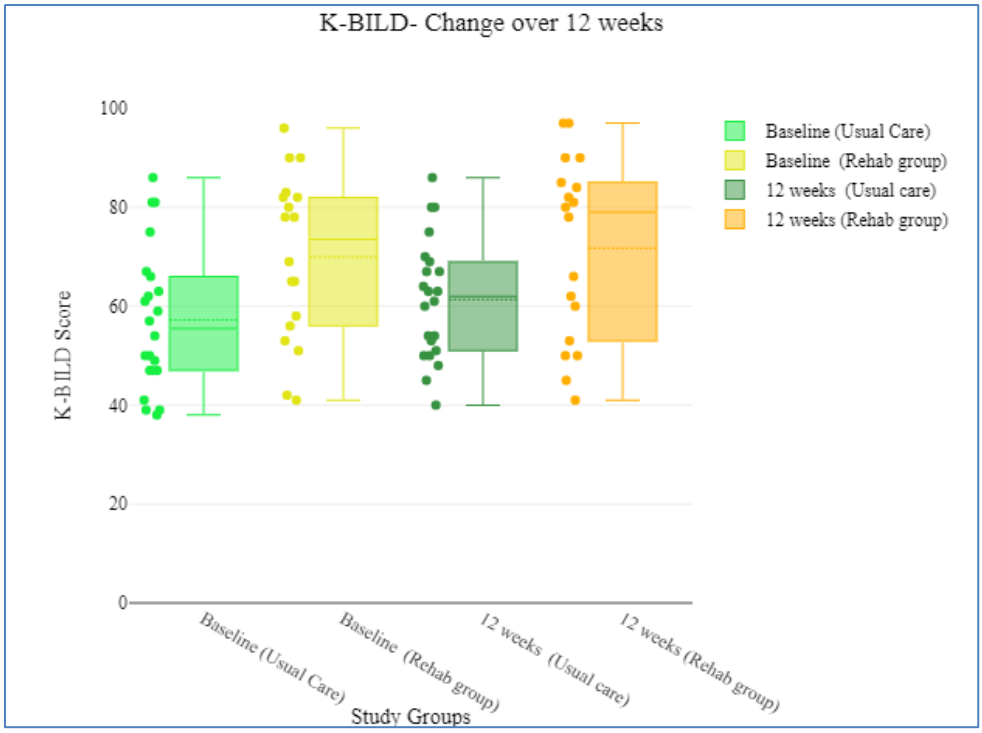


Figure 9- Box and whisker plot showing change in K-BILD score in both groups over 12 weeks

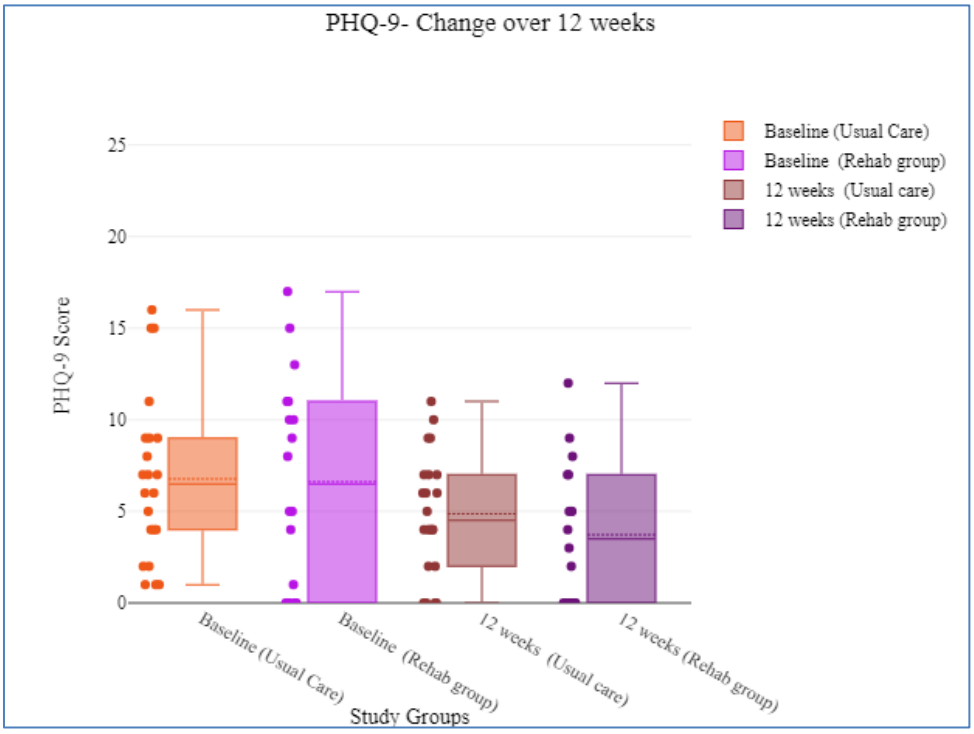


Figure 10- Box and whisker plot showing change in PHQ-9 score in both groups over 12 weeks

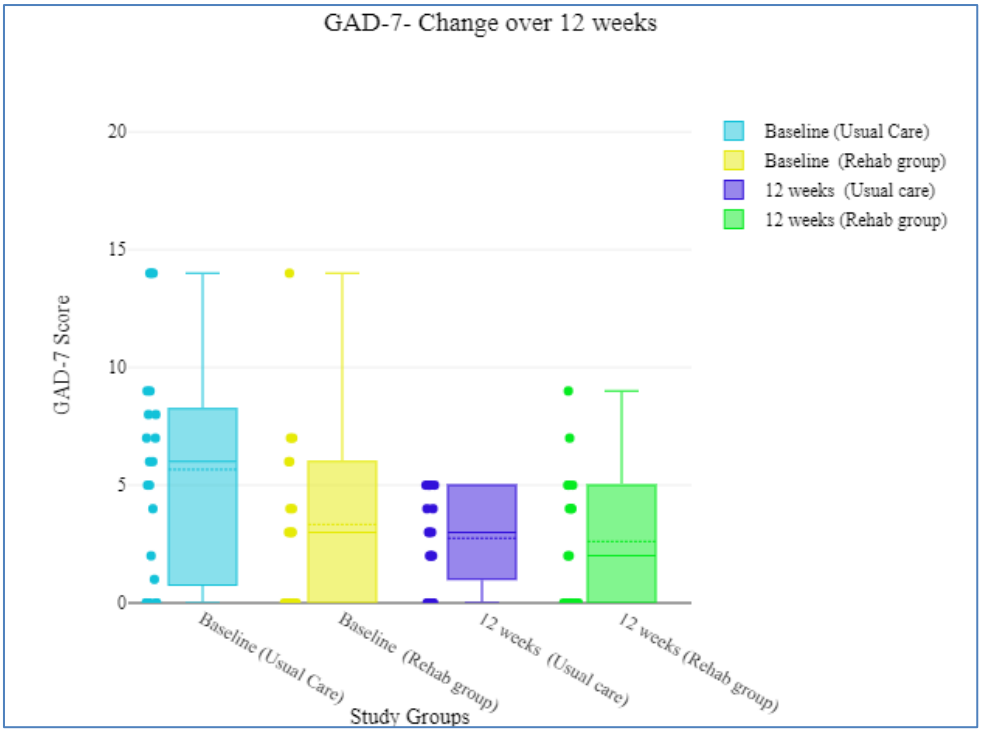


Figure 11- Box and whisker plot showing change in GAD-7 score in both groups over 12 weeks

Analysis of Drop-outs

During the study 17 patients dropped out from the trial, 12 were from the intervention group and 5 patients were from the control group.

The baseline characteristics (recorded at the time of enrollment) of the cohort who dropped out from the study were compared with those who did not drop-out and following table shows the key summary of the same:

Variable	Drop-out = yes n=17		Drop-out = no n=40				
	Mean	SD	Mean	SD	Diff	95%CI	P value
Age (years)	56.0	12.3	55.80	12.20	-0.20	-7.3 to 6.9	0.9551
BMI (kg/m^2)	25.3	6.20	25.2	4.80	-0.1	-3.1 to 3.0	0.9579
Duration of illness (months)	44.6	39.0	44.4	38.4	-0.1	-22.5 to 22.2	0.9902
MMRC median, (IQR)	3(2-4)	-	2(1-2)	-	-	-	0.0014
6-MWD (meters)	137.6	161.2	301.1	116.5	163.5	87.4 to 239.5	0.0001
DLCO (Corrected %)	24.9	24.2	39.2	19.6	14.3	2.0 to 26.5	0.0233
FVC (liters)	1.25	0.77	1.61	0.72	0.36	-0.08 to 0.77	0.1085
K-BILD	54.9	21.1	62.9	16.6	8.0	-2.4 to 18.5	0.1280
PHQ-9	8.3	8.6	6.70	5.0	-1.6	-5.2 to 2.03	0.3830
GAD-7	7.2	7.3	5.0	5.1	-2.2	-5.6 to 1.2	0.1982

Table 10- Comparison in baseline parameters between patients who dropped out with the patients who completed 12 week follow-up

The mean age, duration of illness and BMI was similar between those who dropped out and those who did not. As is clear from the above table, the subjects who dropped out from the study had worse DLCO, FVC and 6-MWD values compared to those

who did not and there was a statistically significant difference between the two groups in DLCO (14.3%, p-value 0.0233) and 6-MWD (163.5m, p-value 0.0001). Though mean FVC in non-dropouts was higher by0.36L, the difference did not reach a statistical significance. Also, the subjects who dropped out had a higher degree of dyspnea as reflected in baseline median dyspnea score by mMRC scale and the difference was also statistically significant (p value-0.0014).

Another key factor in drop-out was patient being on LTOT at the time of randomization. Eight patients in the entire study group were on LTOT and only 2 completed the 12 week follow up. Of the 17 patients who dropped out from the study, 6 patients were on LTOT (p value- 0.0028)

The patients who left the study had a higher baseline score on anxiety and depression questionnaires and scored much worse compared to the other group on quality of life questionnaire but none of these differences reached a statistical significance.

These baseline differences translated into many personal reasons and few unknown reasons for the patient to leave the study. At time of dropping out, patients were asked to elaborate the problems faced by them during the study or the problem due to which they wanted to leave the study. There was no preset pro-forma for recording these causes and they were recorded in patients' words. The reasons elaborated by the patients were clubbed into 9 categories based on similarity of the answers. While some patients had only one reason, many patients had multiple reasons for the dropping out and all were recorded for each patient. The patients who could not be contacted via calls or messages during the follow up or those who did not visit for follow up due to unknown reasons were marked as loss to follow up.

The most commonly reported reasons for dropping out were undue dyspnea provoked by exercise (n=6), problems in travelling to hospital for follow-up (n=5), financial limitations in initiating supplemental oxygen (n=4) and lack of response on call/ loss to follow up (n=4).

Many patients had overlapping reasons like having undue exertional dyspnea with a financial limitation in initiating supplemental oxygen or withdrawal of consent because the patient shifted to another city. Only the patients who could not be

contacted at all, and for whom no cause for absence could be determined were marked as loss to follow up.

Reason for dropping out	Intervention group (n) Total drop-outs =12	Control group (n) Total drop-outs = 5	Total (n)
Financial limitation in initiating supplemental oxygen	4	X	4
Unwillingness to initiate supplemental oxygen during exercise (only in rehabilitation group)	1	X	1
Undue dyspnea on exercise (only in rehabilitation group)	6	X	6
Consent withdrawn	1	1	2
Lack of motivation to exercise (only in rehabilitation group)	1	X	1
Inability to follow up- logistical problems in traveling to the hospital/ too breathless to travel	3	2	5
No response on telephone/ messages, "Loss to follow up"	2	2	4
Hospitalization during the study	1	1	2

Table 11- Reasons for patient drop-out from the study

Patient identified problems in home based rehabilitation: all the patients in the intervention group who were not lost to follow up were asked at the end of the study to describe the key problems faced by them in their own words. This was done with the purpose to identify the barriers to rehabilitation that the patients may face and the following key problems emerged:

1. Long walking distance between the various departments within hospital
2. Dyspnea on exercising leading to worsening of anxiety associated with dyspnea
3. Difficulty in travelling due to dyspnea
4. Lack of adequate finances to arrange for supplemental oxygen for the purpose of maintaining adequate activity
5. Fear and misconceptions about initiating supplemental oxygen therapy.
6. Lack of motivation, persistently poor mood and anxiety

DISCUSSION

This study was done with the intention of assessing the feasibility, safety, and efficacy of a guided home-based rehabilitation program in a heterogeneous group of ILD patients. The study began with the enrollment of 57 consecutive patients who were later randomized to the trial (n=30) and control groups (n=27). The mean age of the group was 55.8 years, with 30 females (52.6%) and 27 males (47.4%). The age and gender distribution of the group were very much similar to the Indian data on the prevalence of ILDs, as reported by Dhooria et al. (8), where they reported around 47% of patients with ILD as males with a mean age of 50.7 years. The slightly higher mean age of our group may have been due to the fact that our group had a mean duration of illness of 44.5 months at the time of recruitment. The second registry of ILD patients in India reported mean age of 55.3 years and 46.2% male patients, which is similar to our study group. (33)

The most common ILD type in the group was hypersensitivity pneumonitis (n=17, 29.8%), followed by NSIP (n=13, 22.8%) and IPF (n=11, 19.3%), organizing pneumonia (n=8, 14%), sarcoidosis (n=3, 5.2%) and two each (3.5%) with mixed pattern (HP/NSIP overlap) and undifferentiated ILD and one patient with post-Covid-19 DPLD. This distribution was significantly different from the prevalence described by a large registry in

India, where sarcoidosis (37.3%) was the most common ILD subtype, followed by connective tissue disease (CTD)-related ILDs (19.3%), idiopathic pulmonary fibrosis (IPF, 17.0%), and hypersensitivity pneumonitis (HP, 14.4%) (8). Another multi-center registry in India (33) reported hypersensitivity pneumonitis (in 47.3%) as the most common ILD, followed by CTD-ILD in 13.9% and idiopathic pulmonary fibrosis in 13.7%. Our group had comparable numbers of patients with CTD-ILD and IPF, but there was a significant discrepancy in the number of patients with HP and sarcoidosis. This can be due to two reasons; first, there is a significant regional difference in the prevalence of HP, and since our study was done only at a single center, the data was more reflective of local prevalence. Second, many cases of sarcoidosis are self-limiting and not all patients develop involvement of lung interstitium, as the study only involved the patients with ILD, many cases with sarcoidosis but without interstitial lung involvement were excluded.

There were a few baseline differences that crept up in the study due to the heterogeneous nature of the population that was included as a part of the trial. The trial included all patients irrespective of their type of ILD or long-term oxygen use. Despite randomization, there were a few significant differences in both groups. More patients with hypersensitivity pneumonitis were randomized to the control group, while the intervention group had more patients on LTOT and patients with a higher baseline dyspnea score. These factors may have influenced a high number of drop-outs from the intervention group. The final analysis showed that patients with higher dyspnea scores, patients on LTOT, and those with lesser 6-MWD had higher chances of dropping out of the study. In a study similar to ours, where home-based rehabilitation was done using video calls, the study had strict inclusion criteria where they included only patients with IPF with DLCO $\geq$ 30% predicted, FVC $\geq$ 50% predicted, six-minute walk test distance (6-MWD) $\geq$ 150 m (18). The aim of our study was to include all patients of ILD irrespective of disease type and severity, which led to these differences. Also, the randomization was done using a random number table which could not account for the differences in these baseline characteristics.

Our study faced a significant problem of drop-outs, 17 total (29.8%), with 12 from the intervention group and five from the control group. Though most participants had resting room air saturation $\geq$92%, there was significant desaturation on 6-minute walk test and on exercises advised as a part of PR program. Most of these patients had a sedentary life due to dyspnea and were not willing to start supplemental oxygen during exercise. Major reasons for this were a lack of adequate finances to arrange for oxygen supplement devices and undue dyspnea on exertion, which worsened the anxiety, and the patients were negatively motivated for rehabilitation. The financial constraints negatively associated with rehabilitation programs have not been discussed in published literature. Another major reason for the loss of follow-up was an inability to travel due to breathlessness. A logistical issue within the hospital also came to our notice, where the patients had to travel a long distance to the rehabilitation department for training and re-training. Though most studies have not reported the data on drop-outs or reported a 100% completion rate for the rehabilitation program, few studies have reported non-completion and drop-outs from both control and intervention groups ranging from 6% to 27.6% (20,25,27). Most numbers of drop-outs were reported by Heras et al., who conducted tele-rehabilitation

and reported 8 of 29 patients not completing the study. As most studies on pulmonary rehabilitation in ILD patients have been done in a hospital-based in-patient or out-patient set-up, problems associated with rehabilitation at home have not been highlighted, and the rate of study completion remains high. This highlights the fact that rehabilitation of ILD patients at home is not the same as a hospital-based rehabilitation program, and many problems which do not seem to arise in a hospital, like the availability of oxygen, may be a limiting factor in a home-based rehabilitation program and a major reason for non-adherence.

Though no study addressed the issues of drop-out from PR programs in ILD patients, indirect data has been reported in some studies. Data from the study by Wallaert et al. showed that ILD patients who completed the PR program had significantly higher baseline FVC and DLCO compared to drop-outs (22). On the other hand, the problem of drop-out from PR programs has been examined in COPD patients. A study by Li et al. assessed the factors of non-adherence to a home-based rehabilitation program in COPD patients and found that lack of motivation (44%), anxiety (23%), lack of social/ family support (16%), and comorbidities were major reasons for the same (34). They also found that non-adherence patients had higher emotional scores and lesser 6-MWD at baseline, which was also seen in our study.

Despite the above limitations, the patients who did complete the 12-week rehabilitation program reported better outcomes compared to the baseline. The changes were more in the quality of life and psychological domains as compared to the physical domain, but most patients who completed the follow-up reported feeling much better after 12 weeks, irrespective of the group they were randomized to. In the physical activity domain, the intervention group had a mean increase in 6-MWD of 16.3 meters after the 12-week PR program. Most studies and a Cochrane review (35) show a net positive benefit of rehabilitation on 6-MWD; the only study done on home rehabilitation showed stabilization of 6-MWD with rehabilitation rather than an improvement(18). This positive change in most can be due to the fact that there is usually no limitation of resources and machines in the hospital, and the rehabilitation program can be customized in real-time based on patients' symptoms and exertional capacity guided by monitoring of vital signs. At the same time, a more aggressive change in exercise regimen in a home-based program may lead to an undue worsening

of the patient's physical condition and may pose a risk to the patient, as real-time monitoring is not feasible. Also, most studies report that the change in 6-MWD is more in the patients with more severe restriction and lesser 6-MWD at baseline (35,36); the studies fail to assess these changes in a resource-limited home-based setting where a lack of support and oxygen supplementation acts a negative factor for continuing physical activity and PR program. As is evident in our study, most patients who dropped out had significantly lesser 6-MWD, FVC, DLCO, and SpO2 and had higher dyspnea scores at baseline. In order to continue the involvement of this subgroup and pass on the benefits of PR, we need to address all of these issues. Also, the larger benefit of cost saving in a home rehabilitation program is offset by a large fund needed to procure the oxygen supplement devices, especially in low-middle income populations where the cost of treatment itself may be more than income.

A less aggressive approach, as in our study, may be safer and more adaptable but probably yields less significant results. Another possible reason for a net positive change reported in the Cochrane review may be due to publication bias, where the studies with insignificant change or a negative change were not published and thus not included in the review. This is evident in the fact that there is only one published study that shows a fall in 6-MWD (Jackson et al.) despite pulmonary rehabilitation (37).

In our study, FVC (liters) and DLCO (%) were used to assess the change in lung function. The mean FVC increase in the intervention and control groups at 12 weeks was 130 ml and 50 ml, respectively. FVC increase in the intervention group was more by 80ml, but the difference between the groups and the change from baseline was not clinically significant. Most studies report stabilization of FVC on rehabilitation, but a statistically significant improvement with PR has not been reported in any study.

Though there was an increase in FVC, DLCO decreased in both groups, but the fall was lesser in the rehabilitation group as compared to the control group (-0.06 vs. -0.36%). The endpoint difference in both the groups was not clinically significant, and there was no effect of PR on improving DLCO. Most studies on PR have not used DLCO measures as a follow-up, and one study showed no improvement in DLCO, but comparative values were not provided in the data(18). A randomized trial on the benefits of rehabilitation in ILD by Dowman et al. (26) showed that both the FVC and

DLCO in the study subjects with IPF had declined despite an increase in 6-MWD and quality of life after rehabilitation. Thus, despite improvement in exercise capacity and quality of life, PR does not have a clinically significant effect on lung function decline, which may, in the best-case scenario, show either a mild improvement or stabilization.

Unlike changes in lung function, the improvement in quality of life with PR is unequivocal. A systematic review has shown that pulmonary rehabilitation begins to positively impact the quality of life immediately after the program (35). Previous studies have used St. George's Respiratory Questionnaire (SGRQ) and Chronic Respiratory Disease Questionnaire (CRDQ) which were not specifically developed for ILD patients. Though these questionnaires did encompass a wide range of domains, including physical symptoms, emotional, and activity, they were not specifically developed for patients with ILD. For our study, we used the K-BILD questionnaire which was specifically designed with ILD patients in mind (32). Irrespective of the scale used, the present study showed a similar result which corroborated the existing evidence that rehabilitation improves the quality of life in patients with ILD. Though the improvement was not clinically significant, it did conform to the rest of our outcome data, where none of the parameters had a significant improvement but achieved stabilization with home-based rehabilitation. There was a paradoxically more improvement in the quality of life domain in the control group which is difficult to explain. A possible placebo effect of inclusion in the study and overall improvement in psychological well-being may have contributed to it, as the patients in the control group also had a greater improvement in anxiety scores compared to the intervention group. Similar to our study, no significant change in K-BILD scores at three months was observed by Heras et al. in their trial (18). One limitation of our study, with respect to the quality of life assessment, was that all the patients with high depression and anxiety scores were referred to a specialist for management irrespective of their randomization status. Psychological intervention rather than rehabilitation may have been a reason for the improvement in QoL scores in these patients. By what degree the psychological intervention without exercise rehabilitation, and vice versa, improves QoL needs further assessment.

The prevalence of depression and anxiety in ILD patients ranges from 14%-49% and 21%-60%, respectively, depending on the scale used for assessment, ILD type, and patient characteristics (6). Multiple scales have been used to assess the psychological outlook of ILD patients, and all have shown a variable but high prevalence of both depression and anxiety in ILD patients. The hospital anxiety and depression scale (HADS) has been used most commonly across all studies. One study by Holland et al. used the HADS score to assess depression and anxiety in 124 ILD patients and found the prevalence of depression to be 23% and anxiety to be 31% (38). Another study by Coelho et al. using the Beck anxiety inventory and Beck depression inventory reported the prevalence of anxiety and depression to be 60% and 57% in ILD patients (39). In our study, we found an overall prevalence of anxiety in ILD patients (using GAD-7 ≥10 as the cutoff) to be 22.8% and a prevalence of depression (using PHQ-9 ≥10 as the cutoff) at 28% which was in agreement with the currently available prevalence data.

PR has been shown to improve depression and anxiety in patients with ILD immediately after rehabilitation and on a short-term follow-up in a few studies, but in none of these studies was it evaluated as a primary outcome (6). Also, all the studies done previously have not mentioned if the improvement in psychological outcome was due to PR only or if any additional intervention, such as pharmacotherapy or behavioral counseling, was done by a specialist. In the present study, we observed improvement in mental well-being across both groups, irrespective of whether physical rehabilitation was done or not. Though both groups showed improvement in PHQ-9 and GAD-7 at the end of 12 weeks, the control group had greater improvement in anxiety scores, whereas the intervention group had more improvement in depression scores. Whether the improvement was due to the exercise program only is difficult to say, but since it was seen in both groups, it may likely be due to psychiatric intervention.

Depression and anxiety have been overlooked and undertreated in patients with ILD, and an active search for these hidden problems is an exception rather than a norm. As we have already discussed, patients with poor mental health are more likely to drop out of the rehabilitation program. Poor mental health in these patients sets up a vicious cycle of worsening depression and anxiety, leading to poor motivation with

declining physical activity. ILD patients should be actively screened for anxiety and depression and referred for treatment if warning signs are present. Improvement in mental health can improve the overall quality of life, and the patient may become more agreeable to a PR program with better adherence once the mood improves and anxiety is allayed.

To summarize, our home-based PR program stabilized the fall in lung function and exercise capacity with an overall improvement in QoL, mental health scores, and dyspnea perception. Though the study was plagued by significant drop-outs, we learned a valuable lesson that home-based rehabilitation is not the same as a hospital-based program. Many logistical, financial, and cultural issues need to be considered and addressed for a home-based program to be widely adopted and accepted, especially in a low-middle-income population. Until we can overcome these barriers, significant inclusion and adhesion to PR program are unlikely to be achieved, and we need studies to find solutions to these problems.

CONCLUSION

Our study suggests that pulmonary home-based rehabilitation in patients with interstitial lung disease stabilizes lung function and exercise capacity and improves the quality of life and mental health in those who complete the program. We also identified significant modifiable factors responsible for the failure of a home-based rehabilitation program, such as exercise induced dyspnea with lack of supplemental oxygen devices, financial constraints, patients' attitude towards starting supplemental oxygen, poor mental health, and problems in traveling due to dyspnea. Evaluation for anxiety and dyspnea should be done in all patients with ILD, and timely referral for treatment can have a significant impact on the quality of life. Also, patients with severe ILD with worse mental health and dyspnea scores, and poorer exercise capacity at baseline, are more likely to drop-out of a home-based rehabilitation program and they should ideally undergo rehabilitation in hospital-based setting.

LIMITATIONS

1. The study group consisted patients with varying types and severity of ILD. The results may not be generalizable to all patients.
2. There were significant baseline differences in distribution by type of ILD in both groups
3. There was significant baseline difference in mean SpO2 and mMRC score between groups which may have led to more patients dropping out of the intervention group
4. More patients with LTOT were randomized to the intervention group which may have led to more drop-outs
5. Significant number of patients dropped out from the study. The intervention group suffered from more drop-outs which may have changed the results and reduced the overall power of the study.
6. High risk patients in both the groups were referred for psychiatric evaluation and management. The change in anxiety and depression scores could be due to psychological intervention and this may have diluted the actual impact that physical rehabilitation alone may have had on mental health.

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ANNEXURE-1

ALL INDIA INSTITUTE OF MEDICAL SCIENCES

JODHPUR

INFORMED CONSENT FORM

I …..…….son/ daughter of…….. a resident of……. hereby declare that I give informed consent to participate in the Thesis study labeled "**Randomized Control Trial on efficacy of home based Pulmonary Rehabilitation program in Interstitial Lung Disease patients."** Dr. Rishabh Kochar has informed me to my full satisfaction, in the language I understand, about the purpose, nature of study and various investigations to be carried out for the study. I have been informed about the duration of the study and possible complications caused by study.

I give full consent for being enrolled in the above study and I reserve my rights to withdraw from the study whenever I wish without prejudice of my right to undergo further treatment at this hospital and its associated hospitals.

_____ _____

Name of Subject Date Signature of subject

We have witnessed that the patient signed the above form in the presence of his/her free will after fully having understood its contents.

_____ _____

Name of Witness Date Signature of witness

_____ _____

Name of Investigator Date Signature of Investigator

ANNEXURE-2

अखिल भारतीय आयुर्विज्ञान संस्थान

जोधपुर

बोधित सहमति प्रपत्र

मैं,_____पुत्र/पुत्री_____

निवासी_____ डॉ. ऋषभ कोचर द्वारा शोध-निबंध शीर्षक **"इंटरस्टीशियल लंग डिजीज के मरीजों में घर पर आधारित फुफ्फुसीय पुनर्वास** कार्यक्रम **की प्रभावकारिता पर यादृच्छिक** नियंत्रित **परीक्षण।"** का हिस्सा बनने के लिए मेरी पूर्ण, स्वैच्छिक सहमति देता **हूँ।** निम्नलिखित अध्ययन की प्रक्रिया और प्रकृति **को** मुझे समझ में आने वाली भाषा में मेरी पूर्ण संतुष्टि के लिए समझाया गया है"

मैं किसी भी समय अध्ययन से बाहर निकलने के मेरे अधिकार से अवगत हूं" मैं समझता हूं कि मेरे और मेरे किसी भी मेडिकल रिकॉर्ड के बारे में एकत्र की गई जानकारी एम्स जोधपुर से जिम्मेदार व्यक्ति द्वारा देखी जा सकती है।मैं इन व्यक्तियों के लिए अपने रिकॉर्ड **देखने** की अनुमति देता हूं ।

दिनांक: _____

स्थान : _____ ……..

हस्ताक्षर/ बाएंअंगूठेकीछाप

यह प्रमाणित करने के लिए कि उपर्युक्त सहमति मेरी उपस्थिति में प्राप्त की गई है।

……	……	…….
साक्षी **का नाम**	हस्ताक्षर	दिनांक
डॉ. ऋषभ कोचर	……	…….
(अन्वेषक **का नाम)**	हस्ताक्षर	दिनांक

ANNEXURE-3

PATIENT INFORMATION SHEET

Name of the patient: **Patient ID**:

Randomized Control Trial on efficacy of home based Pulmonary Rehabilitation program in Interstitial Lung Disease patients

1. **Aim of the study**: To compare the effect of home based pulmonary rehabilitation on the exercise capacity and quality of life of ILD patients
2. **Study site**: Out Patient services of Department of Pulmonary, Critical Care and Sleep Medicine, All India Institute of Medical Sciences, Jodhpur, Rajasthan.
3. **Study procedure**: After detailed history, clinical examination and necessary baseline laboratory investigations, patients will be distributed and exercise and standard care group. Necessary monitoring will be done in study period.
4. **Likely benefit**: Study will help to know the effectiveness and feasibility of home based rehabilitation programs on ILD patients
5. **Confidentiality**: All the data collected from each study participant will be kept highly confidential.
6. **Risk**: Enrolment in above study poses no substantial risk to any of the study participant.
7. **Withdrawal from study**: You are free to decide whether to participate or not in the study or withdraw from the study anytime. If you choose not to participate in the study or withdraw from the study, you will continue to receive the same amount of care and treatment at AIIMS, Jodhpur.

Dr. Rishabh Kochar
Phone- 9871215080
Date-

ANNEXURE-4

रोगी सूचना पत्र

रोगी का नाम: रोगी आईडी :

इंटरस्टीशियल लंग डिजीज के मरीजों में घर पर आधारित फुफ्फुसीय पुनर्वास कार्यक्रम **की प्रभावकारिता पर यादृच्छिक** नियंत्रित **परीक्षण।**

1. अध्ययन का उद्देश्य: **आई.एल.डी रोगियों की व्यायाम क्षमता और जीवन की गुणवत्ता पर घर पर आधारित फुफ्फुसीय पुनर्वास के प्रभाव की तुलना करना**
2. अध्ययन स्थल: अखिल भारतीय आयुर्विज्ञान संस्थान, जोधपुर, राजस्थान के **श्वसन, गहन चिकित्सा एवं निद्रा रोग विभाग की बाह्य** रोगी सेवाएं।
3. अध्ययन प्रक्रिया: **विस्तृत इतिहास, नैदानिक परीक्षा और आवश्यक आधारभूत प्रयोगशाला जांच के बाद, रोगियों को व्यायाम और मानक देखभाल समूह में वितरित किया जाएगा । अध्ययन अवधि में आवश्यक निगरानी की जाएगी।**
4. संभावित लाभ: अध्ययन से **आई.एल.डी** रोगियों पर घर आधारित पुनर्वास कार्यक्रमों की प्रभावशीलता और व्यवहार्यता जानने में मदद मिलेगी
5. गोपनीयता: प्रत्येक अध्ययन प्रतिभागी से एकत्र किए गए सभी डेटा को अत्यधिक गोपनीय रखा जाएगा।
6. जोखिम: उपरोक्त अध्ययन में अध्ययन के किसी भी प्रतिभागी के लिए कोई जोखिम नहीं है।
7. अध्ययन से पीछे हटना: आप अध्ययन में भाग लेने या न लेने का निर्णय लेने के लिए स्वतंत्र हैं या अध्ययन से कभी भी पीछे हट सकते हैं। यदि आप अध्ययन में भाग नहीं लेते हैं या अध्ययन से पीछे हटते हैं, तो आपको एम्स, जोधपुर में देखभाल और उपचार की समान मात्रा प्राप्त होती रहेगी।

डॉ. ऋषभ कोचर

दूरभाष - 9871215080. **९८७१२१५०८०**

दिनांक-

ANNEXURE- 5

Pro forma

PROFORMA FOR DATA COLLECTION

Name- …… Age-……years Gender… CR No……..

Hospital ID…… Height……..cm Weight……. BMI……

Contact no- …… Occupation……

Marital status……..… Educational qualification …….

ILD type……...

Disease duration……...

Ongoing Treatment……...

……..

……..

LTOT- YES / NO

If yes, Flow Rate

Investigations

	Week 0	**Week 6**	**Week 12**
Hemoglobin			
TLC			
DLC			
Platelet			
Hematocrit			
Dyspnea on mMRC Scale			
Resting Saturation			
Resting Heart rate			
Resting BP			
Post- Exercise Saturation			
Post- exercise heart rate			

Post- exercise BP			
ECG **(Only if needed)**			
Venous Blood Gas/ Arterial Blood Gas (Only if Needed)			
6- MWD			
KBILD Score			
PHQ-9			
GAD-7 (max- 21)			
DLCO			
Spirometry			
REE			
TEE			

KBILD Questionnaire

1. In the last 2 weeks, I have been breathless climbing stairs or walking up an incline or hill.

1. Every time 2. Most times 3. Several Times 4. Some times
5. Occasionally 6. Rarely 7. Never

2. In the last 2 weeks, because of my lung condition, my chest has felt tight.

1. All of the time 2. Most of the time 3. A good bit of the time 4. Some of the time
5. A little of the time 6. Hardly any of the time 7. None of the time

3. **In the last 2 weeks have you worried about the seriousness of your lung complaint?**

1. All of the time 2. Most of the time 3. A good bit of the time 4. Some of the time
5. A little of the time 6. Hardly any of the time 7. None of the time

4. In the last 2 weeks have you avoided doing things that make you breathless?

1. All of the time 2. Most of the time 3. A good bit of the time 4. Some of the time
5. A little of the time 6. Hardly any of the time 7. None of the time

5. In the last 2 weeks have you felt in control of your lung condition?

1. All of the time 2. Most of the time 3. A good bit of the time 4. Some of the time
5. A little of the time 6. Hardly any of the time 7. None of the time

6. In the last 2 weeks, has your lung complaint made you feel fed up or down in the dumps?

1. All of the time 2. Most of the time 3. A good bit of the time 4. Some of the time
5. A little of the time 6. Hardly any of the time 7. None of the time

7. In the last 2 weeks, I have felt the urge to breathe, also known as 'air hunger'.

1. All of the time 2. Most of the time 3. A good bit of the time 4. Some of the time
5. A little of the time 6. Hardly any of the time 7. None of the time

8. In the last 2 weeks, my lung condition has made me feel anxious.

1. All of the time 2. Most of the time 3. A good bit of the time 4. Some of the time
5. A little of the time 6. Hardly any of the time 7. None of the time

9. In the last 2 weeks, how often have you experienced 'wheeze' or whistling sounds from your chest?

1. All of the time 2. Most of the time 3. A good bit of the time 4. Some of the time
5. A little of the time 6. Hardly any of the time 7. None of the time

10. In the last 2 weeks, how much of the time have you felt your lung disease is getting worse?

1. All of the time 2. Most of the time 3. A good bit of the time 4. Some of the time
5. A little of the time 6. Hardly any of the time 7. None of the time

11. In the last 2 weeks has your lung condition interfered with your job or other daily tasks?

1. All of the time 2. Most of the time 3. A good bit of the time 4. Some of the time
5. A little of the time 6. Hardly any of the time 7. None of the time

12. In the last 2 weeks have you expected your lung complaint to get worse?

1. All of the time 2. Most of the time 3. A good bit of the time 4. Some of the time
5. A little of the time 6. Hardly any of the time 7. None of the time

13. In the last 2 weeks, how much has your lung condition limited you carrying things, for example, groceries?

1. All of the time 2. Most of the time 3. A good bit of the time 4. Some of the time
5. A little of the time 6. Hardly any of the time 7. None of the time

14. In the last 2 weeks, has your lung condition made you think more about the end of your life?

1. All of the time 2. Most of the time 3. A good bit of the time 4. Some of the time
5. A little of the time 6. Hardly any of the time 7. None of the time

15. Are you financially worse off because of your lung condition?

1. A significant amount 2. A large amount 3. A considerable amount
4. A reasonable amount 5. A small amount 6. Hardly at all 7. Not at all

GAD-7 Questionnaire

Over the last 2 weeks, how often have you been bothered by the following problems?	**Not at all**	**Several days**	**More than half the days**	**Nearly every day**
1. Feeling nervous, anxious or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it's hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid, as if something awful might happen	0	1	2	3
Add up your results for each column				
Total score (add column totals together)				

- 0 to 4 = mild anxiety
- 5 to 9 = moderate anxiety
- 10 to 14 = moderately severe anxiety
- 15 to 21 = severe anxiety

PHQ-9 Questionnaire

Over the last 2 weeks, how often have you been bothered by any of the following problems?	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3
	0 + ____ + ____ + ____ = Total Score: ____			

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐

Patient's name:	Date:

ANNEXURE-6

Institutional Ethics Committee Certificate

अखिल भारतीय आयुर्विज्ञान संस्थान, जोधपुर
All India Institute of Medical Sciences, Jodhpur
संस्थागत नैतिकता समिति
Institutional Ethics Committee

No. AIIMS/IEC/2021/2503 **Date: 12/03/2021**

ETHICAL CLEARANCE CERTIFICATE

Certificate Reference Number: **AIIMS/IEC/2021/3338**

Project title: **"Randomized control trial on efficacy of home based guided pulmonary rehabilitation program in interstitial lung disease patients"**

Nature of Project:	**Research Project Submitted for Expedited Review**
Submitted as:	**D.M. Dissertation**
Student Name:	**Dr. Rishabh Kochar**
Guide:	**Dr. Naveen Dutt**
Co-Guide:	**Dr. M.K.Garg, Dr. Nishant Kumar Chauhan, Dr. Ramniwas, Dr. Ravi Gaur & Dr. Mukesh Swami**

Institutional Ethics Committee after thorough consideration accorded its approval on above project.

The investigator may therefore commence the research from the date of this certificate, using the reference number indicated above.

Please note that the AIIMS IEC must be informed immediately of:

- Any material change in the conditions or undertakings mentioned in the document.
- Any material breaches of ethical undertakings or events that impact upon the ethical conduct of the research.
- In case of any issue related to compensation, the responsibility lies with the Investigator and Co-Investigators.

The Principal Investigator must report to the AIIMS IEC in the prescribed format, where applicable, bi-annually, and at the end of the project, in respect of ethical compliance.

AIIMS IEC retains the right to withdraw or amend this if:

- Any unethical principle or practices are revealed or suspected
- Relevant information has been withheld or misrepresented

AIIMS IEC shall have an access to any information or data at any time during the course or after completion of the project.

Please Note that this approval will be rectified whenever it is possible to hold a meeting in person of the Institutional Ethics Committee. It is possible that the PI may be asked to give more clarifications or the Institutional Ethics Committee may withhold the project. The Institutional Ethics Committee is adopting this procedure due to COVID-19 (Corona Virus) situation. If the Institutional Ethics Committee does not get back to you, this means your project has been cleared by the IEC.

On behalf of Ethics Committee, I wish you success in your research.

Dr. Praveen Sharma
Member Secretary
Member secretary
Institutional Ethics Committee
AIIMS,Jodhpur

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