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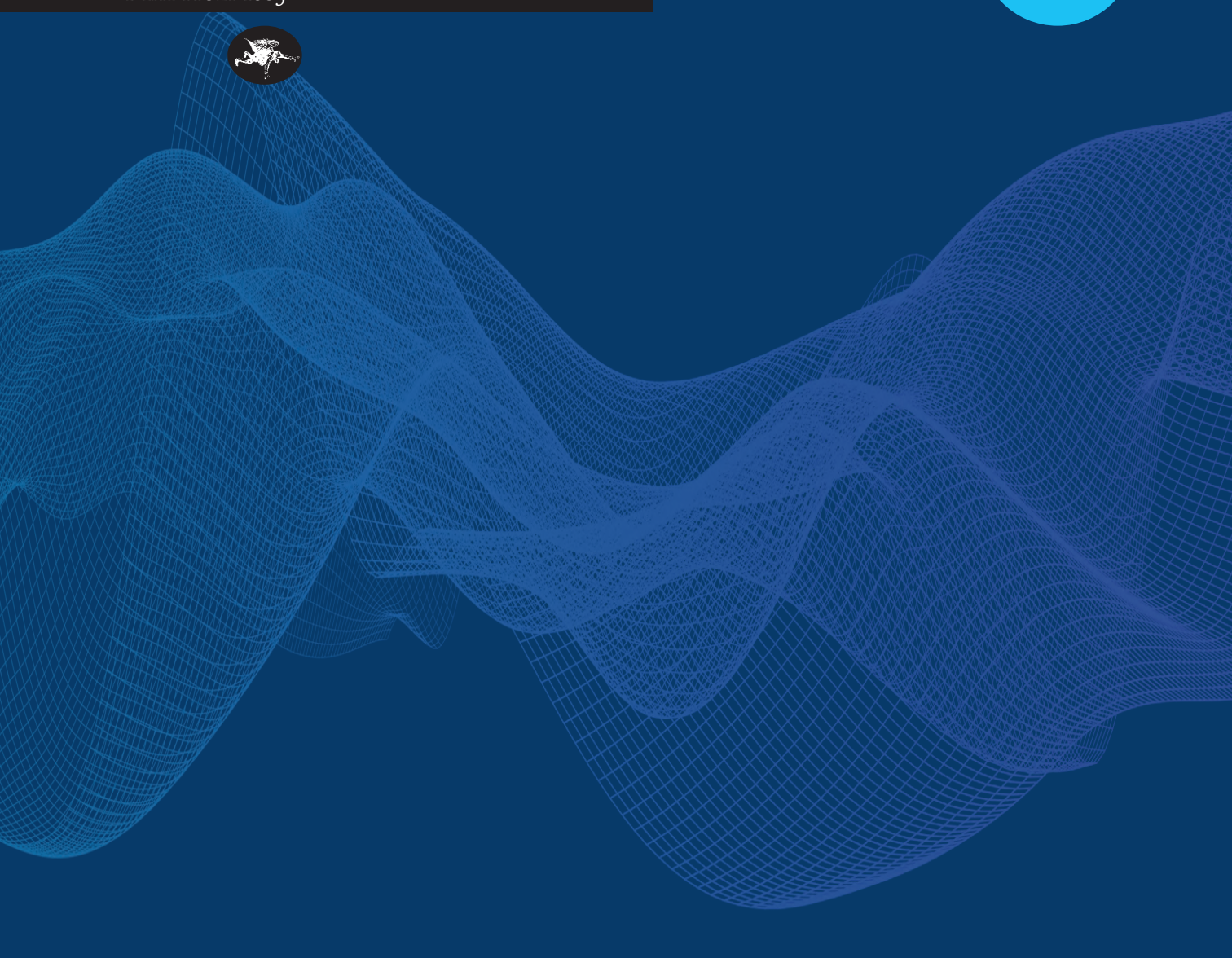

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Multidisciplinary Respiratory Medicine is a peer-reviewed, open access journal encompassing all aspects of respiratory medicine. It has a particular focus on interdisciplinary and translational research. Multidisciplinary Respiratory Medicine is published online at **https://mrmjournal.org/**.

The journal aims to provide a forum for the publication and free access of high quality original scientific articles, reviews and position papers documenting clinical and experimental advances in respiratory medicine, and related fields.

Given the journals interdisciplinary character, the target readership is wider than respiratory medicine, embracing numerous related disciplines (allergology, immunology, internal medicine, geriatrics, infectious diseases, intensive care, etc) and health professionals.

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mRNA vaccines protect from the lung microvasculature injury and the capillary blood volume loss occurring in SARS-CoV-2 paucisymptomatic infections

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ABSTRACT

Introduction: The reduction of lung capillary blood volume (Vc) had been identified as the microvascular injury mostly underlying the respiratory Long-COVID syndrome following post-COVID-19 pneumonia. The same kind of injury has been recently also found in several individuals after milder paucisymptomatic SARS-CoV-2 infections. Though current guidelines strongly recommend vaccination, studies aimed to investigate the *in vivo* protection of anti-SARS-CoV-2 vaccines on lung microvascular targets still are missing to our best knowledge.
Aim: to assess the protection of mRNA vaccines from the reduction of lung capillary blood volume (Vc) caused by paucisymptomatic SARS-CoV-2 infections in vaccinated compared to unvaccinated individuals.
Methods: Non-smoking individuals with recent paucisymptomatic SARS-CoV-2 infection were divided into vaccinated and unvaccinated groups. Lung function parameters, including single-breath diffusing capacity and microvascular blood volume, were compared between groups.
Results: Fifty vaccinated and twenty-five unvaccinated well-matched individuals were studied. Differently than usual lung function parameters, only the single-breath simultaneous assessment of sDL_{CO}, sDL_{NO}/sDL_{CO} ratio and Vc allowed to identify the occurrence of the lung microvascular injury with high sensitivity and specificity ($p<0.001$).
Conclusion: mRNA vaccines proved to exert a high protection from the loss of lung capillary blood volume (Vc) induced by SARS-CoV-2 paucisymptomatic infections ($p<0.001$). The availability of this non-invasive investigational model should be regarded as a very helpful tool for assessing and comparing *in vivo* the protective effect of mRNA vaccines on the human microvascular structures of the deep lung.

Key words: Long COVID; mRNA vaccines; lung function; DL_{NO} and DLco single-breath simultaneous measure; lung microvascular injury; lung capillary blood volume

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Authors' contributions: RWDN planned the study and wrote the manuscript; PT provided contributed to the final version of the manuscript and provided critical feedback; MP carried out all statistical calculations and contributed to the final version of the manuscript. All authors have read and agreed to the published version of the manuscript.

Ethics approval and consent to participate: The study was approved by the Ethical and Scientific Commission of the National Centre for Respiratory Pharmacoeconomics and Pharmacoepidemiology during the session of May 2nd, 2021. At recruitment, all subjects gave their informed consent also to the anonymous use of their own data for research purposes.

Availability of data and material: From the corresponding author on reasonable request.

Conflict of interest: The authors declare no conflict of interest. RWDN is Associate Editor of *Multidisciplinary Respiratory Medicine*.

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Introduction

The SARS-CoV-2 outbreak of late 2019 caused a tremendous public health impact worldwide during the following couple of years, with over half a billion confirmed cases and around seven million deaths as reported by the World Health Organization [1].

SARS-CoV-2 infections showed variable severity, ranging from the serious COVID-19 disease with acute respiratory failure (frequently fatal) to a mild clinical picture mostly involving only upper airways [2-5]. In general, the onset of infection is characterized by fever, dysgeusia, fatigue, anorexia and respiratory symptoms, such as: cough, expectoration, and dyspnea, of variable severity, duration and evolution [6-10].

It was shown that around 40% of patients are still complaining variable dyspnea associated to limitation in their quality of life for several weeks/months after their recovery from COVID-19 pneumonia (the Respiratory Long-COVID Syndrome) [11-14]. Our group demonstrated a substantial reduction of lung capillary blood volume that persists for several weeks in these cases [15].

Though previously underestimated and mostly regarded as merely due to psychological factors [6,16-18], long-lasting dyspnea associated to the same kind of pathophysiological lung disorders was also assessed by our group in a not negligible proportion of subjects following paucisymptomatic COVID-19 syndromes [19,20], thus supporting the occurrence of a substantial reduction of lung capillary blood volume also in these milder conditions.

Current guidelines recommend vaccination against SARS-CoV-2 of all eligible individuals [21-27]. However, despite the huge number of investigations focusing the biological and immunological effects of anti-COVID vaccines, pathogenetic studies aimed to investigate and assess their protection on specific lung structural targets *in vivo* still are missing to our best knowledge. mRNA vaccines are of great interest from this point of view because they were found to be highly effective in preventing the SARS-CoV-2 inflammatory aggression and safe **[**28-30].

Aim of the study was to compare the protection of mRNA vaccines against the reduction of lung capillary blood volume caused by paucisymptomatic SARS-CoV-2 infection in vaccinated and unvaccinated individuals.

Methods

Study design

Non-smoker patients of both genders, aged ≥18 years, referring to our Specialist Medical Centre (CEMS) between September 1, 2021 and June 30, 2023 after a paucisymptomatic SARS-CoV-2 infection (without any pneumonia) managed at home for a few days over the last six months before the date of recruitment were enrolled after their informed consent.

Exclusion criteria were: current and former-smoke habit; age < 18 years; comorbidities able to affect the diffusion capacity, namely: anemia (blood hemoglobin [Hb] <12g/L); heart failure, COPD; lung fibrosis; vasculitis; liver and renal failure; diabetes; any previous hospital admission for COVID pneumonia; any inflammatory parenchymal lesion radiologically (CT scan) documented over the last three months before recruitment; physical and/or cognitive impairment enabling procedures for lung function tests; refusal of consent.

The sample was divided in two groups: 1) vaccinated subjects at least two months before their paucisymptomatic SARS-CoV-2 infection, and: 2) unvaccinated individuals because no-vax, in proportion of 2:1.

The protocol is shortly described further below. All subjects were investigated by means of usual spirometric parameters and current diffusing capacity for carbon monoxide (DL_{CO}), associated with the non-invasive simultaneous single-breath measurements of DL_{CO} (sDL_{CO}) and nitric oxide (sDL_{NO}), the sDL_{NO}/sDL_{CO} ratio, and the lung capillary blood volume (Vc). The simultaneous single-breath method for assessing sDL_{CO} and sDL_{NO} (5 seconds breath hold time) was added to current DLco measures (10 seconds breath hold time) because current DL_{CO} is intrinsically unable to discriminate abnormalities occurring at the alveolar level (such as, the membrane diffusing conductance - DM) from those attaining the vascular side

of the blood gas exchange (such as, the total volume of blood in the lung capillaries exposed to alveolar air - Vc). In fact, as the binding of NO with intracapillary haemoglobin (Hb) is extremely faster than that one of CO, sDL_{NO} mainly informs on the condition of the epithelial surface of the alveolar membrane, while sDL_{CO} mainly informs on the vascular phase of diffusion through the membrane. Moreover, only when sDL_{NO} and sDL_{CO} are simultaneosly measured, the sDL_{NO}/sDL_{CO} ratio can be calculated. Obviously, higher the ratio, lower the value of sDLco, and then of the lung capillary blood volume (Vc). These are the reasons why the single-breath method for assessing sDL_{CO} and sDL_{NO} simultaneously is recommended for investigating the different factors affecting the determinants of diffusing capacity [31].

Current dyspnea was graded at recruitment by means of the Modified British Medical Research Council dyspnea score (mMRC-DS) in all subjects according to the British Thoracic Society (BTS) recommendations [31]. The duration of dyspnea was also calculated in days from the resolution of acute symptoms.

Data collected

Age, sex, body mass index (BMI), blood Hb (in g/L), % O_2 saturation (SpO_2 %), the mMRC-DS and comorbidities were recorded together with the therapeutic approach to the paucisymptomatic COVID infection at home. Information on anti-COVID vaccinations received before the SARS-CoV-2 infection were also collected.

Lung function parameters collected were: Vital Capacity (VC), Forced Expiratory Volume in 1 sec (FEV_1), current DL_{CO}, sDL_{CO} and sDL_{NO}, sDL_{NO}/sDL_{CO} ratio, and Vc. All parameters have been reported as % predicted. A Plethysmography Platinum DX Elite (MedGraphics, USA) was used for assessing spirometric parameters and usual DL_{CO} (10 seconds breath hold time). sDL_{CO} and sDL_{NO} (5 seconds breath hold time) were obtained simultaneously by means of the "Stand-Alone" Hypair Compact System (MGC Diagnostics International, Sorinnes, Belgium) that allows noninvasively the simultaneous assessment of diffusing membrane conductance (DM) and Vc (such as the vascular side of alveolar/capillary membrane) as a function of the standard single-breath method. This method is based on the principle by Roughton & Forster [32,33]: 1/DL=1/DM+1/Ø Vc, where 1/DL is the total resistance to the NO absorption and the CO uptake; 1/DM is the resistance opposed by the alveolar membrane, and 1/Ø Vc is the diffusion resistance to the red cell membrane and Hb combination [32,33]. As NO and CO are characterized by different solubilities for plasma, the method is based on the principle of two distinct reactions of Theta fractions, one for NO and the other for CO, during the same single breath.

Ethics

The study was approved by the Ethical and Scientific Commission of the National Centre for Respiratory Pharmacoeconomics and Pharmacoepidemiology during the session of May 2nd, 2021. At recruitment, all subjects gave their informed consent also to the anonymous use of their own data for research purposes.

Statistical analysis

A pre-specified sample size calculation was performed based on the mean difference of spirometric and diffusive parameters according to the formula for unmatched samples $n=(1+1/c)\ (z_{1-\alpha}+z_{1-\beta})^2/\Delta^2$, where $\alpha=5\%$ and $\beta=20\%$ are the type I and II errors, respectively. Δ is the standardized mean difference defined as the mean difference *d* of each parameter between the two groups divided by its standard deviation, and c is the ratio between vaccinated and unvaccinated patients. As vaccinated patients were expected to be more frequent than unvaccinated patients, a ratio of 2:1 (i.e., c=2) was chosen for the sample size calculation. Conservatively it was assumed that the mean value for each parameter considered in the group of unvaccinated patients would be 10% lower than the corresponding mean value in the group of vaccinated patients (for RV and sDL_{NO}/sDL_{CO} ratio, it was assumed an increase of 10%). The standard deviation of their mean difference was calculated assuming that the standard deviation for each parameter was equal to 40% of the mean value in both groups, and a plausible linear correlation $\rho=0.5$ for each parameter between the two groups. According to these assumptions, a total

of at least 60 patients (40 vaccinated and 20 unvaccinated) should be enrolled in the study.

Continuous data were presented as means and standard deviation (SD), while gender and prevalence of comorbidities as absolute and relative frequencies. Differences assessed in baseline between the two subsets of patients were tested by non-parametric Wilcoxon test (for continuous variables) and Fisher exact test (for gender and comorbidities). Differences in lung function parameters were estimated by a generalized linear model (gamma family) adjusting for all the characteristics available at enrollment. Results were reported as adjusted mean difference (AMD) and confidence intervals (CI). Moreover, the association between lung parameters and dyspnea was also investigated by ANOVA test using the variable mMRC-DS as categorical independent variable. Pairwise comparison (i.e. mMRC-DS=0 vs. mMRC-DS=1, mMRC-DS=0 vs. mMRC-DS=2, etc.) were expressed in terms of p-value adjusted for multiple comparison using the Sidak correction.

A $p < 0.05$ was considered statistically significant. All statistical calculations were carried out by means of STATA (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC).

Results

A total of 75 subjects were recruited: fifty vaccinated and twenty-five unvaccinated individuals. Patients of both groups had been managed at home by their GPs and were prescribed with anti-inflammatory drugs (100%), antimicrobics (64% macrolides; 24% α lactams; 10% quinolones), and systemic steroids (92%) for a few days. The distribution of prescriptions was not significantly different in the two groups (p=ns). Nirmatrelvir/ritonavir had never been used in the patients recruited.

All vaccinated subjects received three doses of mRNA vaccines (two doses and one buster) over an average of 163 days ±39 sd before the onset of their paucisymptomatic COVID syndrome. Vaccines used were Pfizer (55%) and Moderna (44%), respectively.

Baseline characteristics of subjects are reported in Table 1. At recruitment, the two groups were well matched for age, sex, BMI, Hb and prevalence of comorbidities. Moreover, the distribution of comorbidities was comparable in the two groups, such as: bronchial asthma (6); overweight (5), and blood hypertension (4) in the group of vaccinated subjects, while bronchial asthma (3); overweight (2), and blood hypertension (2) in the unvaccinated group, respectively. The mean dyspnea score was 0.3 (SD=0.5) in vaccinated subjects, while 1.1 (SD=0.8) in unvaccinated individuals ($p<0.0001$). Moreover, mean SpO_2 was higher in vaccinated than in unvaccinated individuals: 97.6% (SD=0.8) and 96.8% (SD=1.4), respectively ($p< 0.0018$).

Mean values of spirometric parameters (namely, VC and FEV_1) were in the normal range in both groups and no statistical difference was found between groups (Table 2). Similarly, no difference was observed

Table 1. Baseline characteristics of patients.

Parameters	Vaccinated	Unvaccinated	p
N	50	25	
Mean age (SD)	57.0 (14.5)	51.5 (11.5)	0.0580
Male (%)	28 (56.0%)	15 (60.0%)	0.4690
Mean BMI (SD)	25.0 (4.5)	26.3 (3.7)	0.2163
Al least 1 comorbidity (%)	21 (42.0%)	6 (24.0%)	0.1000
Mean Hb (SD)	13.9 (0.3)	14.1 (0.3)	0.0571
Mean SpO_2 (SD)	97.6 (0.8)	96.8 (1.4)	0.0018
Mean mMRC-DS (SD)	0.3 (0.5)	1.1 (0.8)	<0.0001

BMI: body mass index; Hb: blood hemoglobin; mMRC-DS: Modified British Medical Research Council dyspnea score; SD: standard deviation; SpO_2: saturation.

Table 2. Comparison of diffusive and spirometric parameters between vaccinated and non-vaccinated patients and statistical significance.

Parameters	Vaccinated	Unvaccinated	MD (95% CI)	AMD (95% CI)
FEV_1	95.4 (14.4)	91.4 (14.0)	4.1 (-2.7 to 10.8), p=0.239	6.2 (-1.0 to 13.4), p=0.093
VC	102.6 (13.5)	98.4 (13.4)	4.2 (-2.2 to 10.7), p=0.195	6.5 (-0.2 to 13.3), p=0.058
DL_{CO}	93.7 (13.7)	90.9 (20.8)	2.8 (-5.0 to 10.6), p=0.480	2.8 (-6.0 to 11.6), p=0.536
sDL_{CO}	82.8 (11.9)	73.6 (10.5)	9.2 (4.0 to 14.5), p=0.001	10.5 (4.4 to 16.7), p=0.001
sDL_{NO}	90.7 (11.6)	82.6 (13.8)	8.1 (2.3 to 14.0), p=0.006	8.8 (2.2 to 15.4), p=0.009
sDL_{NO}/sDL_{CO} ratio	109.9 (6.3)	117.7 (8.6)	-7.8 (-11.3 to -4.3), p<0.001	-8.7 (-12.6 to -4.8), p<0.001
Vc	65.1 (9.9)	54.1 (10.1)	11.0 (6.5 to 15.6), p<0.001	12.0 (7.0 to 16.9), p<0.001

AMD: adjusted mean difference; DL_{CO}: current diffusing capacity for carbon monoxide; FEV_1: Forced Expiratory Volume in 1 sec; MD: mean difference; sDL_{CO}: single-breath diffusing capacity for carbon monoxide; sDL_{NO}: single-breath diffusing capacity for nitric oxide; VC: Vital Capacity; Vc: lung capillary blood volume.

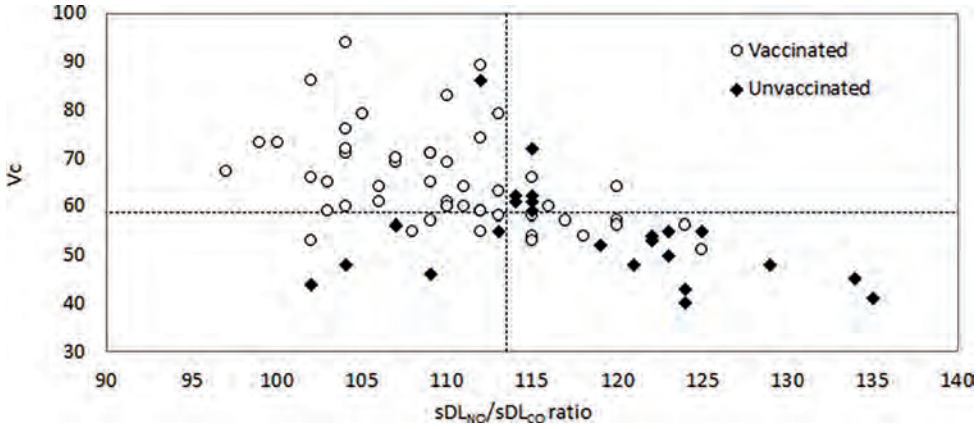

Figure 1. Distributions of vaccinated and unvaccinated subjects according to optimal cut-off values for sDL_{NO}/sDL_{CO} ratio (113.5) and Vc (58.5) [see reference 20].
sDL_{CO}: single-breath diffusing capacity for carbon monoxide; sDL_{NO}: single-breath diffusing capacity for nitric oxide; Vc: lung capillary blood volume.

in the current DL_{CO} between vaccinated and unvaccinated (p< 0.536). Conversely, sDL_{CO}, sDL_{NO}, sDL_{NO}/sDL_{CO} and Vc were highly discriminant, with significant differences in favor of vaccinated subjects (ranging between p<0.009 and p< 0.001) (Table 2). It should be also underlined that the distribution of sDL_{NO}/sDL_{CO} and Vc values below their optimal cut-off values for normality [19,20] appeared quite different between groups and dramatically in favor of vaccinated subjects (Figure 1 and Table 3). Specifically, about two third of vaccinated patients lie in the quadrant sDL_{NO}/sDL_{CO} ratio<113.5 and Vc>58.5, while almost half of the unvaccinated patients lie in the opposite quadrant (i.e., sDL_{NO}/sDL_{CO} ratio>113.5 and Vc<58.5).

The distribution of mean values for each lung function parameter collected are reported by mMRC-DS categories in Figure 2 and comparison among groups is detailed in Table 4.

The distribution of $sDL_{CO,}$ sDL_{NO}/sDL_{CO} ratio and Vc seem to be strongly associated with mMRC-DS categories (ANOVA test p <0.005). After adjusting for multiple comparison, distribution of Vc in patients with MRC-DS=2 is significantly different from the distribution in patients with both MRC-DS=0 and MRC-DS=1, and distribution of sDL_{CO} in patients with MRC-DS=2 is significantly different from the distribution in patients with MRC-DS=0 (Table 4).

Table 3. Distribution of subjects with sDL_{NO}/sDL_{CO} ratio and Vc values under and over optimal cut-off values for normality in both groups (see reference 20).

Vaccinated	ratio<113.5	ratio>113.5	Unvaccinated	Vc<58.5	Vc>58.5
Vc>58.5	66%	6%	**ratio<113.5**	4%	24%
Vc<58.5	10%	18%	**ratio>113.5**	24%	48%

sDL_{CO}: single-breath diffusing capacity for carbon monoxide; sDL_{NO}: single-breath diffusing capacity for nitric oxide; Vc: lung capillary blood volume.

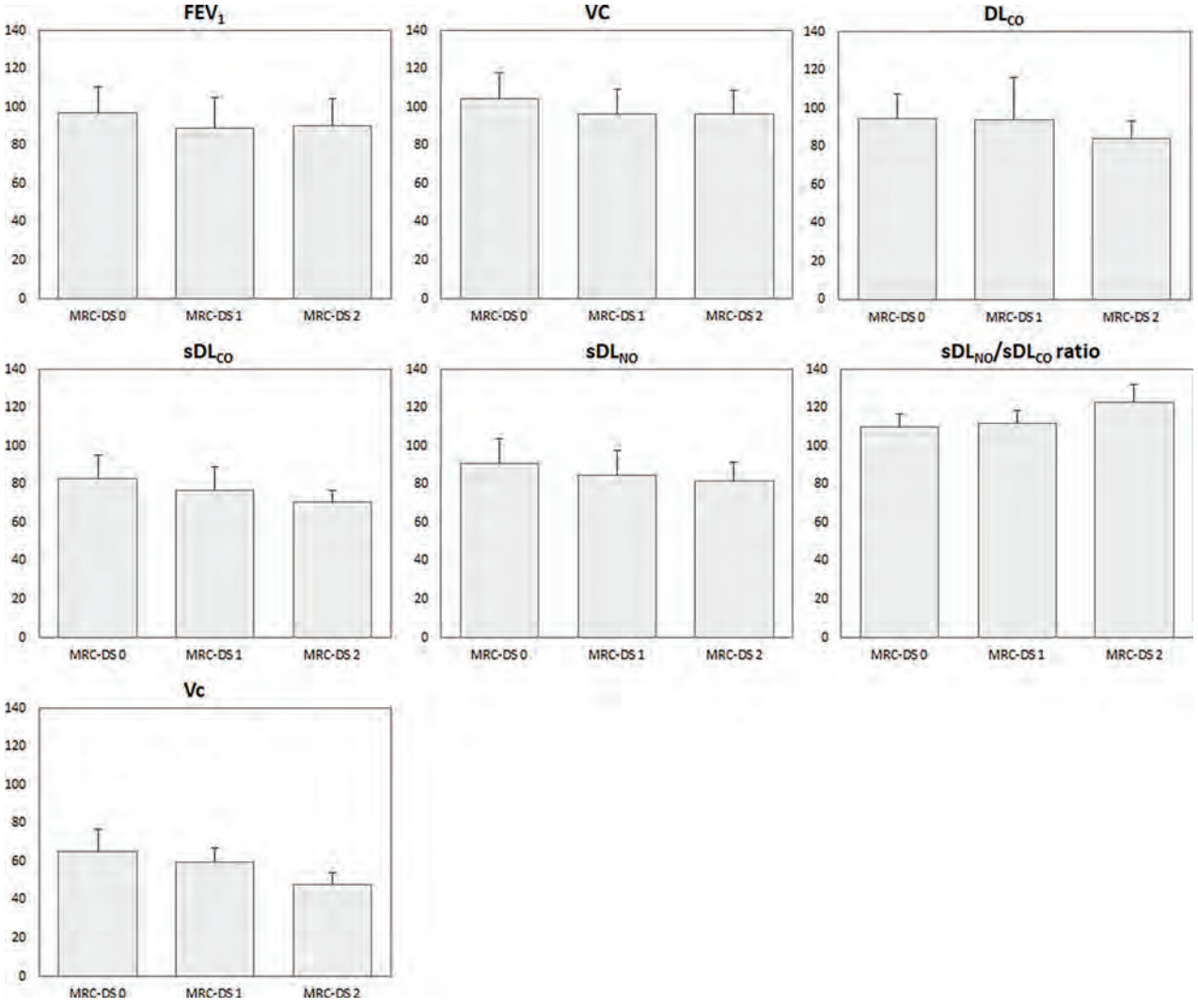

Figure 2. Mean value of diffusive and spirometric parameters according to MRC-DS (bars represent standard deviations).
DL_{CO}: current diffusing capacity for carbon monoxide; FEV_1: Forced Expiratory Volume in 1 sec; sDL_{CO}: single-breath diffusing capacity for carbon monoxide; sDL_{NO}: single-breath diffusing capacity for nitric oxide; VC: Vital Capacity; Vc: lung capillary blood volume.

Table 4. Comparison between diffusive and spirometric parameters among the MRC-DS groups: data expressed as mean (standard deviation). Comparisons among groups are expressed in terms of p adjusted for multiple comparison (Sidak correction).

Parameters	mMRC-DS 0	mMRC-DS 1	mMRC-DS 2	ANOVA test	mMRC-DS 1 vs. 0	mMRC-DS 2 vs. 0	mMRC-DS 2 vs. 1
FEV_1	97.3 (13.2)	89.4 (15.6)	90.7 (13.6)	p=0.0778	p=0.101	p=0.462	p=0.992
VC	104.6 (13.4)	96.7 (12.7)	96.4 (12.4)	p=0.0381	p=0.071	p=0.216	p=0.999
DL_{CO}	94.3 (13.4)	93.7 (22.3)	83.9 (9.2)	p=0.1819	p=0.998	p=0.195	p=0.309
sDL_{CO}	83.3 (11.8)	77.0 (12.4)	70.8 (6.3)	p=0.0048	p=0.113	p=0.008	p=0.409
sDL_{NO}	91.1 (12.7)	84.8 (12.9)	81.7 (10.2)	p=0.0427	p=0.166	p=0.105	p=0.890
sDL_{NO}/sDL_{CO} ratio	**110.3 (6.4)**	**112.0 (6.9)**	**122.8 (9.4)**	**p<0.0001**	**p=0.749**	**p<0.001**	**p<0.001**
Vc	**65.5 (11.2)**	**59.8 (7.0)**	**47.7 (6.4)**	**p<0.0001**	**p=0.081**	**p<0.001**	**p=0.004**

DL_{CO}: current diffusing capacity for carbon monoxide; FEV_1: Forced Expiratory Volume in 1 sec, mMRC-DS: Modified British Medical Research Council dyspnea score; sDL_{CO}: single-breath diffusing capacity for carbon monoxide; sDL_{NO}: single-breath diffusing capacity for nitric oxide; VC: Vital Capacity; Vc: lung capillary blood volume.

When compared to current DLco, the diffusive parameters obtained by the simultaneous single-breath method, such as the $sDL_{CO,}$ sDL_{NO}, sDL_{NO}/sDL_{CO} ratio and Vc, confirmed their high discriminant power in identifying the occurrence of the lung microvascular involvement and the loss of the microvascular blood volume (Table 4).

Respiratory structures (and those of the deep lung in particular) are the first human targets of the corona virus aggression. It is then easily presumable that long-term respiratory consequences of variable severity may occur in these circumstances [1, 34, 35], thus contributing to the onset of the respiratory Long-COVID syndrome.

Discussion

Long-term pulmonary symptoms (mostly dyspnea for several weeks) had been reported in several patients after SARS-CoV-2 infections, though paucisymptomatic [34,35]**.** As the aggression of SARS-CoV-2 to the lung structures recognizes alveolar damage, pulmonary congestion, and diffuse microvascular thrombosis in particular, as the major lung injuries occurring [4,36-40], long-term respiratory consequences in gas transfer may frequently occur and can be expected in a wide range of COVID severity, the paucisymptomatic syndromes included [19-20], due to ventilation/perfusion mis-match, being long-lasting dyspnoea the most frequent clinical sign.

Unfortunately, as mentioned above, these persisting troubles in blood gas transfer cannot be fully identified neither by spirometric procedures nor by current DL_{CO} measure due to their low specificity and sensitivity [13,41-43]. In particular, due to the slow binding of CO with intracapillary Hb, current measures of DL_{CO} proved insufficient to discriminate disorders of diffusing membrane conductance (DM) from those involving the vascular side of alveolar/capillary membrane and then for investigating and defining the underlying cause of ventilatory/perfusion mis-match occurring in these cases [31,33,44-47].

The persistent reduction of lung capillary blood volume (Vc), such as the total volume of blood in the lung capillaries exposed to alveolar air, has been recently identified as the peculiar pathophysiological disorder that is able to characterize and grade the respiratory Long-COVID syndrome in subjects still complaining long-lasting dyspnea also following paucisymptomatic SARS-CoV-2 infections. In other words, the microangiopathy originally occurred in the deep lung and the consequent drop in pulmonary volume of capillary blood correspond to the major pathogenetic events sustaining the previously unexplained long-lasting abnormalities in gas transport (namely, dyspnea) in these cases, regardless their normal lung volumes.

The single-breath simultaneous assessment of sDL_{CO}, sDL_{NO}/sDL_{CO} ratio and Vc allowed to identify *in vivo*, non-invasively, in short time, at

low cost and with high sensitivity and specificity the persisting underlying impairment of pulmonary microvasculature also due to paucisymptomatic SARS-CoV-2 infections, otherwise undetectable and then neglected [19,20,45,46]. In other words, also mild SARS-CoV-2 infections can alter the integrity of the lung microvasculature and consequently to lead to the inadequate response to tissue metabolic demands in some patients (as indicated by the persistency of their dyspnea) [19,20]. This aspect is crucial because the capillary blood volume proves reduced within the deep lung likely due to microvascular destruction. As a consequence, the vascular side of the diffusive function can result substantially affected also after milder SARS-CoV-2 infections. This peculiar pathophysiologial disorder can be used as a marker of SARS-CoV-2 injury of the lung and for checking the effect of possible preventive and/or therapeutic interventions. Data of the present investigation are further supported by the results of an elegant capillaroscopic study that described in various tissue samples the occurrence of a long-lasting reduction in vascular density and the persistent capillary rarefication as the two peculiar features that characterize both the acute SARS-CoV-2 infection and the Long-COVID syndrome [48].

In the present pivotal investigation *in vivo*, the difference between vaccinated and unvaccinated individuals proved dramatically in favor of the former groups of subjects. In other words, the mean extent of microvascular blood loss and the prevalence of cases characterized by diffusive values frankly lower the optimal cut-off limits for normality proved quite lower in vaccinated subjects. Present data are clearly suggesting that the microvascular derangement occurring in the lung can be largely prevented by anti-COVID vaccinations, in particular by mRNA vaccines. On the other hand, two-dose regimens of the Moderna and Pfizer-BioNTech mRNA vaccines (such as those vaccine that give your cells instructions for how to make the S protein found on the surface of the COVID-19 virus) had been documented to be able in providing a good protection (of around 90%) against severe COVID-19 in real-life, both in terms of mortality and morbidity [49]. Moreover, mRNA vaccines highly contributed to protect the economies worldwide and to implement public health measures according to innovative protocols of intervention.

Though the main goal of vaccines is to limit the spread of a pathogen within a population [50-52], the identification of a lung tissular target where their specific tissular protection could be assessed is of equal importance in our opinion, particularly when the parameters to use are easy to obtain, not time consuming and highly specific. This aspect assumes further importance when we consider that several factors can contribute to bias the general evidence of real efficacy and effectiveness of vaccination (namely, patients' different immune conditions and response; technical aspects; social and political issues, etc.). On the other hand, an autopsy-based analysis documented the importance of vaccine-induced immunity in protecting from the effects of the inflammatory viral-induced aggression, thus supporting the importance and the efficacy of the vaccination against SARS-CoV-2 pulmonary and cardiac injury [53]. Unfortunately, poor evidence is still available for *in vivo* specific tissular responses to anti-COVID-19 vaccinations in humans.

The present investigation is providing the first *in vivo* evidence to our best knowledge concerning the efficacy of mRNA vaccines in preserving specific biological structures of the deep lung. This recent evidence can represent a quite relevant human model for investigating and quantifying in short time and non-invasively the *in vivo* efficacy of anti-COVID vaccines in preserving from those long-lasting microvascular injuries and hidden alveolar-perfusion abnormalities that underly SARS-CoV-2 infections, though of "apparent" mild clinical severity.

The present study recognizes some points of weakness: it consists of a monocentric investigation and the sample size is obviously limited. Moreover, only two mRNA vaccines were used because only those two were provided by our Public Health Institutions over the study period.

On the other hand, points of strength are: the strict selection of subject investigated; the pivotal method for the non-invasive lung function measurements; the identification of a specific lung tissular disorder (such as, of lung microvasculature) for testing the protection power of mRNA, never investigated before.

Conclusions

Paucisymptomatic SARS-CoV-2 infections can cause long-lasting troubles in gas transfer and consequent long-lasting dyspnea in more than 40% of unvaccinated individuals.

The pathogenesis of these respiratory disorders proved mainly related to the reduction of lung microvascular blood volume occurring in the deep lung. These features, previously unknown and undetected, can now be easily identified by means of the single-breath simultaneous assessment of sDL_{CO}, sDL_{NO}/sDL_{CO} ratio and Vc with high sensitivity and specificity, being the lung microvascular injury, the main feature underlying.

The main and unprecedented message emerging from the present study is that mRNA vaccines provide high protection of the deep lung from the long-lasting loss of lung microvascular blood volume induced by SARS-CoV-2 infections, though paucisymptomatic.

The study protocol was basically based on the Roughton & Forster equation that underlies the simultaneous single-breath assessment of DL_{NO} and DLco. Even if small discrepancies vs conventional DLco measurements are possible due to some methodological differences (mainly to different gas sampling and breath-holding time, virtually slightly affecting the values for alveolar volume), the simultaneous single-breath assessment of DL_{NO} and DLco has been recognized as able to provide different physiological information that provide a better understanding of lung involvement in respiratory diseases [54].

Even if further studies are needed, mRNA vaccines provide high protection from the long-lasting loss of lung microvascular blood volume induced by paucisymptomatic SARS-CoV-2 infections.

The availability of this human *in vivo* lung model for assessing and comparing non-invasively the protection of mRNA vaccines on deep lung structures assumes high relevance in our opinion because the morbidity of SARS-CoV-2 infections is still high in the general population and specific mRNA vaccinations can easily prevent their persisting lung tissular consequences and minimize their public health burden.

Abbreviations

BMI: body mass index
Hb: hemoglobin
SpO_2 %: % O_2 saturation
mMRC-DS: modified British Medical Research Council dyspnea score
VC: vital capacity
FEV_1: forced expiratory volume in 1 second
DL_{CO}: current measure of diffusion capacity for carbon oxyde
sDL_{CO}: non-invasive simultaneous single-breath measurements of diffusion for carbon oxide
sDL_{NO}: the non-invasive simultaneous single-breath measurements of nitric oxyde
sDL_{NO}/sDL_{CO} ratio: the ratio between sDL_{NO}/sDL_{CO} values
Vc: the lung capillary blood volume
mRNA vaccines: messenger RNA vaccines

References

1. Ashhurst AS, Johansen MD, Maxwell JWC, Stockdale S, Ashley CL, Aggarwa A, et al. Mucosal TLR2-activating protein-based vaccination induces potent pulmonary immunity and protection against SARS-CoV-2 in mice. Nature Commun 2022;13:6972.
2. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. China Novel Coronavirus Investigating and Research Team. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020;382: 27-33.
3. Matricardi PM, Dal Negro RW, Nisini R. The first, comprehensive immunological model of COVID-19: implications for prevention, diagnosis, and public health measures. Pediatr Allergy Immunol 2020:31(5):454-70. doi:10.1111/pai.13271.
4. Guan W, Ni Z, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382:1708-20. https://doi.org/10.1056/NEJMo a2002032
5. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497-506.
6. Akbarialiabad H, Taghrir MH, Abdollahi A, Ghahramani N, Kumar M, Paydar S, et al. Long COVID, a comprehensive systematic scoping review. Infection 2021;49:1163-86.
7. Fernandez-de-las-Penas C. Long-COVID: current definition. Infection 2022;50:285-6.
8. Joshee S, Vatti N, Chang C. Long-Term effects of COVID-19. Mayo Clin. Proc 2022;97: 579-99.
9. Yong SJ. Long COVID or post-COVID-19 syndrome: putative pathophysiology, risk factors, and treatments. Infect Dis 2021;53(10):737-54.
10. Castanares-Zapatero P, Chalon L, Kohn M, Dauvrin M, Detollenaere J, Maertens de Noordhout C, et al. Pathophysiology and mechanism of long COVID: a comprehensive review. Ann Med 2022;54:1473-87.

11. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020;323:1061-69.
12. Iba T, Connors JM, Levy JH. The coagulopathy, endotheliopathy, and vasculitis of COVID-19. Inflamm Res 2020;69: 1181-9.
13. Mo X, Jian W, Su Z, Chen M, Peng H, Peng P, et al. Abnormal pulmonary function in COVID-19 patients at time of hospital discharge. Eur Respir J 2020;55,2001217. https://doi.org/10.1183/13993 003.01217 -2020;
14. National Institute for Health and Care Excellence, Scottish Intercollegiate Guidelines Network, Royal College of General practitioners. COVID-19 rapid guideline managing the long-term effects of COVID-19. Dec. 18, 2020. https//www.nice.org.uk/guidance/ng188 (accessed April 30, 2022).
15. Dal Negro RW, Turco P, Povero M. Long-lasting dyspnea in patients otherwise clinically and radiologically recovered from COVID pneumonia: a probe for checking persisting disorders in capillary lung volume as a cause. Multidiscip Respir Med 2022;17(1):875. doi: 10.4081/mrm.2022
16. Haque AH, Pant AB. Long COVID: untangling the complex syndrome and the search for therapeutics. Viruses 2023;15:42. https://doi.org/10.3390/v15010042
17. Halpin SJ, McIvor C, Whyatt G, Adams A, Harvey O, McLean L, et al. Post-discharge symptoms and rehabilitation needs in survivors of COVID-19 infection: a cross-sectional evaluation. J Med Virol 2021;93(2):1013-1022. doi: 10.1002/jmv.26368.
18. Sykes DL, Holdsworth L, Jawad N, Gunasekera P, Morice AH, Crooks MG. Post-COVID-19 symptom burden: what is Long-COVID and how should we manage it? Lung 2021;199:113-9.
19. Dal Negro RW, Turco P, Povero M. Phenotyping lung function disorders in respiratory Long-COVID**.** Brit J Multidisc Adv Studies 2023;4:71-83.
20. Dal Negro RW, Turco P, Povero M. Persistent Reduction of Lung Capillary Blood Volume as the Major "Deep Lung" Disorder Underlying Respiratory Long-COVID Syndrome. Am J Med and Public Health 2024;5(1):1-8.
21. Food and Drug Administration. Learn more about COVID-19 vaccines from the FDA. Silver Spring, MD: US Department of Health and Human Services, Food and Drug Administration; 2021. Accessed August 23, 2021. https://www.fda.gov/consumers/consumer-updates/learn-more-about-covid-19-vaccines-fda
22. CDC. COVID-19: different COVID-19 vaccines. Atlanta, GA: US Department of Health and Human Services, CDC; 2021. Accessed August 25, 2021. https://www.cdc.gov/coronavirus/2019-ncov/vaccines/different-vaccines.html
23. Krammer F. SARS-CoV-2 vaccines in development. Nature 2020;586:516-27.
24. Lavelle EC, Ward RW. Mucosal vaccines — fortifying the frontiers. Nat Rev Immunol 2022;22:236-50.
25. Haas EJ, Angulo FJ, McLaughlin JM, Anis E, Singer SR, Khan F, Brooks, et al. Impact and effectiveness of mRNA BNT162b2 vaccine against SARS-CoV-2 infections and COVID-19 cases, hospitalisations, and deaths following a nationwide vaccination campaign in Israel: An observational study using national surveillance data. Lancet 2021;397:1819-29.
26. Dagan N, Barda N, Kepten E, Miron O, Perchik S, Katz MA, et al. BNT162b2 mRNA COVID-19 Vaccine in a Nationwide Mass Vaccination Setting. N Engl J Med 2021;384:1412-23.
27. Chung H, He S, Nasreen S, Sundaram ME, Buchan SA, Wilson, SE, et al. Canadian Immunization Research Network (CIRN) Provincial Collaborative Network (PCN) Investigators. Effectiveness of BNT162b2 and mRNA-1273 COVID-19 vaccines against symptomatic SARS-CoV-2 infection and severe COVID-19 outcomes in Ontario, Canada: Test negative design study. BMJ 2021;374:n1943.
28. Lauring AS, Tenforde MW, Chappell JD, Gaglani M, Ginde AA, Tresa McNeal T, et al. Clinical severity of, and effectiveness of mRNA vaccines against Covid-19 from omicron, delta, and alpha SARS-CoV-2 variants in the United States: prospective observational study. BMJ 2022;376:e069761. http://dx.doi.org/10.1136/bmj-2021-069761)
29. Angel Y, Spitzer A, Henig O, Saiag E, Sprecher E, Padova H, et al. Association Between Vaccination With BNT162b2 and Incidence of Symptomatic and Asymptomatic SARS-CoV-2 Infections Among Health Care Workers. JAMA 2021;325:2457-65.
30. Pilishvili T, Gierke R, Fleming-Dutra KE, Farrar JL, Mohr NM, Talan DA, et al. Vaccine Effectiveness among Healthcare Personnel Study Team Effectiveness of mRNA COVID-19 Vaccine among, U.S. Health Care Personnel. N Engl J Med 2021;385:e90.
31. Mahler DA, Wells CK. Evaluation of clinical methods for rating dyspnoea. Chest 1988;93:580-6.
32. Roughton FJ, Forster RE. Relative importance of diffusion and chemical reaction in determining rate of exchange of gases in the human lung. J Appl Physiol 1957;11:290-302.
33. Graham BL, Brusasco V, Burgos F, Cooper BG, Jensen R, Kendrick A, et al. ERS/ATS standards for single-breath carbon monoxide uptake in the lung. Eur Respir J 2017;49(1):1600016. doi: 10.1183/13993003.00016-2016
34. van Kessel SAM, Olde Hartman TC, Lucassen PLBJ, van Jaarsveld CHM. Postacute and long-COVID-19 symptoms in patients with mild diseases: a systematic review. Fam Pract 2022;39:159-67.
35. Huang C, Huang L, Wang Y, Li X, Ren L, Gu X, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet 2021;397:220-32**.**
36. Tian S, Xiong Y, Liu H, Niu L, Guo J, Liao M, et al. Pathological study of the 2019 novel coronavirus disease (COVID-19) through postmortem core biopsies. Mod Pathol 2020; 33(6):1007-1014. https://doi.org/10.1038/s4137 9-020-0536

37. Dhawan RT, Gopalan D, Howard L, Vicente A, Park M, Manalan K, et al. Beyond the clot: perfusion imaging of the pulmonary vasculature after COVID-19. Lancet Respir Med 2021;9:107-16.
38. Wickman D, Sperhake JP, Lutgehetmann M, Steurer S, Edler C, Heinemann A, et al. Autopsy findings and venous thromboembolism in patients with COVID-19: a prospective cohort study. Ann Intern Med 2020;173:268-77.
39. Libby P, Luscher T. COVID-19 is in the end, an endothelial disease. Eur Heart J 2020;41:3038-44.
40. Iba T, Connors JM, Levy JH. The coagulopathy, endotheliopathy, and vasculitis of COVID-19. Inflamm Res 2020;69:1181-9.
41. Frija-Masson J, Debray MP, Gilbert M, Lescure FX, Travert F, Borie R, et al. Functional characteristics of patients with SARS-CoV- 2 pneumonia at 30 days post-infection. Eur Respir J 2020;56:2001754. https://doi.org /10.1183/13993 003.01754.
42. Mo X, Jian W, Su Z, Chen M, Peng H, Peng P, et al. Abnormal pulmonary function in COVID-19 patients at time of hospital discharge. Eur Respir J 2020;55:2001217. https://doi.org/10.1183/13993 003.01217 -2020)
43. Gibson QH, Roughton FJW. The kinetics and equilibria of the reactions of nitric oxide with sheep haemoglobin. J Phys 1957;136:507-24.
44. Zavorsky GS, van der Lee I. Can the measurement of pulmonary diffusing capacity for nitric oxide replace the measurement of pulmonary diffusing capacity for carbon monoxide? Respir Physiol Neurobiol 2017;241:9-16.
45. Zavorsky GS, Hsia CCW, Hughes MB, Borland CD, Guénard H, van der Lee I, et al. Standardization and application of the single-breath determination of nitric oxide uptake in the lung. Eur Respir J 2017;49:1600962. doi: 10.1183/13993003.00962-2016
46. Borland CDR, Hughes JMB. Lung diffusing capacities (DL) for nitric oxide (NO) and carbon monoxide (CO): The evolving story. Compr Physiol 2020;10:73-97.
47. George PM, Barratt SL, Condliffe R, Desai SR, Devaraj A, Forrest I, et al. Respiratory follow-up of patients with COVID-19 pneumonia. Thorax 2020;75:1009-16.
48. Osiaevi I, Schulze A, Evers G, Harmening K, Vink H, Kumpers P, et al. Persistent capillary rarefication in long COVID syndrome. Angiogenesis 2023 Feb;26(1):53-61. doi: 10.1007/s10456-022-09850-9.
49. Self WH, Tenforde MW, Rhoads JP, Gaglani M, Adit A, Ginde AA et al. Comparative Effectiveness of Moderna, Pfizer-BioNTech, and Janssen (Johnson & Johnson) Vaccines in Preventing COVID-19 Hospitalizations Among Adults Without Immunocompromising Conditions — United States, March–August 2021. MMWR 2021;70(38):1337-43.
50. Graham BS. Advances in antiviral vaccine development. Immunol Rev 2013;255(1):230-42. https://doi.org/10.1111 /imr.1209890
51. Notarte KI, Catahay JA, Velasco JV, Pastrana A, Ver AT, Pangilinan FC, et al. Impact of Covid-19 vaccination on the risk of developing long-COVID and on existing long-COVID symptoms. A systematic review. EClinicalMedicine 2022;53:101624.
52. Haque AH, Pant AB. Long COVID: untangling the complex syndrome and the search for therapeutics. Viruses 2023;15:42. https://doi.org/10.3390/v15010042
53. Colombo D, Del Nonno F, Marchioni L, Lalle E, Gallì P, Vaia F, et al. Autopsies Revealed Pathological Features of COVID-19 in Unvaccinated vs. Vaccinated Patients. Biomedicines 2023;11:551. https://doi.org/10.3390/bio medicines11020551
54. Kang M-Y, Grebenkov D, Guénard H, Katz I, B Sapoval B - The Roughton-Forster equation for DL_{CO} and DL_{NO} re-examined. Respir Physiol Neurobiol 2017:241: 62-71.

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Original Research Article

Post-COVID conditions response: a collaborative approach to establishing multidisciplinary clinics in Ecuador

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ABSTRACT

Introduction: Worldwide, 3.7% (144.7 million) of people diagnosed with COVID-19 developed Post-COVID Conditions (PCC). Therefore, creating and implementing multidisciplinary rehabilitation clinics is important to address the needs of patients and improve overall recovery. This study was made possible with support from the United States Agency for International Development funded RISE program, under the terms of the cooperative agreement 7200AA19CA00003.

Methods: This case study was conducted in Ecuador and describes the creation and implementation of 21 PCC rehabilitation clinics in primary healthcare centers and secondary level hospitals in 7 provinces across the country. Data was gathered for the identification of partnering health facilities and needs, for the evaluation of knowledge enhancement in health professionals after a specific training program, and for the measurement of key performance indicators. This article emphasizes the organization, educational strategies, and implementation of rehabilitation programs tailored specifically for the management of Post-COVID Conditions in Ecuador.

Results: The implementation of PCC rehabilitation clinics involved a collaborative effort between the Ministry of Public Health (MOPH), the private sector and a non-governmental organization (Jhpiego). Twenty-one health facilities from the primary and secondary level of care were selected, and PCC rehabilitation implemented in 7 provinces of Ecuador. Additionally, 133 health providers were trained and a total of 13,846 patients treated, among whom 859 had a diagnosis of PCC. Medical doctors outperformed nurses in both pre- and post-tests scores. However, all healthcare professionals demonstrated comparable improvement in knowledge acquisition. Rehabilitation manuals were developed and adopted by the MOPH, rehabilitation equipment was donated and a mobile application, "RESPIRA", was developed and disseminated free of charge.

Conclusion: The establishment of PCC rehabilitation clinics in Ecuador was successful in identifying patients in need of early rehabilitation. The insights of this study can serve as a guide for the development of similar initiatives in other countries. Tailored courses are essential to address disparities and ensure comprehensive skill development and promote equitable healthcare delivery.

Key words: Multidisciplinary care; post-COVID Conditions; rehabilitation; specialized care; under-resourced settings

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Ethics approval and consent to participate: This study was approved by Universidad San Francisco de Quito ethics committee (2022-68M).

Data availability statement: All data generated or analyzed during this study are included in this published article as supplementary information. The datasets generated during and/or analyzed during the current study are available from the corresponding author

on reasonable request. These databases don't contain patient data; instead, they delve into the structure, educational strategies, and implementation of programs designed for the development and implementation of multidisciplinary clinics for the management of Post-COVID Conditions in Ecuador.

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Introduction

Globally, 3.7% (144.7 million) of people diagnosed with COVID-19 developed Post- COVID Conditions (PCC) [1]. Although the clinical presentation of acute COVID-19 varies from asymptomatic to critical, about 80% of patients have mild to moderate infections with symptoms lasting 4-5 days and with full recovery 7-10 days post-infection [2]. However, among follow up of recovering patients, persisting symptoms can be identified longer than 12 weeks after the acute infectious period, leading to Post-COVID Conditions (PCC) [3]. Although a correlation between severity of acute infection and likelihood of developing PCC has not been clearly established [3-5], there is evidence of persisting dyspnea following COVID-19 pneumonia [6]. These symptoms are not restricted solely to pulmonary effects but may span across multiple organ systems [2, 3, 7]. Post-COVID Condition develops after SARS-CoV-2 infection and is diagnosed due to the persistence of symptoms after 12 weeks of the onset of the disease [8]. Symptoms vary in severity and include but are not limited to reported symptoms such as shortness of breath, fatigue, changes in taste or smell, and joint or muscle pain [9].

The multi-system nature of PCC has placed a burden on both patients and health systems requiring specialized teams to tackle a plethora of multi-organ symptoms involved. Hence the relevance of establishing PCC rehabilitation clinics to strengthen rehabilitation care in Ecuador and specifically to introduce multidisciplinary rehabilitation for patients with PCC. Unfortunately, Ecuador is under-resourced and understaffed, rehabilitation services are scarce and in many geographical areas inexistent. To this end, in this article we depict key steps in establishing PCC rehabilitation clinics in Ecuador, including creating governmental alliances, educating, and training healthcare staff to identify and manage PCC patients.

Methods

Project background

RISE is a global program funded by the U.S. President's Emergency Plan for AIDS Relief

(PEPFAR) and the U.S. Agency for International Development (USAID) that supports over 20 countries worldwide in both attaining and maintaining epidemic control through collaboration with strong local partners managing sustainable, self-reliant, and resilient health systems by 2024. Within the RISE expansion of COVID-19 response in Ecuador, one of the objectives was to increase and potentiate national capacity in case management, coordination, and operations for COVID-19 rehabilitation and home-based care. This objective was achieved with USAID´s support and in collaboration with the Ministry of Public Health, through the selection of facilities, equipment procurement and subsequent training of health providers.

Additionally, protocols, standards of practice, guidelines and digital tools were developed for case management.

Study setting

In Ecuador, the health system is organized into different levels of care, ranging from the primary level to the tertiary level. Our study focuses on primary and secondary level of care. The primary level of care provides primary and preventive medical care. It includes health centers and medical units located in communities and rural areas and offers basic health services. The secondary level of care comprises general and specialized hospitals for medical and surgical services. These facilities offer specialties such as surgery, gynecology, pediatrics, and internal medicine, among others.

Implementation of multidisciplinary PCC rehabilitation clinics in Ecuador

Identification and selection of public health facilities

RISE developed a program titled: "Functional recovery of COVID-19 and PCC" that included a series of ten webinars provided by national and international experts to raise awareness and disseminate evidence-base knowledge about PCC. The webinars were conducted via Zoom© and transmitted by Facebook© Live through the Universidad San Francisco de Quito's (USFQ) School of Medicine homepage. A total of 4,930 individual health professionals attended. This program allowed us to identify the need for additional training and capacity building, through the development and implementation of multidisciplinary rehabilitation clinics (Figure 1).

After the program completion, and in collaboration with the Ministry of Public Health (MOPH), a facility level assessment focusing on rehabilitation services was completed online by 123 publicly funded health facilities around the country. The assessment results and the facility treatment of patients with diagnosis of COVID-19 determined the selected institutions where the PCC rehabilitation clinics would be implemented.

In consultation with the Ministry of Public Health (MOPH), 18 of 123 health facilities throughout 7 provinces in Ecuador were selected for expanded services, rehabilitation, and treatment of PCC. Furthermore, after the implementation of these first

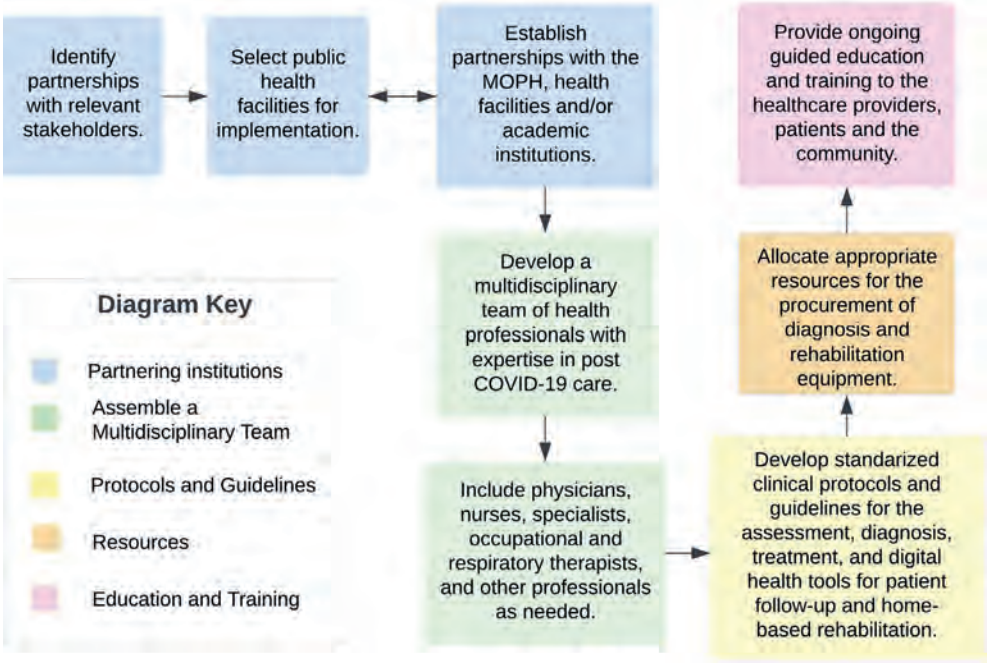

Figure 1. Key steps to establish a PCC rehabilitation clinic.

clinics, the Municipality of the Metropolitan District of Quito requested RISE to develop PCC rehabilitation clinics in three Metropolitan Health Units, located at the North, Center and South of Quito, increasing the total number to 21, located in 7 provinces of the country (Figure 2).

Development of multidisciplinary teams

Health professionals working in the selected facilities received further on-site training, taking into consideration their availability and willingness to work in a high-demand environment and in a multidisciplinary team. Health facilities were under-staffed, and training was challenging as it had to be individualized to each health provider´s area of competence which wasn´t represented in all facilities. Training was provided to health postgraduate students, physiatrists, family physicians, attending physicians, general practitioners, rural physicians, interns (medical students in the last year of their career), psychologists, psychiatrists, pediatricians, nurses, technicians, physical therapists, respiratory therapists, and paramedics.

Equipment donation

Although PCC affects diverse organs and effective treatment relies on a multidisciplinary approach, respiratory equipment was specifically selected for donation in Ecuador, as the devices were scarce and/or new to the country. Therefore, donations included spirometers, oximeters, non-invasive gas analyzers, and inspiratory muscle trainers (IMT). These devices play a crucial role in evaluating respiratory function, lung volumes, monitoring oxygen levels, analyzing gas exchange and improving respiratory muscle strength.

Based on the identified needs, RISE prepared a comprehensive procurement plan, considering equipment specifications, quantity, estimated costs, and timelines. The project followed processes and guidelines

Figure 2. Location of health facilities where the PCC rehabilitation clinics were implemented.

aligning with the donor´s and the MOPH´s policies and evaluating the equipment for quality and appropriateness. The donated equipment was allocated to 21 health facilities and healthcare staff received training on equipment use, ensuring seamless integration and improved patient care. RISE continuously monitored and evaluated the impact of the donation for potential adjustments and additional support.

Development of a mobile application for PCC: RESPIRA APP

RISE developed a mobile application for Android and iOS mobile devices, called RESPIRA.

RESPIRA informs patients about symptoms inherent to PCC and provides rehabilitation exercises that can be done at home. RESPIRA supports domiciliary rehabilitation with the supervision of a health provider and has multimedia content such as illustrations, photos, audio, and videos.

Android users can download RESPIRA App for free by clicking on the following link:

https://play.google.com/store/apps/details?id=com.app.postcvid

For iOS devices, it can be downloaded from the following link:

https://apps.apple.com/ec/app/respira/id6446152507?l=en

Development of standardized protocols, guidelines, and tools for patient assessment

RISE developed evidence-based PCC rehabilitation manuals for health providers and patients that were adopted by the MOPH, nationally. RISE developed infographics that health providers offered to the patients, increasing access to timely rehabilitation and home care (Figure S1 in the appendix supplementary material).

Ongoing guided education and training to healthcare providers

RISE developed the training package: "Identification and management of Post COVID-19 Conditions in Ecuador" to provide tools for health professionals and patients to gain understanding and knowledge of PCC. Additionally, a "Post COVID-19 Conditions Rehabilitation Manual" in two versions (one for health professionals and one for patients) was developed. While both manuals focus on PCC rehabilitation, with a multidisciplinary and multisystemic approach, the interventions of respiratory rehabilitation have been used as a guide for other pulmonary conditions. Moreover, training courses based on constructivism, were created along with the manuals, to encourage participants to build their knowledge based on their experiences and newly acquired knowledge. These courses applied methodological resources such as practice-based education, experiential learning, virtual learning, and case analysis, which allowed for the development of decision-making and teamwork. All training topics adhered to current management guidelines and biosafety protocols [10]. The training consisted of two modalities: in-person and virtual.

The virtual modules were delivered daily by Zoom©, for two hours, during three consecutive days and provided a theoretical background of PCC, including symptoms, signs, and multi- system manifestations. The goal was to enable early diagnosis and timely management.

The on-site training strengthened and deepened the knowledge acquired in the virtual meetings, through participatory discussions with questions and answers and practice-based learning involving rehabilitation procedures and techniques. The same participants that attended a virtual component attended the in-person training, which lasted 12 hours in total. The training schedule and topics are depicted (Table S1 in the appendix supplementary material).

Evaluation

The practical sessions were done on-site, which included 3 sessions of 4 hours each. The methodology included practice-based education. During these sessions, participant's new knowledge was reinforced and evaluated through simulated clinical case presentations. A moderator provided a brief introduction and discussion on the most important components of the case presentations. Participants were divided into smaller groups and were assessed on procedures such as the 6-minute gait test [11], the proper use of Inspiratory

Muscle Training, IMT, breathing exercises, early mobilization, the Sit to Stand Test [12], Barthel Index, and the Post COVID-19 Functional Status Scale [13].

To evaluate knowledge acquisition, participants were given questionnaires consisting of 15 questions written by local experts. Each questionnaire included the material detailed in the course and was applied twice, before the training and immediately after completing all the course components (theoretical, practical, virtual and in-person). The evaluation was applied through Qualtrics, with the aim to increase participant´s engagement and accessibility from any mobile device.

Data collection tool

After the overall implementation of the 21 post COVID-19 rehabilitation clinics (training, guidelines, manuals, and equipment), a survey was generated on the KOBO platform that allowed the determination of the number of patients with a diagnosis and who received treatment for PCC. Due to the lack of an established protocol or clinical practice guidelines in the health facilities, the diagnostic criteria were determined according to evidence-based information available at that moment, from the PCC manuals created by RISE (Figure S2 in the appendix supplementary material).

Follow up

After completing the overall implementation of the PCC rehabilitation clinics, a comprehensive follow up assessment was conducted and RISE worked with each institution´s team to create tailored flowcharts that addressed the unique needs and capabilities of each healthcare center and hospital, ensuring a seamless and efficient process for referring patients to the appropriate area of need.

Results

Participant demographics

From July 2022 to February 2023, RISE conducted three in-person theoretical and practical training sessions including 133 participants from 21 facilities. Out of these, 50 (37.59%) were physical therapists, 42 (31.58%) medical doctors, 8 (6.02%) respiratory therapists, 4 (3.01%) occupational therapists, 2 (1.50%) speech therapists, 12 (9.02%) nurses and 15 (11.28%) had other health professions. The cohort was mainly female (71%).

Knowledge acquisition

Evaluation of knowledge acquisition was done before and after the training, to determine the impact of the theoretical and practical sessions through a 15-question evaluation. On average, the participants showed an increase of 2.47 points when comparing average scores from the pre-test (7.95) to post-test (10.42), with a maximum score of 15 points (Figure 3). Additionally, our results evidenced a more homogenous distribution of the post-test scores vs pre-test scores. Although this suggests a significant impact ($p = 0.0000003$) on knowledge acquisition, the higher variance values portray variability on an individual level within the groups. Overall, we could determine that the training sessions provided knowledge acquisition regarding identification and management of patients with PCC.

Additionally, three distinct statistical analyses were conducted to determine any difference in prior knowledge and acquired knowledge among categories of healthcare professionals. These professionals were classified into four groups: medical doctors, nurses, respiratory therapists, and others. The initial analysis reviewed pre-test scores across professional categories, revealing a statistically significant difference between medical doctors and nurses, with medical doctors exhibiting higher scores. Contrary, no significant difference was observed when comparing the other group of professionals. A second analysis of post-test scores demonstrated similar findings, with medical doctors achieving significantly higher scores compared to nurses, while other comparisons remained statistically equivalent. Finally, the third analysis evaluated participants' knowledge acquisition, calculated by subtracting post-test scores from pre-test scores. This analysis indicated no statistical disparity among healthcare

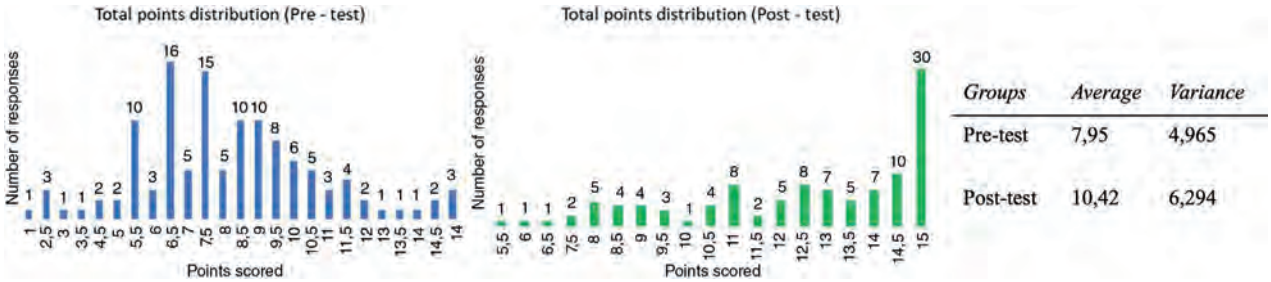

Figure 3. Recorded scores of participants' pre and post-test.

Table 1. Patients cared for in the PCC rehabilitation clinics (from July 5, 2022, to March 31, 2023).

Patients care by RISE supported facilities		
Facility	**Patients**	**Post COVID-19 Patients**
Hospital Docente De Calderón	5,090	157
CS Tabacundo	2,181	61
CS La Troncal	1,973	23
Hospital Vicente Corral Moscoso	1,648	109
Hospital Básico Yaruqui	1,540	191
CS Nabón	399	47
Hospital San Luis De Otavalo	202	65
Hospital General San Vicente De Paul	171	20
CS Comité Del Pueblo	148	25
CS San Antonio De Pichincha	137	14
Hospital Isidro Ayora De Loja	126	88
Cs Catamayo	90	25
Unidad Metropolitana Centro	50	12
CS Ponce Enríquez	46	4
CS Calderón	30	6
Unidad Metropolitana Norte	10	9
Hospital General Enrique Ortega	3	2
Unidad Metropolitana Sur	2	1
Total	**13,846**	**859**

Table 2. Patients cared by age group.

Patients cared by age group		
Age group	**Patients**	**Percentage**
0-19 years	4,528	32.7%
20-39 years	1,924	13.9%
40-64 years	5,165	37.3%
65 years or more	2,229	16.1%

professionals, suggesting that all groups demonstrated comparable improvement following the training.

Patient outcomes

Up to March 31, 2023, 13,846 patients received care in the areas of physical and respiratory rehabilitation within the RISE project facilities. From these, 859 patients (6.2%) met criteria for post COVID-19 condition (Table 1). Data was uploaded daily by health providers. Of the total of patients cared for at the PCC rehabilitation clinics 32.7% were children and adolescents, 51.2% adults, 16.1% older adults (Table 2) and 54% were women, while 46% were men.

Discussion and conclusion

The impact of the COVID-19 pandemic can still be seen in patients exhibiting long-lasting effects on their overall health. Although, initially, identification of these patients was essential, it was clear that establishing specialized and multidisciplinary centers for their rehabilitation was required [14, 15]. Health organizations worldwide have invested in the creation of these clinics, and although pioneer services were developed in countries such as the USA, Canada and the UK [16] it was essential to bring this care for patients to Latin America where resources are scarce. Additionally, rehabilitation is an area that requires strengthening in Ecuador, and due to the PCC cases reported, an opportunity to implement rehabilitation clinics in the country was evident [9]. Our approach in

Ecuador was to create PCC rehabilitation clinics that included the procurement of specific equipment, and the development of guidelines and training healthcare personnel for adequate treatment of patients, due to an ever-growing demand from the population [17].

Initially, it was essential to establish the clinics in health facilities, mainly in public institutions, and the MOPH. The relevance of establishing the clinics in both primary health care centers and secondary-level hospitals lies in the ability to refer patients with more extended needs or specialized care to hospitals, while patients with less severe needs could be cared for in primary health centers, avoiding saturation of hospitals [18]. The MOPH and Municipality´s support enabled us to establish 21 PCC rehabilitation clinics in 7 provinces. The public sector collaboration increased the sheer area of impact; moreover, the clinics were free of charge, therefore ensuring patients all over the country equal access to high quality and specialized care after COVID-19.

The equipment acquisition for the PCC clinics was primarily centered around respiratory rehabilitation (spirometers, pulse oximeters, inspiratory muscle trainers and gas analyzers) due to the prevalence of respiratory sequela in patients recovering from COVID-19 [6] and due to the lack of overall respiratory rehabilitation in the country [19]. Effective implementation of clinics involves not only equipment but also comprehensive training for health personnel. This training ensures accurate device usage, data interpretation, and high-quality care delivery. The need for these clinics is visible, particularly when considering aging populations that were severely affected during the pandemic [17]. Thus, creating these spaces and tools to continue healthcare professional training and education can benefit not only patients suffering from PCC, but also a population of non-COVID patients who need respiratory rehabilitation but haven't had access to such a service previously. Although COVID-19 has a particular impact on the respiratory system, many PCC clinics apply a multidisciplinary approach, including neurological, psychological, sport medicine, physiotherapy, and nutritional care, as it is evident that PCC can affect a variety of organs and systems [20].

The training sessions conducted by RISE saw the participation of 133 individuals from 21 health facilities, representing various health professions. Evaluation of knowledge acquisition, assessed through a pre-and post-training test, revealed a significant improvement in participants' average scores, indicating the effectiveness of the theoretical and practical sessions. Despite the overall positive findings, there was statistical variability in individual performance within groups. Statistical analyses revealed that medical doctors achieved higher scores than nurses in both pre-tests and post-tests. However, when assessing knowledge acquisition, no significant difference was observed among healthcare professionals, suggesting that all groups benefited equally from the training. This suggests the need for targeted courses and programs tailored to nurses' needs, ensuring comprehensive skill enhancement across all healthcare disciplines.

PCC multidisciplinary rehabilitation clinics, situated within the public sector, provide inclusive access to care regardless of financial status. The proactive identification of over 800 patients with PCC between July 2022 and March 2023 highlights the clinics' crucial role in addressing long-term impacts and reducing pressure on referral hospitals. In a future study we will analyze the effectiveness of targeted rehabilitation of the patients attending to the post-COVID-19 clinics. However, overall, PCC rehabilitation clinics represent a holistic and innovative approach to patient recovery in the country.

Additionally, PCC rehabilitation clinics play a role in COVID-19 education and prevention [20], and, by providing information on disease symptoms and prevention measures, they may contribute to reducing the spread of the disease and minimizing its further impact on the population. This preventative approach, in addition to the collaboration between primary healthcare centers and hospitals, helps alleviate the burden on referral hospitals. In conclusion, the establishment of PCC rehabilitation clinics was successful in identifying patients with PCC for early rehabilitation and strengthened respiratory rehabilitation for patients with additional diseases in Ecuador. The insights of this study can serve as a guide for the development of similar initiatives in other countries.

Key summary points

- Post-COVID Conditions (PCC), have placed a burden on both patients and health systems as multidisciplinary treatments are needed that require specialized teams to tackle a plethora of multi-organ symptoms involved.
- This article provides a post implementation reflection that seeks to describe the processes, infrastructure requirements, training needs and the challenges faced in developing and implementing multidisciplinary rehabilitation clinics for patients with PCC, in an under-resourced setting.
- Twenty-one post COVID-19 rehabilitation clinics were established in primary healthcare centers and second level hospitals in 7 out of 24 provinces of Ecuador.
- The establishment of PCC clinics in Ecuador was successful in identifying patients for early rehabilitation.
- The implementation of PCC rehabilitation clinics involved a collaborative effort between the Ministry of Public Health, the private sector and a non-governmental organization.
- The insights of this study can serve as a guide for the development of similar initiatives in other countries.

Abbreviations

PCC: Post COVID Condition
PEPFAR: President's Emergency Plan for AIDS Relief
USAID: U.S. Agency for International Development
RISE: Reaching Impact, Saturation and Epidemic Control
MOPH: Ministry of Public Health
Jhpiego: Johns Hopkins Program for International Education in Gynecology and Obstetrics
IMT: Inspiratory muscle trainers

References

1. Walvekar SS, Mohite VR. Tracking Health Beyond Recovery: A Study on Identifying Post-COVID Syndrome Symptoms. Indian J Crit Care Med 2024;28(2):170–4.
2. Raveendran AV, Jayadevan R, Sashidharan S. Long COVID: An overview. Int J Diabetes Metab Syndr 2021;15(3):869–75.
3. Castanares-Zapatero D, Chalon P, Kohn L, Dauvrin M, Detollenaere J, Maertens De Noordhout C, et al. Pathophysiology and mechanism of long COVID: a comprehensive review. Ann Med 2022;54(1):1473–87.
4. Fernández-de-las-Peñas C, Palacios-Ceña D, Gómez-Mayordomo V, Cuadrado ML, Florencio LL. Defining Post-COVID Symptoms (Post-Acute COVID, Long COVID, Persistent Post-COVID): An Integrative Classification. Int J Environ Res Public Health 2021; 18(5):2621.
5. Soriano JB, Ancochea J. On the new post COVID-19 condition. Arch Bronconeumol 2021;57(12):735–6.
6. Dal Negro RW, Turco P, Povero M. Long-lasting dyspnoea in patients otherwise clinically and radiologically recovered from COVID pneumonia: a probe for checking persisting disorders in capillary lung volume as a cause. Multidiscip Respir Med 2022;17:875. Available from: https://mrmjournal.org/mrm/article/view/875
7. Crook H, Raza S, Nowell J, Young M, Edison P. Long covid-mechanisms, risk factors, and management. BMJ 2021;374:n1648. doi: 10.1136/bmj.n1648.
8. Nalbandian A, Desai AD, Wan EY. Post-COVID-19 Condition. Annu Rev Med 2023;74(1):55–64.
9. Battistella LR, Imamura M, De Pretto LR, Van Cauwenbergh SKHAA, Delgado Ramos V, Saemy Tome Uchiyama S, et al. Long-term functioning status of COVID-19 survivors: a prospective observational evaluation of a cohort of patients surviving hospitalisation. BMJ Open 2022;12(7):e057246.
10. Rajan S, Khunti K, Alwan N, Steves C, MacDermott N, Morsella A, et al. In the wake of the pandemic: Preparing for Long COVID [Internet]. Copenhagen (Denmark): European Observatory on Health Systems and Policies 2021 [cited 2023 Dec 4]. (European Observatory Policy Briefs). Available from: http://www.ncbi.nlm.nih.gov/books/NBK569598/
11. Enright PL. The six-minute walk test. Respir Care 2003;48(8):783–5.
12. Zhang Q, Li Y xia, Li X lian, Yin Y, Li R lan, Qiao X, et al. A comparative study of the five-repetition sit-to-stand test and the 30-second sit-to-stand test to assess exercise tolerance in COPD patients. COPD 2018;13:2833–9.
13. Klok FA, Boon GJAM, Barco S, Endres M, Geelhoed JJM, Knauss S, et al. The Post-COVID-19 Functional Status scale: a tool to measure functional status over time after COVID-19. Eur Respir J 2020;56(1):2001494.
14. Barker-Davies RM, O'Sullivan O, Senaratne KPP, Baker P, Cranley M, Dharm-Datta S, et al. The Stanford Hall consensus statement for post-COVID-19 rehabilitation. Br J Sports Med 2020;54(16):949–59.
15. Spruit MA, Holland AE, Singh SJ, Tonia T, Wilson KC, Troosters T. COVID-19: interim guidance on rehabilitation in the hospital and post-hospital phase from a

European Respiratory Society- and American Thoracic Society-coordinated international task force. Eur Respir J 2020;56(6):2002197.
16. Venkatesan P. NICE guideline on long COVID. Lancet Respir Med 2021;9(2):129.
17. De Biase S, Cook L, Skelton DA, Witham M, Ten Hove R. The COVID-19 rehabilitation pandemic. Age Ageing 2020;49(5):696–700.
18. Kearon J, Risdon C. The Role of Primary Care in a Pandemic: Reflections During the COVID-19 Pandemic in Canada. J Prim Care Community Health 2020;11:215013272096287.
19. Gloeckl R, Leitl D, Jarosch I, Schneeberger T, Nell C, Stenzel N, et al. Benefits of pulmonary rehabilitation in COVID-19: a prospective observational cohort study. ERJ Open Res 2021;7(2):00108–2021.
20. Sisó-Almirall A, Brito-Zerón P, Conangla Ferrín L, Kostov B, Moragas Moreno A, Mestres J, et al. Long Covid-19: Proposed Primary Care Clinical Guidelines for Diagnosis and Disease Management. Int J Environ Res Public Health 2021;18(8):4350.

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Supplementary Material

Figure S1: Infographic

Figure S1: Infographic *(continued)*

Table S1: Schedule of activities

SCHEDULE OF ACTIVITIES			
Description of the Activity	**Session 1**	**Session 2**	**Session3**
Definitions of post COVID-19 condition	X		
Identify risk factors and symptoms	X		
Diagnostic studies and differential diagnosis	X		
Functional tests		X	
General treatment		X	
Universal Rehabilitation		X	
Targeted Rehabilitation			X
Evaluation and Vaccination			X
Practical training			X

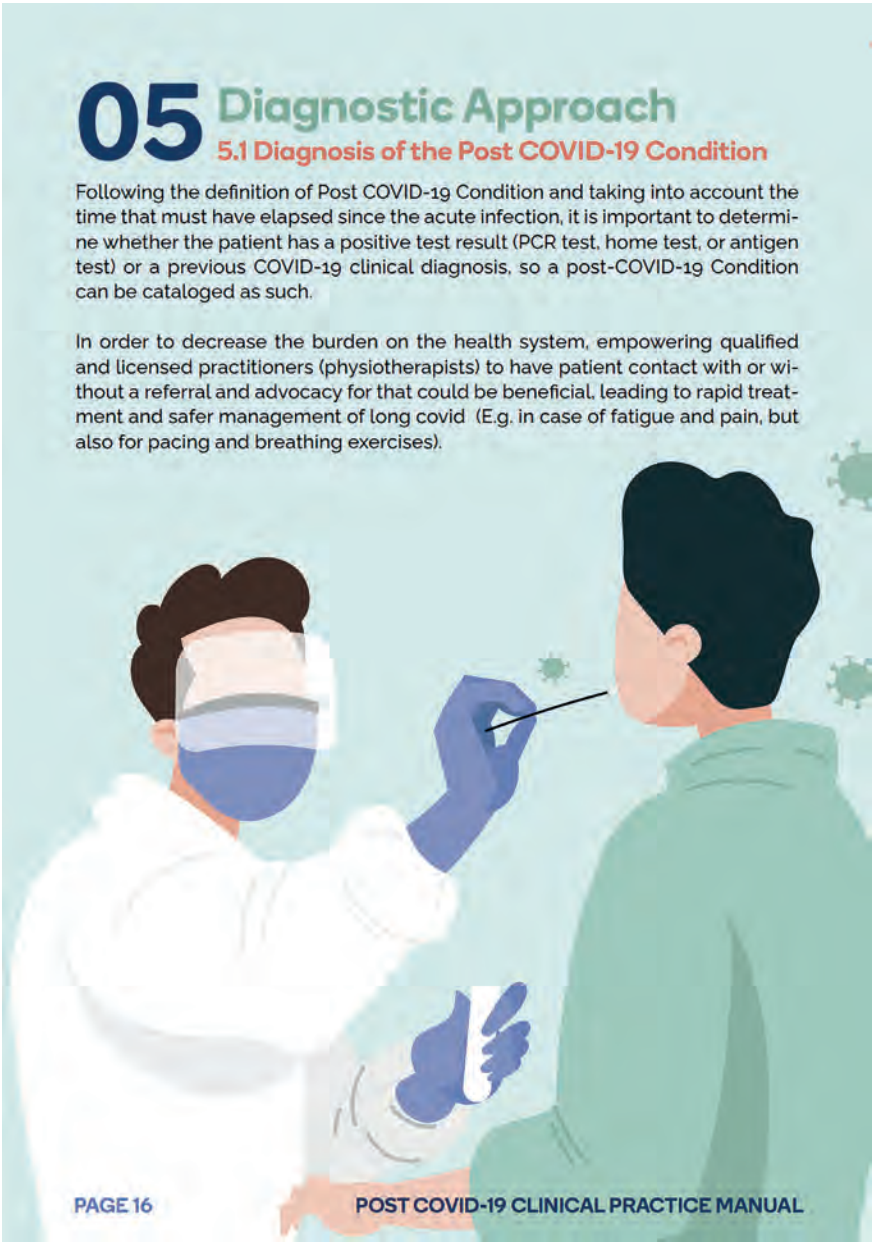

Figure S2: Diagnostic criteria

Figure S2: Diagnostic criteria *(continued)*

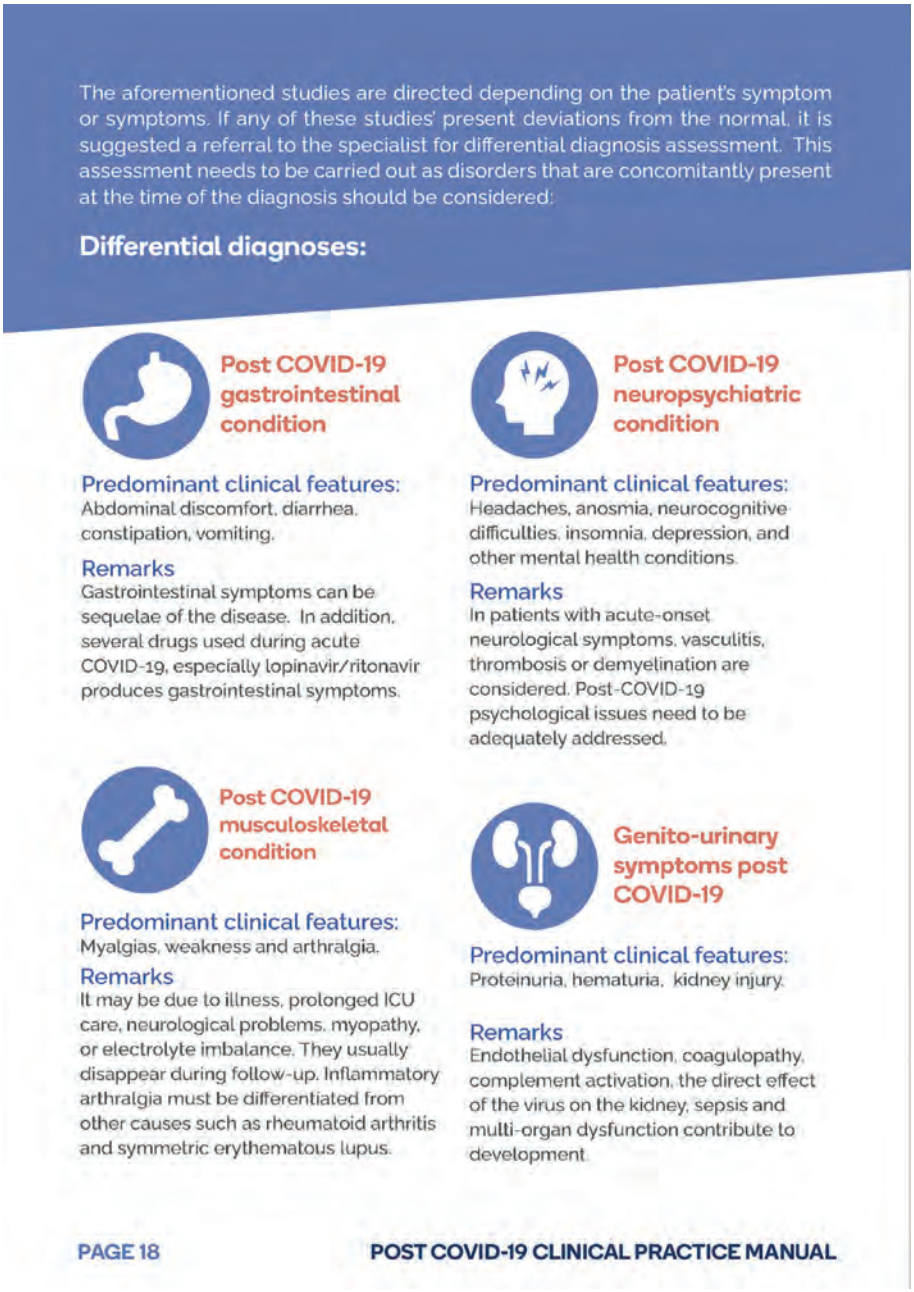

Figure S2: Diagnostic criteria *(continued)*

Original research article

OPEN ACCESS

Evaluation of screening tools for primary ciliary dyskinesia in Egypt: single center study

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ABSTRACT

Background: Primary ciliary dyskinesia (PCD) is a chronic respiratory illness that places significant strain on the healthcare system due to the complexity and expense of its diagnosis and treatment methods. The diagnostic process typically requires skilled technicians and an assortment of intricate, costly, and time-consuming approaches. Implementing screening tools can enhance efficiency by focusing the diagnostic process on those strongly suspected of having PCD. Tools such as the PCD Rule (PICADAR), North America Criteria Defined Clinical Features (NA-CDCF), the Clinical Index Score (CI), and the newly proposed CI_{new13} could potentially serve as useful screening tools. This study aims to examine the effectiveness of these tools individually, compare their performance against each other, and assess their results relative to prior research.

Methods: We conducted a diagnostic accuracy test on 83 Egyptian patients referred to Alexandria University Children's Hospital for potential PCD diagnosis between January 2015 and December 2022. The scores obtained from the screening tools were calculated and assessed.

Results: Of the initial group, 10 patients were ruled out because they fit other diagnostic parameters. Forty-three cases received a confirmed diagnosis, while 30 did not. Notably, the confirmed cases consistently scored higher on our screening tools than those that remained unconfirmed (p <.001, for all tested scores). We used receiver operating characteristic curves to assess and compare the effectiveness of each tool. The NA-CDCF had the smallest area under curve 0.736 (95% confiedence interval 0.619-0.832); in contrast, the CI score had the largest 0.898 (95% confidence interval 0.808-0.957).

Conclusion: All the tools tested were effective in identifying suitable patients for PCD testing at statistically significant levels. However, the PICADAR and NA-CDCF scores' performance did not significantly differ in the current study. The CI and CI_{new13} scores, on the other hand, outperformed both.

Key words: Primary ciliary dyskinesia, Diagnosis, Screening, Egypt

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Authors' contributions: AGE: collected data, calculated the scores and wrote the initial manuscript. WS, MARE and IE: revised statistics and edited the manuscript. AK: revised and edited the manuscript. NF: planned the research methodology, revised and edited the manuscript. All the authors have approved submission in its final form.

Ethics approval and consent to participate: An approval has been granted from the Alexandria University Ethics Committee (IRB number: 00012098, serial number: 0306441). Consent to participate was not applicable because the data were collected from medical records.

Conflict of interest: The authors declare that there are no competing interests.

Availability of data and materials: The data are available upon request. AK is a member of the Editorial Board of Multidisciplinary Respiratory Medicine.

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Introduction

Primary Ciliary Dyskinesia (PCD) is a rare genetic disease with diverse symptoms that adversely impact health [1]. Typically affecting the respiratory system, PCD presents differently in every patient due to the disrupted motion of cilia [2-4]. Potential symptoms may include constant wet cough, persistent runny nose with or without blockages, middle ear complications that could impair hearing, defects in laterality, recurring chest infections, neonatal respiratory distress, and fertility problems during reproductive years [5].

Diagnosing PCD is a demanding, costly, and time-intensive process. The lack of a universally accepted diagnostic test, combined with the inability of a single test or combination of tests to conclusively rule out the condition, exacerbates the challenge [2, 3]. Various screening tools have been developed and validated to identify patients with a high likelihood of having PCD [6, 7]. These include the PICADAR questionnaire, the NA-CDCF score, and the CI score (Supplementary material Tables 1, 2, and 3) [8-10]. Numerous PCD centers employ these measures to target diagnostic efforts on those most likely to benefit from the rigorous diagnostic process [11]. CI_{new13} (Supplementary material Table 4) is a recently suggested screening tool, tested and proposed by Martinů et al. [7].

The current study aims to evaluate the performance of these tools within our study group, comparing their effectiveness with each other and with previous research.

Patients

This study comprised 83 patients from 75 distinct families, all evaluated for PCD between January 2015 and December 2022. These patients were suspected of PCD based on criteria from the European Respiratory Society (ERS) Task Force. The ERS suggests a PCD diagnosis when several symptoms, such as chronic moist coughing, persistent rhinorrhea, laterality defects, newborn respiratory distress, auditory issues, unexplained bronchiectasis, and congenital heart malformation, exist concurrently [2]. Patients diagnosed with conditions other than PCD were excluded from the study. Infants under one year of age were also excluded due to insufficient medical data for accurate clinical score assessment.

Methods

Study design

Diagnostic test accuracy study.

Study setting

Tertiary health care facility.

Recruiting location

Respiratory Department, Alexandria University Children's Hospital. We obtained permission from the Ethics Committee of Alexandria University before conducting the study (IRB number: 00012098).

Outcome measures

We collected information on age, sex, and history of parental consanguinity. We calculated primary outcomes using various screening tools, namely the PICADAR score, the NA-CDCF score, the CI score, and the newly proposed CI_{new13} score. Responses to these questionnaires and diagnostic test results were retrieved from medical records.

Statistical analysis

We used the Statistical Package for Social Science (SPSS) program (ver 27) to collect and analyze data [12]. We performed diagnostic test accuracy analysis and generated the area under the receiver operator (ROC) characteristics curve (AUC) using MedCalc software (ver 20) [13]. The Kolmogorov-Smirnov test showed the distribution of variables to be normal, warranting the use of parametric statistics [14]. Accordingly, we conducted both parametric and non-parametric analyses [14, 15]. For sample size calculation, we accepted a beta error of up to 20%, setting the study's

power at 80%, resulting in a minimum sample size of 62 patients. We designated an alpha level of 5% and a significance level of 95%. Statistical significance was identified at a p of <0.05 [16].

Results

The study initially included 83 patients, but ten were excluded; five due to severe allergic rhinitis and asthma, four with cystic fibrosis, and one with an immune deficiency disorder. Thus, the study comprised 73 patients: 33 males (45.21%) and 40 females (54.79%). Their mean age was approximately 8.09 years, with a standard deviation of 4.34. Table 1 includes more demographic details of the group.

PCD was confirmed in 43 patients, referred to as "definite PCD", while the remaining 30 could not be definitively diagnosed and were labeled as "possible PCD or undefined". The confirmation of PCD was based on either a distinctive ciliary axonemal defect detected by transmission electron microscopy as per international consensus guidelines in two cases [14], bi-allelic pathologic mutations in a PCD-associated gene in 25 cases, or a combination of both in the remaining 16 cases.

Table 2 juxtaposes the PICADAR, NA-CDCF, CI, and CI_{new13} scores for confirmed and non-confirmed cases. In confirmed cases, the PICADAR, NA-CDCF, CI, and CI_{new13} had median values of 9, 3, 6, and 9, respectively. Whereas, the median values among non-confirmed cases for the PICADAR, NA-CDCF, CI, and CI_{new13} were 6, 2, 3, and 7, respectively. There was a statistically significant difference in the scores of confirmed cases compared to non-confirmed ones for each tested score (p <.001 for all scores).

The receiver operating characteristic curves for the various screening tools were compared, as depicted in Figure 1. The areas beneath these curves were calculated and are displayed in Table 3. The NA-CDCF had the smallest area (0.736, 95% CI 0.619-0.832); in contrast, the CI score had the largest (0.898, 95% CI 0.808-0.957). Based on the existing data, the cut-off value with the highest combined sensitivity and specificity was determined for each of the four tools tested; their performance is outlined in Table 3. These values were >7 for the PICADAR, >2 for the NA-CDCF, >4 for the CI score, and >7 for the CI_{new13}. These are

Table 1. Some demographic data for the study cohort.

	All children (n=73)	Confirmation for PCD		Test of significance p
		Not confirmed (n=30)	Confirmed (n=43)	
Age at enrollment (year)				
• Min-Max	1.17-16.00	2.00-15.00	1.17-16.00	
• Mean±SD	8.09±4.34	7.08±4.09	8.80±4.42	$t_{(df=71)}$ =1.686
• SE of Mean	0.51	0.75	0.67	p=.096 NS
• 95.0% CI of the mean	7.08-9.11	5.55-8.61	7.44-10.16	
• 25th Percentile – 75th Percentile	5.00-12.00	3.00-10.00	6.00-12.00	
Sex				
• Male	33 (45.21%)	15 (50.00%)	18 (41.86%)	χ^2(df=1)=0.473
• Female	40 (54.79%)	15 (50.00%)	25 (58.14%)	p=.492 NS
Consanguinity				
• No	19 (26.03%)	12 (40.00%)	7 (16.28%)	χ^2(df=1)=5.165, **p=.023***
• Yes(R)	54 (73.97%)	18 (60.00%)	36 (83.72%)	Z=3.359, **p<.001*** **OR: 3.429** 95% CI: 1.152-10.202

n, number of patients; PCD, Primary Ciliary Dyskinesia; TEM, Transmission Electron Microscope; Min-Max, Minimum to Maximum; SD, Standard deviation; SE, Standard error; CI, Confidence interval; t, Independent Sample t test; χ^2, Pearson Chi-Square; df, degree of freedom; Z, Z score for absolute difference between groups (p for significance of 95% CI difference); OR, Odds Ratio; NS, Statistically not significant (p≥.05); *, Statistically significant (p<.05); R, Risk category.

Table 2. Comparison between the values for the PICADAR, NA-CDCF, CI, and CI_{new13} scores between confirmed and non-confirmed cases.

		Confirmation		
	All children (n=73)	**Not confirmed (n=30)**	**Confirmed (n=43)**	**Test of significance *p***
PICADAR total score (out of 14)				
• Min-Max	2.00-14.00	2.00-14.00	4.00-14.00	Z(MW)=3.532 *p*<.001*
• Median	8.00	6.00	9.00	
• 95.0% CI of the Median	8.00-10.00	5.00-8.00	8.00-10.00	
• 25th Percentile – 75th Percentile	6.00-10.00	5.00-8.00	7.00-11.00	
NA-CDCF total score (out of 4)				
• Min-Max	1.00-4.00	1.00-4.00	2.00-4.00	Z(MW)=3.624 *p*<.001*
• Median	3.00	2.00	3.00	
• 95.0% CI of the Median	3.00-4.00	2.00-3.00	3.00-4.00	
• 25th Percentile – 75th Percentile	2.00-3.00	2.00-3.00	3.00-4.00	
CI total score (out of 7)				
• Min-Max	2.00-7.00	2.00-6.00	3.00-7.00	Z(MW)=5.877 *p*<.001*
• Median	5.00	3.00	6.00	
• 95.0% CI of the Median	5.00-6.00	3.00-4.00	6.00-7.00	
• 25th Percentile – 75th Percentile	4.00-6.00	3.00-4.00	5.00-6.00	
CI_{new13} total score (out of 13)				
• Min-Max	4.00-13.00	4.00-13.00	7.00-13.00	Z(MW)=5.071 *p*<.001*
• Median	9.00	7.00	9.00	
• 95.0% CI of the Median	9.00-10.00	7.00-9.00	9.00-10.00	
• 25th Percentile – 75th Percentile	7.00-10.00	6.00-8.00	9.00-11.00	

PICADAR, Primary ciliary dyskinesia rule; NA-CDCF, North America criteria defined clinical features; CI, Clinical index; CI_{new13}, Clinical $index_{new13}$; n, number of patients; Min-Max, Minimum to Maximum; CI, Confidence interval; $Z_{(MW)}$, Z of Mann-Whitney U test; *, Statistically significant (*p*<.05).

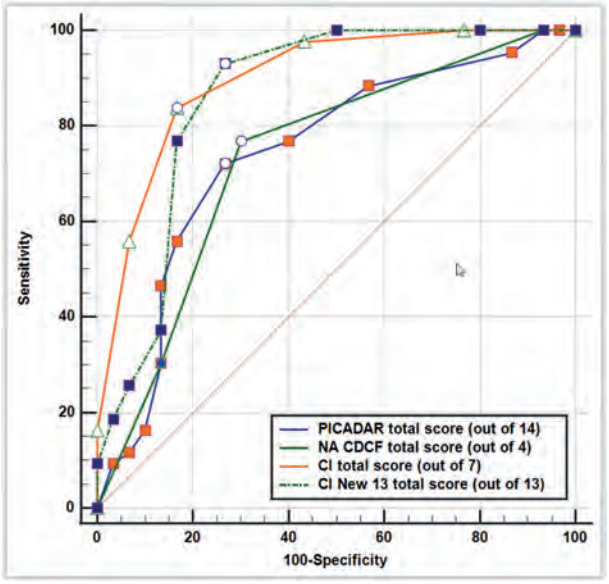

Figure 1. ROC curves for the PICADAR, NA-CDCF, CI, and CI_{new13} scores to discriminate between the confirmed and the non-confirmed cases.

suggested as the new threshold cut-offs for testing Egyptian patients suspected of PCD.

Figure 2 presents a Venn diagram, delineating the similarities and differences among four screening tools. The tools agreed on results for 52 patients when using the original, recommended cut-off points. Figure 3 displays box and whisker plots of the calculated scores for each tool, distinguishing between confirmed and not-confirmed cases. These plots are based on both the originally suggested cut-offs (red line) and the best-performing cut-offs from our study cohort (blue lines).

Discussion

Diagnosing PCD is particularly challenging in low and middle-income countries due to the costly and complex diagnostic tools [17]. In this study, we evaluated the effectiveness of various predictive tools

Table 3. Area under the ROC curves for the different screening tools and the best detected cut-off thersholds among the study cohort.

Index	AUC (%) (95% CI)	Z	Cut-off Value(YI)	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)	Overall Test Accuracy (%) (95% CI)
PICADAR[a,b]	0.743 (0.627-0.838)	3.957 (p=.0001*)	>7	72.09 (56.33-84.67)	73.33 (54.11-87.72)	79.49 (67.54-87.83)	64.71 (51.99-75.64)	72.60 (60.91-75.64)
NA-CDCF[a,b]	0.736 (0.619-0.832)	3.809 (p=.0001*)	>2	76.74 (61.37-88.24)	70.00 (50.60-85.27)	78.57 (67.45-86.65)	67.74 (53.76-79.14)	73.97 (62.38-83.55)
CI[c,d]	0.898 (0.808-0.957)	10.907 (p<0001*)	>4	83.72 (69.30-93.19)	83.33 (65.28-94.36)	87.80 (76.19-94.19)	78.12 (64.03-87.76)	83.56 (73.05-91.21)
CI_{new13}[c,d]	0.862 (0.761-0.932)	7.251 (p<0001*)	>7	93.02 (80.94-98.54)	73.33 (54.11-87.72)	83.33 (73.31-90.10)	88.00 (70.68-95.71)	84.93 (74.64-92.23)

Cut-off value (YI), the value at which the diagnostic test is able to discriminate the outcome i.e. for PICADAR; test (>7), total score of >7 (i.e. starting from 8 because the score has no decimal points) is able to discriminate Primary Ciliary Dyskinesia. YI, Youden index J. Different superscript letters indicate significant difference according to pairwise comparison of ROC curves [18].

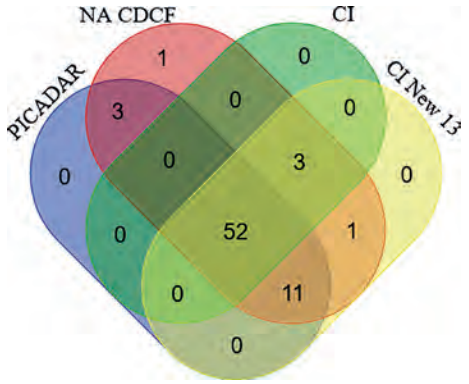

Figure 2. Venn diagram for the tested screening tools. When applying the originally proposed cut-offs, 52 PCD patients tested positive with the four screening tools, while 11 had positive results with the PICADAR, NA-CDCF, and CI_{new13} but not the CI score. Three patients had positive results with the NA-CDCF, CI, and CI_{new13} but not with PICADAR. Another 3 patients tested positive for PICADAR and NA-CDCF but neither CI nor CI_{new13}.

within our study group, comparing their performance with each other and with previously published data. This research could streamline the diagnostic process by identifying those who truly need to navigate the rigorous diagnostic pathway.

In the present study, median scores for the screening tools (PICADAR, NA-CDCF, CI, and the newly proposed CI_{new13}) were much higher in confirmed cases (9, 3, 6, and 9, respectively) than in non-confirmed ones (6, 2, 3, and 7, respectively); this was statistically relevant with p <.001 for all scores. This is in line with the original articles and subsequent validation studies [7-11]. However, we observed that the median value of each individual score was higher for both PCD and non-PCD patients compared to what was reported in the previous validation studies. This discrepancy could be due to the fact that our study cohort was younger than those in prior studies (range from 1.17 to 16.00 years with a median value of 8). This age range may have facilitated a more accurate recall of neonatal and infancy histories, key components of the screening scores, which may often be overlooked by adults. A recent external validation was carried out by Martinů et al. [7] on 1,834 patients, with ages ranging from 0 to 70.90 years and a median age of 6.1 years. In this validation, the median values for PCD patients were significantly higher than non-PCD patients (for PICADAR 7 vs.3, NA-CDCF 3 vs. 2, and the CI score of 5 vs. 3, p <.001 for the three scores).

The current study demonstrated that the PICADAR score achieved its maximum combined sensitivity and specificity at a cut-off point of >7 (meaning 8, as the score does not include decimal points). The sensitivity and specificity were 72.09% and 73.33%, respectively. Using this cut-off would result in 39 patients testing positive and being referred for PCD testing, with 31 of them receiving a confirmed diagnosis,

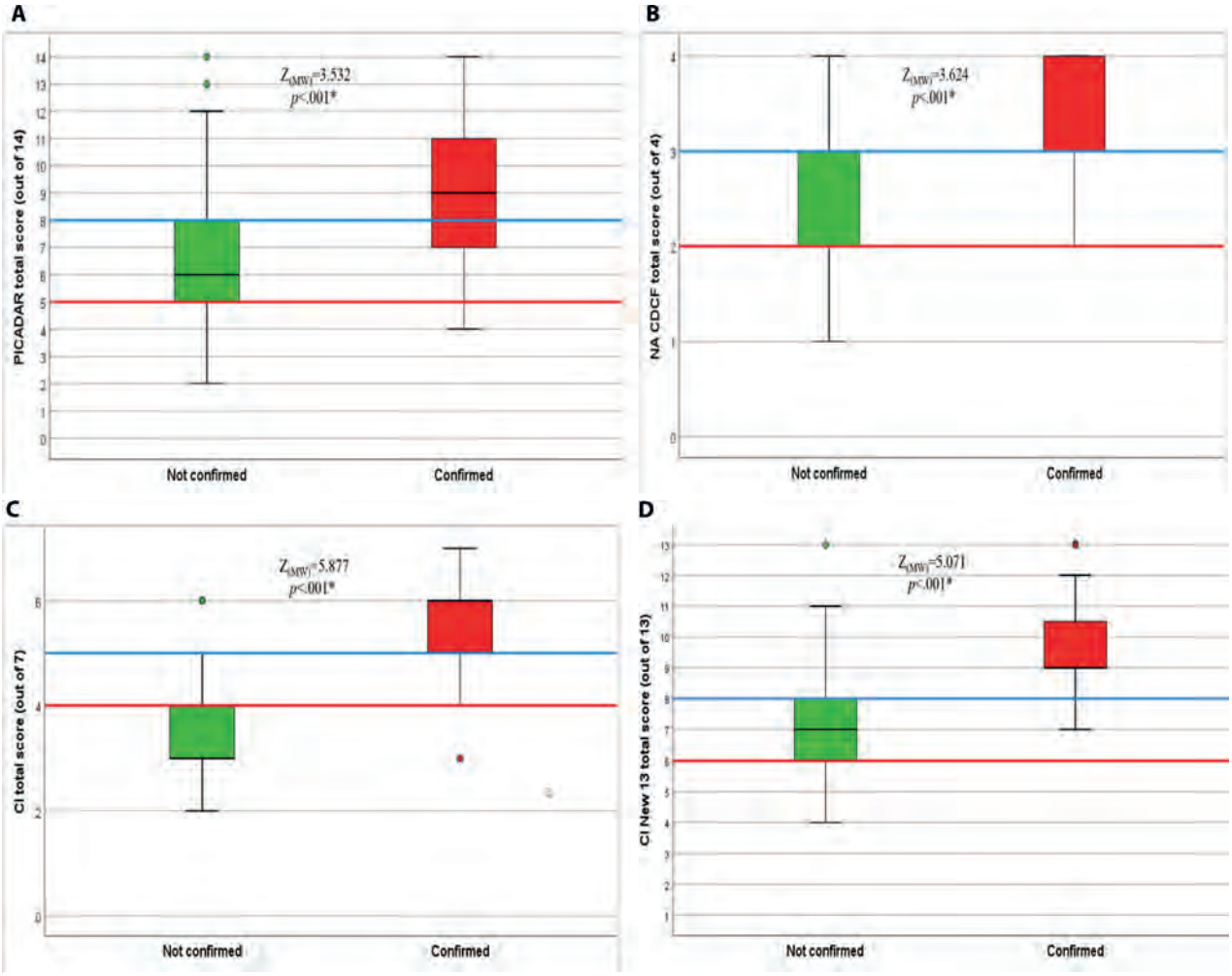

Figure 3. Box and whisker graph of the different screening tools (a: PICADAR, b: NA-CDCF, c: CI score, and d: CI_{new13}) in the studied group. The thick line in the middle of the box represents the median, the box represents the inter-quartile range (from 25th to 75th percentiles), and the whiskers represent the minimum and maximum after excluding outliers (circles). The horizontal red line represents the original cut-off value, while the horizontal blue line represents the cut-off with the best performance among the study cohort.

resulting in a positive predictive value (PPV) of 79.49%. A study conducted by Martinů et al. [7] demonstrated that the best predictive characteristics were achieved at a cut-off threshold of 6.

When we applied the cut-off threshold of 5, initially proposed by Behan et al. [10] to our patients, 67 tested positive and were referred for PCD evaluation. Of these, 41 were confirmed diagnoses. The sensitivity stood at 95.35%, surpassing the original article's 90% in its validation group. In contrast, the specificity was 13.33%, below the 75% reported in the original article's validation group [10].

In the present study, the greatest combined sensitivity and specificity for the NA-CDCF score were observed at a cut-off of >2 (effectively starting at 3, as the score does not include decimal points). This resulted in a sensitivity of 76.74% and a specificity of 70.0%. Using this value, 42 patients would test positive and be referred for PCD testing. Of these, 33 would receive a confirmed diagnosis, leading to a PPV of 78.57%. Similarily, Martinů et al. [7] found that a cut-off threshold of 3 yielded the most accurate predictive characteristics.

Applying the initial cut-off threshold value of 2, proposed by Leigh et al. [9] our study would yield positive

test results for 71 patients, 43 of whom would indeed be diagnosed with PCD. The sensitivity would be 100%, exceeding the 80% reported in Leigh's article. However, the specificity would drastically drop to 6.67%, significantly lower than the 72% reported in the initial study [9].

In this study, we found the optimal combined sensitivity and specificity score for the CI to be above 4 (due to the score not having decimal points, it started from 5). The sensitivity was 83.72%, and specificity was 83.33%. Applying this score would result in 41 patients testing positive and being referred for PCD testing. Out of these, 36 would receive a confirmed diagnosis, leading to an 87.80% PPV. On the other hand, Martinů et al. [7] showed that a cut-off value of 4 produced the best predictive characteristics.

Applying the original article's [8] suggested cut-off of 4 to our study would result in 55 patients being recommended for PCD testing, 42 of whom would receive a confirmed diagnosis. This cut-off provides a sensitivity of 97.67%, surpassing the 95.52% from the original article. However, its specificity, at 56.67%, falls short of the original's 72.49% [8].

Martinů et al. [7] proposed the CI_{new13} as a potential new predictive tool for PCD. When applied to the present cohort, this tool demonstrated the utmost combined sensitivity and specificity at a cut-off value greater than 7 (meaning it starts from 8 as the score does not accommodate decimal points). The sensitivity was measured at 93.02%, while the specificity came in at 73.33%. Previously, Martinů et al. [7] had reported that the CI_{new13} recorded its best performance at a cut-off value of 6, yielding an impressive 95.5% sensitivity alongside a 68.7% specificity.

The current study shows that while all four examined screening tools had adequate discriminative power for PCD, the CI and the newly proposed CI_{new13} tools outperformed both the PICADAR and NA-CDCF tools in terms of sensitivity and specificity. Despite this, the ease of use of the CI score makes it the preferred screening tool for PCD among suspected Egyptian patients. It only requires seven question-based clinical data and does not need further investigations. This is consistent with other research results [7]. Utilizing the CI score with a new suggested cut-off threshold greater than 4 (i.e., 5) will result in 13 patients being referred for unnecessary testing (false positives) while potentially missing one PCD patient (false negative) in the diagnostic process. The newly suggested CI_{new13} did not add significant benefit over the CI score and this goes with what was reported by Martinů et al. [7]. Moreover, this study, similar to the findings of Palmas et al. [11] shows no significant difference between the PICADAR and NA-CDCF scores, possibly due to overlapping parameters in both scores.

This study's notable achievement is being the first to evaluate the effectiveness of PCD screening tools in Egyptian pediatric patients. However, our work has been somewhat constrained by the relatively small sample size (73 patients) from a single-center in comparison to 1,834, and 211 patients in Martinů et al. [7] and Palmas et al. [11] external validations, respectively. Hence, we strongly recommend additional studies with larger populations and multiple centers across Egypt.

Conclusion

The PICADAR, NA-CDCF, CI, and the recently proposed CI_{new13} scores may significantly predict which patients are suitable for PCD examination. In this study, the performance of PICADAR and NA-CDCF did not show any significant differences, but the CI and CI_{new13} scores were superior. Although PICADAR and NA-CDCF are commonly used, employing the CI score could reduce unneeded testing, while using the NA-CDCF might decrease the chance of undetected cases.

Abbreviations:

AUC: Area under curve
CI: Clinical index
ERS: European Respiratory society
NA-CDCF: North America criteria defined clinical features
PCD: Primary ciliary dyskinesia
PICADAR: Primary ciliary dyskinesia rule
PPV: Positive predictive value
ROC: Receiver operating characteristic curve

References

1. Goutaki M, Shoemark A. Diagnosis of Primary Ciliary Dyskinesia. Clin Chest Med 2022; 43(1):127–40.

2. Kuehni CE, Lucas JS. Diagnosis of primary ciliary dyskinesia: summary of the ERS Task Force report. Breathe 2017; 13(3):166–78.
3. Lucas JS, Leigh MW. Diagnosis of primary ciliary dyskinesia: searching for a gold standard. Eur Respiratory Soc 2014; 44(6):1418–22.
4. Mirra V, Werner C, Santamaria F. Primary Ciliary Dyskinesia: An Update on Clinical Aspects, Genetics, Diagnosis, and Future Treatment Strategies. Front Pediatr 2017; 5:135.
5. Goutaki M, Meier AB, Halbeisen FS, Lucas JS, Dell SD, Maurer E, et al. Clinical manifestations in primary ciliary dyskinesia: systematic review and meta-analysis. Eur Respir J 2016; 48(4):1081–95.
6. Kuehni CE, Lucas JS. Toward an Earlier Diagnosis of Primary Ciliary Dyskinesia. Which Patients Should Undergo Detailed Diagnostic Testing? Ann Am Thorac Soc 2016; 13(8):1239–43.
7. Martinů V, Bořek-Dohalská L, Varényiová Ž, Uhlík J, Čapek V, Pohunek P, et al. Evaluation of a Clinical Index as a Predictive Tool for Primary Ciliary Dyskinesia. Diagnostics (Basel) 2021; 11(6):1088.
8. Djakow J, Rozehnalova E, Havlisova M, Svobodova T, Pohunek P. Clinical index to evaluate the risk of primary ciliary dyskinesia in children. Eur Respiratory Soc 2012; 40:2844.
9. Leigh MW, Ferkol TW, Davis SD, Lee HS, Rosenfeld M, Dell SD, et al. Clinical Features and Associated Likelihood of Primary Ciliary Dyskinesia in Children and Adolescents. Ann Am Thorac Soc 2016; 13(8):1305–13.
10. Behan L, Dimitrov BD, Kuehni CE, Hogg C, Carroll M, Evans HJ, et al. PICADAR: a diagnostic predictive tool for primary ciliary dyskinesia. Eur Respir J 2016; 47(4):1103–12.
11. Palmas K, Shanthikumar S, Robinson P. Assessment of primary ciliary dyskinesia predictive tools. Eur Respir J 2020; 56(6):1–3.
12. IBM Corp. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp; Released 2020.
13. Patton S, Bassaly R. Urinary incontinence. In: Kellerman RD, Rakel DP, Heidelbaugh JJ, EM L (eds). Conn's Current Therapy. Philadelphia, PA: Elsevier; 2023. 1174–6.
14. Field A. Discovering Statistics Using IBM SPSS Statistics. 4th ed. London: SAGE Publications Ltd; 2013.
15. Greenland S, Senn SJ, Rothman KJ, Carlin JB, Poole C, Goodman SN, et al. Statistical tests, P values, confidence intervals, and power: a guide to misinterpretations. Eur J Epidemiol 2016; 31(4):337–50.
16. Curran-Everett D. Evolution in statistics: P values, statistical significance, kayaks, and walking trees. Adv Physiol Educ 2020; 44(2):221–4.
17. Zhao X, Bian C, Liu K, Xu W, Liu Y, Tian X, et al. Clinical characteristics and genetic spectrum of 26 individuals of Chinese origin with primary ciliary dyskinesia. Orphanet J Rare Dis 2021; 16(1):293.
18. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 1988; 44(3):837–45.

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Appendix

Supplementary files

Table S1. PICADAR.

Does the patient have a daily wet cough that started in early childhood?	Yes – complete PICADAR No – STOP. PICADAR is not designed for patients without a wet cough	
Was the patient born full term or preterm?	Term	2
Did the patient experience chest symptoms in the neonatal period (e.g. tachypnea, cough, Pneumonia)?	Yes	2
Was the patient admitted to a neonatal unit?	Yes	2
Does the patient have a situs abnormality (Situs Inversus or Heterotaxy)?	Yes	4
Does the patient have a congenital heart defect?	Yes	2
Does the patient have persistent perennial rhinitis?	Yes	1
Does the patient experience chronic ear or hearing symptoms (e.g. glue ear, serous otitis media, hearing loss, and ear perforation)?	Yes	1
Total score		**14**

Behan L, Dimitrov BD, Kuehni CE, Hogg C, Carroll M, Evans HJ, et al. PICADAR: a diagnostic predictive tool for primary ciliary dyskinesia. Eur Respir J 2016; 47(4):1103-12.

Table S2. NA-CDCF score

Features
Unexplained neonatal respiratory distress in a full-term newborn with need for supplemental oxygen for ≥ 1 day and no meconium aspiration
Early-onset (before 6 months), year-round wet cough
Early-onset (before 6 months), year-round nasal congestion
Laterality defect

Leigh MW, Ferkol TW, Davis SD, Lee HS, Rosenfeld M, Dell SD, et al. Clinical Features and Associated Likelihood of Primary Ciliary Dyskinesia in Children and Adolescents. Ann Am Thorac Soc 2016; 13(8):1305-13.

Table S3. CI score

Clinical Index 7-Item Questionnaire (Each YES = 1 Point)
Did the child manifest with significant respiratory difficulties with breathing after birth?
Did the child have rhinitis or excessive mucus production in the first 2 months of life?
Did the child suffer from pneumonia?
Did the child present with 3 or more episodes of bronchitis?
Was the child treated for chronic secretory otitis or suffered from >3 episodes of acute otitis?
Does the child have a year-round nasal discharge or nasal obstruction?
Was the child treated with antibiotics for acute upper respiratory tract infection >3 times?

Djakow J, Rozehnalova E, Havlisova M, Svobodova T, Pohunek P. Clinical index to evaluate the risk of primary ciliary dyskinesia in children. Eur Respiratory Soc 2012; 40:2844.

Table S4. CI_{new13}.

Is the child full term?
Neonatal respiratory symptoms
Unexplained neonatal respiratory distress
Admission to a neonatal intensive care unit
Early-onset year-round wet cough
Rhinitis or nasal congestion in the first 2 months of life
Pneumonia in childhood
3 or more bronchitis episodes in childhood
Laterality defect
Congenital heart defect
Antibiotic therapy for rhinosinusitis > 3 times
Persistent year-round rhinitis
Chronic ear or hearing symptoms

Martinů V, Bořek-Dohalská L, Varényiová Ž, Uhlík J, Čapek V, Pohunek P, et al. Evaluation of a Clinical Index as a Predictive Tool for Primary Ciliary Dyskinesia. Diagnostics (Basel) 2021; 11(6):1088.

Original research article

OPEN ACCESS

Lung ultrasound in respiratory therapy: a global reflective survey

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ABSTRACT

Background: Lung ultrasound (LUS) is a noninvasive point-of-care diagnostic tool used to assess the presence and severity of various lung disorders and has been widely used in acute care settings for more than two decades. Respiratory therapists (RTs) play a vital role in managing patients on ventilation and other patients requiring respiratory support. However, the incorporation of LUS into the scope of practice of RTs has not been well highlighted despite the prominence of their practice in acute care. This international cross-sectional survey was specifically designed to evaluate the knowledge, attitude, and practice of RTs with respect to lung ultrasonography.
Methods: This observational cross-sectional study was conducted among RTs from different parts of the world using a questionnaire-based study tool. In total, 514 RTs responded to all the questions and were considered for statistical analysis. Descriptive statistics, analysis of variance, Fisher's exact, Chi-square, Bonferroni *post-hoc* analysis, and binomial logistic regression analyses were performed to identify the significance of the data.
Results: The majority of the 514 RTs who responded to the survey were from Middle Eastern countries. Out of the 514 responders, 44.9% of the responders were in the age group of 23-30 years; 67.1% were bachelor's degree holders; and 40.9% of participants had more than 10 years of experience. The knowledge-based questions revealed that RTs with higher experience and academic qualification provided more positive responses while in the attitude-related domain it was observed that standardized training in LUS helps them to enhance the current practice and to add LUS to the academic curriculum of respiratory therapy schools. However, barriers to practice LUS remains based on their responses. The practice-based questions revealed that RTs expected some additional seminars/workshops/webinars to be conducted on LUS. More than half of the participants were found to be knowledgeable with a positive attitude and working towards the inclusion of LUS in the respiratory therapy profession.
Conclusion: RTs have a positive attribute towards the inclusion of LUS in their clinical practice. Providing more structured training for professional RTs and including LUS modules in the respiratory therapy school curriculum may facilitate mastering their diagnostic skills, thereby expanding the scope of practice.

Key words: Respiratory therapists; Lung ultrasound; Survey; Knowledge; Attitude; Practice

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Authors' contributions: CSM, conceptualization, methodology, investigation, manuscript original drafting, review and editing, supervision, project administration; ED, conceptualization, methodology, validation, manuscript original drafting, review and editing; JKS, data collection, supervision, manuscript review and editing; MAA, data collection, supervision, manuscript review and editing; LT, data collection, supervision, manuscript review; AW, data collection, supervision, manuscript review; MK, supervision, manuscript review and editing. All authors read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Ethics approval and consent to participate: The study was approved by the institutional ethical committee of Srinivas University, India (SUEC:2018/001). An informed consent was obtained from all the participants.

Conflict of interest: The authors declare that they have no conflicts of interest.

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Background

Over the past two decades, the utility of lung ultrasound (LUS) has revolutionized and is now an inevitable tool in assessing and managing critically ill patients [1]. LUS is a radiation-free imaging tool that is noninvasive, portable, and rapid, allowing the real-time examination of pulmonary and related structures. Many studies, including meta-analyses, that compared LUS with chest X-ray suggested its higher sensitivity and similar specificity in detecting disorders such as pleural effusion, pneumonia, pneumothorax, and pulmonary edema [2-5]. LUS also provides vital information at the bedside on lung aeration, ventilation distribution, and respiratory complications in ventilated patients [6-10]. Moreover, a comprehensive ultrasonographic approach, including LUS, echocardiography, and diaphragmatic ultrasound, offers detailed information that could help clinicians individualize ventilator settings in these patients.

Apart from acute care areas, LUS is found to be beneficial in other related clinical settings such as cardiology and rheumatology to assess the presence and severity of diverse related lung conditions. Integrating LUS with traditional echocardiography provides an integrated cardiopulmonary analysis and facilitates cardiologists in the diagnosis and management of acute and chronic cardiopulmonary conditions [11]. Similarly, LUS was also found to have a high diagnostic accuracy and significant correlation with the high-resolution computed tomography findings, thereby playing an important role in the diagnosis and management of rheumatoid disorders like interstitial lung diseases [12].

Respiratory therapists (RTs) are healthcare professionals who specialize in the evaluation and treatment of patients of diverse age groups presenting with respiratory and related disorders. They possess the knowledge, skill, and ability to offer a wide scope of diagnostic and therapeutic procedures based on the requirements. Evidence supports the importance of RTs and RT-driven care in improving patient outcomes and reducing morbidities [13-15]. It is also of interest that an outcome with decreasing costs and increased compliance with established practice guidelines without any increase in adverse events was observed in RT-driven care compared to the care directed by physicians [16]. RTs, as one of the primary practitioners of mechanical ventilation, play a pivotal role in identifying and fixing various ventilator/ventilation-related disorders, and LUS may facilitate their diagnostic abilities in the diagnosis of various respiratory derangements such as pneumothorax, pulmonary edema, etc. [17]. Nevertheless, it is not currently included as one of the standard practices in respiratory therapy profession.

Despite the paucity of literature on international consensus on education, assessment of competencies, and certification on LUS, these available studies described the need for training sessions of 1-3 days with alternating theoretical and hands-on sessions [18-21]. Anecdotal studies have also shown the positive outcomes of a 1-day training for physicians [22], 2-day training session for paramedics [23], and 0-12 hours of training for nurses and medical students resulting in the identification of B-lines and pleural effusions [24]. Another training study on a multidisciplinary group of professionals including physicians and RTs concluded the effectiveness of LUS training with a 2-hour video lecture, followed by 25 supervised scans [25].

In one of the pioneering studies on LUS training for RTs, the authors concluded that RTs trained in ultrasound are independently capable of performing LUS with an accuracy of > 95% [26]. Another recently published study concluded that a 2-day (16 hours) of training resulted in a post-test outcome of > 60% of the total score in 96% of the participants, reflecting the importance of didactic theory sessions and practical sessions [27]. A scoping review published on the involvement of RTs in LUS identified seven papers that incorporated different approaches of ultrasound training for RTs and concluded that training LUS skills for RTs seems feasible but needs global standardization [28].

It is evident that despite the increasing trend of the potential of LUS in the diagnostics and therapeutic areas of respiratory care, a global standardization of including this tool within the scope of practice of RTs is yet to be achieved. Therefore, this first cross-sectional international survey designed specifically for RTs was performed to set a benchmark regarding their insights on the knowledge, attitude, and practice regarding LUS. We understand that such a survey will

give understanding to the global practice, and specific measures might be considered to include this imaging tool within the scope of practice of RTs. We also anticipate that the outcome of this project will serve as a point of reference for policy makers and for the upcoming investigations related to the subject matter.

Methods

Study design

This observational cross-sectional survey adopted snowball sampling techniques through emails, professional social networks, respiratory therapy professional societies, and RTs of various countries. The survey targeted RTs worldwide with diverse educational backgrounds, age groups, and sex. We developed the survey on an online survey platform (Google Forms). The study was conducted from January 2022 to May 2022. The study was approved by the institutional ethical committee of Srinivas University, India (SUEC:2018/001).

Study participants

The targeted participants were RTs with no restrictions to age, sex, educational background, professional experience, and country where they work. An informed consent was obtained from all the participants. RTs who gave the consent to participate and were working in academic and clinical settings were included in the study. RTs who denied the consent to participate and those who did not complete the survey were automatically excluded from the study.

Questionnaire development

The survey questionnaire was created in English. Previous studies describing the applications of LUS and the competencies required were reviewed [14-18]. The authors and two critical care physicians, who are experienced in LUS and research, developed the questionnaire to investigate the objectives of the study. A five-member panel of experienced critical care physicians and senior RTs carried out the content validation of the questionnaire. The panel examined the core content, language, appropriateness of questions for various domains, scoring patterns, etc. A pilot survey was conducted with an experimental group of 20 randomly selected participants of various ages, sex, qualification, and experience. The internal consistency of the responses to the questions of knowledge, attitude, and practice domains in the pilot group was analyzed using Cronbach's alpha reliability test, with an acceptable result of 0.736 (> 0.6).

The survey was segregated into the demographic and questionnaire segments. In the demographic segment, respondents' basic information such as sex, age, nationality, geographical location, educational qualification, and work experience in years were collected. The questionnaire segment contained 18 questions, with 6 questions each in knowledge, attitude, and practice sections. The objective of the questionnaire (Supplementary file 1) was to assess the knowledge, attitude, and practice of RTs regarding LUS, to compare the knowledge, attitude, and practice regarding LUS amongst RTs across the world, and to investigate the factors that can facilitate LUS practice in the RT profession.

1. Knowledge: This domain focused on the technical and clinical knowledge of RTs in LUS.
2. Attitude: This domain focused on the subjective perspectives of the RTs regarding the training, clinical, and future application of LUS.
3. Practice: The practice domain focused on the subjective exposure, training, and practice sessions of the RTs with LUS.

Data analysis

All data was populated in Microsoft Excel (2013, Redmond, WA, United States) and then transferred to SPSS statistical software (SPSS, v.28; IBM, Armonk, NY, United States) for analysis. The distribution of all qualitative variables, both demographic and other variables (i.e., close-ended) of samples were examined with frequency tables. The descriptive statistics was done using mean and standard deviation or median and quartile deviation. The mean score of survey domains were

compared between sexes using independent sample *t*-test. Analysis of variance (ANOVA) was used to find the difference among demographic information such as age, work country, educational qualifications, and their experience based on knowledge, attitude, and practice scores. Bonferroni *post-hoc* analysis was performed to determine the significant difference between groups. Chi-square and Fisher's exact tests were performed to find the association between demographic domains and the 'barriers to practice' related question. Statistical significance was set at p (two-tailed) < 0.05. Binomial logistic regression analysis was also performed between the dependent and independent variables to explore the values of the study outcome.

Results

A total of 514 RTs from 22 countries responded to this survey. The age of the participants ranged from 23-50, and most respondents were between 23-30 years (n = 231, 44.9%). The sex distribution was comparable between males (n = 250, 48.6%) and females (n = 260, 50.6%), with four respondents preferring not to disclose their sex. Most of the respondents were bachelor's degree holders (n = 345, 67.1%) followed by diploma holders. Though the group was small, there were doctorate degree holders (n = 7, 1.4%) among the respondents. Most RTs were highly experienced with more than 10 years (n = 210, 40.9%). More RTs working in the Kingdom of Saudi Arabia responded to the survey (n = 109, 21.2%), followed by the United Arab Emirates, India, the United States, and Canada. The distribution of the demographic variables (age, sex, academic qualification, years of experience, and work country) were examined with frequency tables presented in Table 1.

Descriptive statistics were calculated with mean and standard deviation for the knowledge domain questions. The correct answer rates of the six questions on the LUS knowledge questions ranged between 0-100%. The mean knowledge score was 2.80 ± 1.49 (range: 0-6) suggesting an overall 46.60% correct rate on the knowledge domain. Median and quartile deviation was calculated for attitude and practice-based questions as these domains were measured on an ordinal scale (Table 2). One of the attitude-based questions (Q. 12) related to the 'barriers' was analyzed separately due to its nature.

The frequency for each question under knowledge, attitude, and practice were calculated and presented in Table 3. The right and wrong answers in the

Table 1. Demographic details of the participants.

Demographic characteristics	Frequency	Percentage
Age		
23-30	231	44.9
>30-40	187	36.4
>40-50	78	15.2
> 50	18	3.5
Sex		
Male	250	48.6
Female	260	50.6
Prefer not to say	4	0.8
Academic qualification		
Bachelor's	345	67.1
Diploma/Associate's	83	16.1
Intern	15	2.9
Master's	57	11.1
On-the-job trainee	7	1.4
Ph.D.	7	1.4
Years of experience		
0-2 years	104	20.2
>2-5 years	99	19.3
>5-10 years	101	19.6
>10 years	210	40.9
Country where the respondent currently works		
Bahrain	11	2.1
Canada	56	10.9
India	86	16.7
KSA	109	21.2
Philippines	18	3.5
Qatar	44	8.6
UAE	89	17.3
USA	75	14.6
Others	26	5.1

Ph.D., Doctor of Philosophy; KSA, Kingdom of Saudi Arabia; UAE, United Arab Emirates; USA, United States of America.

Table 2. Response rate of the participants.

Dependent variables	Mean ± SD	Median (Quartile Deviation)
Knowledge	2.80 ± 1.49	
Attitude	4.18 ± 1.29	5.00 (4.00-5.00)
Practice	2.19 ± 1.73	2.00 (1.00-4.00)

SD, Standard deviation.

Table 3. Knowledge, attitude, and practice questionnaire analysis.

Knowledge-based questions	Correct, *n* (%)	Incorrect, *n* (%)
Q1: LUS emits radiation (No)	387 (75.3)	127 (24.7)
Q2: Image identification (Pleural reverberation artifacts)	164 (31.9)	350 (68.1)
Q3: Image identification (Bat sign)	276 (53.7)	238 (46.3)
Q4: Image identification (Pleural effusion)	214 (41.6)	300 (58.4)
Q5: Image identification (Pulmonary edema)	198 (38.5)	316 (61.5)
Q6: Sea shore in M-mode (Normal lung)	198 (38.5)	316 (61.5)
Attitude-based questions	**Yes, *n* (%)**	**No/not sure, *n* (%)**
Q7: LUS within the scope of RTs?	430 (83.7)	84 (16.3)
Q8: LUS promotes safety culture?	439 (85.4)	75 (14.6)
Q9: Need of training for RTs?	454 (88.3)	60 (11.7)
Q10: RTs are competent to do LUS?	377 (73.3)	137 (26.7)
Q11: LUS module in RT school curriculum?	446 (86.8)	68 (13.2)
Q12: Barriers for RTs to do LUS?		
Practice-based questions	**Yes, *n* (%)**	**No, *n* (%)**
Q13: Previous learning in LUS?	267 (51.9)	247 (48.1)
Q14: Any formal certification in LUS?	36 (7.0)	478 (93.0)
Q15: Any hands-on experience in LUS?	134 (26.1)	380 (73.9)
Q16: Any feedback on your experience in LUS?	176 (34.2)	338 (65.8)
Q17: Any assistance offered to others in LUS?	244 (47.5)	270 (52.5)
Q18: Ever been an advocate for LUS in RT profession?	269 (52.3)	245 (47.7)

LUS, Lung ultrasound; RT, Respiratory therapist.

knowledge-based domain and the responses of the attitude-based and practice-based domains were recorded individually with frequency and percentage to validate the strength of each question.

In question 1, the majority of the respondents were aware that LUS does not emit radiation (*n* = 387, 75.3%). Question 9 regarding the requirement of LUS training for RTs (*n* = 454, 88.3%) and question 11 on the inclusion of an LUS module to RT school curriculum (*n* = 446, 86.8%) were found to have a more positive attitude in the group of attitude-based questions. Similarly, among the practice-based questions, question 18 on the advocacy of LUS in the RT profession (*n* = 269, 52.3%) and question 13 regarding previous learning in LUS (*n* = 267, 51.9%) reflected the keenness of the respondents to learn LUS and involve LUS in their practices. More than half of the participants were found to be knowledgeable with positive attitudes and working towards including LUS in the RT profession.

The mean score of knowledge, attitude, and practice were compared between male and female sexes

Table 4. Comparison of sex in the knowledge, attitude, and practice scores.

Domain	Sex	*n*	Mean	SD	*t*	*p*
Knowledge	Male	250	2.6080	1.55951	2.55	0.01*
	Female	260	2.9423	1.39516		
Attitude	Male	250	4.0280	1.49538	3.23	0.001*
	Female	260	4.3808	0.91175		
Practice	Male	250	2.3680	1.69590	2.06	0.04*
	Female	260	2.0538	1.74786		

*, Statistically significant. SD, Standard deviation.

Table 5. Comparison of age groups in the knowledge, attitude, and practice scores.

Domain	Age Group	*n*	Mean	SD	SE	*F*	*p*
Knowledge	23-30	231	2.6797	1.54398	0.10159	1.68	0.17
	>30-40	187	2.8075	1.44257	0.10549		
	>40-50	78	2.9872	1.46379	0.16574		
	>51	18	3.3333	1.37199	0.32338		
	Total	514	2.7957	1.49303	0.06585		
Attitude	23-30	231	4.1602	1.18519	0.07798	0.05	0.98
	>30-40	187	4.1872	1.39208	0.10180		
	>40-50	78	4.1667	1.39029	0.15742		
	>51	18	4.2778	1.22741	0.28930		
	Total	514	4.1751	1.29344	0.05705		
Practice	23-30	231	2.4156	1.74469	0.11479	4.92	0.002*
	>30-40	187	2.1979	1.74701	0.12775		
	>40-50	78	1.7051	1.59633	0.18075		
	>51	18	1.3333	1.37199	0.32338		
	Total	514	2.1907	1.73223	0.07641		

*, Statistically significant. SD, Standard deviation; SE, Standard error.

using independent sample *t*-test (Table 4). Knowledge, attitude, and practice scores significantly differed between males and females ($p < 0.05$). Knowledge and attitude scores regarding LUS were highest among females: (2.94 ± 1.40) and (4.38 ± 0.91), respectively. Practice scores on LUS were higher for males (2.37 ± 1.70). The mean scores of knowledge, attitude, and practice were compared between age groups using ANOVA (Table 5). There was a significant difference ($p < 0.05$) between age groups for practice scores regarding LUS. The youngest age group (23-30) had a higher mean score (2.42 ± 1.74) than other age groups. Multiple comparisons between the age groups on the responses of various domains were performed using Bonferroni *post-hoc* analysis. We observed a significant difference in the responses of the practice domain between the age groups of 23-30 and 41-50 ($p < 0.05$). The comparison between the rest of the groups was not significant. Knowledge, attitude, and practice scores significantly differed between work countries ($p < 0.05$) by applying ANOVA (Table 6). The mean scores of participants from India were found to be highest in all the domains such as knowledge (3.24 ± 1.45), attitude (4.51 ± 0.84), and practice (3.34 ± 1.51) compared to participants from the rest of the countries. The *post-hoc* analysis revealed a significant difference in the

Table 6. Comparison of country in the knowledge, attitude, and practice scores.

Domains	Work country	*n*	Mean	SD	*F*	*p*
Knowledge	Bahrain	11	2.2727	1.61808	3.92	< 0.001*
	Canada	56	3.0536	1.36741		
	India	86	3.2442	1.45470		
	KSA	109	2.3394	1.34178		
	Philippines	18	1.8333	1.09813		
	Qatar	44	2.8636	1.19283		
	UAE	89	2.8764	1.62243		
	USA	75	2.8133	1.51295		
	Others	26	3.1154	1.90425		
	Total	514	2.7957	1.49303		
Attitude	Bahrain	11	3.8182	1.16775	7.77	< 0.001*
	Canada	56	4.6250	.61975		
	India	86	4.5116	.83658		
	KSA	109	3.5413	1.69166		
	Philippines	18	4.3333	.48507		
	Qatar	44	4.5227	.90190		
	UAE	89	3.8202	1.51928		
	USA	75	4.5333	1.08221		
	Others	26	4.3846	1.13409		
	Total	514	4.1751	1.29344		
Practice	Bahrain	11	2.0909	1.51357	8.58	< 0.001*
	Canada	56	1.7500	1.68685		
	India	86	3.3372	1.50771		
	KSA	109	1.8532	1.60915		
	Philippines	18	1.7222	1.40610		
	Qatar	44	2.0909	1.50686		
	UAE	89	1.6067	1.74263		
	USA	75	2.3467	1.69653		
	Others	26	2.8462	1.91191		
	Total	514	2.1907	1.73223		

*, Statistically significant. SD, Standard deviation; KSA, Kingdom of Saudi Arabia; UAE, United Arab Emirates; USA, United States of America.

response was observed between India and the Kingdom of Saudi Arabia and the Philippines ($p < 0.05$), and the differences among the other countries were insignificant among the responses in the knowledge domain. In the attitude domain, a significant difference was observed between Canada and the Kingdom of Saudi Arabia and the United Arab Emirates, India and the Kingdom of Saudi Arabia and the United Arab Emirates, the Kingdom of Saudi Arabia and Qatar, and the United Arab Emirates and the United States ($p < 0.05$). In the practice domain, we observed a significant difference between India and Canada, the Kingdom of Saudi Arabia, the Philippines, Qatar, the United Arab Emirates, and the United States ($p < 0.05$). ANOVA was applied to qualifications and domains. Knowledge and practice scores were

Table 7. Comparison of academic qualification in knowledge, attitude, and practice scores.

Domains	Academic qualification	*n*	Mean	SD	*F*	*p*
Knowledge	Bachelor's	345	2.6696	1.50419	6.11	< 0.001*
	Diploma/associate	83	2.7108	1.33005		
	Intern	15	2.3333	1.44749		
	Master's	57	3.7544	1.37945		
	Trainee	7	2.5714	0.97590		
	Ph.D.	7	3.4286	1.51186		
	Total	514	2.7957	1.49303		
Attitude	Bachelors	345	4.0464	1.39482	2.85	0.02*
	Diploma/Associate	83	4.5181	0.83171		
	Intern	15	4.4667	0.63994		
	Masters	57	4.4035	1.23722		
	Trainee	7	3.5714	1.51186		
	Ph.D.	7	4.5714	0.78680		
	Total	514	4.1751	1.29344		
Practice	Bachelors	345	2.1797	1.69203	5.08	< 0.001*
	Diploma/Associate	83	1.7711	1.72729		
	Intern	15	1.9333	1.22280		
	Masters	57	3.1228	1.85232		
	Trainee	7	1.4286	1.13389		
	Ph.D.	7	1.4286	1.61835		
	Total	514	2.1907	1.73223		

*, Statistically significant. SD, Standard deviation; Ph.D., Doctor of Philosophy.

the highest among respondents with master's degree (3.75 ± 1.38 and 3.12 ± 1.85, respectively), whereas the attitude score was the highest among the Ph.D. group (4.57 ± 0.79) (Table 7).

After *post-hoc* analysis, we observed a significant difference in the responses of the practice domain between master's degrees and interns, diploma, and bachelor's degrees ($p < 0.05$). A significant difference in the attitude responses was observed between bachelor's degree holders and diploma holders ($p < 0.05$). In the practice domain, there was a significant difference between master's degree holders and diploma and bachelor's degree holders ($p < 0.05$). There was a significant difference ($p < 0.05$) in knowledge regarding LUS. We observed that respondents with more than 10 years of experience had a higher score (3.02 ± 1.47) than the other groups. The group with 6-10 years of experience scored higher than other groups in the practice questions. Attitude scores were not correlated with years of experience. We observed a significant difference in the practice responses between the 0-2 years of experience and > 10 years of experience ($p < 0.05$) after *post-hoc* analysis. No statistical significance was observed in the attitude responses amongst the groups of years of experience ($p > 0.05$). In the practice domain, there was a significant difference between those with 6-10 years and > 10 years of experience ($p < 0.05$) (Table 8). Logistic regression analysis was performed between the dependent and independent variables to predict the values of the study outcome. The dependent variables were years of experience (up to 5 years and above 5 years of experience) and academic qualifications (qualifications less than bachelor's degree and bachelor's degree and above). The independent variables were the knowledge, attitude, and practice scores. We attained a regression

Table 8. Comparison of years of experience in knowledge, attitude, and practice scores.

Domains	Years of experience	*n*	Mean	SD	*F*	*p*
Knowledge	0-2	104	2.5288	1.56389	2.99	0.03*
	>2-5	99	2.6869	1.59493		
	>5-10	101	2.7129	1.31405		
	>10	210	3.0190	1.46722		
	Total	514	2.7957	1.49303		
Attitude	0-2	104	3.8942	1.37183	2.34	0.07
	>2-5	99	4.2222	1.13888		
	>5-10	101	4.3465	1.22013		
	>10	210	4.2095	1.34268		
	Total	514	4.1751	1.29344		
Practice	0-2	104	2.4519	1.61233	3.98	0.01*
	>2-5	99	2.1212	1.76284		
	>5-10	101	2.5446	1.81397		
	>10	210	1.9238	1.69827		
	Total	514	2.1907	1.73223		

*, Statistically significant. SD, Standard deviation.

Table 9. Regression analysis among knowledge, attitude, and practice scores and years of experience.

Independent variable	B	SE	Wald	Degrees of freedom	*p*	Odds Ratio	95% CI	
							Lower	Upper
Knowledge	0.155	0.064	5.920	1	0.015*	1.167	1.031	1.322
Attitude	0.121	0.072	2.847	1	0.092	1.128	0.981	1.298
Practice	-0.105	0.055	3.634	1	0.057	0.900	0.808	1.003
Constant	-0.272	0.330	0.680	1	0.410	0.762	NA	NA

*, Statistically significant. CI, Confidence interval; SE, Standard error.
NA, Not applicable.

Table 10. Regression analysis among knowledge, attitude, and practice scores and academic qualifications.

Independent variable	B	SE	Wald	Degrees of freedom	*p*	Odds Ratio	95% CI	
							Lower	Upper
Knowledge	0.065	0.080	0.655	1	0.418	1.067	0.912	1.247
Attitude	-0.343	0.114	9.023	1	0.003*	0.710	0.568	0.888
Practice	0.224	0.071	9.848	1	0.002*	1.251	1.088	1.439
Constant	2.200	0.524	17.625	1	0.000	9.021		

*, Statistically significant. CI, Confidence interval; SE, Standard error.

output that concluded knowledge and attitude had a positive impact on the years of experience, as higher experience resulted in an increase in knowledge and attitude, whereas practice questions had a negative impact on the years of experience (Table 9). Regression analysis with academic qualification concluded that knowledge and practice have a positive impact with the higher academic qualification, whereas attitude has a negative impact with the academic qualification (Table 10).

Question on barriers to practice LUS

There was a question in the attitude domain as follows: "*If formally certified in lung ultrasound to enhance the scope of practice, do you think that there will be barriers for RTs to perform lung ultrasound?*" The options were: *a) Yes b) No c) Not sure.* Table 11 shows that 50% of the respondents mentioned that there might be barriers for the RTs to practice LUS, even if they were formally certified. All the independent variables such as demographic details were analyzed against the attitude-based question on barriers to practice LUS. Fisher's exact test was applied to find the association between age groups and barriers to practice. No significant difference (Fisher's exact test = 11.59; p value = 0.07) was found between these two variables, concluding that there was no association between age group of the RTs and barriers to practice LUS (Figure 1, Table 12). The association between sex and barriers to practice was analyzed using the chi-square test. Overall, 52.4% of the male and 48.8% of the female RTs reported that there were barriers to LUS. No significant difference (Chi-square = 5.44; p = 0.07) was observed, concluding that there was no association between sex and perception of barriers to practice LUS (Figure 2, Table 13). Fisher's exact test was performed to find the association between academic qualifications and the barriers to practice-related question. A significant difference (Fisher's exact = 18.73; p = 0.04) was found indicating that there is an association between academic qualification of the RTs and barriers to practice LUS (Figure 3, Table 14). The association between the years of experience of the RTs and their attitude towards the barriers to practice LUS was assessed using the chi-square test. RTs who had more than 10 years of experience in the field agreed that barriers to practicing LUS remain even though they are experienced. We identified a significant difference (p < 0.05) between the years of experience and the attitude towards barriers to practice LUS (Figure 4, Table 15). Fisher's exact test was applied to find the association between work countries and barriers to practice-related question. Nearly 50.2% of the RTs reported that barriers exist for them to use the LUS irrespective of the work country, while 27.0% of them responded that there were no barriers. The remaining respondents were unsure. There was a significant difference (Fisher's exact = 46.68; p = 0.001) (Figure 5, Table 16).

Table 11. Attitude domain question on barriers to practice lung ultrasound.

Answer	Frequency	Percent
No	139	27.0
Not sure	117	22.8
Yes	258	50.2
Total	514	100.0

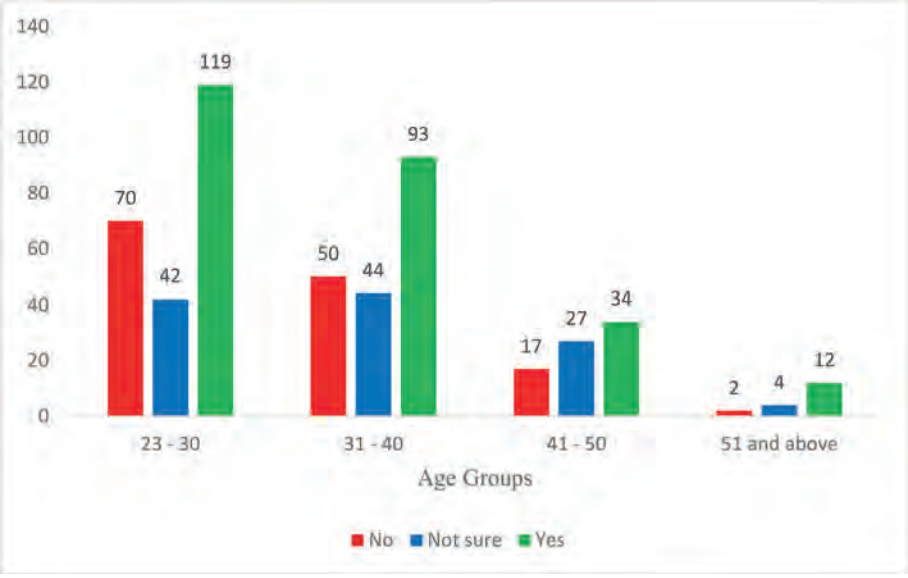

Figure 1. Insight of respondents on the barriers to practice lung ultrasound based on age groups.

Table 12. Cross tabulation between age and barrier-related question.

Parameter		If formally certified in lung ultrasound to enhance the scope of practice, do you think that there will be barriers for respiratory therapists to use this diagnostic tool?			Total
		No	Not Sure	Yes	
Age group in years	23-30	70 (30.3)	42 (18.2)	119 (51.5)	231
	>30-40	50 (26.7)	44 (23.5)	93 (49.7)	187
	>40-50	17 (21.8)	27 (34.6)	34 (43.6)	78
	>51	2 (11.1)	4 (22.2)	12 (66.7)	18
Total		139	117	258	514

Fisher's exact test = 11.59; $p = 0.07$.

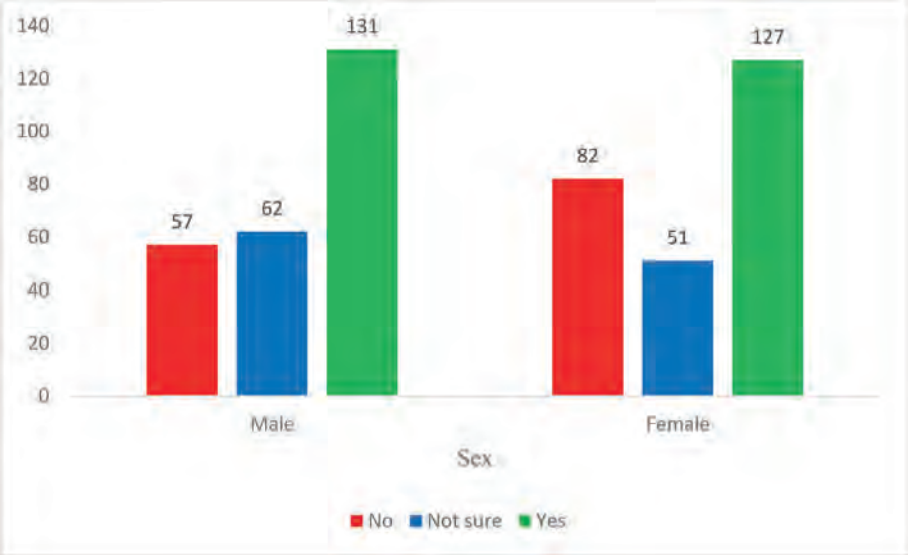

Figure 2. Insight of respondents on the barriers to practice lung ultrasound based on sex.

Table 13. Cross tabulation between sex and barrier-related question.

Sex	If formally certified in lung ultrasound to enhance the scope of practice, do you think that there will be barriers for respiratory therapists to use this diagnostic tool?			Total
	No	Not sure	Yes	
Male	57 (22.8)	62 (24.8)	131 (52.4)	250
Female	82 (31.5)	51 (19.6)	127 (48.8)	260
Total	139 (27.3)	113 (22.2)	258 (50.6)	510

Chi-square = 5.44; $p = 0.07$.

Discussion

The scope of practice of RTs has been expanding with the evolution of new related technologies in medicine. LUS appears to be a promising tool in the diagnostic and prognostic aspects of respiratory disorders, especially in acute care settings. Considering the pivotal role of RTs in acute care settings, it is recommended that RTs should master the knowledge and skills related to LUS [28, 29]. It is suggested that as the primary caregivers of ventilated patients, RTs trained in LUS will have specific beneficial outcomes in terms of early recognition of pneumothorax, facilitation of weaning, and optimization of the positive-end expiratory pressure in worsening acute respiratory distress syndrome patients [28].

This study was the first international survey specifically conducted for RTs to capture a diverse range of practices, challenges, and insights, offering a comprehensive view of how LUS is utilized worldwide by RTs. Even though the sample size was small compared

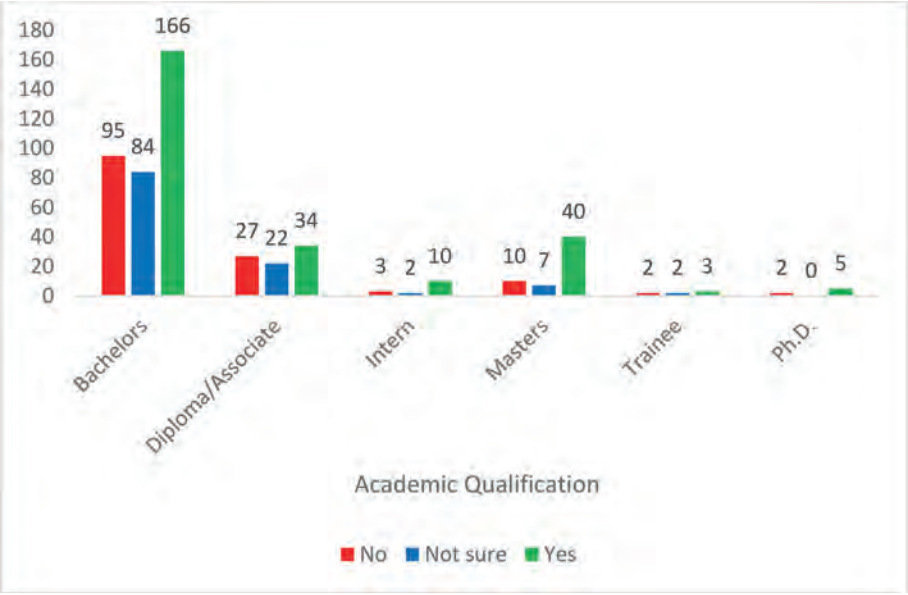

Figure 3. Insight of respondents on the barriers to practice lung ultrasound based on educational qualifications (Ph.D., Doctor of Philosophy).

Table 14. Cross tabulation between qualification and barrier-related question.

	If formally certified in lung ultrasound to enhance the scope of practice, do you think that there will be barriers for respiratory therapists to use this diagnostic tool?			
Academic qualification	**No**	**Not sure**	**Yes**	**Total**
Bachelors	95 (27.5)	84 (24.3)	166 (48.1)	345
Diploma/Associate	27 (32.5)	22 (26.5)	34 (41.0)	83
Intern	3 (20.0)	2 (13.3)	10 (66.7)	15
Master's	10 (17.5)	7 (12.3)	40 (70.2)	57
Trainee	2 (28.6)	2 (28.6)	3 (42.9)	7
Ph.D.	2 (28.6)	0 (0)	5 (71.4)	7
Total	139	117	258	514

Fisher's exact = 18.73; $p = 0.04$. Ph.D., Doctor of Philosophy.

to the number of RTs globally, the survey had participation from many countries where the practice exists, providing important insights into their shared perspectives on LUS. The survey reflected all age groups, with considerable participation from the young RTs. Sex-wise, the samples were comparable. RTs with diverse qualifications participated in the survey, with prominent representation from bachelor's degree holders. From an experience perspective, the groups with less than 10 years were comparable, but a striking participation was noted from the senior RTs with more than 10 years of experience. RTs working in diverse geographical regions responded to the survey, with higher responses from the Middle Eastern countries.

From the knowledge domain analysis, the mean score of 2.80 ± 1.49 (range: 0-6) reflected the insufficiency of LUS knowledge that the RTs possess. One of the alarming parts of the knowledge domain was about the 'seashore sign,' in which only 38.5% of the RTs correctly mentioned it as a normal lung pattern

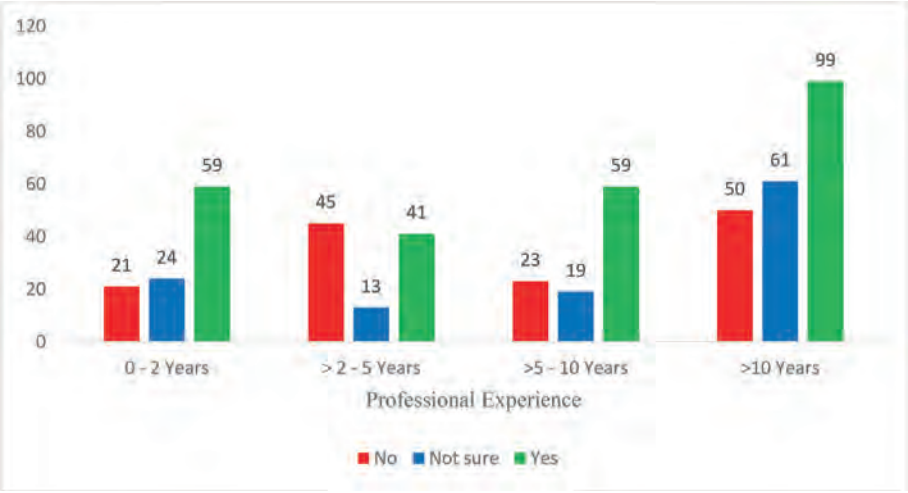

Figure 4. Insight of respondents on the barriers to practice lung ultrasound based on years of experience.

Table 15. Cross tabulation between years of experience and barrier-related question.

	If formally certified in lung ultrasound to enhance the scope of practice, do you think that there will be barriers for respiratory therapists to use this diagnostic tool?			
Years of experience	**No**	**Not sure**	**Yes**	**Total**
0-2	21 (20.2)	24 (23.1)	59 (56.7)	104
>2-5	45 (45.5)	13 (13.1)	41 (41.4)	99
>5-10	23 (22.8)	19 (18.8)	59 (58.4)	101
> 10	50 (23.8)	61 (29.0)	99 (47.1)	210
Total	139	117	258	514

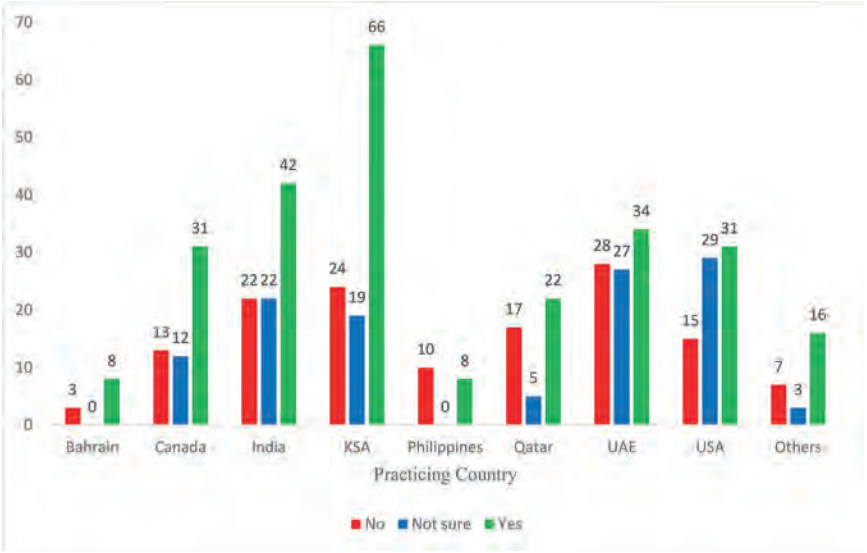

Figure 5. Insight of respondents on the barriers to practice lung ultrasound based on the country they work. (KSA, Kingdom of Saudi Arabia; UAE, United Arab Emirates; USA: United States of America).

Table 16. Cross tabulation between work country and barriers for lung ultrasound.

Country where the respondent currently works	If formally certified in lung ultrasound to enhance the scope of practice, do you think that there will be barriers for respiratory therapists to use this diagnostic tool?			Total
	No	Not sure	Yes	
Bahrain	3 (27.3)	0 (0)	8 (72.7)	11
Canada	13 (23.3)	12 (21.4)	31 (55.4)	56
India	22 (25.6)	22 (25.6)	42 (48.8)	86
KSA	24 (22.0)	19 (17.4)	66 (60.6)	109
Philippines	10 (55.6)	0 (0)	8 (44.4)	18
Qatar	17 (38.6)	5 (11.4)	22 (50.0)	44
UAE	28 (31.5)	27 (30.3)	34 (38.2)	89
USA	15 (20.0)	29 (38.7)	31 (41.3)	75
Others	7 (26.9)	3 (11.5)	16 (61.5)	26
Total	139 (27.0)	117 (22.8)	258 (50.2)	514

Fisher's exact = 46.68; $p = 0.000$. KSA, Kingdom of Saudi Arabia; UAE, United Arab Emirates; USA, United States of America.

from the options given. It is understood that the paucity of focused training and position statements specific for the RTs to perform LUS might have led to the ambiguity as reflected in the responses of the knowledge domain. Additionally, this uncertainty in the knowledge-related domain of RTs might perpetuate considering their naiveness in LUS and the infancy of the profession in some parts of the world [30].

The mean attitude score in this survey was 4.18 ± 1.29 (range: 0-5) reflecting the positive approach of RTs toward LUS. The majority (83.7%) stand with the idea of including LUS within their scope of practice. In general, the attitude of respondents was suggestive of the need to empower the RTs with LUS with proper training to enhance patient care and safety culture. We agree with a previous similar study that such an extended scope can be developed only through proper training pathways to set up a clear structure focusing on the outcome, i.e., patient care.

The mean practice score was 2.19 ± 1.73 (range: 0-6), indicating an insufficient exposure and practice of LUS by the RTs. It is of great interest that 51.9% of RTs have initiated efforts to practice LUS by learning through workshops/ journals/ textbooks/ webinars/ YouTube. However, only 7.0% of the RTs have some certification in LUS, with only 26.1% of them having hands-on experience. The enthusiasm to learn LUS and their interest to include LUS in the profession was visible in their responses related to assisting the LUS-related procedures and their interaction on LUS with other healthcare professionals.

In our study, the positively attributed responses in the knowledge and practice domains were high among the RTs who have completed their master's and Ph.D. This corresponded to the years of clinical exposure they possess. This reflects that the learning trajectory in any areas such as LUS progresses from basic principles and techniques to more advanced concepts and skills [31]. Like any other technique, the process of the LUS learning curve typically starts with exploring the technical aspects of the equipment and by obtaining and interpreting basic ultrasound images. With experience, they may move on to more advanced techniques, such as using ultrasound to guide procedures or to assess specific respiratory conditions.

The results obtained from knowledge-based questions was comparable to a prospective cohort study conducted by See et al., in which RT trainees were examined with the same pre-performance and post-performance-based test in identifying ultrasound images after undergoing a didactic session, self-learning module, and practical assessment. It was found that the trainees were 95% successful in interpreting the images, and the performance score was directly

proportional to the number of training cases attended by the trainees [26]. Hence, systematic training and practice are essential to master LUS, as the goal of LUS training is to enable healthcare professionals like RTs to use ultrasound effectively and confidently in their clinical practice [32].

The attitude of the working professional RT regarding the need for the inclusion of LUS curriculum in RT school reflected the necessity of the same. This finding was backed by another cross-sectional study that focused on the RTs working in Saudi Arabia where the results showed the need of integrating LUS into RT curriculum [30].

Hands-on experience is an important part of training in LUS [33], and we applaud the positive responses of our respondents related to attitude and practice reflecting their interest towards the learning process. One of the ways RTs can gain hands-on experience in LUS includes the observation of experienced practitioners while they perform LUS exams, which can provide valuable insight into the technique and help to build an understanding of the process [34]. Another method is to practice LUS on simulated models, which helps to develop technical skills and confidence [35].

The practice-based responses in our study are in accordance with a study where the trainees including RTs were exposed to a didactic session with video lecture, hands-on session at the bedside, and practical assessments of LUS. When the trainee's knowledge was assessed, almost 80% of the trainees were able to identify the normal lungs and lungs with interstitial-alveolar syndrome after a few examinations and supervisions, reflecting the importance of exposure and training [25]. The most comprehensive way to gain hands-on experience in LUS is to perform supervised exams or performance-based assessment on real patients. This can provide valuable experience in working with patients and applying the knowledge and skills learned [36].

To address the identified gaps noted from our survey, regarding knowledge and practice of RTs, it is important to implement comprehensive and targeted professional development programs. Strategies to facilitate this include standardized training programs with a comprehensive curriculum, hands-on workshops, and simulation-based education [37, 38]. Additionally, continuing education programs such as workshops, online courses, and certification programs are crucial [39, 40]. Interdisciplinary training through collaborative learning with other professionals and case-based learning can also enhance RTs' skills [41, 42]. Moreover, mentorship and peer learning opportunities should be provided to support ongoing professional growth [43, 44].

An area of concern identified was the barriers to practice LUS. In our study, irrespective of diverse demographic details, half of the total respondents agreed that there might exist barriers for the RTs to practice LUS, and the other half had mixed opinions. Even though the survey did not subcategorize the types of expected barriers, the potential barriers to RTs' involvement in LUS practice, as reflected from the literature include lack of formal training and curriculum, lack of resources and mentors, time constraints, lack of accreditation or standardization, resistance to practice, and lack of confidence [30]. Strategies to overcome these barriers include investing in equipment and resource sharing, providing integrated training sessions and hybrid self-paced programs, implementing standardized training guidelines and tailored certification programs, offering evidence-based education and inclusive approaches, and providing frequent practice opportunities and mentorship [37, 39, 40, 43]. If RTs, even with formal certification, continue to have barriers to practice, then this points at the need of competency assessments with the endorsement from the respective professional societies or regulatory bodies.

Due to the nature of their educational background and professional practice, RTs are eligible candidates to learn and practice LUS. However, the extent and duration of training/learning, the frequency of scans to be done, and the competency-based assessment specific to RTs are still unknown with some repositioned statements related to other professions.

It has been reported from a few anecdotal experiences and conference abstracts that LUS skills can be satisfactorily achieved with a training duration ranging from 2 hours to 4 months and with 20-80 supervised scans [36, 45-47]. Even though the learning curve associated with the application of LUS is relatively short, the diagnostic yield of LUS depends primarily on the

clinician's expertise [48-50]. It was highlighted from a multicentered study with multidisciplinary trainees including RTs that a training curriculum consisting of theoretical modules and 25 LUS exams under expert supervision is optimal to attain the basic skills for identifying normal lung aeration, interstitial-alveolar syndrome, and consolidation in acutely ill patients [25].

There is evidence to support the involvement of non-physician healthcare professionals such as nurses, paramedics, and physiotherapists in the practice of ultrasonography [51-53], and some articles reflect the need of inclusion of LUS into the scope of practice of RTs [17, 28-30]. It was reiterated in these articles that considering the nature of the profession, equipping RTs with LUS knowledge will be an added value in improving the quality of patient care and patient safety.

Conclusion

Foreseeing professional advancement and better patient outcomes, this study suggested that RTs perceive value in the inclusion of a comprehensive respiratory care-related ultrasound training module within existing respiratory therapy curriculums internationally. This study also suggests that a well-structured respiratory-related ultrasound training module for the practicing RTs may serve to augment their technical and clinical decision-making skills for safer practice. Building on this broader understanding, additional study on LUS is warranted in specific countries/healthcare authorities to understand the nuances of RT practice in those contexts. Barriers to implement the practice of routine use of LUS ultrasonography by the RTs remains. However, the involvement of professional organizations of the respective countries, medical education departments, and credentialing and privileging committees play a pivotal role in this process to reflect the benefit-risk ratio of including RTs in the imaging taskforce.

Need of future research

This study aimed at exploring the potential and the outlook of RTs in the practice of LUS. Although LUS clearly has an impact on respiratory care practices, there are substantial gaps, as identified from the available literature. Future research focusing on randomized controlled academic and clinical trials with the inclusion of LUS as a tool of practice for RTs is highly recommended. There also exists a need for multicentered prospective studies to propose and standardize the training and competency requirement in LUS for RTs. Everything starts at the school level, and we highlight the need to include LUS modules in respiratory therapy curriculum across the globe.

Strengths and limitations of this study

This is the first international survey conducted to explore the objective and subjective responses of RTs on LUS. Since this survey only addressed qualified respiratory therapy professionals, the responses might be considered as their global feedback on this imaging tool. However, we consider the number of participants in this study to be low compared to the worldwide number of RTs. We assume this to be due to the specific nature of the topic, where the practice of LUS by the RTs is still naïve in many parts of the world. This might have led to a bias of interest in the topic. Another reason might be survey fatigue as the coronavirus disease 2019 pandemic caused a surge in survey-based research activities.

References

1. Lerchbaumer MH, Lauryn JH, Bachmann U, Enghard P, Fischer T, Grune J et al. Point-of-care lung ultrasound in COVID-19 patients: inter- and intra-observer agreement in a prospective observational study. Sci Rep 2021; 11(1):10678.
2. Ebrahimi A, Yousefifard M, Mohammad Kazemi H, Rasouli HR, Asady H, Moghadas Jafari A, et al. Diagnostic Accuracy of Chest Ultrasonography versus Chest Radiography for Identification of Pneumothorax: A Systematic Review and Meta-Analysis. Tanaffos 2014;13(4):29-40.
3. Lichtenstein D, Goldstein I, Mourgeon E, Cluzel P, Grenier P, Rouby JJ. Comparative diagnostic performances of auscultation, chest radiography, and lung ultrasonography in acute respiratory distress syndrome. Anesthesiology 2004;100(1):9-15.
4. Maw AM, Hassanin A, Ho PM, McInnes MDF, Moss A, Juarez-Colunga E, et al. Diagnostic Accuracy

of Point-of-Care Lung Ultrasonography and Chest Radiography in Adults with Symptoms Suggestive of Acute Decompensated Heart Failure: A Systematic Review and Meta-analysis. JAMA Netw Open 2019;2(3):e190703.
5. Ye X, Xiao H, Chen B, Zhang S. Accuracy of Lung Ultrasonography versus Chest Radiography for the Diagnosis of Adult Community-Acquired Pneumonia: Review of the Literature and Meta-Analysis. PLoS One 2015;10(6): e0130066
6. Via G, Lichtenstein D, Mojoli F, Rodi G, Neri L, Storti E, et al. Whole lung lavage: a unique model for ultrasound assessment of lung aeration changes. Intensive Care Med 2010;36(6):999-1007.
7. Chiumello D, Mongodi S, Algieri I, Vergani GL, Orlando A, Via G, et al. Assessment of Lung Aeration and Recruitment by CT Scan and Ultrasound in Acute Respiratory Distress Syndrome Patients. Crit Care Med 2018;46(11):1761-68.
8. Dubé BP, Dres M, Mayaux J, Demiri S, Similowski T, Demoule A. Ultrasound evaluation of diaphragm function in mechanically ventilated patients: comparison to phrenic stimulation and prognostic implications. Thorax 2017;72(9):811-8.
9. Lichtenstein D, Mézière G, Biderman P, Gepner A, Barré O. The comet-tail artifact. An ultrasound sign of alveolar-interstitial syndrome. Am J Respir Crit Care Med 1997;156(5):1640-6.
10. Mongodi S, Via G, Girard M, Rouquette I, Misset B, Braschi A, et al. Lung Ultrasound for Early Diagnosis of Ventilator-Associated Pneumonia. Chest 2016;149(4): 969-80.
11. Bianco F, Bucciarelli V, Ricci F, De Caterina R, Gallina S. Lung ultrasonography: a practical guide for cardiologists. J Cardiovasc Med (Hagerstown) 2017;18(7):501-9.
12. Song G, Bae SC, Lee YH. Diagnostic accuracy of lung ultrasound for interstitial lung disease in patients with connective tissue diseases: a meta-analysis. Clin Exp Rheumatol 2016;34(1):11-16.
13. Stoller JK. 2000 Donald F. Egan Scientific Lecture. Are respiratory therapists effective? Assessing the evidence. Respir Care 2001;46(1):56-66.
14. Stoller JK. The effectiveness of respiratory care protocols. Respir Care 2004;49(7):761-5.
15. Kollef MH, Shapiro SD, Clinkscale D, Cracchiolo L, Clayton D, Wilner R, et al. The effect of respiratory therapist-initiated treatment protocols on patient outcomes and resource utilization. Chest 2000;117(2):467-75.
16. Stoller JK, Mascha EJ, Kester L, Haney D. Randomized controlled trial of physician-directed versus respiratory therapy consult service-directed respiratory care to adult non-ICU inpatients. Am J Respir Crit Care Med 1998;158(4):1068-75.
17. Karthika M, Wong D, Nair SG, Pillai LV, Mathew CS. Lung ultrasound: the emerging role of respiratory therapists. Respir Care 2019;64(2):217-29.
18. Oveland NP, Sloth E, Andersen G, Lossius HM. A porcine pneumothorax model for teaching ultrasound diagnostics. Acad Emerg Med 2012;19(5):586-92.
19. Connolly K, Beier L, Langdorf MI, Anderson CL, Fox JC. Ultrafest: a novel approach to ultrasound in medical education leads to improvement in written and clinical examinations. West J Emerg Med 2015;16(1):143-8.
20. Dinh VA, Giri PC, Rathinavel I, Nguyen E, Hecht D, Dorotta I, et al. Impact of a 2-Day Critical Care Ultrasound Course during Fellowship Training: A Pilot Study. Crit Care Res Pract 2015; 2015:675041.
21. Greenstein YY, Littauer R, Narasimhan M, Mayo PH, Koenig SJ. Effectiveness of a Critical Care Ultrasonography Course. Chest 2017;151(1):34-40.
22. House DR, Amatya Y, Nti B, Russell FM. Lung ultrasound training and evaluation for proficiency among physicians in a low-resource setting. Ultrasound J 2021; 13(1):34.
23. Guy A, Bryson A, Wheeler S, McLean N, Kanji HD. A Blended Prehospital Ultrasound Curriculum for Critical Care Paramedics. Air Med J 2019;38(6):426-30.
24. Swamy V, Brainin P, Biering-Sørensen T, Platz E. Ability of non-physicians to perform and interpret lung ultrasound: A systematic review. Eur J Cardiovasc Nurs 2019; 18(6):474-83.
25. Arbelot C, Dexheimer Neto FL, Gao Y, Brisson H, Chunyao W, Lv J, et al. APECHO Study Group. Lung Ultrasound in Emergency and Critically Ill Patients: Number of Supervised Exams to Reach Basic Competence. Anesthesiology 2020;132(4):899-907.
26. See KC, Ong V, Wong SH, Leanda R, Santos J, Taculod J, et al. Lung ultrasound training: curriculum implementation and learning trajectory among respiratory therapists. Intensive Care Med 2016;42(1):63-71.
27. Mathew CS, Dias E, Wong D, Karthika M. Lung Ultrasound in Respiratory Therapy: A Pre- and Post-Training Analysis. Indian J Respir Care 2023;12(2):151-62.
28. Kappel C, Chaudhuri D, Hassall K, Theune S, Sharif S, Alhazzani W, et al. Point-of-care ultrasound training for respiratory therapists: A scoping review. Can J Respir Ther 2022; 58:28-33.
29. Liu K, Yao YL, Wang YX, Wei BL, Li LC, Wang QX. A cross-sectional survey on the lung ultrasound training and practice of respiratory therapists in mainland China. BMC Pulm Med 2022;22(1):425.
30. Sreedharan JK, Karthika M, Alqahtani JS, AlRabeeah SM, Alnasser M, Alqahtani AS. Routine Application of Lung Ultrasonography in Respiratory Care: Knowledge, Perceptions, and Barriers to Instigate. Adv Med Educ Pract 2022; 13:1395-406.
31. Barnes TA, Kacmarek RM, Durbin CG. Survey of respiratory therapy education program directors in the United States. Respir Care 2011;56(12):1906-15
32. Smallwood N, Matsa R, Lawrenson P, Messenger J, Walden A. A UK wide survey on attitudes to point of care ultrasound training amongst clinicians working on the Acute Medical Unit. Acute Med 2015;14(4):159-64
33. Pietersen PI, Madsen KR, Graumann O, Konge L, Nielsen BU, Laursen CB. Lung ultrasound training: a systematic review

of published literature in clinical lung ultrasound training. Crit Ultrasound J 2018;10(1):23.
34. Keene S, McHenry KL, Byington RL, Washam M. Respiratory therapists as physician extenders: perceptions of practitioners and educators. Respir Care Educ Ann 2015; 24:20-7.
35. Mastmeyer A, Wilms M, Fortmeier D, Schröder J, Handels H. Real-Time Ultrasound Simulation for Training of US-Guided Needle Insertion in Breathing Virtual Patients. Stud Health Technol Inform 2016; 220:219-26.
36. Mukherjee T, Mehta S, Walker D. The development of an in-house thoracic ultrasound teaching programme on a UK intensive care unit. Intensive Care Med 2011; 37:1
37. Volpicelli G, Elbarbary M, Blaivas M, Lichtenstein DA, Mathis G, Kirkpatrick AW, et al; International Liaison Committee on Lung Ultrasound (ILC-LUS) for International Consensus Conference on Lung Ultrasound (ICC-LUS). International evidence-based recommendations for point-of-care lung ultrasound. Intensive Care Med 2012;38(4):577-91.
38. Blehar DJ, Barton B, Gaspari RJ. Learning curves in emergency ultrasound education. Acad Emerg Med 2015; 22(5):574-82.
39. Bahner DP, Adkins EJ, Hughes D, Barrie M, Boulger CT, Royall NA. Integrated medical school ultrasound: development of an ultrasound vertical curriculum. Crit Ultrasound J 2013;5(1):6.
40. Moore CL, Copel JA. Point-of-care ultrasonography. N Engl J Med 2011 24;364(8):749-57.
41. Thistlethwaite J. Interprofessional education: a review of context, learning and the research agenda. Med Educ 2012;46(1):58-70.
42. Mantuani D, Frazee BW, Fahimi J, Nagdev A. Point-of-Care Multi-Organ Ultrasound Improves Diagnostic Accuracy in Adults Presenting to the Emergency Department with Acute Dyspnea. West J Emerg Med 2016;17(1):46-53.
43. Kelm DJ, Ratelle JT, Azeem N, Bonnes SL, Halvorsen AJ, Oxentenko AS, et al. Longitudinal Ultrasound Curriculum Improves Long-Term Retention Among Internal Medicine Residents. J Grad Med Educ 2015;7(3):454-7.
44. Dickerson J, Paul K, Vila P, Whiticar R. The role for peer-assisted ultrasound teaching in medical school. Clin Teach 2017;14(3):170-4.
45. Chalumeau-Lemoine L, Baudel JL, Das V, Arrive´ L, Noblinski B, Guidet B, et al. Results of short-term training of naïve physicians in focused general ultrasonography in an intensive-care unit. Intensive Care Med 2009;35(10):1767-71.
46. Uppalapati A, Oropello J, Mukkera SR, Jamkhana ZA, DelGiudice R, Sherman B. Efficacy of a training program to achieve competence in lung and pleural ultrasound. Chest 2011;140(4):1033.
47. UAP Flato, HP Guimara~es, G Petisco, F Bezerra, AB Cavalcante, O Berwanguer. Use of lung ultrasonography in the detection of pneumothorax among medical students and emergency physicians. Crit Care 2011;15(S2):46.
48. Mayo PH, Goltz HR, Tafreshi M, Doelken P. Safety of ultrasound guided thoracentesis in patients receiving mechanical ventilation. Chest 2004;125(3):1059-62.
49. Poletti PA, Kinkel K, Vermeulen B, Irmay F, Unger PF, Terrier F. Blunt abdominal trauma: should US be used to detect both free fluid and organ injuries? Radiology 2003; 227(1):95-103.
50. Ojaghi Haghighi SH, Morteza Begi HR, Sorkhabi R, Tarzamani MK, Kamali Zonouz G, Mikaeilpour A, et al. Diagnostic Accuracy of Ultrasound in Detection of Traumatic Lens Dislocation. Emerg (Tehran) 2014;2(3):121-4.
51. Rooney KP, Lahham S, Lahham S, Anderson CL, Bledsoe B, Sloane B, et al. Pre-hospital assessment with ultrasound in emergencies: implementation in the field. World J Emerg Med 2016;7(2):117-23.
52. Leech M, Bissett B, Kot M, Ntoumenopoulos G. Lung ultrasound for critical care physiotherapists: A narrative review. Physiother Res Int 2015;20(2):69–76.
53. Henderson SO, Ahern T, Williams D, Mailhot T, Mandavia D. Emergency department ultrasound by nurse practitioners. J Am Acad Nurs Pract 2010;22(7):352–5.

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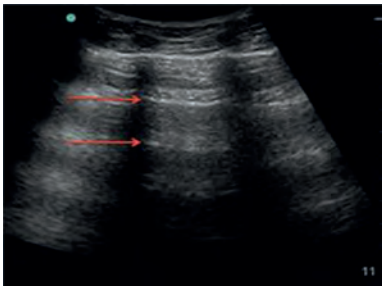
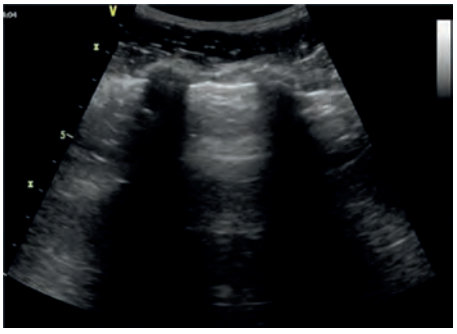
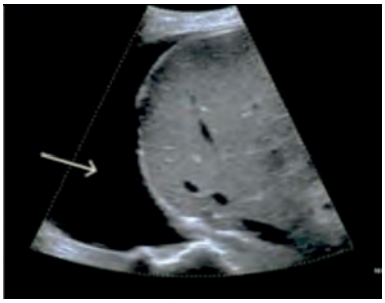
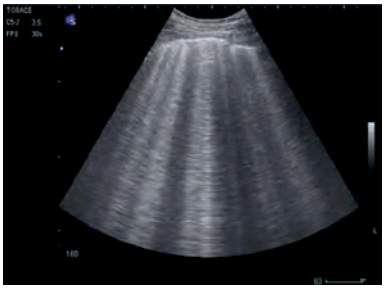
APPENDIX

SUPPLEMENTARY FILE 1: SURVEY QUESTIONNAIRE

Questions		Answer Options [Italic Bold-Correct Answer]
Knowledge-Based Questions		
Q1	Lung ultrasound emits radiation.	a. Yes b. ***No*** c. Maybe
Q2	The bright horizontal lines represented by the arrows indicates _____ 	a. Lung tissue artifacts b. ***Pleural reverberation artifacts*** c. Endotracheal Tube artifacts d. Rib shadows
Q3	What normal / abnormal sign is visible in the following lung ultrasound image? 	a. Seashore sign b. ***Bat sign*** c. Quad sign d. B-lines
Q4	What normal/ abnormal sign is indicated by the arrow? 	a. Pulmonary Edema b. ***Pleural Effusion*** c. Pneumothorax d. Atelectasis

Questions		Answer Options
Knowledge-Based Questions		**[Italic Bold-Correct Answer]**
Q5	What is the most likely clinical condition reflected by the vertical lines in this lung ultrasound image of a patient in respiratory distress? 	a. ***Pulmonary Edema*** b. Pleural Effusion c. Pneumothorax d. Normal Lung
Q6	Seashore sign in M-mode of Lung ultrasound indicates _____	a. Pulmonary Edema b. Pleural Effusion c. Pneumothorax d. ***Normal Lung***
Attitude-Based Questions		**Answer Options**
Q7	Do you think that Lung Ultrasound should be included within the scope of practice of RTs?	a. Yes b. No c. Not sure
Q8	Do you think that RT performed lung ultrasound can promote safety culture in ICU, especially in case of ventilated patients?	a. Yes b. No c. Not sure
Q9	Do you think that there is a need of development of training-based certification on Lung Ultrasound for the currently practicing RTs?	a. Yes b. No c. Not sure
Q10	Do you think that your academic and clinical knowledge can make you competent to perform lung ultrasound?	a. Yes b. No c. Not sure
Q11	Do you think that lung ultrasound needs to be included in the curriculum of RT schools?	a. Yes b. No c. Not sure
Q12	If formally certified in lung ultrasound to enhance the scope of practice, do you think that there will be barriers for RTs to perform lung ultrasound?	a. Yes b. No c. Not sure
Practice-Based Questions		**Answer Options**
Q13	Have you ever learnt about Lung Ultrasound in any workshops/ journals/ textbooks/ webinars/ YouTube?	a. Yes b. No
Q14	Do you have any formal certification in Lung Ultrasound?	a. Yes b. No
Q15	Do you have any hands-on experience in Lung Ultrasound?	a. Yes b. No
Q16	Have you ever been asked by the Physicians/ Nurses/ Other Healthcare Professionals, regarding your knowledge on Lung Ultrasound?	a. Yes b. No
Q17	Have you ever assisted the Physicians in performing Lung Ultrasound/ prepared the Ultrasound Machine?	a. Yes b. No
Q18	Have you ever interacted/ recommended the scope of Lung Ultrasound in RT Profession, to Colleagues/ Supervisors/ Other Healthcare Professionals/ Management?	a. Yes b. No

Original Research Article

OPEN ACCESS

Effect of Home-Based Pulmonary Rehabilitation on Pulmonary Fibrosis

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ABSTRACT

Background: Pulmonary fibrosis is a chronic, progressive lung condition that involves lung tissue scarring and thickening. The effects of home-based pulmonary rehabilitation (PR) in post-COVID pulmonary fibrosis (PCPF) and other forms of fibrosis together have not been evaluated. This study aims to evaluate the effectiveness of home-based pulmonary rehabilitation on pulmonary function, functional capacity, and health-related quality of life in people with pulmonary fibrosis [post-COVID pulmonary fibrosis, pulmonary fibrosis secondary to pulmonary tuberculosis (TB), pulmonary fibrosis secondary to interstitial lung disease (ILD), pulmonary fibrosis secondary to bronchiectasis].

Methods: A single-group pretest–posttest experimental study was performed after recruiting 98 pulmonary fibrosis subjects from K.M.C hospitals. After being screened for the inclusion and exclusion criteria, 45 subjects were analyzed, and 6 subjects were lost to follow up. A home-based pulmonary rehabilitation program was carried out for 8 weeks (warm-up, stretching exercises, aerobic exercise, strength training for upper limb and lower limb, breathing exercises mainly involved; others: energy saving techniques, controlled coughing techniques, dyspnea relieving positions). The program was supervised via weekly phone calls. Pulmonary function (Pulmonary function test), exercise capacity (6-minute walk test), dyspnea (modified Borg scale), and health-related quality of life (SF-36) were evaluated before and after the intervention. During the enrollment and after the 6-minute walk test, saturation of peripheral oxygen (SPO_2) level was also evaluated pre-intervention and after the 8-weeks program.

Results: Pulmonary function [FVC(L) t = -12.52, p<0.05; FEV_1(L) t = -2.56, p<0.05; FEV_1/FVC t = 7.98, p<0.05 and DL_{CO} (ml/min/mmHg) t = -5.13, p<0.05], 6MWD [MD 88.66; p<0.05] and HRQOL measured by SF-36 scores (p<0.05) were improved significantly. Both the baseline SPO_2 level before the 6MWT [MD 1.07, p<0.05] and the SPO_2 level after the 6MWT [MD 1.16, p<0.05] showed a significant improvement. The rating of perceived exertion(dyspnea) [MD 1.30, p<0.05] was reduced significantly after the 8-week program.

Conclusion: Our study shows that home-based pulmonary rehabilitation is an effective option for improving lung function and physical functional capacity by reducing dyspnea perception and improving the saturation of peripheral oxygen (SPO_2) level, and enhancing the quality of life in people with pulmonary fibrosis.

Key words: home-based pulmonary rehabilitation, post-COVID pulmonary fibrosis, idiopathic pulmonary fibrosis, interstitial lung disease, pulmonary function test, quality of life.

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Authors' contributions: All the authors contributed to the conceptualization. Data collection, delivery of protocol, and execution were done by Ms. Rashmita Saha. Dr. Vijay Pratap Singh and Dr. Stephen Rajan Samuel supervised all aspects of its implementation. All the authors contributed equally to data analysis, formulation of results, and proofreading of the manuscript. Compilation and writing of the manuscript were done by Ms. Rashmita Saha and Dr. Vijay Pratap Singh. All authors read and approved the final manuscript.

Ethics approval and consent to participate: This study had been reviewed and approved by the Institutional Ethics Committee, Kasturba Medical College, Mangalore (Protocol No: IEC KMC MLR 01/2022/18). All participating subjects had received a verbal explanation, written detailed information on the study, and signed consent forms for the participation. The processing of sensitive personal data was based on following the Helsinki Declaration's ethical principles.

Consent for publication: Written informed consent was obtained from all individuals participating in the study and all authors in this study provided formal consent for publication.

Availability of data and material: The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Conflict of interest: All authors declare that they have no competing interests.

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Background

Pulmonary Fibrosis (PF) is the common term used to describe a large family of diseases that causes inflammation and scarring of the lung. It is typically not a primary disease but rather develops as a result of other respiratory or interstitial lung disorders [1–3]. Worldwide, pulmonary fibrosis has a high prevalence and mortality rate [4]. In the post-COVID era, the healthcare system has been changed by post-COVID complications [5]. One of them is post-COVID Pulmonary Fibrosis (PCPF) [6]**.** However, pulmonary fibrosis is caused not just by post-COVID or interstitial lung diseases but also by other lung diseases such as bronchiectasis and pulmonary tuberculosis (TB).

Basically, the extracellular matrix (ECM) becomes coated with abnormal collagens, causing pulmonary fibrosis. This results in a stiff lung that lacks the compliance (or "stretchability") required for regular breathing [7]. Lung scarring blocks the pathways necessary for deactivating pro-fibrotic cells and eliminating the proliferating matrix. This intricate process includes myofibroblast transition of epithelial cells, a procoagulant framing in the lung, oxidative signaling, supported by the accumulation of reactive oxygen species in the lungs, and replacement of the normal type I alveolar epithelium with hyperplastic type II cells [8]. It is driven by neutrophils and macrophages because of their released cytokines (IL-6, IL-2, IL-1, and TNFα) and chemokines (IL-8 and oxanthin) [9].

People with pulmonary fibrosis seek medical attention for their progressive, persistent coughs and dyspnea. Dyspnea and fatigue impair the functional capacity and quality of life of pulmonary fibrosis patients. Individuals with pulmonary fibrosis gradually become less physically active and unable to do daily living activities as fibrosis advances, dyspnea, and exhaustion worsen [10].

Pulmonary rehabilitation (PR) is one of the advantageous management techniques to improve shortness of breath, health status, exercise tolerance, etc. In 2013, the 'American Thoracic Society (ATS)' defined pulmonary rehabilitation as - "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 emotional condition of people the long-term adherence of health-enhancing behaviors" [11].

As a homecare-based rehabilitation purpose, patients with pulmonary fibrosis (post-COVID pulmonary fibrosis, pulmonary fibrosis secondary to TB, pulmonary fibrosis secondary to ILD, pulmonary fibrosis secondary to bronchiectasis) frequently require assistance from family members, who can be trained by health professionals in their own home environment. Basically, home-based programs are a good and suitable option for pulmonary rehabilitation in everyday life [12]. Furthermore, these programs are effective, useful, simple, cost-effective, and practical [13, 14].

A standard home-based pulmonary rehabilitation program for patients with pulmonary fibrosis (post-COVID pulmonary fibrosis, pulmonary fibrosis secondary to TB, pulmonary fibrosis secondary to ILD, pulmonary fibrosis secondary to bronchiectasis) has not been studied in India. Therefore, this study aimed to investigate the effectiveness of home-based pulmonary rehabilitation for pulmonary fibrosis patients. As we included patients with post-COVID pulmonary

fibrosis, pulmonary fibrosis due to TB, pulmonary fibrosis secondary to ILD, and pulmonary fibrosis secondary to bronchiectasis; our study differs from earlier studies in these areas.

Methods

The study was approved by the Institutional Ethics Committee of Kasturba Medical College, Mangalore (Protocol number: IEC KMC MLR 01/2022/18) and complied with the Declaration of Helsinki (as revised in 2013). The trial was registered at www.clinicaltrials.gov (CTRI/2022/03/041284).

Study Design

A single group pretest-posttest experimental study was conducted in the KMC hospitals (OPD), Ambedkar Circle and Attavar, Mangalore. It was performed between February 2022 to January 2023.

Participant selection

Study participants were recruited from KMC hospitals, Mangalore, those were visiting the outpatient department (OPD) diagnosed with pulmonary fibrosis referred by pulmonologists based on standard diagnostic criteria [15]. Prior to the start of the 8-week home-based pulmonary rehabilitation program, a total of 98 pulmonary fibrosis participants were achieved. However, 37 of them were eliminated since 32 did not match the inclusion criteria, and 5 did not want to take part in this study.

Inclusion criteria

a. Pulmonary Fibrosis secondary (2°) to interstitial lung disease (ILD).
b. Pulmonary Fibrosis post-COVID.
c. Pulmonary Fibrosis secondary (2°) to other lung disease like bronchiectasis, tuberculosis, etc.
d. Age: 18-80 years
e. Moderate to severe diagnosed through PFT (FEV_1<50).
f. Independent ambulation.

Exclusion criteria

a. Cardiac conditions (Moderate to severe) like coronary artery disease and congestive heart failure.
b. Respiratory conditions like chronic obstructive pulmonary disease (COPD), asthma, lung cancer, severe pulmonary hypertension.
c. Other neuromuscular conditions affecting respiratory as well as physical function.

Procedures

Subjects were included based on the inclusion criteria. They were screened for points mentioned in the exclusion criteria. Eligible subjects were called on a subsequent day and explained about this research study if the patient voluntarily agreed, then they were asked to sign a written informed consent in English and their vernacular language. Pre-testing was done before starting the home-based pulmonary rehabilitation program and all outcomes were recorded. Pulmonary Function Test (PFT), SF-36 scale, and 6 MWT were conducted. Readings were recorded and stored for statistical analysis. The intervention was started at the home of the candidate, and all the guidelines of the American Thoracic Society (ATS) for home-based pulmonary rehabilitation were followed [13, 16, 17]. We had developed a home-based pulmonary rehabilitation protocol based on previous literature and expert advice. Patients were provided with a booklet to refer at home with a family member supervising. After 8 weeks later, a post-test was conducted, and readings were recorded. Based on the pre-readings and post-readings, statistical analysis was done.

Intervention

Over the course of the 8-week program, the patients were instructed about the benefits and importance of adhering to the pulmonary rehabilitation program. The patient and patient's party who was there in the hospital was taught about the benefits of the program, and we asked the patient party to supervise the program at their home. Participants and

the participant's party were provided with a catalogue which had detailed instructions for the exercise program. The patients and patient's party were given a notebook or diary in which the patient was marked after doing performance, daily, and patient's party also had to signed. The patients were instructed to do all the exercises at least six days a week in three sessions with ten repetitions each. If the significant fatigue or shortness of breath, they were advised to take a rest and to keep doing the exercises according to their fatigue tolerance level. The supervision of the program was done by phone calls once a week and daily exercise queries. Once in a week, when we had called, we spoke to both patients and patient's party about the program, and any distress, progression, and hindrance (Figure 1).

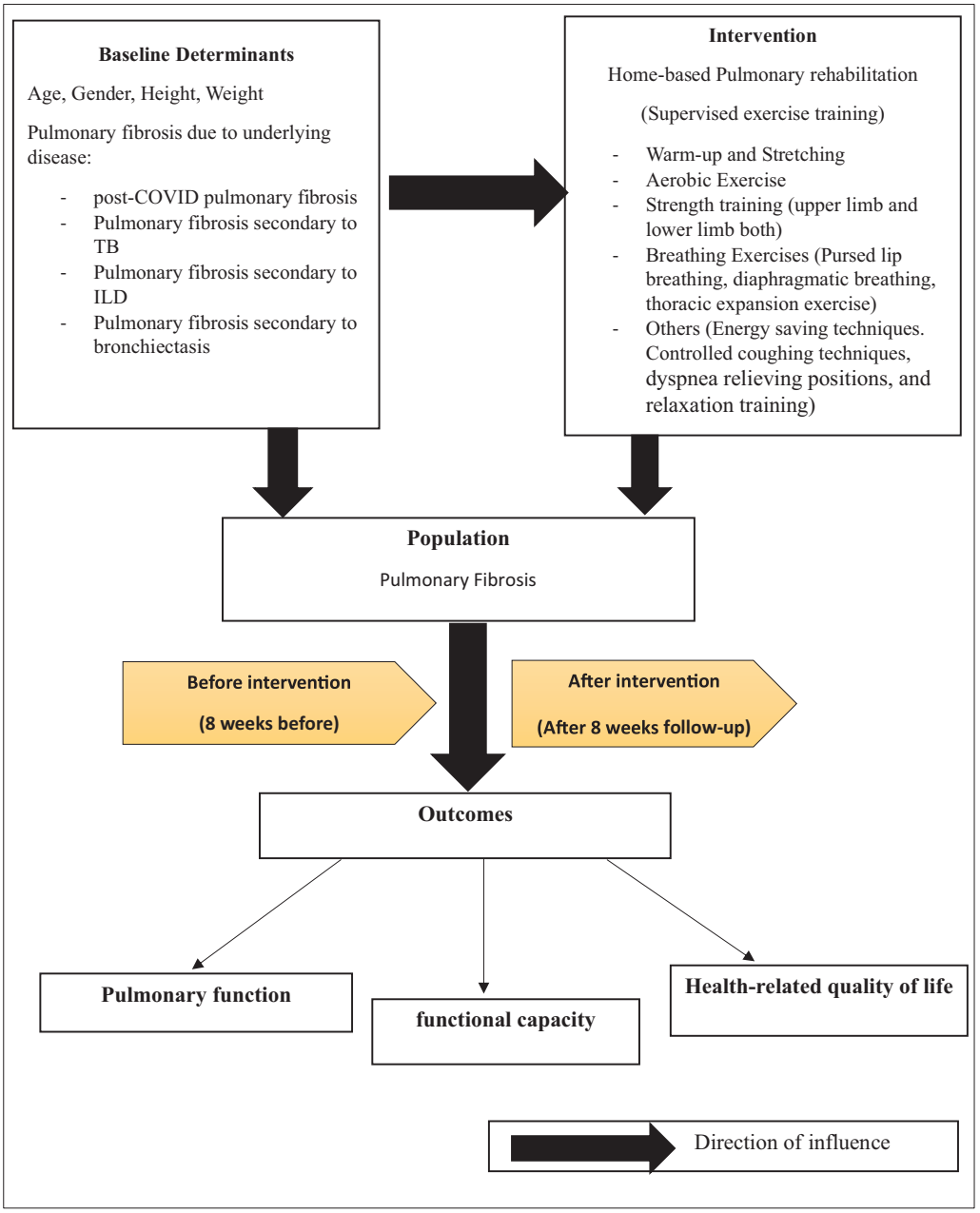

Figure 1. Framework for the effect of home-based pulmonary rehabilitation on pulmonary fibrosis (Authors creation of the figure).

Warm-up and stretching

The warm-up was for ~ 5min. It was composed of active upper and lower limb exercises. Stretching was ~ 5min, including the pectoralis major, trapezius, quadriceps, hamstrings, and gastrocnemius (calf) muscles. Each stretch posture was maintained for the 30s [18].

Aerobic exercises

Aerobic exercises consisted of walking and slow jogging. The training intensity was light (≤ 3 on modified Borg scale).

Time was at least for 20-30 min. And the exercise frequency was 1-2 times per day for 8 weeks [18, 10].

Strength training

For upper limb strengthening

Shoulder flexion, extension, abduction, elbow flexion, elbow extension with free weight; 8-10 rep. for each movement 2-3 sets, 2 times/day for 8 weeks [10, 13].

For lower limb strengthening

Seated dynamic quadriceps, hamstrings strengthening, hip abductors strengthening with weight cuff, heal raises 8-10 reps. for each and 2-3 sets, 2 times/day for 8 weeks. Sit-to-Sand exercise 3sets, 10 reps. 2 times/day for 8 weeks [18, 13, 10].

For strength training we checked for 1 RM. Since, these subjects are having pulmonary fibrosis, we further saw which weight subjects can do 7-10 repetitions for 1 set twice a day.

Progression

For progression at home, subjects were instructed that if given weight will be too easy to do and perceived dyspnea was ≤ 3 on the modified Borg scale (0-10), then increase the weight by adding another ½ kg. These clarifications were also done during follow up through telerehabilitation. This was done to ensure patient safety.

Others

It consists of teaching breath control (pursed lip breathing, diaphragmatic breathing), thoracic expansion exercise 10 reps, 2-3 sets /day for 8weeks, energy-saving techniques, and controlled coughing exercises. Coping strategies to deal with shortness of breath and relaxation training were taught to the patients [10, 19].

Termination criteria

- Dyspnoea more than 3 on 'modified Borg scale (0-10)'.
- Chest tightness, blurring of vision, profuse sweating, giddiness, and any balance problem.
- Patient decision to stop.

Outcome measures

Before and after the 8 weeks home-based pulmonary rehabilitation program, all patients were assessed using the same criteria.

Primary Outcomes

Pulmonary Function Test (PFT)

The forced expiratory volume in 1 second (FEV_1) ratio of FEV_1 to FVC (FEV_1/FVC) and carbon monoxide diffusing capacity (DL_{CO}) values were recorded. It was carried out by an expert in accordance with the ATS standards [20].

Instrument used: The instrument used for pulmonary function test was spirometry (EasyOne Pro Lab) *Portable Pulmonary Function Testing Machine - EasyOne Pro® | ndd Medical* ID:3100-1.

6-minute walk test

Exercise capacity was measured using the 6 min walk test(6 MWT). It was performed once at the starting and at the end of the pulmonary rehabilitation program, according to the guidelines of the American Thoracic Society [21]. Before and after the 6 MWT, the saturation of peripheral oxygen (SPO_2) level was assessed by using pulse oximeter (Omron CMS50N) [10].

Secondary Outcomes

Modified Borg scale (0-10)

Dyspnoea severity/rate of perceived exertion was measured by using a 'modified borg scale (0-10)' [22].

SF -36

Health-related quality of life was measured using the '36 -item Short Form Survey (SF-36) questionnaire' [23].

Saturation of peripheral oxygen (SPO2) level

Before and after the 6 MWT, the saturation of peripheral oxygen (SPO_2) level was assessed [10].

Data Analysis

Statistical analysis was done for all the variables in the study. Data was checked for normal distribution. All the variables under this study for pre to post changes had achieved normal distribution with a bell-shaped curve, then paired-t test was used to see the changes (pre to post) after 8 weeks of intervention. Descriptive statistics were used to analyze the demographic and baseline characteristics. Variables studied as outcomes (pre and post) for 8 weeks are presented as mean, standard deviation, confidence interval (C.I.), and p. P (<0.05) was considered significant. Data was analyzed using the software IBM SPSS version 26.0.1 (Statistical Package for the Social Sciences).

Results

A total sample size of 98 participants were achieved prior to the commencement of 8 weeks home-based pulmonary rehabilitation program. Out of 98, 37 participants were excluded as 32 were not meeting the exclusion criteria, and 5 refused to participate in this study. Out of 32, 27 participants were excluded due to medical conditions, 3 participants due to FEV_1>50%, and 2 participants due to age criteria. We analyzed 45 subjects because 6 subjects were lost to follow up. Figure 2 shows the recruitment process in the CONSORT flow diagram [24, 25].

Baseline characteristics of participants

Table 1 summarizes the demographic and baseline characteristics of the subjects in this study. The data analysis was performed on the 45 subjects (25 male, 20 female) (mean age 62.0±11.0 years) who completed the 8 weeks home-based pulmonary rehabilitation program. No adverse events were observed during the 8 weeks rehabilitation program. The causes of pulmonary fibrosis were post-COVID pulmonary fibrosis (35.6%), Pulmonary fibrosis secondary to TB (22.2%), Pulmonary Fibrosis secondary to ILD (33.3%), Pulmonary Fibrosis Secondary to bronchiectasis (8.9%). In this 8-week home-based pulmonary rehabilitation program, the completion rate is 74%, and the dropout rate is 26%.

Primary Outcome

6 MWT was performed using the standard test protocol (American Thoracic Society ATS guidelines) before and after 8 weeks of the intervention [21]. Table 2 describes the results of 6 MWT conducted pre-intervention and post-8 weeks of intervention. After the intervention, significant improvement in walking distance in the 6 MWT was found (MD 88.6 m), ($p<0.05$).

Table 3 describes the results of the pulmonary function test (PFT) conducted pre-intervention and post-8 weeks. After the home-based exercise program, pulmonary function test results (PFT) were significantly improved for FVC (1.29 liters vs. 1.38 liters, $p<0.05$), FEV_1(1.13 liters vs. 1.18 liters, $p<0.05$) FEV_1/FVC (0.84 vs. 0.82, $p<0.05$) and DL_{CO} (6.32 ml/min/mmHg vs. 6.7 ml/min/mmHg, $p<0.05$).

Secondary Outcome

Health-related quality of life (HRQOL) assessment was also done along with other outcome measure assessments. The analysis was divided into 9 domains of the scale respectively (Table 4). A significant improvement was found in physical functioning, role limitations due to physical health, role limitations due to emotional health, emotional well-being, social functioning, pain, general health, and health change

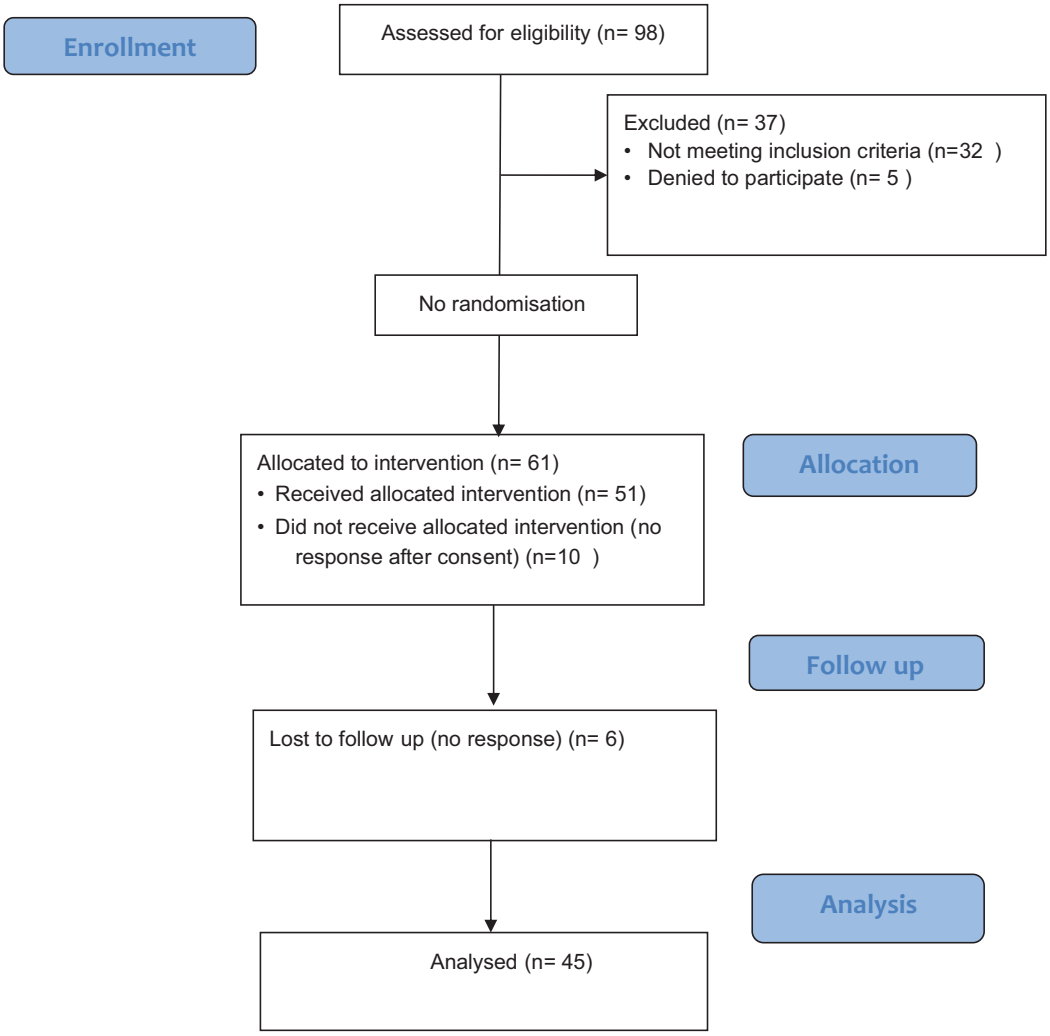

Figure 2. CONSORT Flowchart for Single-Arm Study. n= number of samples. Modified from [24].

Table 1. Demographic and baseline characteristics of the subjects in this study.

Characteristics	n	Value
Age (Years)	45	62.0±11.0
Gender (M: F)	45	25:20 (55.6%:44.4%)
Height (cm)	45	157.5±7.0
Weight (Kgs)	45	60.9±8.0
Pulmonary Fibrosis due to underlying disease		
1. Post-COVID Pulmonary Fibrosis	16	35.6%
2. Pulmonary Fibrosis secondary to TB	10	22.2%
3. Pulmonary Fibrosis secondary to ILD	15	33.3%
4. Pulmonary Fibrosis Secondary to bronchiectasis	4	8.9%

Table 2. 6 Minute Walk Test results before and after the home-based pulmonary rehabilitation.

Variable		n	Mean±S.D	MD	S.D of difference	C.I. at 95% of the difference		t	P
						Lower	Upper		
6MWT	Pre- Intervention	45	185.0±45.2	88.66	30.39	-97.80	-79.53	-19.56	0.000*
	post-Intervention	45	273.6±66.2						

*p<0.05, n, number of samples; SD, standard deviation; MD, mean difference; C.I, confidence interval; t, test statistic; p, level of significance.

Table 3. Pulmonary function test results (PFT) results before and after the home-based pulmonary rehabilitation.

Variables		Mean±S.D	MD	S.D of difference	C.I. at 95% of the difference		t	P
					Lower	Upper		
FVC(L)	Pre- Intervention	1.29±0.36	0.08	0.04	-0.09	-0.06	-12.52	0.000*
	post-Intervention	1.38±0.38						
FVC (% pred)	Pre- Intervention	42.88±4.70	2.71	1.10	-3.04	-2.38	-16.53	0.000*
	post-Intervention	45.60±4.63						
FEV_1 (L)	Pre- Intervention	1.13±0.31	0.05	0.14	-0.09	-0.01	-2.56	0.014*
	post-Intervention	1.18±0.37						
FEV_1 (% pred)	Pre- Intervention	45.86±4.35	3.11	1.86	-3.67	-2.55	-11.2	0.000*
	post-Intervention	48.97±4.58						
FEV_1/FVC	Pre- Intervention	0.84±0.05	0.019	0.016	0.014	0.024	7.98	0.000*
	post-Intervention	0.82±0.05						
FEV_1/FVC (% pred)	Pre- Intervention	110.7±7.81	2.86	2.22	2.19	3.53	8.65	0.000*
	post-Intervention	107.9±7.03						
DL_{CO} (ml/min/mmHg)	Pre- Intervention	6.32±1.34	0.45	0.59	-0.63	-0.27	-5.13	0.000*
	post-Intervention	6.78±1.73						
DL_{CO} (% pred)	Pre- Intervention	25.35±4.86	1.80	2.43	-2.53	-1.06	-4.95	0.000*
	post-Intervention	27.15±6.53						

*p<0.05, SD, standard deviation, MD, mean difference, C.I., confidence interval, t, test statistic, p, level of significance.

scores (p<0.05), but energy/fatigue domain score was not statistically significant. (>0.05). The highest difference was noted in the domains of role limitations due to emotional health (33.94 MD, p<0.05) and general health (35.45 MD, p<0.05).

The rate of perceived exertion (RPE) was taken using the 'Modified Borg scale' (0-10) after 6MWT. Table 5 shows the RPE changes taken before and after 8 weeks of intervention. MD of 1.3 (p<0.05) was observed. Table 6 and Table 7 show the distribution of subjects based on RPE scores pre-intervention and post-intervention.

Peripheral oxygen saturation (SPO_2) level was taken before and after the 6MWT(Immediately, 3min and 5min). Table 8 shows the SPO_2 level variation before and after the 8-week of intervention. A significant improvement was found for baseline SPO_2 level before the 6MWT [MD 2.73, p<0.05] , immediately after the 6MWT [MD 3.47, p<0.05], 3 min after the 6MWT [MD 3.57, p<0.05] and 5 min after the 6MWT [MD 3.65, p<0.0]. Figure 3 gives a graphical representation of SPO_2 level results taken at pre-intervention and after 8 weeks post-intervention.

Table 4. Quality of life (SF-36) results before and after the home-based pulmonary rehabilitation.

Domains		Mean±S.D	MD	S.D of difference	C.I. at 95% of the difference		t	P
					Lower	Upper		
physical functioning %	Pre- Intervention	21.33±10.02	28.11	14.78	-32.55	-23.67	-12.757	0.000*
	post-Intervention	49.44±16.62						
role limitations due to physical health %	Pre- Intervention	41.66±19.21	28.88	24.97	-36.39	-21.38	-7.760	0.000*
	post-Intervention	70.55±15.34						
role limitations due to emotional health %	Pre- Intervention	45.39±22.26	33.94	25.81	-41.69	-26.18	-8.821	0.000*
	post-Intervention	79.33±17.77						
energy/fatigue %	Pre- Intervention	50.55±9.54	0.88	11.14	-4.23	2.45	-0.535	0.595
	post-Intervention	51.44±6.79						
emotional well-being %	Pre- Intervention	54.13±9.51	8.35	10.64	-11.55	-5.15	-5.26	0.000*
	post-Intervention	62.48±7.64						
social functioning %	Pre- Intervention	56.28±12.35	27.34	13.38	-31.36	-23.32	-13.702	0.000*
	post-Intervention	83.63±7.92						
pain %	Pre- Intervention	82.50±18.27	13.16	17.88	-18.54	-7.79	-4.93	0.000*
	post-Intervention	95.66±7.21						
general health %	Pre- Intervention	27.55±9.45	35.44	11.47	-38.89	-31.99	-20.72	0.000*
	post-Intervention	63.00±7.02						
Health change %	Pre- Intervention	22.22±10.95	26.11	19.18	-31.87	-20.34	-9.13	0.000*
	post-Intervention	48.33±18.76						

*p<0.05, SD, standard deviation; MD, mean difference; C.I., confidence interval; t, test statistic; p, level of significance.

Table 5. Rate of Perceived Exertion (RPE) before and after the home-based pulmonary rehabilitation.

		n	Mean±S.D	MD	S.D of difference	C.I. at 95% of the difference	t	P
Rating of Perceived Exertion (RPE)	Pre-intervention	45	3±0.82	1.30	0.49	1.15-1.44	17.68	0.000*
	Post-intervention	45	1.7±0.73					

*p<0.05, n, number of samples; SD, standard deviation; MD, mean difference; C.I., confidence interval; t, test statistic; p, level of significance.

Table 6. Subjects distribution based on Rating of Perceived Exertion (RPE)scores before the home-based pulmonary rehabilitation.

Grade	n	Values (%)
2-3	32	71.1
4-5	13	28.9

Table 7. Subjects distribution based on Rating of Perceived Exertion (RPE)scores after the home-based pulmonary rehabilitation.

Grade	n	Values (%)
0-1	18	40
2-3	27	60

Table 8. SPO_2 results before and after the home-based pulmonary rehabilitation.

Variables (SPO_2 %)	Intervention	n	Mean±S.D	MD	S.D of difference	C.I. at 95% of the difference	t	P
Baseline before 6MWT	Pre-intervention	45	93.20±1.33	2.73	1.07	2.41-3.05	17.06	0.0001*
	Post-intervention	45	95.93±0.88					
Immediate after 6MWT	Pre-intervention	45	90.22±1.02	3.47	1.16	3.21-3.82	20.05	0.0001*
	Post-intervention	45	93.69±1.01					
3 min after 6MWT	Pre-intervention	45	91.56±0.78	3.57	1.07	3.25-3.90	22.30	0.0001*
	Post-intervention	45	95.13±0.86					
5 min after 6MWT	Pre-intervention	45	92.62±0.88	3.65	1.15	3.29-3.99	21.24	0.0001*
	Post-intervention	45	96.27±0.91					

*p<0.05, SD, standard deviation; MD, mean difference; C.I., confidence interval; t, test statistic; p, level of significance.

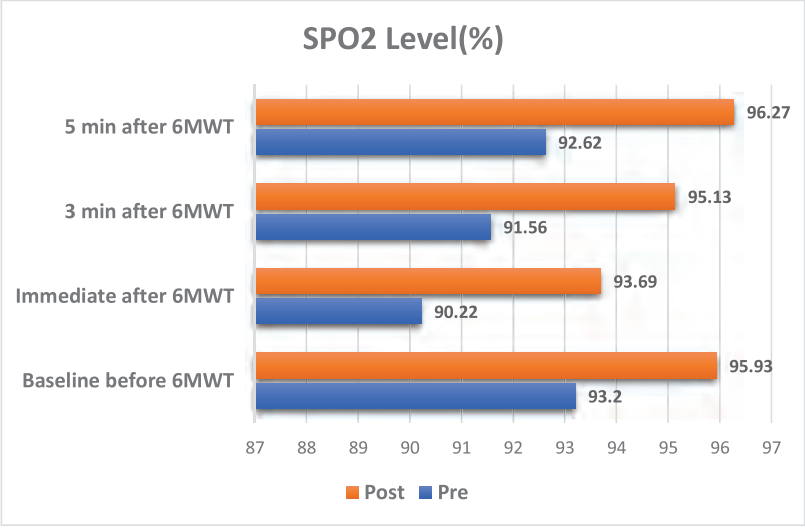

Figure 3. SPO_2 Level (%) pre- post intervention.

Subgroups: outcomes for pulmonary fibrosis due to underlying disease.

MDs for each outcome measures were estimated in the subgroups [post-COVID pulmonary fibrosis, pulmonary fibrosis secondary to TB, pulmonary fibrosis secondary to ILD, and pulmonary fibrosis secondary to bronchiectasis]; because the improvement results for each form of pulmonary fibrosis caused by the different pathological condition were not equal. However, due to the limited and uneven sample size no subgroup analysis (paired t-test) for post-COVID pulmonary fibrosis, pulmonary fibrosis secondary to TB, pulmonary fibrosis secondary to ILD, or pulmonary fibrosis secondary to bronchiectasis were not performed.

Primary outcomes for subgroups

Table 9 illustrates the MDs for PFT (Pulmonary function test) before and after the 8-week intervention in each kind of pulmonary fibrosis caused by an underlying condition. For each kind of pulmonary fibrosis, the FVC, FEV_1, FEV_1/FVC, and DL_{CO} data obtained before and eight weeks after the intervention are shown graphically in Figure 4-7.

Table 9. Pulmonary function test results (PFT).

	Pulmonary Fibrosis due to underlying disease											
	Post-COVID PF			PF secondary to TB			PF secondary to ILD			PF Secondary to bronchiectasis		
	Intervention (n=16)			Intervention (n=10)			Intervention (n=15)			Intervention (n=4)		
Variables (PFT)	Pre (n=16) Mean±S.D	Post (n=16) Mean±S.D	MD	Pre (n=10) Mean±S.D	Post (n=10) Mean±S.D.	MD	Pre (n=15) Mean±S.D	Post (n=15) Mean±S.D	MD	Pre (n=4) Mean±S.D	Post (n=4) Mean±S.D	MD
FVC(L)	1.42±0.27	1.51±0.28	0.09	1.12±0.35	1.20±0.38	0.08	1.44±0.32	1.53±0.34	0.09	1.05±0.39	1.11±0.40	0.06
FVC (% pred)	42.13±6.04	45.06±6.30	2.93	44.68±2.70	47.31±2.21	2.63	43±3.91	45.75±3.77	2.75	41.1±4.88	43.6±4.47	2.50
FEV_1(L)	1.26±0.33	1.34±0.36	0.08	0.95±0.25	1.00±0.27	0.05	1.20±0.17	1.26±0.18	0.06	0.98±0.30	1.00±0.42	0.02
FEV_1 (% pred)	44.2±6.86	47.73±7.35	3.53	46±3.16	48.75±3.30	2.75	47.06±1.84	50.31±1.92	3.25	46.4±1.64	48.8±1.75	2.40
FEV_1/FVC	0.83±0.05	0.81±0.04	0.02	0.85±0.08	0.83±0.07	0.02	0.83±0.03	0.82±0.02	0.01	0.84±0.05	0.82±0.04	0.02
FEV_1/FVC (% pred)	109.75±1.89	108.25±1.5	1.50	108.56±5.08	105.62±4.39	2.93	111.06±6.79	108.2±6.46	2.86	114.3±12.63	111±11.13	3.3
DL_{CO} (ml/min/ mmHg)	6.13±2.31	6.78±3.03	0.65	6.42±0.18	6.8±0.25	0.38	6.41±0.51	6.8±0.47	0.39	6.43±0.25	6.77±0.36	0.34
DL_{CO} (% pred)	24.73±8.19	27.46±11.19	2.73	25.6±1.64	27.1± 1.66	1.50	26.75±3.59	28.25± 4.57	1.50	25.43±1.26	26.62±1.36	1.19

*MD, mean difference for each type of pulmonary fibrosis due to underlying disease; *SD, standard deviation.

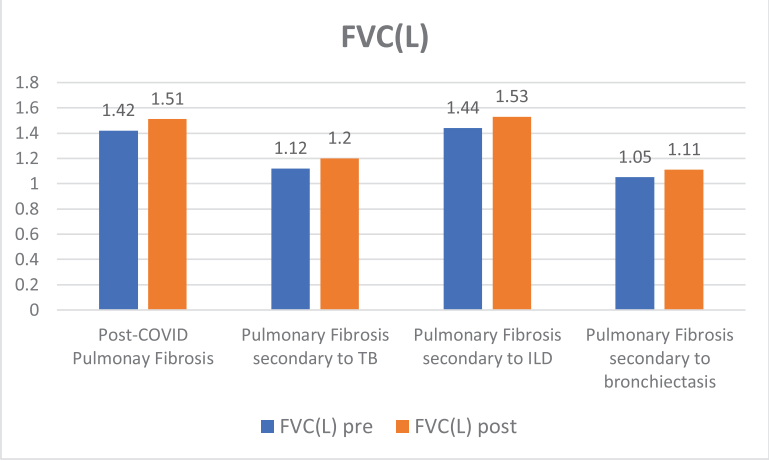

Figure 4. FVC(L) pre- post-intervention for each type of pulmonary fibrosis due to underlying disease.

Table 10 depicts the MDs for 6MWT distance before and after the 8-week intervention in each type of pulmonary fibrosis induced by an underlying disease. Figure 8 shows a graphical representation of 6MWT distance data acquired before and after 8 weeks of intervention for each type of pulmonary fibrosis due to different pathological condition. After the home-based exercise program, 6MWT distance results were improved for each type of pulmonary fibrosis [post-COVID pulmonary fibrosis 193.46 vs 291.27, MD 97.81 meter; pulmonary fibrosis secondary to TB 174 vs 258.5, MD 84.5 meter; Pulmonary fibrosis secondary to ILD 182.8 vs 270, MD 87.2 meter; pulmonary fibrosis secondary to bronchiectasis 187 vs 255, MD 68 meter].

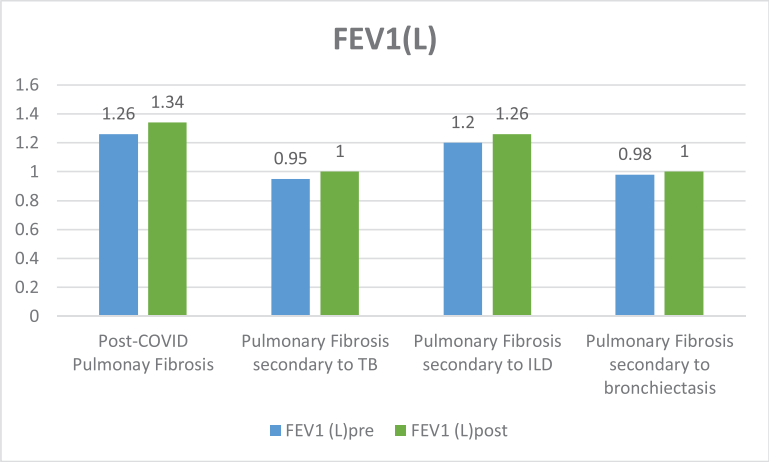

Figure 5. FEV_1(L) pre- post-intervention for each type of pulmonary fibrosis due to underlying disease.

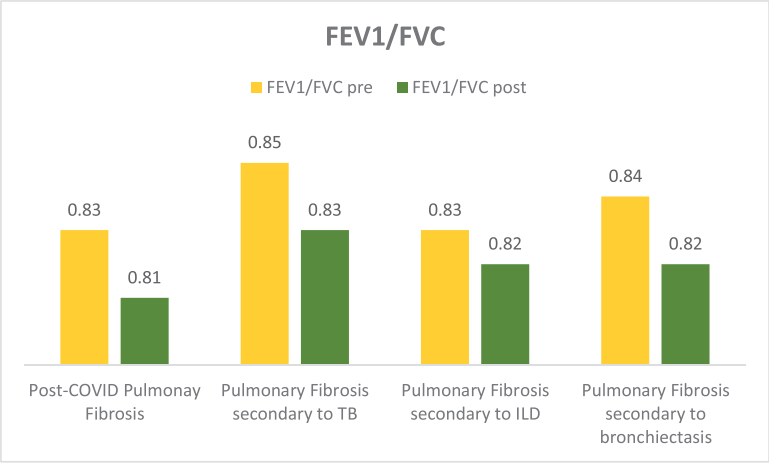

Figure 6. FEV_1/FVC pre- post-intervention for each type of pulmonary fibrosis due to underlying disease.

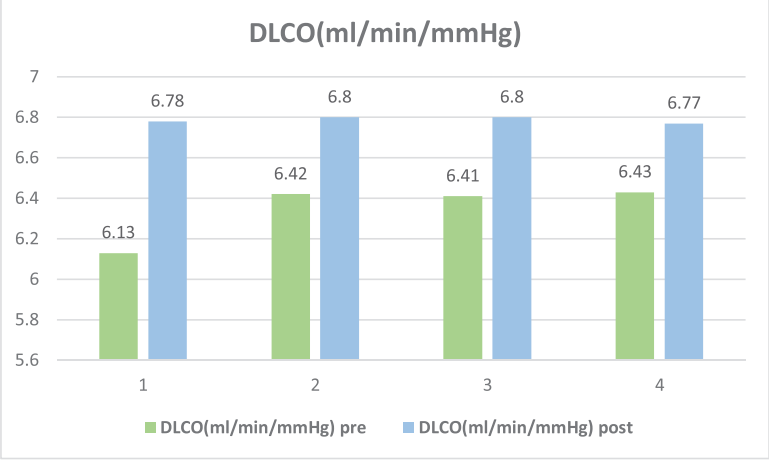

Figure 7. DL_{CO} pre- post-intervention for each type of pulmonary fibrosis due to underlying disease.

Table 10. 6MWT.

	Pulmonary Fibrosis due to underlying disease											
	Post-COVID PF			PF secondary to TB			PF secondary to ILD			PF Secondary to bronchiectasis		
	Intervention (n=16)			Intervention (n=10)			Intervention (n=15)			Intervention (n=4)		
Variables	Pre (n=16) Mean±S.D	Post (n=16) Mean±S.D	MD	Pre (n=10) Mean±S.D	Post (n=10) Mean±S.D.	MD	Pre (n=15) Mean±S.D	Post (n=15) Mean±S.D	MD	Pre (n=4) Mean±S.D	Post (n=4) Mean±S.D	MD
6MWT	193.46±49.18	291.27±67.58	97.81	174±31.60	258.5±37.27	84.5	182.8±51.05	270±80.26	87.2	187±44.07	255±66.08	68

*MD, mean difference for each type of pulmonary fibrosis due to underlying disease; *SD, standard deviation; *PF, pulmonary fibrosis.

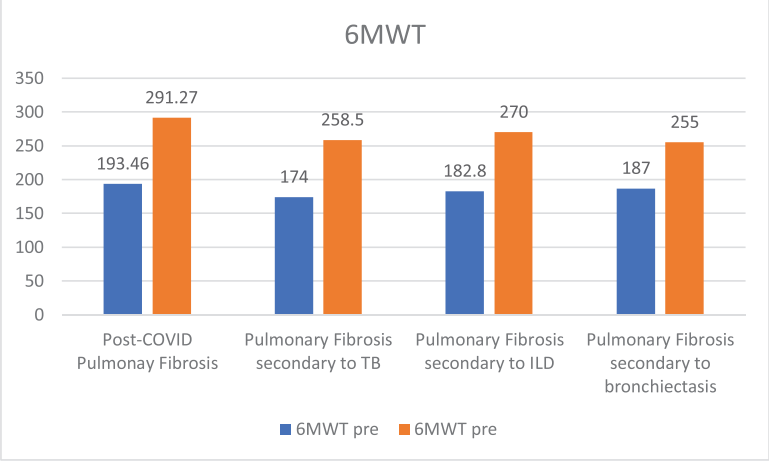

Figure 8. 6MWT Distance pre- post-intervention for each type of pulmonary fibrosis due to underlying disease.

SECONDARY OUTCOMES FOR SUBGROUPS:

Table 11 shows the MDs in 9 domains for SF-36 scale before and after the 8-week intervention in each type of pulmonary fibrosis caused by an underlying condition. The SF-36 scale measures health-related quality of life (HRQOL), which illustrates improvement in each of the nine domains pre and post intervention. An improvement was found in physical functioning, role limitations due to physical health, role limitations due to emotional health, emotional well-being, energy/fatigue, social functioning, pain, general health, and health change score. The highest difference was noted in the post-COVID pulmonary fibrosis group for the domains of role limitations due to physical health % (MD 45.32) and health change % (MD 31.25).

The MDs for rate of perceived exertion (RPE) in each form of pulmonary fibrosis caused by an underlying condition before and after the 8-week intervention are shown in Table 12. After the home-based exercise programme, RPE values were improved for each type of pulmonary fibrosis [post-COVID pulmonary fibrosis 2.87 vs 1.53, MD 1.34; pulmonary fibrosis secondary to TB 2.90 vs 1.60, MD 1.30; Pulmonary fibrosis secondary to ILD 3.20 vs 1.93, MD 1.27; pulmonary fibrosis secondary to bronchiectasis 3 vs 1.75, MD 1.25].

After the home-based exercise programme, baseline SPO_2 levels before the 6MWT and SPO_2 levels after the 6MWT were improved for each type of pulmonary fibrosis. Table 13 shows the MDs for SPO_2 level before and after the 8-week intervention for each type of pulmonary fibrosis induced by an underlying disease. Baseline SPO_2 levels before the 6MWT versus SPO_2 levels after 6MWT for each kind of pulmonary fibrosis conditions pre and post treatments were post-COVID pulmonary fibrosis (MD 3.75 vs MD 4); pulmonary fibrosis related to (TB MD 3 vs

Table 11. SF-36.

	Pulmonary Fibrosis due to underlying disease											
	Post-COVID PF			PF secondary to TB			PF secondary to ILD			PF Secondary to bronchiectasis		
	Intervention (n=16)			Intervention (n=10)			Intervention (n=15)			Intervention (n=4)		
Domains (SF-36)	**Pre (n=16) Mean±S.D**	**Post (n=16) Mean±S.D**	**MD**	**Pre (n=10) Mean±S.D**	**Post (n=10) Mean±S.D.**	**MD**	**Pre (n=15) Mean±S.D**	**Post (n=15) Mean±S.D**	**MD**	**Pre (n=4) Mean±S.D**	**Post (n=4) Mean±S.D**	**MD**
physical functioning %	22.50±14.38	49.69±16.48	27.19	19±8.90	48±20.03	29	21±6.32	50.67±17.10	29.67	23.75±4.78	47.5±10.40	23.75
role limitations due to physical health %	32.81±19.83	78.13±15.48	45.32	47.50±21.89	67.50±12.08	20	46.67±16	63.33±12.91	16.66	43.75±12.5	75±20.41	31.25
role limitations due to emotional health %	43.71±20.10	81.35±16.99	37.64	44.36±20.55	76.88±22.50	32.52	48.88±27.81	75.67±15.19	26.79	41.65±16.7	91.67±16.65	50.02
energy /fatigue %	50.63±9.10	51.56±6.25	0.93	52±12.52	51±4.59	1	50.33±9.15	51.67±9.19	1.34	47.5±6.45	51.25±4.78	3.75
emotional well-being %	53.25±11.47	63±9.52	9.75	55.20±10.46	64±5.65	8.8	53.07±7.47	61.60±7.52	8.53	59±6	60±4.61	1
social functioning %	55.19±11.93	82.84±9	27.65	52.50±9.86	85±7.90	32.5	59.17±15.28	84.20±5.74	25.03	59.37±6.25	81.25±12.5	21.88
pain %	86.25±13.26	97.34±6.28	11.09	77.75±15.52	92.25±9.23	14.5	81.33±25.70	97.33±4.57	16	83.75±7.21	91.25±10.89	7.5
general health %	27.81±11.54	65±7.52	37.19	29.50±6.85	58.50±6.68	29	26.33±9.34	64±6.03	37.67	26.25±8.53	62.5±6.45	36.25
Health change %	23.44±11.06	54.69±22.76	31.25	20±10.54	47.50±14.19	27.5	20±10.35	41.67±15.43	21.67	31.25±12.5	50±20.41	18.75

*MD, mean difference for each type of pulmonary fibrosis due to underlying disease; *SD, standard deviation; *PF, pulmonary fibrosis.

Table 12. Rate of Perceived Exertion (RPE).

	Pulmonary Fibrosis due to underlying disease											
	Post-COVID PF			PF secondary to TB			PF secondary to ILD			PF Secondary to bronchiectasis		
	Intervention (n=16)		MD	Intervention (n=10)		MD	Intervention (n=15)		MD	Intervention (n=4)		MD
Variables	Pre (n=16) Mean±S.D	Post (n=16) Mean±S.D		Pre (n=10) Mean±S.D	Post (n=10) Mean±S.D.		Pre (n=15) Mean±S.D	Post (n=15) Mean±S.D		Pre (n=4) Mean±S.D	Post (n=4) Mean±S.D	
Rate of Perceived Exertion (RPE)	2.87±1.02	1.53±0.90	1.34	2.90±0.56	1.60±0.51	1.30	3.20±0.77	1.93±0.59	1.27	3±0.81	1.75±0.95	1.25

*MD, mean difference for each type of pulmonary fibrosis due to underlying disease; *SD, standard deviation; *PF, pulmonary fibrosis.

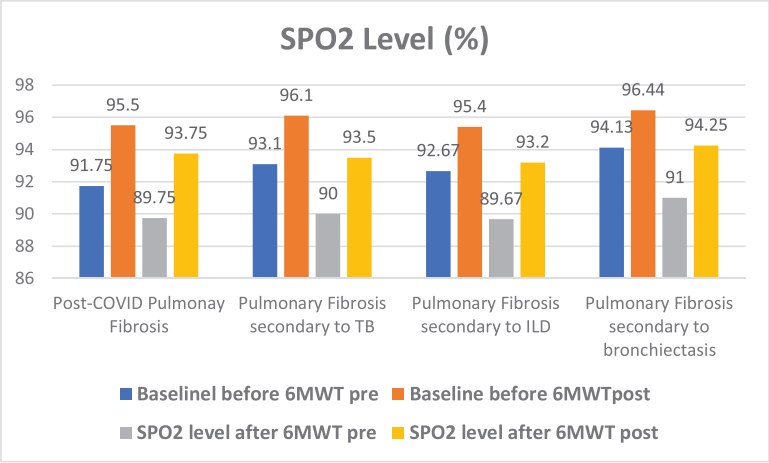

Figure 9. SPO_2 level(%) pre- post-intervention for each type of pulmonary fibrosis due to underlying disease.

MD 3.5); pulmonary fibrosis secondary to ILD (MD 2.73 vs MD 3.53); and pulmonary fibrosis secondary to bronchiectasis (MD 2.31 vs MD 3.25). Figure 9 depicts a graphical representation of SPO_2 level fluctuations prior to and after 8 weeks of intervention for each kind of pulmonary fibrosis caused by a distinct pathological condition.

Discussion

Our study shows that home-based pulmonary rehabilitation effectively improves pulmonary function, physical functional capacity, and quality of life in patients with pulmonary fibrosis. This study also indicates that a home-based pulmonary rehabilitation program is feasible (with a high adherence rate) and safe for pulmonary fibrosis patients.

To the best of our knowledge, this is the first interventional study investigating the effects of a home-based pulmonary rehabilitation in patients with pulmonary fibrosis due to underlying disease (post-COVID pulmonary fibrosis, pulmonary fibrosis secondary to TB, pulmonary fibrosis secondary to ILD, pulmonary fibrosis secondary to bronchiectasis).

This study has shown an increase in the 6 MWD after 8 weeks of the home-based pulmonary rehabilitation program. The mean difference obtained in our study was 88.66 meters which was above the minimal clinically significant differences (MCID) value(30m) [26]. Sevgi Ozalevli et al. conducted a prospective study on IPF patients by giving home-based pulmonary rehabilitation. The study demonstrated an increase in the 6 MWT distance(MD 45 meters) [10]. These findings are in-line with this study. However, it should be noted that the study of Sevgi Ozalevli et al.

Table 13. SPO_2 level (%).

Variables (SPO_2 level %)	Pulmonary Fibrosis due to underlying disease											
	Post-COVID PF			PF secondary to TB			PF secondary to ILD			PF Secondary to bronchiectasis		
	Intervention (n=16)			Intervention (n=10)			Intervention (n=15)			Intervention (n=4)		
	Pre (n=16) Mean±S.D	Post (n=16) Mean±S.D	MD	Pre (n=10) Mean±S.D	Post (n=10) Mean±S.D.	MD	Pre (n=15) Mean±S.D	Post (n=15) Mean±S.D	MD	Pre (n=4) Mean±S.D	Post (n=4) Mean±S.D	MD
Baseline before 6MWT	91.75±0.50	95.50±0.57	3.75	93.10±1.19	96.10±0.87	3	92.67±1.23	95.40±0.63	2.73	94.13±1.02	96.44±0.89	2.31
Immediate after 6MWT	89.75±0.50	93.75±0.51	4	90±0.66	93.5±0.70	3.5	89.67±0.97	93.20±0.86	3.53	91±0.89	94.25±1.18	3.25
3 min after 6MWT	90.75±0.50	95.25±0.95	4.5	91.10±0.31	95±0.66	3.9	91.33±0.61	94.87±0.63	3.54	92.25±0.68	95.44±1.09	3.19
5 min after 6MWT	92±0.5	96.25±0.98	4.25	92.70±0.67	96.30±0.68	3.6	92.13±0.64	95.93±0.70	3.8	93.19±0.98	96.56±1.15	3.37

*MD, mean difference for each type of pulmonary fibrosis due to underlying disease; *SD, standard deviation; *PF, pulmonary fibrosis.

differed from our study as it had less sample size of 17 IPF, and the home-based pulmonary rehabilitation program was of 12-week duration [10].

Marc Spielmanns et al. performed a prospective study in severe post-COVID patients compared with other lung diseases with a sample size of 99 for post-COVID-19 patients and 419 for other lung diseases patients by giving comprehensive pulmonary rehabilitation which showed significant improvement in 6MWD [27]. Li Shen et al. also performed a randomized control trial (RCT) on idiopathic pulmonary fibrosis patients [19]. At the 12 months after pulmonary rehabilitation, they found a substantial improvement in 6MWD for the exercise group compared to the control group. The reduction in 6MWD was significantly less in the exercise group than in the control group from the baseline. Seema K. Singh et al. showed significant improvement in 6MWD (MD 38 meters) in patients with chronic lung impairment from pulmonary tuberculosis [28]. In this study, we found that the post-COVID pulmonary fibrosis group showed the greatest mean difference (MD 97.81) compared to other pulmonary fibrosis groups after 8 weeks of intervention.

The improvements in the walking distance could be due to the improved cellular bioenergetics that occurred during 8 weeks of exercise-based pulmonary rehabilitation [29]. Physical deconditioning caused due to the disease pathology could be one of the reasons for impaired cellular bioenergetics in the skeletal muscles [29, 30]. The reason for improvements in the 6 MWT distance also indicates improvement in aerobic capacity over time [31]. On the other hand, the reasons for the improvement in physical functioning may be because of improvement in neuromuscular performance [32, 33]. The post-COVID pulmonary fibrosis group showed more improvement in 6MWT distance might due to improvement of cellular bioenergetics in the skeletal muscles, neuromuscular performance and lung function capacity compared to the other group.

A retrospective study done by Sevgi Ozalevli et al. showed that PFT were not changed after the home-based exercise program [10]. Seema K. Singh et al. also showed no significant improvement in PFT in patients with chronic lung impairment from pulmonary tuberculosis [28]. Anyway, this study shows significant improvement in PFT for FVC, FEV_1, FEV_1/FVC, and DL_{CO} after 8 weeks of intervention. The reasons for the improvement may be due to the large sample size in this study compared to the Sevgi Ozalevli et al. and Seema K. Singh et al. study [10, 28]. In this study, we included not only IPF patients but also post-COVID pulmonary fibrosis, pulmonary fibrosis secondary to TB, pulmonary fibrosis secondary to ILD, and pulmonary fibrosis secondary to bronchiectasis patients were included. On the other hand, a RCT study conducted by Li Shen et al. showed improvement in pulmonary function test results [19]. These findings are in-line with this study. Exercise protocol, including aerobic and breathing exercises, can slow the decline of

lung functional capacity [21, 34, 35]. So, the improvement of pulmonary functional capacity may be helpful to prevent the further progression of lung fibrosis [36, 37].This study has shown FVC value was more improved in post-COVID pulmonary fibrosis (MD 0.09 litres) and pulmonary fibrosis secondary to ILD (MD 0.09 litres) groups. FEV_1 improved better in post-COVID pulmonary fibrosis (MD 0.08 litres) group. Greater improvement was observed for FEV_1/FVC pulmonary fibrosis secondary to ILD (MD 0.01) in comparison to other categories of pulmonary fibrosis. For DL_{CO} (MD 0.65 ml/min/mmHg) post-COVID pulmonary fibrosis group showed more recovery compared to other groups. post-COVID pulmonary fibrosis and pulmonary fibrosis secondary to ILD showed more improvement may be because these two groups had more samples compared to other subgroups. However, there were only minor changes observed in all four subgroups of pulmonary fibrosis (post-COVID pulmonary fibrosis, pulmonary fibrosis secondary to ILD, pulmonary fibrosis secondary to TB, and pulmonary fibrosis secondary to bronchiectasis). This could be because all subgroups underwent in the same home exercise program for eight weeks.

In this study, we found a mean difference of 1.30 units in RPE scores after 8 weeks of intervention which was above the MCID value [38]. Rate of Perceived Exertion (RPE) scores are more reduced after 8 weeks of intervention in post-COVID pulmonary fibrosis group (MD 1.34).This might be because these groups were showed more improvement in their lung functional capacity.

Rogliani et al. conducted an observational study on patients recovering from COVID-19 [39]. This study showed that the sensation of dyspnoea after post-6MWT was clinically and statistically significant. (Δ pre-post 6MWT Borg scale: median 1.5, IQR 0.3-2, range 0-5) [39]. These results were consistent with our study. Ozalevli et al. reported that the perceived dyspnea severity during daily activities was significantly reduced [10].

The rate of perceived exertion interprets the individual's efforts, breathlessness, fatigue, and levels of perceived exertion [22]. The overall reduction in the levels of perceived exertion may be due to an alteration in breathing patterns and an improvement of pulmonary functional capacity [40]. On the other hand, the increase in the tolerance for dyspnoea may have also helped reduce the levels of perceived exertion [30, 40]. Exercise protocol, including lower limb strengthening, may have also helped improve RPE scores [18, 41].

Holland et al. explained that the functional capacity is improved through the contribution of peripheral muscle adaption [42]. Previous studies in ILD and COPD have shown that weakness of peripheral muscles indicates exercise intolerance and exercise capacity improvement following pulmonary rehabilitation because of peripheral muscle adaptation [43- 45].

According to our study, after 8 weeks of intervention, there was a substantial improvement in both the baseline saturation of peripheral oxygen level (SPO_2) and after the 6MWT SPO_2 level (MD 2.73% vs. MD 3.47%, $p<0.05$). According to Ozalevli et al., individuals with idiopathic pulmonary fibrosis had a substantial ($p<0.05$) rise in peripheral oxygen saturation (SPO_2) levels [10].These results are consistent with our study. Our study revealed that the SPO_2 level of post-COVID pulmonary fibrosis patients (before 6MWT MD 3.75% vs. after 6MWT MD 4%) improved more than the other subgroups. This improvement may be due to enhanced lung function capacity, which stops the lung fibrosis from progressing further.

HRQOL was assessed using the SF-36 questionnaire version 1.0, which covers total 9 domains. The score of each domain is depicted as a percentage of the overall impairments on a scale of 0-100%, where a lower score indicates reduced health status [46, 47]. Greater, more significant improvements were observed in the domains of Role limitations due to physical health (MD 28.88), Role limitations due to emotional health (MD 33.94), and general health (MD 35.44). Energy/fatigue domains were clinically significant. Improvements in domains are depicted in Table 4. The post-COVID pulmonary fibrosis group exhibited greater improvement in the categories of role limitations due to physical health % (MD 45.32) and health change % (MD 31.25), which may be related to improvement in exercise capacity and lung function.

Ozalevli et al. showed that physical role, general health, and emotional role domains were significantly improved [10]. These findings are in-line with

this study. On the other hand, Gloeckl et al. proved that SF-36 mental components were significantly improved [36]. Improvements in QOL can be attributed to exercise-based pulmonary rehabilitation programs and its benefits, breathing control due to breathing, exercises, and overall fitness and wellness [48–50].

One of the strengths of our study is the physical exercise training protocol, which is used in home-based pulmonary rehabilitation programs for pulmonary fibrosis patients. We have developed a low-cost program to perform, making it easy for the participants to understand. In this study, we included pulmonary fibrosis patients with the full spectrum of underlying disease (post-COVID pulmonary fibrosis, pulmonary fibrosis secondary to TB, pulmonary fibrosis secondary to ILD, pulmonary fibrosis secondary to bronchiectasis).

Limitations

The most relevant limitations of our study are the absence of randomization and a control group. This study also has a smaller sample size. Subgroup analysis for post-COVID pulmonary fibrosis, pulmonary fibrosis secondary to TB, pulmonary fibrosis secondary to ILD, and pulmonary fibrosis secondary to bronchiectasis was not done due to the small and unequal sample size in these subgroups.

Moreover, this study did not investigate the long-term effects of the home-based pulmonary rehabilitation program on pulmonary fibrosis patients.

Future recommendations

For future research, we recommend more extensive studies with a control group, and individual studies for each category of pulmonary fibrosis patients are warranted with a large sample size. More variables like peripheral muscle strength and peripheral oxygen saturation can be incorporated with functional capacity and quality of life for each category of pulmonary fibrosis, giving a better insight into clinical improvement in the future.

Conclusions

Therefore, a home-based pulmonary rehabilitation program is effective, safe, and feasible and can be used to treat pulmonary fibrosis patients secondary to ILD, post-COVID pulmonary fibrosis, pulmonary fibrosis secondary to TB secondary to bronchiectasis in the Indian setup. It may provide beneficial effects in improving these patients' pulmonary function as well as aerobic conditioning, physical functional capacity by decreasing dyspnea severity and increasing the SPO_2 level, and quality of life.

Abbreviations

PF: Pulmonary Fibrosis
PCPF: post-COVID Pulmonary Fibrosis
ILD: Interstitial Lung Disease
IPF: Idiopathic Pulmonary Fibrosis
COVID-19: Corona Virus-19
HRQoL: Health-Related Quality of Life
SF-36: Short Form-36
6 MWT: 6-Minute walk test
6 MWD: 6-Minute walk distance
RPE: Rate of Perceived Exertion
ATS: American Thoracic Society
PFT: Pulmonary Function Test
FVC: Forced Vital Capacity
FEV: Forced Expiratory Volume
FEV_1: Forced Expiratory Volume in the first second
DL_{CO}: Diffusing Capacity of the Lungs for Carbon Monoxide

References

1. Raghu G, Remy-Jardin M, Richeldi L, Thomson CC, Antoniou KM, Bissell BD, et al. Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults: An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med 2022;205(9):E18–47.
2. Nashatyreva MS, Trofimenko IN, Chernyak BA, Avdeev SN. Pulmonary Fibrosis and Progressive Pulmonary Fibrosis in a Prospective Registry of Interstitial Lung Diseases in Eastern Siberia. Life 2023;13(1):1–11.
3. Tran S, Ksajikian A, Overbey J, Li P, Li Y. Pathophysiology of Pulmonary Fibrosis in the Context of COVID-19 and Implications for Treatment: A Narrative Review. Cells 2022;11(16):1–10.
4. Maher TM, Bendstrup E, Dron L, Langley J, Smith G, Khalid JM, et al. Global incidence and prevalence of

idiopathic pulmonary fibrosis. Respir Res [Internet] 2021;22(1):1–10. Available from: https://doi.org/10.1186/s12931-021-01791-z
5. Oronsky B, Larson C, Hammond TC, Oronsky A, Kesari S, Lybeck M, et al. A Review of Persistent Post-COVID Syndrome (PPCS). Clin Rev Allergy Immunol [Internet] 2023;64(1):66–74. Available from: https://doi.org/10.1007/s12016-021-08848-3
6. Ambardar SR, Hightower SL, Huprikar NA, Chung KK, Singhal A, Collen JF. Post-COVID-19 pulmonary fibrosis: Novel sequelae of the current pandemic. J Clin Med 2021;10(11):2452.
7. Meyerholz DK. Rigid respiration: fulminant pulmonary fibrosis after COVID-19. eBioMedicine [Internet] 2023;87:104428. Available from: https://doi.org/10.1016/j.ebiom.2022.104428
8. Oatis D, Simon-Repolski E, Balta C, Mihu A, Pieretti G, Alfano R, et al. Cellular and Molecular Mechanism of Pulmonary Fibrosis Post-COVID-19: Focus on Galectin-1, -3, -8, -9. Int J Mol Sci 2022;23(15):8210.
9. Hirawat R, Jain N, Aslam Saifi M, Rachamalla M, Godugu C. Lung fibrosis: Post-COVID-19 complications and evidences. Int Immunopharmacol [Internet] 2023;116:109418. Available from: https://doi.org/10.1016/j.intimp.2022.109418
10. Ozalevli S, Karaali HK, Ilgin D, Ucan ES. Effect of home-based pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis. Multidiscip Respir Med 2010;5(1):31–7.
11. Singh SJ, ZuWallack RL, Garvey C, Spruit MA, Brindicci C, Higenbottam T, et al. Learn from the past and create the future: The 2013 ATS/ERS statement on pulmonary rehabilitation Eur Respir J 2013;42(5):1169–74.
12. Holland AE, Singh SJ, Casaburi R, Clini E, Cox NS, Galwicki M, et al. Defining modern pulmonary rehabilitation: An official American thoracic society workshop report. Ann Am Thorac Soc 2021;18(5):E12–29.
13. Ranaweera A. American Thoracic Society. Int J Pharm Med 2005;19(3):173–7.
14. Uzzaman MN, Agarwal D, Chan SC, Engkasan JP, Habib GMM, Hanafi NS, et al. Effectiveness of home-based pulmonary rehabilitation: systematic review and meta-analysis. Eur Respir Rev [Internet] 2022;31(165). Available from: http://dx.doi.org/10.1183/16000617.0076-2022
15. Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, et al. Diagnosis of idiopathic pulmonary fibrosis An Official ATS/ERS/JRS/ALAT Clinical practice guideline. Am J Respir Crit Care Med 2018;198(5):e44–68.
16. Nici L, Donner C, Wouters E, Zuwallack R, Ambrosino N, Bourbeau J, et al. American thoracic society/European respiratory society statement on pulmonary rehabilitation. Am J Respir Crit Care Med 2006;173(12):1390–413.
17. Rochester CL, Vogiatzis I, Holland AE, Lareau SC, Marciniuk DD, Puhan MA, et al. An official American Thoracic Society/European Respiratory Society policy statement: Enhancing implementation, use, and delivery of pulmonary rehabilitation. Am J Respir Crit Care Med 2015;192(11):1373–86.
18. José A, Holland AE, Selman JPR, Camargo CO De, Fonseca DS, Athanazio RA, et al. Home-based pulmonary rehabilitation in people with bronchiectasis: a randomised controlled trial. ERJ Open Res 2021;7(2):00021-2021. Available from: http://dx.doi.org/10.1183/23120541.00021-2021
19. Shen L, Zhang Y, Su Y, Weng D, Zhang F, Wu Q, et al. New pulmonary rehabilitation exercise for pulmonary fibrosis to improve the pulmonary function and quality of life of patients with idiopathic pulmonary fibrosis: A randomized control trial. Ann Palliat Med 2021;10(7):7289–97.
20. Graham BL, Steenbruggen I, Barjaktarevic IZ, Cooper BG, Hall GL, Hallstrand TS, et al. Standardization of spirometry 2019 update an official American Thoracic Society and European Respiratory Society technical statement. Am J Respir Crit Care Med 2019;200(8):E70–88.
21. Issues S, Test MW, Equipment R, Preparation P. American Thoracic Society ATS Statement : Guidelines for the Six-Minute Walk Test 2002;166:111–7.
22. Williams N. The Borg Rating of Perceived Exertion (RPE) scale. Occup Med (Chic Ill) 2017;67(5):404–5.
23. Lins L, Carvalho FM. SF-36 total score as a single measure of health-related quality of life: Scoping review. SAGE Open Med 2016;4:205031211667172.
24. Eldridge SM, Chan CL, Campbell MJ, Bond CM, Hopewell S, Thabane L, et al. CONSORT 2010 statement: Extension to randomised pilot and feasibility trials. BMJ 2016;355:i5239.
25. Lancaster GA. Guideliens for reporting non randomised 2019;1:1–6.
26. Puente-Maestu L, Palange P, Casaburi R, Laveneziana P, Maltais F, Neder JA, et al. Use of exercise testing in the evaluation of interventional efficacy: An official ERS statement. Eur Respir J [Internet] 2016;47(2):429–60. Available from: http://dx.doi.org/10.1183/13993003.00745-2015
27. Spielmanns M, Pekacka-Egli AM, Schoendorf S, Windisch W, Hermann M. Effects of a comprehensive pulmonary rehabilitation in severe post-COVID-19 patients. Int J Environ Res Public Health 2021;18(5):1–14.
28. Singh SK, Naaraayan A, Acharya P, Menon B, Bansal V, Jesmajian S. Pulmonary Rehabilitation in Patients with Chronic Lung Impairment from Pulmonary Tuberculosis. Cureus 2018;10(11).
29. Sala E, Roca J, Marrades RM, Alonso J, Gonzalez De Suso JM, Moreno A, et al. Effects of endurance training on skeletal muscle bioenergetics in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1999;159(6):1726–34.
30. Jahn K, Sava M, Sommer G, Schumann DM, Bassetti S, Siegemund M, et al. Exercise capacity impairment after COVID-19 pneumonia is mainly caused by deconditioning. Eur Respir J 2022;59(1).
31. Jolley SE, Bunnell AE, Hough CL. ICU-Acquired Weakness. Chest [Internet] 2016;150(5):1129–40. Available from: http://dx.doi.org/10.1016/j.chest 2016.03.045

32. Spruit MA, Thomeer MJ, Gosselink R, Troosters T, Kasran A, Debrock A, et al. Skeletal muscle weakness in patients with sarcoidosis and its relationship with exercise intolerance and reduced health status. Thorax 2005;60(1):32–8.
33. Watanabe F, Taniguchi H, Sakamoto K, Kondoh Y, Kimura T, Kataoka K, et al. Quadriceps weakness contributes to exercise capacity in nonspecific interstitial pneumonia. Respir Med [Internet] 2013;107(4):622–8. Available from: http://dx.doi.org/10.1016/j.rmed.2012.12.013
34. Hanada M, Kasawara KT, Mathur S, Rozenberg D, Kozu R, Ahmed Hassan S, et al. Aerobic and breathing exercises improve dyspnea, exercise capacity and quality of life in idiopathic pulmonary fibrosis patients: Systematic review and meta-analysis. J Thorac Dis 2020;12(3):1041–55.
35. Gomes-Neto M, Silva CM, Ezequiel D, Conceição CS, Saquetto M, MacHado AS. Impact of Pulmonary Rehabilitation on Exercise Tolerance and Quality of Life in Patients with Idiopathic Pulmonary Fibrosis A SR and M-A. J Cardiopulm Rehabil Prev 2018;38(5):273–8.
36. Gloeckl R, Leitl D, Jarosch I, Schneeberger T, Nell C, Stenzel N, et al. Benefits of pulmonary rehabilitation in COVID-19: a prospective observational cohort study. ERJ Open Res 2021;7(2):00108–2021.
37. Yu X, Li X, Wang L, Liu R, Xie Y, Li S, et al. Pulmonary Rehabilitation for Exercise Tolerance and Quality of Life in IPF Patients: A Systematic Review and Meta-Analysis. Biomed Res Int 2019;2019.
38. Ries AL. Minimally clinically important difference for the UCSD Shortness of Breath Questionnaire, Borg Scale, and Visual Analog Scale. COPD J Chronic Obstr Pulm Dis 2005;2(1):105–10.
39. Rogliani P, Calzetta L, Coppola A, Puxeddu E, Sergiacomi G, D'Amato D, et al. Are there pulmonary sequelae in patients recovering from COVID-19? Respir Res 2020;21:(1):286.
40. Gigliotti F, Coli C, Bianchi R, Romagnoli I, Lanini B, Binazzi B, et al. Exercise training improves exertional dyspnea in patients with COPD: Evidence of the role of mechanical factors. Chest 2003;123(6):1794–802.
41. Cook H, Reilly CC, Rafferty GF. A home-based lower limb-specific resistance training programme for patients with copd: An explorative feasibility study. ERJ Open Res 2019;5(2).
42. Holland AE, Hill CJ, Conron M, Munro P, McDonald CF. Short term improvement in exercise capacity and symptoms following exercise training in interstitial lung disease. Thorax 2008;63(6):549–54.
43. Nishiyama O, Taniguchi H, Kondoh Y, Kimura T, Ogawa T, Watanabe F, et al. Quadriceps weakness is related to exercise capacity in idiopathic pulmonary fibrosis. Chest [Internet] 2005;127(6):2028–33. Available from: http://dx.doi.org/10.1378/chest.127.6.2028
44. Bernard S, Leblanc P, Whittom F, Carrier G, Jobin J, Belleau R, et al. Peripheral muscle weakness in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1998;158(2):629–34.
45. Seymour JM, Spruit MA, Hopkinson NS, Natanek SA, Man WDC, Jackson A, et al. The prevalence of quadriceps weakness in COPD and the relationship with disease severity. Eur Respir J 2010;36(1):81–8.
46. Cox IA, Arriagada NB, De Graaff B, Corte TJ, Glaspole I, Lartey S, et al. Health-related quality of life of patients with idiopathic pulmonary fibrosis: A systematic review and meta-analysis. Eur Respir Rev [Internet] 2020;29(158): 1–22. Available from: http://dx.doi.org/10.1183/16000617.0154-2020
47. Swigris J, Olson AL, Brown K. Understanding and optimizing health-related quality of life and physical functional capacity in idiopathic pulmonary fibrosis. Patient Relat Outcome Meas 2016;29.
48. Wallaert B, Duthoit L, Drumez E, Behal H, Wemeau L, Chenivesse C, et al. Long-term evaluation of home-based pulmonary rehabilitation in patients with fibrotic idiopathic interstitial pneumonias. ERJ Open Res [Internet] 2019;5(2). Available from: http://dx.doi.org/10.1183/23120541.00045-2019
49. Vainshelboim B. Exercise training in idiopathic pulmonary fibrosis: Is it of benefit? Breathe 2016;12(2):130–8.
50. Essam H, Wahab NHA, Younis G, El-Sayed E, Shafiek H. Effects of different exercise training programs on the functional performance in fibrosing interstitial lung diseases: A randomized trial. PLoS One [Internet] 2022;17:1–14. Available from: http://dx.doi.org/10.1371/journal.pone.0268589

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Original Research Article

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Characteristics of culture-negative subclinical pulmonary tuberculosis: a single-center observation

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ABSTRACT

Background: Little is known about culture-negative subclinical pulmonary tuberculosis (TB), and its diagnosis remains challenging. Therefore, this study aimed to identify the characteristics and the extent of disease associated with culture-negative subclinical pulmonary TB.

Methods: This retrospective cohort study was conducted on immunocompetent individuals with subclinical pulmonary TB at a university hospital in Thailand from January 2014 to December 2019. Subclinical pulmonary TB was diagnosed based on the presence of radiographic abnormalities consistent with TB in the absence of TB symptoms. All subjects demonstrated significant improvement or resolution of radiographic abnormalities following the completion of treatment. At least two negative sputum cultures were needed to fulfill the definition of culture-negative pulmonary TB. Data were analyzed using univariate and multiple logistic regression analyses to determine the characteristics of those with culture-negative subclinical pulmonary TB compared to culture-positive ones.

Results: Out of the 106 individuals identified with subclinical pulmonary TB, 84 met the criteria for inclusion in the analysis. The study found lower radiographic extent and increasing age were key attributes of culture-negative subclinical pulmonary TB. The odds ratios (95% confidence interval) were 7.18 (1.76 to 29.35) and 1.07 (1.01 to 1.13), respectively. They tend to have lower rates of bilateral involvement in both chest x-ray (8.5% vs. 32.0%, p=0.006) and computed tomography (15.4% vs. 42.9%, p=0.035). However, no other specific radiographic findings were identified.

Conclusions: People with culture-negative subclinical pulmonary TB were likely to have less radiographic severity, reflecting early disease. Nevertheless, no radiographic patterns, except for unilaterality, were related to culture-negative subclinical pulmonary TB.

Key words: Mycobacterium infections; Tuberculosis; Asymptomatic diseases; Radiography.

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Ethics approval and consent to participate: The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Siriraj Hospital, Mahidol University (SIRB 635/2564). Informed consent was waived due to the retrospective nature of this study. All relevant patients consented to have their details and accompanying images published.

Data availability statement: The authors declare that the data supporting the findings of this study are available within the article.

Conflict of interest: The authors have no conflicts of interest to declare.

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Introduction

Tuberculosis (TB) remains a major public health concern worldwide [1]. Early TB detection to interrupt *Mycobacterium tuberculosis* (Mtb) transmission is a cornerstone for TB control [2]. Historically, TB was categorized into binary stages, including latent infection and active disease. Nevertheless, it has recently been conceptualized as a spectrum of disease stages, including latent TB infection, subclinical (i.e., asymptomatic) TB disease, and clinical or active (i.e., symptomatic) TB disease [3]. A better understanding of this emerging trajectory is needed to end the global TB epidemic.

Subclinical TB is considered an early-stage disease prior to the development of active TB [3]. This is supported by the evidence that subclinical pulmonary TB tends to be less severe than active pulmonary TB, as demonstrated by lower rates of multiple pulmonary lesions [4,5]. Previous studies showed that the prevalence of the subclinical disease among individuals with pulmonary TB varied from 18% to 68%, with a vast proportion of smear and culture positivity [4-6]. Moreover, owing to the lack of noticeable symptoms, subclinical pulmonary TB is less likely to be detected by symptom-based or passive case-finding [7]. As a result, they can by far pose a risk of transmission, especially through unrecognizable respiratory symptoms such as unrelated cough [8]. A recent analysis in Vietnam also demonstrated that people with subclinical pulmonary TB are able to spread through household contact [9]. Noteworthily, a retrospective study in Canada found that approximately three-quarters of pulmonary TB patients were identified through active case-finding [10].

The TB epidemic is still ongoing in Thailand, as classified among the thirty nations with the highest TB burden, with an incidence of 155 per 100,000 population in 2022 [1]. Studies on healthcare workers in university hospitals in Bangkok, Thailand, have revealed even more overall TB incidences of 164 to 200 per 100,000 persons based on data between 2011 and 2020 [11,12]. Notably, a substantial proportion of these cases (up to 44%) were identified as subclinical and detected through routine health checks [11,12]. Similarly, cross-sectional research conducted at a university hospital in Bangkok found that nearly half of patients with co-infection of COVID-19 and microbiologically confirmed TB did not have symptoms consistent with TB [13]. As a result, these findings emphasize the intensification of an active case-finding strategy by vigilant screening for subclinical TB. This also aligns with the Thailand Operational Plan to End Tuberculosis (2023-2027) [14] and appears vital in efforts to combat TB, especially in high TB burden countries.

The diagnosis of culture-negative subclinical pulmonary TB is particularly slippery. It has been proposed that culture-negative disease is the very early disease stage that later progresses to culture-positive disease, which may contribute to a higher risk of transmission [8]. Still, the data supporting this statement has yet to be explored. Previous studies on culture-negative pulmonary TB have not solely included those asymptomatic and most presented symptoms [15,16]. Distinguishing its characteristics would extend the understanding of natural history and help enhance the detection rate, implicating a more efficient TB control strategy. We hypothesized that those with culture-negative subclinical pulmonary TB had less

extensive disease than those with culture-positive disease. Therefore, the aim of this study was to determine the characteristics and the extent of radiographic abnormalities associated with culture-negative subclinical pulmonary TB.

Methods

Study design and population

This retrospective cohort study was conducted at a 2,000-bed university hospital in Bangkok, Thailand. We reviewed the medical records of all consecutive pulmonary TB-diagnosed patients registered at the health checkup clinic between January 2014 and December 2019. The health check-up clinic operates within the Department of Preventive and Social Medicine at our institute. It serves as a primary facility providing health maintenance services to both outpatients and hospital employees. Additionally, the clinic offers other relevant health check services, such as pre-employment examinations. As part of its standard practice, the clinic routinely conducts screening chest x-rays (CXR) during health assessments.

Those with abnormal screening CXR were referred to two qualified pulmonologists, each with 23 and 25 years of experience, respectively. All individuals with pulmonary TB or suspicion of having pulmonary TB were routinely asked to provide three initial cough-up sputum specimens for microbiological studies. The local National Tuberculosis Control Program Guideline recommended that at least two sputum specimens, including spot and collected morning sputum, should be acquired [17]. Further, those with an equivocal diagnosis of pulmonary TB underwent chest computed tomography (CT) to ensure the diagnosis before or at the time of anti-TB treatment initiation. The pulmonologists regularly recorded all presented symptoms among all patients.

The study included subjects diagnosed with pulmonary TB who met all the following: age 18 years and over, had no symptoms suggestive of TB, and had a significant improvement of radiographic abnormalities after anti-TB treatment completion. Subjects lost to follow up were excluded. Two physicians independently screened the subjects' eligibility, ensuring the observed abnormalities were TB-related. Disagreements were subsequently resolved through a consensus discussion. Specifically, the follow up radiological assessments were conducted in accordance with the Thai National TB Control Program Guideline [17], which recommends evaluations at 2- and 6-months post-treatment initiation. The standard treatment regimen for pulmonary TB typically comprises an initial two months of the intensive phase of isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA), and ethambutol (EMB) and the subsequent continuation phase of four months of INH and RIF.

Definitions

Subclinical pulmonary TB was defined as the absence of symptoms suggestive of TB while demonstrating radiographic abnormalities consistent with TB. TB-related symptoms include chest symptoms such as cough, hemoptysis, dyspnea, and chest pain, as well as constitutional symptoms such as fever, weight loss, malaise, and night sweats, irrespective of duration. In terms of radiographic features, CXR findings highly suggestive of pulmonary TB include the presence of air-space nodules/clustered nodules or consolidation predominantly in the upper or mid lung zones. In addition, cavities with surrounding consolidation are commonly observed in those with pulmonary TB [18].

A diagnosis of culture-negative pulmonary TB requires at least two separate sputum specimens with negative results for Mtb cultures. This definition is founded on the principle that TB patients may exhibit radiographic evidence of the disease without symptoms or positive microbiological findings [8]. In contrast, culture-positive pulmonary TB was diagnosed when the initial sputum specimens yielded a positive Mtb culture result.

Following the completion of a full course of anti-TB treatment, all cases exhibited significant radiographic improvement or the resolution of radiographic abnormalities when compared to the initial images. This differentiation increased the certainty that the observed changes were distinct from any pre-existing chest radiographic abnormalities.

Data collection

Covariates collected were as follows: demographics and comorbidities (age, sex, smoking status, diabetes mellitus [DM], previous pulmonary TB, being a hospital employee); the radiographic extent of pulmonary lesions (CXR severity grade, CT severity score); CXR findings (patchy opacities, reticulonodular opacities, nodules, cavitation, enlarged hilar shadow, and bilateral involvement); chest CT findings (consolidation, tree-in-bud pattern, ground glass opacities [GGO], nodules, mass, cavitation, adenopathy, bronchiectasis, calcified nodules, calcified lymph node, upper lobe involvement, bilateral involvement, and multilobar involvement [2 lobes or more]).

Radiologic assessment

This study selected chest images prior and closest to the date of initiation of treatment. One radiologist and one pulmonologist (with experience of 20 and 25 years, respectively) reviewed and interpreted all images. Any discrepancies were settled by mutual consensus. The extent of the disease was quantified by using the scoring systems adapted from the previous studies [19,20]. Although originally developed for idiopathic pulmonary fibrosis, this CT severity scoring method was utilized in the present study due to the lack of validated systems for pulmonary TB on CT images, to our knowledge. Additionally, its clinical relevance in assessing pulmonary lesion involvement has been demonstrated through its correlation with histopathology sections [20]. The radiologic assessments are followings:

1. CXR severity grading: the lung fields were divided into six zones. Grade 1 for the involvement of one zone without cavitation; grade 2 for two or three zones, or one zone with cavitation; grade 3 for more than three zones regardless of cavitation.
2. Chest CT severity scores: each lobe was graded according to a percentage of the affected area with a score of 0 to 5; 0 for no involvement; 1 for <5% of a lobe; 2 for 5%-25% of a lobe; 3 for 26%-49% of a lobe; 4 for 50%-75% of a lobe; 5 for >75% of a lobe. Hence, the total possible score ranges from 0 to 25.

Laboratory processing

A 2-5 ml sputum specimen characterized by its mucoid and viscous nature was collected. The specimen was delivered within the standardized containers to the laboratory as soon as possible after collection. If immediate delivery was not possible, it was refrigerated at a temperature of 4 to 8 °C for a maximum duration of 7 days. Importantly, the TB laboratory at our institute, which is responsible for TB diagnostic tests, is certified in compliance with ISO15189:2012 and ISO15190:2020 standards. Internal audits and external quality control checks are conducted annually for every test.

Mtb culture was conducted using either solid media, such as Löwenstein-Jensen (LJ) medium, or liquid media, such as MGIT 960 tubes (Becton Dickinson, Buenos Aires, Argentina). When using LJ medium, 200 µl of the decontaminated sample was inoculated, and TB growth was monitored weekly. A negative result was concluded if no growth was observed after 60 days. Meanwhile, when using MGIT 960 tubes, 500 µl of the decontaminated sample was inoculated, and growth was monitored daily. A negative result was determined if no growth was observed after 42 days. In cases of suspected TB based on positive culture results, confirmation was achieved through acid-fast bacilli (AFB) staining and MPT64 antigen testing.

Statistical analysis

Characteristics, extent, and radiographic findings were compared between culture-negative and culture-positive groups. Continuous variables were shown as means with standard deviations (SD) or medians with interquartile ranges (IQR). Categorical variables were shown as counts with percentages. The t-test or Mann-Whitney U test was used for continuous data, depending on the data distribution. The Chi-square or Fisher's exact test was used for categorical data, as appropriate. Subsequently, variables related to demographics and comorbidities, and radiographic extent, with a $p<0.15$, were entered in the multiple logistic regression. Odds ratios (ORs) with 95% confidence intervals (95% CIs) for having culture-negative subclinical pulmonary TB were calculated, compared to culture-positive subclinical pulmonary TB. A two-sided p below 0.05 was

considered statistically significant. All analyses were performed using IBM SPSS Statistics (version 18, IBM Corp., Armonk, NY, USA).

Results

During the six-year period, 106 individuals with subclinical pulmonary TB were identified, all of whom were identified through screening CXR during routine checkups. Out of these, a total of 84 subjects met the criteria for the main analysis (Figure 1). The age ranged from 18 to 61 years, with a median of 31 years. The proportion of culture positivity was 29.8% (25/84). No subjects known to have human immunodeficiency virus (HIV) infection or severely immunosuppressed states were identified. Regarding the radiographic extent, most had a relatively low severity disease; 83.3% had grade 1 CXR severity, and CT severity scores ranged from 1 to 14 with a median of 2. Patchy opacities were the most frequent CXR findings (67.9%), followed by reticulonodular opacities (36.9%). A tree-in-bud pattern and nodules were the most common CT patterns, contributing 92.5% and 58.5%, respectively. In addition, a miliary pattern was not detected in any subject. Figure 2 and Figure 3 reveal pre- and post-treatment chest images of two patients with culture-positive and culture-negative subclinical pulmonary TB.

In the univariable analysis, subjects with culture-negative subclinical pulmonary TB were slightly older (35 years vs. 26 years, p=0.047). Moreover, they also had a lower degree in the extent shown by a higher proportion of grade 1 CXR severity (89.8% vs. 68.0%, p=0.014). After analyzing the multiple logistic regression, significant variables associated with culture-negative subclinical pulmonary TB remained an increasing age (OR 1.07; 95% CI 1.01 to 1.13) and grade 1 CXR severity (OR 7.18; 95% CI 1.76 to 29.35) (Table 1).

Most radiographic patterns between the two groups did not statistically differ (Table 2), predominant with patchy opacities and tree-in-bud patterns in CXR and chest CT, respectively. However, the culture-negative group had lower rates of bilateral pulmonary involvement in both CXR (8.5% vs. 32.0%, p=0.006) and chest CT (15.4% vs. 42.9%, p=0.035). Although statistical significance was not achieved, multilobar involvement in the chest CT tended to be more commonly found in the culture-positive group (23.1% vs. 50.0%, p=0.060).

Discussion

Consistent with the hypothesis, the present study showed that culture-negative subclinical pulmonary TB had significantly milder radiographic grading and

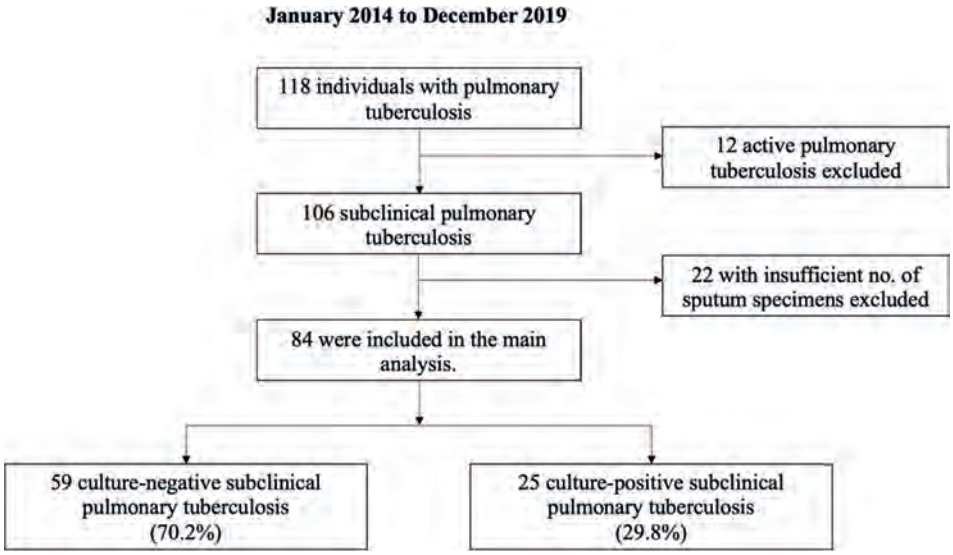

Figure 1. Flow Diagram of the Study.

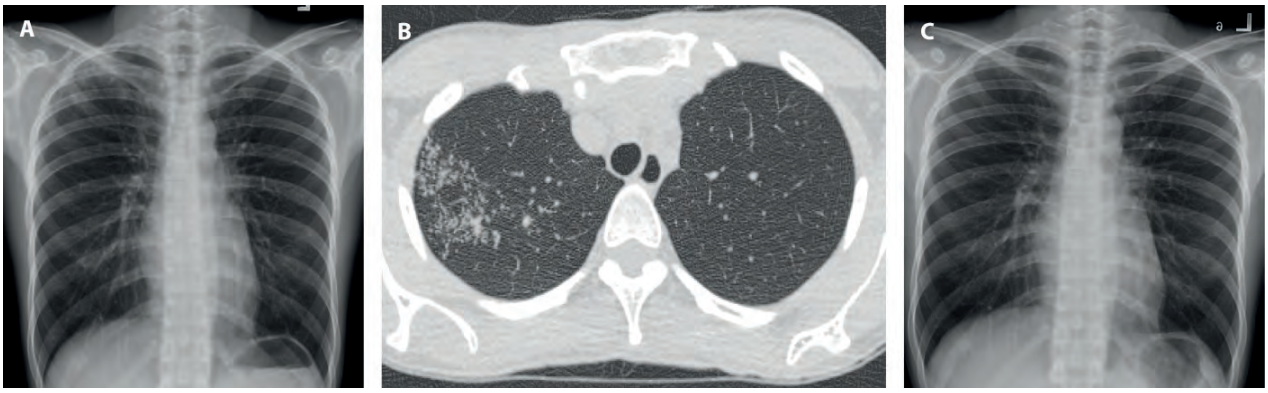

Figure 2. A-C) Pre- and post-treatment chest images of a 26-year-old female with culture-positive subclinical pulmonary TB. A) Pre-treatment chest radiograph shows reticulonodular opacities at the right apical lung. B) Axial CT image in lung window performed 1 month after A. reveals multiple centrilobular nodules with tree-in-bud pattern in the apical segment of the right upper lobe. C) Post-treatment chest radiograph (7 months after A.) shows resolution of the abnormalities of the right apical lung.

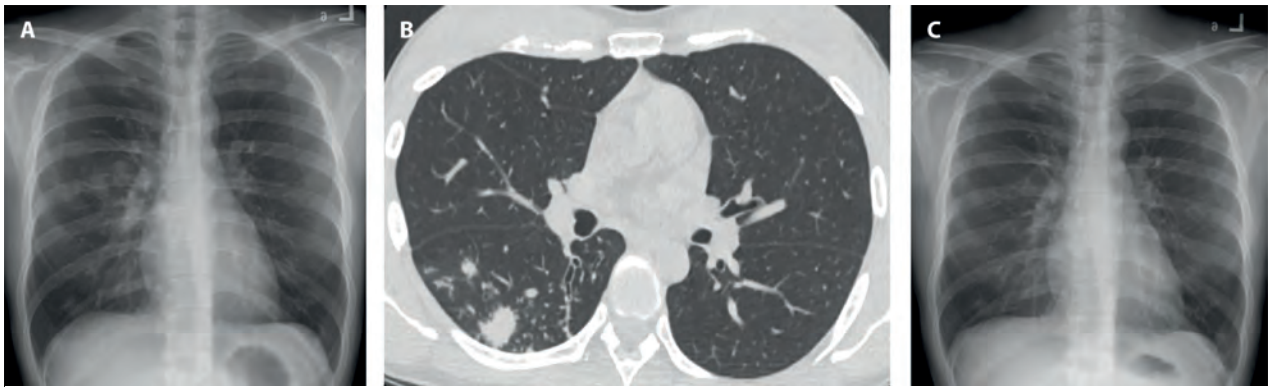

Figure 3. A-C) Pre- and post-treatment chest images of a 32-year-old female with culture-negative subclinical pulmonary TB. A) Pre-treatment chest radiograph shows patchy nodular opacities at the right middle lung zone. B) Axial CT image in lung window performed on the same date as A. reveals solid pulmonary nodules with adjacent centrilobular and tree-in-bud opacities in the superior segment of the right lower lobe as well as bronchial wall thickening and bronchiectasis. C) Post-treatment chest radiograph (10 months after A.) shows resolution of the abnormalities with minimal residual fibrosis at the right middle lung zone.

less frequent bilateral patterns. However, the study did not find other radiographic patterns specific to the culture-negative disease.

This study found that grade 1 CXR severity was strongly related to culture-negative subclinical pulmonary TB, indicating that they were likely to have less extent of the disease than those with culture-positive subclinical pulmonary TB. This aligns with the statement that Mtb may be contained within granuloma in the early stage, resulting in minimal pathology and a lack of symptoms [8]. Interestingly, prior studies also found that individuals with culture-negative pulmonary TB had fewer cavitary lesions than culture-positive ones, reflecting less extensive tissue damage [15,16]. However, the present study revealed a few such lesions exclusively in the culture-negative group, though not statistically significant due to their rarity. Still, the overall evidence suggests that culture-negative subclinical pulmonary TB might represent an earlier stage of TB disease compared to culture-positive cases.

Concerns may arise regarding the adequacy of sputa in subclinical TB patients. However, this study adhered to standardized collection procedures and provided patients with proper instructions, as detailed previously. Furthermore, the TB laboratory at our

Table 1. Univariable and multivariable analyses of factors associated with culture-negative subclinical pulmonary tuberculosis.

	Total (N=84)	Culture-negative (N=59)	Culture-positive (N=25)	P	Multivariable analysis	
					AOR (95% CI)	P
Age (years)	31 (25,38.5)	35 (28,40)	26 (24,30)	0.047†	1.07 (1.01-1.13)¶	0.022
Male sex	19 (22.6)	16 (27.1)	3 (12.0)	0.162‡	-	-
Diabetes	2 (2.4)	-	2 (8.0)	0.086‡	-	-
Previous pulmonary TB	2 (2.4)	2 (3.4)	-	1.000‡	-	-
Smoking status						
Never-smokers	76 (90.5)	53 (89.8)	23 (92.0)	1.000‡	-	-
Ever-smokers	8 (9.5)	6 (10.2)	2 (8.0)			
Being hospital employee	71 (84.5)	51 (86.4)	20 (28.2)	0.456§	-	-
CXR severity grading						
Grade 1	70 (83.3)	53 (89.8)	17 (68.0)	0.014§	7.18 (1.76-29.35)	0.006
Grade 2 and 3	14 (16.7)	6 (10.2)	8 (32.0)		Reference	
No. of CT performed	53 (63.1)	39 (66.1)	14 (56.0)	0.380§	-	-
CT severity score	2 (2,3)	2 (2,3)	2 (2,4)	0.186†	-	-

AOR, adjusted odds ratio; 95% CI, 95% confidence interval. †Data were shown as median (Q1,Q3); P was obtained from the Mann-Whitney U test. ‡Data were shown as n (%); P was obtained from the Fisher's exact test. §Data were shown as n (%); P was obtained from the Chi-square test. ¶For an increase by 1 year.

Table 2. Radiologic features of culture-negative subclinical pulmonary tuberculosis.

CXR findings	**Total (N=84)**	**Culture-negative (N=59)**	**Culture-positive (N=25)**	**P**
Patchy opacities	57 (67.9)	41 (69.5)	16 (64.0)	0.622‡
Reticulonodular opacities	31 (36.9)	19 (32.2)	12 (48.0)	0.170‡
Nodules	4 (4.8)	2 (3.4)	2 (8.0)	0.579†
Cavitation	1 (1.2)	1 (1.7)	-	1.000†
Enlarged hilar shadow	1 (1.2)	1 (1.7)	-	1.000†
Bilateral involvement	13 (15.5)	5 (8.5)	8 (32.0)	0.006‡,*
Chest CT findings	**Total (N=53)**	**Culture-negative (N=39)**	**Culture-positive (N=14)**	**P**
Consolidation	13 (24.5)	9 (23.1)	4 (28.6)	0.725†
Tree-in-bud pattern	49 (92.5)	35 (89.7)	14 (100.0)	0.563†
Ground glass opacities	1 (1.9)	-	1 (7.1)	0.269†
Nodules	31 (58.5)	25 (64.1)	6 (42.9)	0.166†
Mass	1 (1.9)	1 (2.6)	-	1.000†
Cavitation	2 (3.8)	2 (5.1)	-	1.000†
Adenopathy	5 (9.4)	3 (7.7)	2 (14.3)	0.599†
Bronchiectasis	7 (13.2)	5 (12.8)	2 (14.3)	1.000†
Calcified nodules	14 (26.4)	9 (23.1)	5 (35.7)	0.358‡
Calcified lymph node	5 (9.4)	3 (7.9)	2 (14.3)	0.599†
Upper lobe involvement	46 (86.8)	35 (89.7)	11 (78.6)	0.364†
Bilateral involvement	12 (22.6)	6 (15.4)	6 (42.9)	0.035‡,*
Multilobar involvement	16 (30.2)	9 (23.1)	7 (50.0)	0.060‡

*†Data were shown as n (%); P was obtained from the Fisher's exact test. ‡Data were shown as n (%); P was obtained from the Chi-square test. *Statistically significant.*

institute upholds rigorous standards undergoing internal audits and external quality control checks to ensure optimal performance. Correspondingly, the observation of milder radiographic severity in culture-negative disease implies potentially lower bacterial loads, which in turn supports the accuracy of the culture results.

Increasing age is the other factor related to culture-negative subclinical pulmonary TB in this study. The average age of the culture-negative group was higher than the culture-positive group. However, this may not be clinically important and the explanation for this association has been unclear. Most studies that compared culture-negative and culture-positive pulmonary TB did not show a remarkable association between age and culture positivity [15,16,21]. Hence, the relationship between age and culture positivity needs to be clarified, particularly in subclinical disease.

Regarding the radiographic characteristics, the study demonstrated that subjects with culture-negative subclinical pulmonary TB had lower rates of bilateral pulmonary involvement. Again, this displays the progression of the disease from the culture-negative to culture-positive stages and corresponds with our results on the extent of TB lesions discussed earlier. In addition, multilobar involvement in chest CT was less frequent in the culture-negative group; however, the difference failed to reach statistical significance. Likewise, median CT severity scores were similar between the two groups. Such findings might be due to a small proportion of subjects that received CT scanning. It is also worth noting that prior research did not find differences in laterality and multilobar involvement proportions between culture-negative and culture-positive cases [21], of which the inclusion of symptomatic participants might attenuate the result.

In the present study, other radiologic patterns in both imaging modalities, namely CXR and CT, were indistinguishable between the two groups. In the same way, a study in Thailand found that there were no radiographic manifestations specific to smear-negative TB [22]. Meanwhile, a Korean study demonstrated that patchy opacities predicted positive mycobacterial culture (OR 2.14; 95% CI 1.19 to 3.83) [21]. Nevertheless, neither restricted the participants to only subclinical cases. Noteworthily, findings consistent with previous TB, including bronchiectasis, calcified nodules, and calcified lymph nodes, support that spontaneous regression occurs as part of the TB spectrum depicted by Drain and colleagues [3]. From a biological aspect, mycobacterial burden and immune activities play a role in cycling through the emerging TB stages [3].

Importantly, treating TB disease earlier will accelerate TB control at the population level. Establishing a diagnosis of subclinical pulmonary TB without microbiological confirmation is a clinical dilemma. Alternative diagnoses must always be considered in such cases [23]. A study comparing CXR and CT features of subclinical pulmonary TB also underscored that undetectable TB-related pulmonary lesions by CXR were major [24]. Therefore, we proposed leveraging a CT scan could aid the diagnosis in this clinical situation where available. A low-dose CT (LDCT) scan is a useful option as it performs well in detecting pulmonary TB with the advantage of lower radiation compared to conventional CT [25]. According to a study in China, the sensitivity and positive predictive value of using LDCT alone to diagnose pulmonary TB among healthcare workers were 100% and 86.4%, respectively [25]. Based on our facility's pricing, an LDCT scan of the chest costs approximately 6,050 Thai Baht or 165 USD per scan. Of note, the clinical decisions in this study, conducted in the context of a high TB burden country, were rooted in the pre-test probability of TB, alongside the diagnostic information provided by CT findings, which were highly suggestive of TB. This approach strengthened the accuracy of the diagnostic methods utilized.

To our knowledge, this is one of the first studies exclusively conducted on subclinical pulmonary TB cases comparing culture-negative and culture-positive diseases. In addition, the subjects were initially referred from the health checkups. As a result, they provided us with essential information on the very early stage of TB disease.

Several limitations due to the retrospective nature of this study should be considered. First, the study was conducted at a single center with a small sample size, causing decreased robustness and generalizability. Nonetheless, the study presents novel insights into the subclinical disease, serving as a notion for subsequent research. Second, approximately 40% of the participants did not undergo a chest CT scan, resulting

in insufficient power to detect the difference in CT findings accordingly. Even so, this reflects the normal practice that not all cases receive or require a CT scan, such as people who cannot access such investigation and whose CXR findings are typical for pulmonary TB. Third, the study design might not have captured all potential health and comorbidity variables. However, the focus on subjects from health checkup clinics suggests they were generally immunocompetent and healthy. Furthermore, the study accounted for diabetes, a well-established risk factor for TB progression. Replication studies are still crucial.

Conclusions

In conclusion, the authors believe that the present study adds evidence to the knowledge of the earlier stage of TB. To bring about widespread TB elimination, an active case-finding approach in settings with high TB prevalence and advocacy to enhance clinicians' awareness about subclinical, bacteriologically negative pulmonary TB are warranted.

References

1. Global tuberculosis report 2023. Geneva: World Health Organization [cited 2024 Apr 7]; 2023. Licence: CC BY-NC-SA 3.0 IGO. Available from: https://iris.who.int/bitstream/handle/10665/373828/9789240083851-eng.pdf?sequence=1
2. Uplekar M, Weil D, Lonnroth K, Jaramillo E, Lienhardt C, Dias HM, et al. WHO's new end TB strategy. Lancet 2015;385(9979):1799–801. doi:10.1016/S0140-6736(15)60570-0.
3. Drain PK, Bajema KL, Dowdy D, Dheda K, Naidoo K, Schumacher SG, et al. Incipient and subclinical tuberculosis: A clinical review of early stages and progression of infection. Clin Microbiol Rev 2018;31(4):e00021-18. doi:10.1128/CMR.00021-18.
4. Tang P, Liang E, Zhang X, Feng Y, Song H, Xu J, et al. Prevalence and risk factors of subclinical tuberculosis in a low-incidence setting in China. Front Microbiol 2022;12:731532. doi:10.3389/fmicb.2021.731532.
5. Min J, Chung C, Jung SS, Park HK, Lee SS, Lee KM. Clinical profiles of subclinical disease among pulmonary tuberculosis patients: a prospective cohort study in South Korea. BMC Pulm Med 2020;20(1):316. doi:10.1186/s12890-020-01351-z.
6. Kendall EA, Shrestha S, Dowdy DW. The epidemiological importance of subclinical tuberculosis. A critical reappraisal. Am J Respir Crit Care Med 2021;203(2):168–74. doi:10.1164/rccm.202006-2394PP.
7. Frascella B, Richards AS, Sossen B, Emery JC, Odone A, Law I, et al. Subclinical tuberculosis disease—A review and analysis of prevalence surveys to inform definitions, burden, associations, and screening methodology. Clin Infect Dis 2021;73(3):e830–41. doi:10.1093/cid/ciaa1402.
8. Esmail H, Macpherson L, Coussens AK, Houben RMGJ. Mind the gap – Managing tuberculosis across the disease spectrum. EBioMedicine 2022;78:103928. doi:10.1016/j.ebiom.2022.103928.
9. Nguyen HV, Tiemersma E, Nguyen NV, Nguyen HB, Cobelens F. Disease transmission by patients with subclinical tuberculosis. Clin Infect Dis 2023;76(11):2000–6. doi: 10.1093/cid/ciad027.
10. Lau A, Lin C, Barrie J, Winter C, Armstrong G, Egedahl ML, et al. The radiographic and mycobacteriologic correlates of subclinical pulmonary TB in Canada. Chest 2022;162(2):309–20. doi:10.1016/j.chest.2022.01.047.
11. Mingchay P, Paitoonpong L, Kawkitinarong K, Ohata PJ, Suwanpimolkul G. Tuberculosis at a university hospital, Thailand: A surprising incidence of TB among a new generation of highly exposed health care workers who may be asymptomatic. PLoS One 2022;17(8):e0273027. doi: 10. 1371/journal.pone.0273027.
12. Pongwittayapanu P, Anothaisintawee T, Malathum K, Wongrathanandha C. Incidence of newly diagnosed tuberculosis among healthcare workers in a teaching hospital, Thailand. Ann Glob Health 2018;84(3):342–7. doi: 10.29024/aogh.2304.
13. Siranart N, Sowalertrat W, Sukonpatip M, Suwanpimolkul G, Torvorapanit P. First case series and literature review of coronavirus disease 2019 (COVID-19) associated pulmonary tuberculosis in Southeast Asia: Challenges and opportunities. J Infect Public Health 2023;16(1):80–9. doi: 10.1016/j.jiph.2022.11.029.
14. Division of Tuberculosis, Department of Disease Control, Ministry of Public Health. Thailand Operational Plan To End Tuberculosis, Phase 2 (2023 – 2027) [cited 2024 Apr 7]; 2023. Available from: https://www.tbthailand.org
15. Nguyen MVH, Levy NS, Ahuja SD, Trieu L, Proops DC, Achkar JM. Factors associated with sputum culture-negative vs culture-positive diagnosis of pulmonary tuberculosis. JAMA Netw Open 2019;2(2):e187617. doi:10.1001/jamanetworkopen.2018.7617.
16. Chen J, Marusinec R, Brown R, Shiau R, Jaganath D, Chitnis AS. Epidemiology of culture-negative pulmonary tuberculosis—Alameda county, 2010-2019. J Public Health Manag Pract 2023;29(3):353–60. doi:10.1097/PHH.0000000000001715.
17. Division of Tuberculosis. National Tuberculosis Control Programme Guideline, Thailand 2021 [cited 2023 Oct 19]. Bangkok: Division of Tuberculosis; 2021. Available from:

https://ddc.moph.go.th/uploads/publish/1253220220330064337.pdf
18. Bhalla AS, Goyal A, Guleria R, Gupta AK. Chest tuberculosis: Radiological review and imaging recommendations. Indian J Radiol Imaging 2015;25(03):213–25. doi: 10.4103/0971-3026.161431.
19. Willcox PA, Ferguson AD. Chronic obstructive airways disease following treated pulmonary tuberculosis. Respir Med 1989;83(3):195–8. doi:10.1016/s0954-6111(89)80031-9.
20. Kazerooni EA, Martinez FJ, Flint A, Jamadar DA, Gross BH, Spizarny DL, et al. Thin-section CT obtained at 10-mm increments versus limited three-level thin-section CT for idiopathic pulmonary fibrosis: correlation with pathologic scoring. AJR Am J Roentgenol 1997;169(4):977–83. doi:10.2214/ajr.169.4.9308447.
21. Lee CH, Kim WJ, Yoo CG, Kim YW, Han SK, Shim YS, et al. Response to empirical anti-tuberculosis treatment in patients with sputum smear-negative presumptive pulmonary tuberculosis. Respiration 2005;72(4):369–74. doi:10.1159/000086250.
22. Chierakul N, Boonsuk J, Muangman N, Totanarungroj K. Radiographic features for predicting smear-negative pulmonary tuberculosis. J Med Assoc Thai 2016;99(6):697–701. PMID: 29901318.
23. Nahid P, Dorman SE, Alipanah N, Barry PM, Brozek JL, Cattamanchi A, et al. Official American thoracic society/Centers for Disease Control and Prevention/Infectious Diseases Society of America clinical practice guidelines: Treatment of drug-susceptible tuberculosis. Clin Infect Dis 2016;63(7):e147–95. doi:10.1093/cid/ciw376.
24. Lau A, Lin C, Barrie J, Winter C, Armstrong G, Egedahl ML, et al. A comparison of the chest radiographic and computed tomographic features of subclinical pulmonary tuberculosis. Sci Rep 2022;12(1):16567. doi:10.1038/s41598-022-21016-7.
25. He W, Chen BD, Lv Y, Zhou Z, Xu JP, Lv PX, et al. Use of low-dose computed tomography to assess pulmonary tuberculosis among healthcare workers in a tuberculosis hospital. Infect Dis Poverty 2017;6(1):68. doi:10.1186/s40249-017-0274-6.

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Review

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Pharmacological treatment in Idiopathic Pulmonary Fibrosis: current issues and future perspectives

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ABSTRACT

Abstract: Idiopathic pulmonary fibrosis (IPF) represents a fibrotic interstitial lung disease characterized by uncertain etiology and poor prognosis. Over the years, the path to effective treatments has been marked by a series of advances and setbacks. The introduction of approved antifibrotic drugs, pirfenidone and nintedanib, marked a pivotal moment in the management of IPF. However, despite these advances, these drugs are not curative, although they can slow the natural progression of the disease. The history of drug therapy for IPF goes together with the increased understanding of the pathogenic mechanisms underlying the disease. Based on that, current research efforts continue to explore new therapies, possible personalized treatment strategies, drug combinations, and potential biomarkers for diagnosis and prognosis. In this review, we outline the route that led to the discover of the first effective therapies, ongoing clinical trials, and future directions in the search for more effective treatments.

Key words: idiopathic pulmonary fibrosis, IPF, treatment, therapy, future perspectives

Introduction

Idiopathic Pulmonary Fibrosis (IPF) is a fibrotic interstitial lung disease of uncertain origin, exhibiting radiological and histological characteristics consistent with usual interstitial pneumonia (UIP)[1]. It is a rare condition with an estimated global prevalence of about 4 cases per 10,000 persons [2], with a poor prognosis considering a median survival of 3-5 years since diagnosis [3].

IPF predominantly impacts the elderly population, affecting lungs insidiously and revealing itself through exertional breathlessness and a non-productive cough. As the disease advances, individuals may encounter a reduction in exercise capacity, eventually culminating in respiratory failure. IPF should be considered in adult patients with unexplained, persistent exertional breathlessness, cough, bibasilar inspiratory crackles, without constitutional or other symptoms indicative of a multisystem disorder [1].

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The clinical trajectory is further complicated by concurrent conditions such as pulmonary hypertension and emphysema, leading to heightened morbidity and mortality [3–6]. Accurate and timely diagnosis of IPF is crucial for implementing appropriate management strategies. High-resolution computed tomography (HRCT) scans and lung biopsy remain integral to the diagnostic process, and the recent guidelines provide a structured approach for their administration [1,7].

Over the years, the management of IPF has undergone significant developments, especially in the realm of pharmacological therapy aimed at slowing the disease progression and trying to improve patients' quality of life. The history of pharmacological therapy in IPF has witnessed significant advancements over the years, increasing the focus on understanding the underlying pathogenetic mechanisms responsible for disease progression, with the goal of developing novel targeted therapies. The introduction of the U.S. Food and Drug Administration and European Medicines Agency-approved antifibrotic drugs pirfenidone and nintedanib has marked a turning point in IPF management. Pirfenidone, a collagen synthesis inhibitor, has undergone thorough clinical investigations, including the CAPACITY study, demonstrating its ability to slow disease progression and improve patient survival [8,9]. Similarly, nintedanib, a multikinase inhibitor, has shown efficacy in reducing lung function decline in studies such as INPULSIS [10]. These molecules, through their antifibrotic action, have provided a solid foundation for current therapeutic guidelines[1,7]. Despite these advances, pirfenidone and nintedanib are not able to reverse or resolve pre-existing fibrosis. Thus, patients continue to experience lung function deterioration while on treatment, which remains focused on slowing progression of fibrosis, maintaining comfort and, in late stages, on palliative care.

To find a cure for this debilitating and fatal disease, it is imperative to deepen our understanding of the pathogenetic mechanisms underlying IPF, including altered cell-cell crosstalk and secretion of pathogenic molecules in the fibrotic milieu. Ongoing research continues to explore novel therapeutic options, personalized strategies and therapeutic combinations as well as possible biomarkers of diagnosis and/or predictors of treatment efficacy [11]. In this review, we provide a comprehensive summary of the current pharmacological treatments of IPF, clinical trials and future directions.

Pathogenesis and molecular pathways involved in lung fibrosis

IPF is characterized by the accumulation of collagen-producing fibroblasts and myofibroblasts, resulting in aberrant production and deposition of extracellular matrix, including collagens and fibronectin, leading to a progressive and irreversible fibrogenic process and loss of organ function [12]. Although several risk factors, including cigarette smoke, air pollution, and aging, are known to be involved in the development of IPF, the causes of IPF remain unknown[13–15]. Currently, the most accredited hypothesis is that, in genetically predisposed individuals, recurrent alveolar epithelial cells damage may lead to an increased release of cytokines and chemokines by alveolar epithelial cells and recruitment of cells responsible for perpetuating damage and incessant production of extracellular matrix [16]. This mechanism determines an increased secretion of fibrogenic signaling molecules, such as transforming growth factor-β (TGF-β) by activated macrophages that promote recruitment, proliferation and differentiation of fibroblast into myofibroblasts (Figure 1) and alter the balance between collagen synthesis and collagen degradation[17,18]. Moreover, TGF-β acts as an inducer for other fibrogenic molecules secretion such as connective tissue growth factor (CTGF), fibroblast growth factor (FGF), insulin-like growth factor (IGF) and platelet-derived growth factor (PDGF). In addition, telomerase gene mutation, short telomeres, aging, and cellular senescence play a role in the pathogenesis of IPF decreasing the population of type II alveolar epithelial cells and reducing their role in tissue injury repair[19].

IPF treatment in the past: more shadows than lights

The inflammatory model

From its initial characterization, the treatment of IPF has traditionally relied on the assumption that

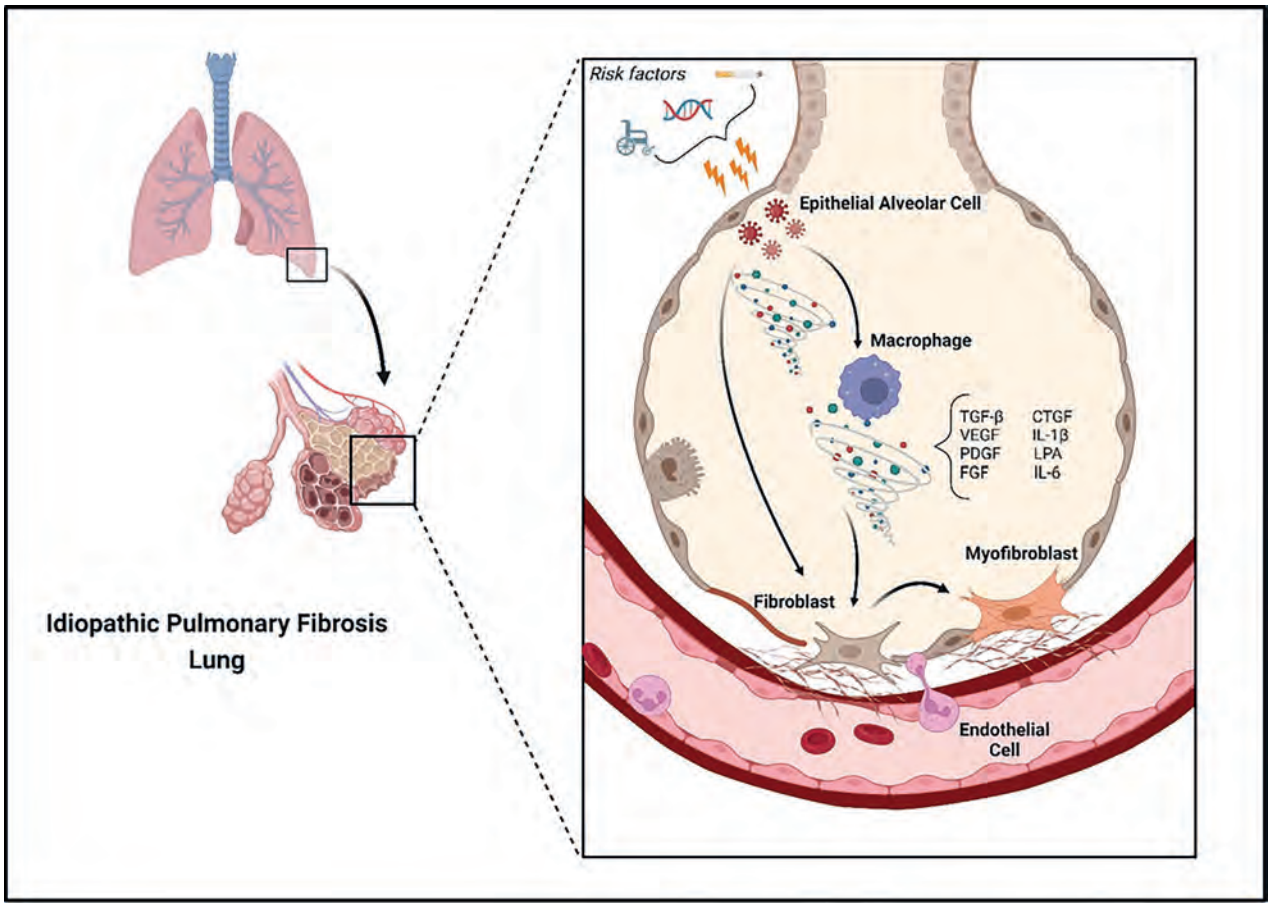

Figure 1. Cell types and cytokines involved in the pathogenesis of IPF. Lung fibrosis is the result of different pathways, assuming a possible trigger related by risk factors (as aging, smoking or genetic mutations) and the uncontrolled secretion of cytokines by epithelial alveolar cells, macrophages and endothelial cells responsible for the activation of fibroblasts and their transition to myofibroblasts. Legend: TGF-β, transforming growth factor-β; VEGF, vascular endothelial growth factor; PDGF, platelet-derived growth factor; FGF: fibroblast growth factor; CTGF: connective tissue growth factor; IL-1β, Interleukyn-1β, LPA, lysophosphatidic acid; IL-6, Interleukyn-6. Created with Biorender.com; all rights reserved.

injury leads to inflammation and fibrosis [20]. Consequently, corticosteroids have been the mainstay of IPF treatment for several years, even because no pharmacological therapy has been proven to alter or reverse the inflammatory process of IPF.

Until 1999, treatment options included corticosteroids, immunosuppressive/cytotoxic agents (e.g., azathioprine, cyclophosphamide), and antifibrotic agents (e.g., colchicine or d-penicillamine) either alone or in combination [21–27].

In 2000, for the first time an International Statement Consensus recommended a combined therapy involving corticosteroid and either azathioprine or cyclophosphamide. However, it acknowledged the high risk of treatment failure due to insufficient data from randomized clinical trials (RCTs)[28].

Supporting the inflammatory pathogenesis hypothesis, the IFIGENIA study, a multicenter, randomized, double-blind, placebo-controlled investigation, assessed outcomes in individuals receiving either N-acetylcysteine (NAC) or a placebo plus prednisone and azathioprine. The trial revealed a diminished rate of decline in Forced Vital Capacity (FVC) and Diffusing Capacity of the Lungs for Carbon Monoxide (DL_{CO}) among patients treated with NAC, although no improvement in one-year survival was observed [29].

A more definitive response regarding steroids and immunomodulating agents came by PANTHER-IPF, a multicenter randomized controlled trial to assess the efficacy of prednisone, azathioprine, and NAC. In the PANTHER-IPF trial, patients with IPF and mild-to-moderate lung function impairment, underwent randomization into three groups: prednisone, azathioprine, and NAC (combination therapy); NAC alone; or placebo. Combination therapy with prednisone, azathioprine and NAC, compared with placebo, was associated with increased all-cause mortality, all-cause hospitalizations and treatment-related severe adverse events. It was observed that elevated mortality and hospitalization rates manifested early in the trial, closely aligning with the period of escalated prednisone dosage, tapered over the initial 4-6 months to a minimal daily dose[30]. This observation implies that the heightened toxicity seemed to be attributed to high-dose corticosteroids rather than the azathioprine and low-dose prednisone.

Role of interferon gamma as a potential inhibitor of profibrotic cytokines

The imbalance between pro-fibrotic and anti-fibrotic cytokines in the pathogenesis of IPF prompted the exploration of interferon gamma (IFN-γ) in clinical trials. IFN-γ has exhibited the capacity to inhibit fibroblast proliferation and reduce the expression of TGF-β, PDGF, and various other pro-fibrotic interleukins in both *in vitro* and *in vivo* investigations [31]. After an encouraging preliminary study limited by a small number of patients enrolled [32], a placebo-controlled trial demonstrated that interferon gamma-1b did not affect progression-free survival or pulmonary function [33]. However, the larger prospective INSPIRE study did not demonstrate any survival advantage with subcutaneous IFN-γ treatment [34].

A change of target: endothelin system and phosphodiesterase-5 inhibitor

Several studies had demonstrated the profibrotic role of endothelin-1, molecule secreted by fibroblasts, endothelial cells, alveolar macrophages, epithelial cells and polymorphonuclear leukocytes, and able to increase collagen production and reduce synthesis of interstitial collagenase [35–38]. Based on these premises, the BUILD-1 trial sought to prove the efficacy of bosentan, a dual endothelin receptor antagonist (ERA), on exercise capacity and time to disease progression in patients with IPF[39]. Treatment with bosentan in IPF patients did not show superiority over placebo in the primary endpoint of change from baseline to month 12 in the 6-minute walk test (6MWT) distance. However, a trend favoring bosentan was observed in the secondary endpoint related to time to IPF worsening or death [39]. This endpoint was re-evaluated in another clinical trial (BUILD-3) with a larger number of patients, where drug tolerability was demonstrated, but the primary objective was not achieved [40].

Among endothelin receptor antagonists, ambrisentan, an ETA receptor-selective antagonist, was also assessed in a clinical trial to evaluate its efficacy in reducing the progression rate of IPF patients. In this trial, ARTEMIS-1, ambrisentan was terminated early due to a lack of efficacy in treating IPF and an increased risk of disease progression and respiratory hospitalizations [41].

The MUSIC trial was a phase II randomized controlled trial aimed at examining the effectiveness and safety of dual endothelin receptor antagonist, macitentan (10 mg once daily) on forced vital capacity (FVC), in individuals with histologically confirmed IPF compared to placebo. Although the promising preliminary data, the primary objective of the MUSIC trial was not achieved as no notable difference between treatments was observed in the primary outcome of changes from baseline up to month 12 in FVC [42].

Another therapeutical option explored has been sildenafil, a phosphodiesterase-5 inhibitor whose mechanism of action stabilizes the second messenger of nitric oxide, cyclic guanosine monophosphate, which leads to pulmonary vasodilatation [43]. It was evaluated in an RCT, based on the hypothesis that it might improve blood flow to well-ventilated regions of the lung, improving ventilation/perfusion ratio, in patients with advanced idiopathic pulmonary fibrosis. The study, including 180 patients, did not show benefits for patients underwent treatment with sildenafil,

not reaching the primary endpoint settled as increase in 6MWT distance [44].

Current approved therapies

With an evolving understanding of the role of fibroblasts and TGF-β, the search for a truly effective drug for pulmonary fibrosis, going beyond the purely inflammatory hypothesis considered up to then, has focused on the anti-fibrotic role of the molecules under study. The first antifibrotic molecule studied was pirfenidone, tested in murine models of bleomycin-induced fibrosis [45] and then its activity had been confirmed in human cells [45]. Pirfenidone demonstrated effective inhibition of fibronectin and the synthesis of α-smooth muscle actin (α-SMA), a critical factor in the fibroblast-to-myofibroblast transition, as induced by TGF-β in human lung fibroblasts. Furthermore, pirfenidone exhibited suppressive effects on fibrotic alterations mediated by TGF-β in human fetal lung fibroblasts [46,47]. In 1999, the first open-label study evaluating efficacy and safety of pirfenidone for IPF patients, showed the capacity to arrest the further decline of lung function in most patients with acceptable tolerability and minimal side effects [48]. Another encouraging result derives from a second open-label study in patients with advanced IPF with effects on stabilization of disease, but survival was not prolonged, probably due to the short treatment duration of 1 year [49]. Subsequent studies confirmed efficacy of pirfenidone, demonstrating an increased progression-free survival time and slowing down vital capacity (VC) deterioration [50,51]

Two Phase III international randomized double-blind placebo trials (CAPACITY 004 and CAPACITY 006) tried to evaluate change in percent predicted forced vital capacity (ppFVC) [52]. The CAPACITY 004 study included 435 patients treated with high-dose pirfenidone (2,403 mg/day), low-dose pirfenidone (1,197 mg/day) or placebo, while the CAPACITY 006 study included 344 patients treated with exclusively high-dose pirfenidone or placebo. While the CAPACITY 004 trial demonstrated a significant difference in FVC% and progression-free survival from baseline over 72 weeks between high-dose pirfenidone and the placebo arm, the CAPACITY 006 trial showed a difference in the reduction in FVC% rate of decline up to week 48 in the pirfenidone group, with no difference at week 72, thus failing the primary endpoint.

Subsequently another randomized, double-blind, placebo-controlled Phase III trial was conducted in 2014 to support the approval of pirfenidone for IPF therapy. In ASCEND trial, treatment with pirfenidone resulted in a significant between-group difference in the change from baseline to week 52 in the percentage of the predicted FVC versus placebo. Patients treated with pirfenidone also recorded a significant reduction in decline of the 6MWT distance and a longer progression-free survival, with gastrointestinal and skin-related side effects rarely causing discontinuation [53].

Further analysis of population of CAPACITY and ASCEND trials proved that pirfenidone significantly reduced the relative risk of all-cause mortality at 1 year by 48% and the risk of IPF-related mortality at 1 year by 68% [54].

Finally, real-world data has shown overall efficacy and tolerability of pirfenidone on reducing FVC decline in patients with IPF [55–57].

Riding the hypothesis of the role of TGF- β in lung fibrogenesis, scientific research evaluated the role of tyrosine kinase inhibitors as a possible therapeutic option. Protein kinases have been associated with the fibrogenic process mediated by growth factors like TGF-β [58]. In the management of IPF, tyrosine kinase inhibitors (TKIs) have been employed to selectively inhibit the function of fibroblasts, pivotal effector cells in the progression of IPF. Imatinib mesylate is a TKI with activity against the platelet-derived growth factor receptors (PDGFR-α and -β), discoidin domain receptors (DDR1 and DDR2), c-kit, and c-Abl [59]. A randomized, placebo-controlled trial evaluated safety and clinical effects of imatinib in patients with mild to moderate IPF followed for 96 weeks, but among all patients, 29% discontinued the study causing the failure to achieve the primary endpoint. The results of this trial showed that imatinib did not affect either survival or lung function [60].

On the other hand, the beginning of cellular signaling cascades via tyrosine kinases like vascular endothelial growth factor (VEGF), FGF and PDGF

has been implicated in pathogenesis of IPF [61]. Nintedanib is an intracellular antagonist that selectively targets a spectrum of tyrosine kinases, including the receptors for VEGF, FGF, and PDGF [62,63].

Based on these fundamental concepts, it was suggested that nintedanib could have a role in slowing FVC decline in patients with IPF. In TOMORROW trial, a phase II trial, four oral doses of nintedanib were compared to placebo in patients with IPF, demonstrating that a dose of 150 mg twice daily of nintedanib, compared with placebo, was associated with a slower loss of lung function (benefit of 68.4%, p = 0.06). The same dosage also led to a markedly reduced occurrence of acute exacerbations (p = 0.02) and enhanced quality of life (as assessed by the St. George's Respiratory questionnaire) compared to the placebo (p = 0.007) [64]. Those encouraging data stimulate the investigation of phase III trials, in INPULSIS-1 and INPULSIS-2 trial, that were both one year-long randomized, placebo-controlled trials examining the efficacy of 150 mg twice daily, using as primary endpoint the annual rate of decline in FVC [10]. In both trials nintedanib significantly reduced the rate of FVC decline, with the adjusted annual change in the nintedanib group that was -114.7 mL compared to -239.9 mL in the placebo group (p < 0.001) in INPULSIS-1, and -113.6 mL in the nintedanib group versus -207.3 mL in the placebo group in INPULSIS-2. The most frequent adverse event in the nintedanib groups was diarrhea, with rates of 61.5% and 18.6% in the nintedanib and placebo groups in INPULSIS-1, and 63.2% and 18.3% in the two groups, respectively, in INPULSIS-2. Adverse events led to discontinuation in less than 5% of patients [10].

Although nintedanib and pirfenidone showed a reduced rate of diseases progression in patient with IPF, those therapies remain an option for increases survival but they are not curative; in fact the disease was still progressive and led to death for respiratory failure. In 2018, with the availability of two antifibrotic drugs recommended for the treatment of IPF, an approach based on a combination therapy was proposed. The hypothesis was that an add-on therapy might provide a synergic effect with more benefit compared to monotherapy with one only antifibrotic drug. The INJOURNEY trial aimed to evaluate safety and tolerability in patient treated with nintedanib and add-on pirfenidone (titrated to 801 mg three times daily) versus nintedanib alone, enrolling patients who completed 4- to 5-weed run-in with nintedanib 150 twice daily who were not required reduction or interruption of treatment during the run-in period [65]. Main results of the trial were that gastrointestinal adverse events were reported in 69.8% of patients treated with nintedanib with add-on pirfenidone and 52.9% treated with nintedanib alone. Exploratory efficacy evaluation demonstrated at week 12 changes from baseline in FVC of -13,2 ml and -40.9 ml in patients treated with nintedanib with add on pirfenidone and nintedanib alone. Despite add-on therapy showed a manageable safety and tolerability profile in patients with IPF and exploratory analysis proved a possible efficacy on FVC decline, no further larger controlled studies has been performed to confirm the benefit/risk ratio of combination therapy.

Last findings and the importance of learning from what went wrong

The introduction of the aforementioned drugs has represented a milestone and a revolution on the history of IPF treatment, although it might be considered only the tip of the iceberg considering the increasing interest and research efforts made by the scientific community since the begin of the third millennium. In fact, according to ClinicalTrial.gov [66], the largest database of clinical research studies supported by the National Institute of Health, only in the last 10 years there have been registered more than 100 phase II and phase III interventional clinical trials evaluating safety and/or efficacy of different treatments in IPF patients, including brand new molecules or already known ones with a possible acting role in the pathophysiology of the disease.

Despite these numbers and although several molecules have shown a promising profile and encouraging results, pirfenidone and nintedanib remain so far, the only two drugs with proven efficacy in IPF [67].

Better understanding of the mechanism behind the development of fibrosis allowed the proposal of drugs with a variety of different targets. The role of the Lysophosphatidic acid (LPA) is one of the most recently studied theme in the onset of lung fibrosis[68].

LPA is a phospholipid mediator able to activate a growth factor-like response in pulmonary fibroblasts, smooth muscle cells and epithelial cells, all expressing a specific receptor, $LPAR_1$[69,70]. It has been demonstrated that both in animal model of lung fibrosis (Bleomycin induced) and in IPF patients' tissue and bronchoalveolar lavage (BAL), LPA have increased concentrations compared to healthy controls [69]. The enzyme responsible for production of LPA is Autotaxin (ATX), a secreted glycoproteic Lysphospholipase D mainly expressed by alveolar epithelial cells, macrophages and weakly in fibroblasts too [71]. As seen for LPA, ATX levels in BAL and lung tissue are higher in IPF than in healthy controls [68], so it has been proposed as potential therapeutical target in IPF with the introduction of its selective inhibitor zirtaxestat. This molecule showed promising efficacy results in the FLORA study, a phase 2a randomized placebo-controlled trial, despite the fact that it was designed to evaluate the safety of zirtaxestat in patients either under standard of care treatment or drug-free [72]. The evaluation of zirtaxestat efficacy in IPF patients was the aim of the ISABELA I and ISABELA II trials, two identically designed phase 3 randomized clinical trials, whose results have been recently published[73]. Unfortunately, both studies have been interrupted early after an interim analysis revealed an increased mortality in the patient group receiving a 600 mg daily dose and a lack of efficacy in all the treatment groups. In fact, ziritaxestat did not improve the annual rate of decline for FVC vs placebo: in the ISABELA 1 trial, the mean rate of decline for FVC at week 52 was −124.6mL (95% CI, −178.0 to −71.2 mL) with 600 mg, −173.9 mL (95% CI, −225.7 to −122.2 mL) with 200 mg, and −147.3mL (95%CI, −199.8 to −94.7 mL) with placebo. In the ISABELA 2 trial, the mean annual rate of FVC decline at week 52 was −173.8 mL (95% CI, −209.2 to −138.4 mL) with 600 mg, −174.9 mL (95% CI, −209.5 to −140.2 mL) with 200 mg, and −176.6 mL (95% CI, −211.4 to −141.8 mL) with placebo [73]. Moreover, pooled data showed all-cause mortality was 8.9% with 600mg and 7.0% with 200mg vs 5.5% with placebo (HR 1.8 [95%CI,1.1 to 3.0] for 600mg of ziritaxestat vs placebo and HR 1.3 [95%CI, 0.8 to 2.3] for 200mg ziritaxestat vs placebo). Furthermore, all secondary outcomes were unmet.

The discrepancy of these findings with what obtained in the FLORA study may be explained by the strong limitations of the phase 2a trial, represented by the small sample size and the short duration. The ISABELA I and ISABELA II trials enrolled 1,306 individuals affected by IPF and the design of the studies has been not considered as a factor leading to these findings [73], but they highlighted the importance of basing phase 3 trial on high-quality preclinical and clinical data, adaptive designs with a Bayesian approach and using biomarker-based enrichment strategies with prognostic biomarkers [73,74].

The ATX/LPA axis is still object of other studies, specifically a phase II RCT on the efficacy and safety of BMS-986278, an antagonist of $LPAR_1$ [74], that has recently completed the recruitment phase (NCT04308681). This study was designed for two cohorts, an IPF cohort and a progressive fibrosing interstitial lung diseases (PF-ILD) cohort[75]. The IPF cohort included three different groups based on daily drug dosage (60mg, 30mg and placebo) with 278 patients randomized and 276 receiving treatment [76]. The primary endpoint was rate of change in percent predicted FVC from baseline through 26 weeks as assessed based on two prespecified estimands [76]: the treatment policy estimand (similar to an Intention-to-Treat [ITT] analysis) included all observed data regardless of dose reduction and provides an estimate of efficacy with dose reduction as part of the treatment regimen; and the while-on-treatment estimand included all observed data prior to dose reduction and provides an estimate of efficacy without dose reduction as part of the treatment regimen. Treatment with 60 mg of BMS-986278 led to a 62% relative reduction in the rate of change in ppFVC versus placebo in the while-on-treatment analysis, and a 54% reduction versus placebo in the treatment policy analysis. A prespecified Bayesian analysis was utilized to provide the probability of a positive treatment difference for BMS-986278 compared to placebo: it showed a greater than 95% probability that 60 mg of BMS-986278 was superior compared to placebo in reducing the rate of decline in ppFVC over 26 weeks in both the while-on-treatment and treatment policy estimands. Subgroup analyses demonstrated a treatment effect of 60-mg BMS-986278 with or without

background antifibrotics. The 30 mg dose was not effective compared to placebo [76]. BMS-986278 was well tolerated in both treatment arms with rates of adverse events, including rates of gastrointestinal side effects, and treatment discontinuation comparable to placebo. These findings represented the basis for the design and initiation of the ongoing phase 3 clinical trial evaluating the effectiveness of BMS-986278 in IPF (NCT06003426).

The study of new and specific targets in the pathways leading to lung fibrosis has allowed the proposal of the use of monoclonal antibodies (MABs) in IPF too, considered as potential tailored therapy with a low rate of adverse events related to their assumption, as shown in other conditions like severe asthma, connective tissue diseases and some forms of cancer [77,78]. Several MABs have been evaluated as candidate treatments for IPF [77], but the only one that has reached and terminated a phase III RCT is pamrevlumab, a fully human recombinant monoclonal antibody against connective tissue growth factor (CTGF), a cytokine produced by fibroblasts, myofibroblasts, and endothelial cells [79]. CTGF is thought to interact with various regulatory modulators, such as TGF-β, vascular endothelial growth factor (VEGF), and receptors such as integrins modulating cellular responses that are associated with aberrant tissue repair and tumorigenesis[80]. The PRAISE study, a phase II RCT, showed that 30mg/kg of pamrevlumab intravenously administered every 3 weeks significantly attenuated the decline in lung function compared with placebo [80], resulting in a mean change in percentage of predicted FVC from baseline to week 48 was −2,9% in the pamrevlumab group compared with −7,2% in the placebo group (between-group difference 4.3% [95% CI 0.4–8.3]; p=0.033), which corresponded to a relative reduction in percentage of predicted FVC decline of 60.3% in patients treated with pamrevlumab. An interesting secondary outcome proposed and met in this trial concerned the imaging with a quantitative score for the lung fibrosis in HRCT (expressed in volume of the classified voxels of lung fibrosis or interstitial lung disease with respect to a segmented whole lung) which resulted significantly lower in the pamrevlumab group than in the placebo group at week 24 (24.8 mL vs 86.4 mL; p=0.009) and this difference was maintained to week 48 (75.4 mL vs 151.5 mL; p=0.038). Due to these findings, the phase III trials Zephyrus I and Zephyrus II (NCT03955146, NCT04419558) were launched to confirm the effectiveness of this drug. In these trials, pamrevlumab treatment did not meet the primary endpoint of change from baseline in forced vital capacity (FVC) at week 48, with a mean decline in FVC from baseline to week 48 of 260 ml in the pamrevlumab group compared to 330 ml in the placebo arm (p=0.29). And, although safety analysis confirmed pamrevlumab was generally safe and well tolerated and the majority of treatment emergent adverse events were mild or moderate, the secondary endpoint considering the disease progression (FVC percent predicted decline of ≥10% or death) was also not met [81].

Another example of a promising molecule whose efficacy has been investigated in a phase III RCT, which unfortunately was discontinued early, is the Recombinant Human Pentraxin-2 (PRM 151). Pentraxin 2, also known as purified serum amyloid P, is a circulating endogenous regulator of tissue repair, able to inhibit the differentiation of monocytes into profibrotic macrophages and fibrocytes, also decreasing the production of TGF- β[82]. It has been demonstrated that serum levels of pentraxin 2 are significantly lower in individuals affected by IPF compared with healthy controls [83]. A phase II trial in which PRM 151 was administered intravenously every 3 weeks, had showed promising results, meeting the primary efficacy end point consisting in a significant difference between the least-squares mean change in percent predicted FVC value from baseline to week 28 in the treatment group compared with the placebo (−2,5% vs −4,8% of the placebo group, difference of -2.3% - 90%CI, 1.1 to 3.5; P= 0.001), and obtaining a positive result considering the Least-Squares mean change in 6-Minutes Walk distance from baseline to week 28 (−0,5 m in the treatment group vs −31.8 m in the placebo arm, with a difference of 31.3 m - 90% CI, 17.4 to 45.1; P < .001) [84]; due to these data the phase III study STARSCAPE (NCT04552899) was subsequently started. In spite of these encouraging findings, in February 2023 the Sponsor decided to interrupt the phase III trial after a futility analysis indicating that the study was unlikely to meet the predefined primary objective of the study.

The reason for this might not have a univocal explanation: while admittedly it could be true that some of the analysed molecules are ineffective in treating IPF, the reverse may still be true; we must still improve on phase II trials to yield more robust and reliable data, which will allow us to design high quality phase III studies. As stated by Podolanczuk et al., the crucial points for avoiding current issues in future clinical trials are several [85]: phase II trials must be sufficiently powered to assess safety and heterogeneity of treatment response considering background antifibrotic use, underlining so the importance of an adequate sample size, considering then ethnic and sex differences, with the option to use reliable biomarkers in future for a precision-based approach. Another point to evaluate is to consider other outcomes: longitudinal change of FVC is recognized as the most clinically relevant parameter in IPF, due to its demonstrated correlation to death; but sometimes its measurement might be susceptible to missing data or patient difficulties in performing spirometry. For this reason, adding other outcome such as death for any causes and hospitalization for worsening of the respiratory condition could be considered in the future, as showed in the CleanUP-IPF, a trial demonstrating the inefficacy of the addition of co-trimoxazole or doxycycline to standard of care for the treatment of IPF [86]. This crucial point in the future of clinical trials in IPF has been the theme of a recent symposium lead by some of the maximum experts of the field, including also regulatory representatives and patients advocates which evaluating the role of functional measurements (FVC, 6MWT), patient reported outcomes (PROs), imaging markers and circulating biomarkers, expressed the need to go beyond FVC as the only primary outcome in RCT [87], underlining the importance of composite outcome and proposing the integration of adequately validated PROs as key-endpoints in the future, making a better understanding of patients feels and function.

Promising molecules in ongoing clinical trials

There are numerous ongoing clinical trials considering the different targetable pathways in idiopathic pulmonary fibrosis. It is important to note that molecules and trials mentioned in this review which have not completed phase 3, are not assessed based on a definitive evaluation of data, but are only considered for their potential, based on the current state of shared information. Table 1 shows the most recent and current phase 3 randomized clinical trials on IPF.

The anti-inflammatory and immunomodulatory function of PDE4 is already documented in literature, leading to its use in COPD and psoriasis/psoriatic arthritis with roflumilast and apremilast, respectively [88,89]. A third PDE4 inhibitor, crisaborole, was approved for topical treatment of mild-to-moderate atopic dermatitis [90]. None of these show any preferential enzymatic inhibition among the four PDE4 subtypes, A–D. Phosphodiesterases (PDEs) mediate the hydrolysis of second messengers, cyclic adenosine monophosphate (cAMP) or cyclic guanosine monophosphate (cGMP). There are 11 gene superfamilies that encode PDEs, comprising various genes (coding for subtypes A, B, C, etc.). These genes also generate alternative mRNA-splicing variants, resulting in around 100 different PDE isoforms [91].

Although there may be some functional redundancy among isoenzymes, most PDE isoforms and variants play specific physiological roles in mammalian cells. This provides an opportunity to create PDE4 inhibitors that target specific subtypes for varied conditions, aiming at optimize effectiveness and tolerance characteristics. Over the past ten years, evidence has grown indicating that PDE4 might have a significant role in fibrosis, supported by animal studies and *in vitro* experiments, examining the impact of PDE4 inhibitors on fibroblasts functionality. The effectiveness of PDE4 inhibitors in reducing lung fibrosis has been observed across diverse experimental setups, notably in rodents experiencing bleomycin-induced fibrosis. In rat models, demonstrated reduction of Ashcroft fibrosis score, hydroxyproline levels, and serum tumour necrosis factor-α (TNF-α) [92,93]. Improvement of lung fibrosis by PDE4 inhibition was not limited to TGF-B1 effects, have been shown to directly influence various functions of fibroblasts in human-derived fibroblast cell lines. Kohyama et al. [94] illustrated the direct impact of PDE4 inhibitors on fibroblasts *in vitro*. In human foetal lung fibroblasts (HFL-1), both rolipram and cilomilast hindered FN-induced chemotaxis and the contraction of collagen gels. The

Table 1. Most recent phase 3 randomized clinical trials on pharmacotherapies for Idiopathic Pulmonary Fibrosis (IPF)

Molecule	Mechanism of Action	Route of Administration	Primary Outcome	Status	ClinicalTrial.Gov Identifier
Zirtaxestat	Selective Autotaxin inhibitor	Oral	Annual Rate of Decline in FVC up to Week 52	Terminated: early discontinuation after interim analysis revealed the increased mortality in the patients group receiving a 600 mg daily dose and a lack of efficacy in all the treatment groups	NCT03711162; NCT03733444
BMS-873786	LPA receptor 1 antagonist	Oral	Absolute change from baseline in forced vital capacity (FVC) measured in mL [to week 52]	Ongoing	NCT06003426
Pamrevlumab	Humanized monoclonal antibody targeting the Connective Tissue Growth Factor (CTGF)	Intravenous	Change From Baseline in Forced Vital Capacity (FVC) at Week 48	Terminated: Zephyrus I did not meet primary endpoint and, based on its results, Zephyrus II has been discontinuated	NCT03955146, NCT04419558
Recombinant Human Pentraxin-2 (rhPTX-2; PRM-151)	Inhibition of TGF-β1 production and differentiation of monocytes into profibrotic fibrocytes	Intravenous	Absolute Change in Forced Vital Capacity (FVC [mL]) [from baseline to week 52]	Terminated: futility analysis outcome indicated that the study was unlikely to meet the predefined primary objective of the study. No new safety concerns were identified.	NCT04552899
Treprostinil	Prostacyclin analogue	Inhalatory	Change in Absolute FVC from Baseline to Week 52	Ongoing	NCT05255991
BI 1015550	Phosphodiesterase 4B (PDE4B) inibitor	Oral	Absolute change from baseline in Forced Vital Capacity (FVC) (mL) at Week 52	Complete (enrollment concluded in June 2023)	NCT05321069
N-acetylcysteine (NAC)	Antioxidant effect tested in a selected cohort of IPF patients with a TOLLIP rs3750920 TT genotype	Oral	Time to one of the following composite endpoint criteria: 10% relative decline in forced vital capacity (FVC), first respiratory hospitalization, lung transplant or death from any cause.	Ongoing	NCT04300920

inhibitory effect of prostaglandin E2 (PGE2) on fibroblast function was enhanced in the presence of PDE4 inhibitors, and the impact of these inhibitors was reduced when endogenous PGE2 was blocked by indomethacin.

BI 1015550, an oral inhibitor, exhibits preferential targeting of PDE4B with around 10 times greater selectivity for inhibiting PDE4B compared to other PDE4 [95] .

FIBRONEER-IPF is a phase III, double blind, randomized, clinical trial conducted across multiple centres worldwide, using a placebo-controlled design. It aims to assess the effectiveness and safety of BI 1015550 in IPF patients, categorized by their utilization of antifibrotic treatments, spanning a period of at least 52 weeks (NCT05321069). The primary endpoint is absolute change from baseline in FVC (mL) at week 52. Started in September 2022, the trial completed its enrolment in June 2023. The intended enrolment targets 963 patients, randomized evenly in a 1:1:1 ratio to receive either 9 mg or 18 mg of BI 1015550 or a placebo administered twice daily. Moreover, the patients have been stratified based on their background use of antifibrotic treatments during screening [96]. The population of included patients is approximately equivalent to those in all the other previously described trials, with minor variations in the FVC and DL_{CO} cut-off values.

Encouraging data came from the phase 2 trial of Fibroneer-IPF that shows among patients without background antifibrotic use, the median change in the FVC was 5.7 mL (95% CI, -39.1 to 50.5) in the BI group and -81.7 mL (95% CI, -133.5 to -44.8) in the placebo group. Among patients with background antifibrotic use, the median change in the FVC was 2.7 ml (95% CI, -32.8 to 38.2) in the BI 1015550 group and -59.2 ml (95% CI, -111.8 to -17.9) in the placebo group (median difference, 62.4 ml; 95% CI, 6.3 to 125.5; probability that BI 1015550 was superior to placebo, 0.986)[97] . Preclinical research indicates that BI 1015550 exhibits complementary actions to nintedanib concerning the transformation of human myofibroblasts and, when used together, they have a synergistic impact on fibroblast proliferation [95,98]. This data leads us to hope for the future possibility of using multiple drugs in synergy to target different pathways simultaneously. On the other hand, the most frequently encountered side effect with PDE4B is diarrhea [97]. Unfortunately, nintedanib commonly presents the same side effect [9], suggesting that in clinical practice, combining the two might be compromised by this common adverse event. Hence, studies and strategies will be necessary to address this possibility and ensure maximum patient adherence to the therapy.

Market-available oral PDE4 inhibitors are linked to side effects such as depression, thoughts of suicide, and related behaviors [99]. During Phase II there was just one report of suicidal ideation that occurred after the residual effect period of BI 1015550 [97]. If the drug will be approved, higher attention in daily clinical practice will be required, in daily clinical practice, to the anxiety/depression and suicidal behavior aspect, conditions that in their reactive form are often associated with idiopathic pulmonary fibrosis [100]. A unique example of a strategy to address anxiety/depression disorder is the one proposed by G. D. Edwards et al. demonstrating a significant reduction in the HADS (Hospital Anxiety and Depression Scale) score through respiratory rehabilitation [101].

IPF is associated with significant risk of comorbidities that may differently influence the prognosis of patients [102]. Pulmonary Hypertension (PH) frequently complicates the course of patients with IPF, with a reported wide prevalence range of 10%–86% [103]. One study demonstrated that IPF patients with PH documented via right heart catheterization had a 1-year mortality of 28% versus those without PH, whose 1-year mortality was only 5.5% [104]. For a long time, it was believed that pulmonary hypertension in idiopathic pulmonary fibrosis (IPF) was caused by the narrowing of blood vessels due to low oxygen and damage to the lung's capillary network from fibrosis. Although these factors probably play a role in the development of pulmonary hypertension in IPF, recent evidences show that other mechanisms are also involved [105]. Drugs approved for pulmonary arterial hypertension have been investigated in several randomized controlled trials in PH-ILD patients, leading to discouraging results until the recent INCREASE study [106–109]. Among individuals suffering from pulmonary hypertension caused by interstitial lung disease, the use of inhaled treprostinil

resulted in enhanced exercise capacity compared to the initial level, as evaluated through a 6-minute walk test [109]. Treprostinil is a stable analogue of prostacyclin, which promotes vasodilation of pulmonary and systemic arterial vascular beds and inhibits platelet aggregation [110]. The INCREASE study was a 16-week research conducted across multiple centers, employing randomization, a double-blind methodology, and a placebo-controlled approach. It aimed to evaluate the safety and effectiveness of inhaled treprostinil in 326 individuals diagnosed with PH-ILD, which includes pulmonary hypertension associated with idiopathic pulmonary fibrosis (IPF) [109]. Apart from achieving the primary goal of assessing the 6-minute walk distance (6MWD) and secondary endpoints, *post hoc* analysis of the INCREASE study revealed that inhaled treprostinil led to notable enhancements in forced vital capacity (FVC) among PH-ILD subjects [111]. Furthermore, when focusing on patients with IPF, FVC improvements of 84.5 mL (SE 52.7; 95% CI −20.4 to 189.5; p=0.11) by week 8 and 168.5 mL (SE 64.5; 95% CI 40.1 to 297.0; p=0.011) by week 16 were observed. There was also a significant reduction in acute disease exacerbations among the IPF patient group compared to the placebo. The enhancements in forced vital capacity (FVC) and the reduction in exacerbations related to the underlying lung condition, as observed in the INCREASE study, indicate that inhaled treprostinil could represent a viable treatment choice for individuals diagnosed with IPF.

Based on these findings, a phase 3 randomized clinical trial, TETON, has been launched as the first clinical trial investigating an inhaled therapy specifically designed for IPF. TETON (NCT04708782) will be a 52-week, randomized, double-blind placebo-controlled, phase 3 study with a nebulized solution of treprostinil in patients with IPF. All subjects will initiate to inhale treprostinil (6 μg/breath) or placebo at a dose of 3 breaths (18 μg) administered four times daily (during waking hours) and will titrate to a target dosing regimen of 12 breaths (72 μg) four times daily. Administering the treatment directly to the lungs might potentially offer added advantages with fewer adverse effects when compared to systemic therapy. This trial aims to investigate the use of inhaled treprostinil in a manner that closely mirrors real-world treatment for IPF by avoiding unnecessary restrictions in the inclusion and exclusion criteria, unlike other IPF studies. Notably, there is not an upper age limit, individuals on the lung transplant list are eligible for participation, and the forced vital capacity (FVC) requirement is set at ≥45% (with no upper limit). Patients may also undergo background therapy with pirfenidone or nintedanib, provided they have been on a stable and optimized dose for a minimum of 30 days before the baseline assessment. Like previous trials, the primary endpoint is the reduction of FVC over 52 weeks. [112] The potential success of the trial could lead to the approval of the first "topical" therapy in IPF, consequently offering a treatment with minimal systemic side effects.

Several interesting phase 2 studies are about to commence their recruitment, focusing on next-generation molecules belonging to the family of monoclonal antibodies, such as vixarelimab (NCT05785624), binding the beta subunit of the oncostatin M receptor, now approved for the treatment of chronic *Prurigo Nodularis* [113] and axatilimab (NCT06132256) directed to colony stimulating factor-1 receptor (CSF-1R), targeting pathways mediated by profibrotic macrophages, that was already demonstrated to be a promising novel treatment strategy for refractory chronic Graft-Versus-Host-Disease [114]. At present, it is not possible to comment on the data and rationale behind these studies as they are still confidential to the sponsoring entities. It will be necessary to wait for the conclusion of these studies to analyze the initial results of these promising new molecules.

The most forward-looking trial stems from a careful observation of the past in IPF therapy. We have previously mentioned the PANTHER study, which demonstrated the failure of combination therapy involving azathioprine, prednisone, and NAC [30]. However, a *post hoc* analysis revealed a potential beneficial effect of NAC in a subgroup of individuals carrying a specific genetic variant, the TOLLIP rs3750920 TT genotype, present in about 25% of patients with IPF [115]. Those patients had a significant reduction of hospitalization, death, transplant, <10% FVC decline compared with those who received placebo. Those with TOLLIP CT genotype (50% of cohort) had similar outcomes to those treated with placebo.

In contrast, the population with the TOLLIP CC genotype (25% of the cohort) indicated a trend for unfavorable outcomes with NAC treatment [115]. The TOLLIP gene encodes a ubiquitin-binding protein, regulating the innate immune response by inhibiting Toll-like receptor (TLR) signaling. TLRs are pivotal in the innate immune response against diverse pathogen-associated molecular patterns. Changes in TLR expression and signaling have been associated with the progression and mortality of IPF [115–117] .

In PRECISIONS-IPF, a phase 3, multi-center, randomized, double-blind, placebo-controlled trial the patients will be selected, for the first time in IPF Trial, by genotyping (NCT04300920). Patient with TOLLIP rs3750920 TT genotype, while receiving standard of care, will be randomized to NAC (600 mg tablets to be taken three times a day) or placebo in a 1:1 ratio and will last 24 months. The study is also at the forefront for its trial procedures; in fact, patients will be offered the opportunity to participate in monitoring through home spirometry three times a week in the morning using a portable spirometer. In well-trained patients, home spirometry has proven to be a reliable tool in monitoring the progression of IPF [118]. The economic aspect of the potential approval of NAC in this population should not be underestimated. A recent published systematic review has shown that NAC + pirfenidone were the most efficacious, tolerable and cost-effective therapy in IPF [119].

The precision medicine approach is still lacking in pulmonary fibrosis, patients with IPF have highly heterogenous clinical trajectories, and prognosis for each individual patient is difficult to predict. These key differences among patients suggest that subgroups of patients may respond differently to treatments.

Another opportunity for IPF therapy is to optimize treatments already approved by exploring alternative administration routes. Pirfenidone stands as the first antifibrotic that received worldwide approval for IPF therapy [120]. Patients undergoing oral pirfenidone therapy may commonly experience gastrointestinal side effects and skin rashes, leading both physician and patient to consider switching to nintedanib or discontinuing antifibrotic treatment [121]. Considering this, a phase 1b trial (AP01-002 ACTRN12618001838202) comparing the safety and tolerability of nebulized AP01 (a novel formulation of inhaled pirfenidone) 50 mg once daily or 100 mg two twice a day has been proposed to evaluate differences in terms of safety of same molecule with different routes of administration. The most common treatment-related adverse events (frequency, % of patients) were all mild or moderate and included cough (14, 15.4%), rash (11, 12.1%), nausea (8, 8.8%), throat irritation (5, 5.5%), fatigue (4, 4.4%) and taste disorder, dizziness and dyspnea (three each, 3.3%). Side effects commonly associated with oral pirfenidone in other clinical trials were less frequent with AP01 [122] .

Research has not focused only on drugs able to target specific pathways involved in the typical progressive scarring of lungs, but also on some important aspects like symptoms and particularly chronic cough [123]), that represents an important cause of quality of life impairment. In IPF cough does not show a clear correlation with pulmonary function, in addition there are some evidence showing an heightened cough reflex sensitivity in this patients and a decrease in cough frequency during sleep suggesting a neurological involvement [127] [128]. Gefapixant, a P2X3 receptor antagonist, has been investigated in patients with treatment-resistant and unexplained chronic cough; unfortunately, it did not meet the pre-specified primary objective of reduction in awake cough frequency [129] . Mixed opioid agonists/antagonists can reduce chronic cough by pharmacologically acting on the opioid system potentially at both peripheral and central nervous system levels [130]. An interim analysis of phase 2 data indicates that NAL ER (Nalbuphine Extended Release) is the first therapy with a significant reduction in IPF-related hourly daytime chronic cough frequency [131]. Based on this evidence a phase 2b trial will commence recruitment in 2024 to confirm and strengthen these findings (NCT05964335).

Another relevant therapeutic issue related to IPF is the treatment of acute exacerbations, dramatic events marked by a rapid clinical and radiological worsening that may lead to death. Unfortunately, there are not effective treatments for patients experiencing acute exacerbation, with only retrospective series providing evidence. Consequently, therapeutic approaches for these patients are often anecdotal or based on personal experience [132]. The 2011 international guidelines on

IPF recommended glucocorticoids for most cases of acute exacerbation; however, this was a weak recommendation relying on expert opinion [120]. Results from EXAFIP trial clarify that cyclophosphamide added to glucocorticoids in AE-IPFs increase 3 months mortality [133]. In 2021 Tejaswini et al. proposed a triple therapy strategy for autoantibody reduction in acute exacerbations, combining therapeutic plasma exchanges (TPE), two doses of rituximab, and four intravenous immunoglobulin (IVIG) infusion. This article shows that this association is related to an improvement in gas exchange, rapid response to therapies, and cumulative one year survival. The data should be assessed with the caveat that the cited study lacked a control cohort [134]. For these reasons, a clinical trial (STRIVE-IPF) is currently recruiting to test this triple therapy with the methodological rigor of randomization placebo/control cohort (NCT03286556).

Conclusion

Pharmacological treatment of IPF remains one the most challenging aspect in the field of ILDs and the entire respiratory medicine. The efforts made by the scientific community in the past led to efficient drugs able to slow down the decline typical of the disease, but it is not enough considering its still unfortunate prognosis. Preclinical studies to better understand the mechanisms underlying this condition are still needed. Meantime, the proposal of several new molecules and the recent new insights in the design of clinical trials represent the basics of promising future results.

References

1. Raghu G, Remy-Jardin M, Richeldi L, Thomson CC, Antoniou KM, Bissell BD, et al. Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults: An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. https://doi.org/10.1164/rccm.202202-0399ST 2022, 205, E18–E47, doi:10.1164/RCCM.202202-0399ST.
2. Maher TM, Bendstrup E, Dron L, Langley J, Smith G, Khalid JM, et al. Global Incidence and Prevalence of Idiopathic Pulmonary Fibrosis. Respir Res 2021;22:197. doi:10.1186/s12931-021-01791-z.
3. Ley B, Collard HR, King TE. Clinical Course and Prediction of Survival in Idiopathic Pulmonary Fibrosis. Am J Respir Crit Care Med 2011;183:431-40, doi:10.1164/RCCM.201006-0894CI.
4. Salonen J, Purokivi M, Bloigu R, Kaarteenaho R. Prognosis and Causes of Death of Patients with Acute Exacerbation of Fibrosing Interstitial Lung Diseases. BMJ Open Respir Res 2020;7. doi:10.1136/bmjresp-2020-000563.
5. Kim HJ, Perlman D, Tomic R. Natural History of Idiopathic Pulmonary Fibrosis. Respir Med 2015;109:661-70. doi:10.1016/j.rmed.2015.02.002.
6. Torrisi SE, Ley B, Kreuter M, Wijsenbeek M, Vittinghoff E, Collard HR, et al. The Added Value of Comorbidities in Predicting Survival in Idiopathic Pulmonary Fibrosis: A Multicentre Observational Study. Eur Respir J 2019;53:1801587. doi:10.1183/13993003.01587-2018.
7. Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, et al. Diagnosis of Idiopathic Pulmonary Fibrosis An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med 2018;198:e44–e68. doi:10.1164/RCCM.201807-1255ST.
8. Noble PW, Albera C, Bradford WZ, Costabel U, Glassberg MK, Kardatzke D, et al. Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis (CAPACITY): Two Randomised Trials. Lancet 2011;377:1760-69. doi:10.1016/S0140-6736(11)60405-4.
9. King TE, Bradford WZ, Castro-Bernardini S, Fagan EA, Glaspole I, Glassberg MK, et al. A Phase 3 Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis. N Engl J Med 2014;370:2083-92. doi:10.1056/NEJMOA1402582.
10. Richeldi L, du Bois RM, Raghu G, Azuma A, Brown KK, Costabel U, et al. Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis. New Engl J Med 2014;370:2071-82. doi:10.1056/NEJMOA1402584/
11. Mondoni M, Varone F, Alfano F, Muscato G, Conti C, Saderi L, et al. Predictors of Stability/Improvement of Forced Vital Capacity in Patients With Idiopathic Pulmonary Fibrosis After One Year of Treatment With Nintedanib. Arch Bronconeumol 2023;59:464-66. doi:10.1016/j.arbres.2023.02.010.
12. Richeldi L, Collard HR, Jones MG. Idiopathic Pulmonary Fibrosis. Lancet 2017;389:1941-52. doi:10.1016/S0140-6736(17)30866-8.
13. Wynn TA. Integrating Mechanisms of Pulmonary Fibrosis. J Exp Med 2011;208:1339-50. doi:10.1084/JEM.20110551.
14. Wilson MS, Wynn TA. Pulmonary Fibrosis: Pathogenesis, Etiology and Regulation. Mucosal Immunol 2009;2:103. doi:10.1038/MI.2008.85.
15. Zaman T, Lee JS. Risk Factors for the Development of Idiopathic Pulmonary Fibrosis: A Review. Curr Pulmonol Rep 2018;7:118-25. doi:10.1007/s13665-018-0210-7.
16. Spagnolo P, Cottin V. Genetics of Idiopathic Pulmonary Fibrosis: From Mechanistic Pathways to Personalised Medicine. J Med Genet 2017;54:93-9. doi:10.1136/jmedgenet-2016-103973.

17. Kropski JA, Blackwell TS. Progress in Understanding and Treating Idiopathic Pulmonary Fibrosis. Ann Rev Med 2019;70:211-24. doi:10.1146/annurev-med-041317-102715.
18. Fernandez IE, Eickelberg O. The Impact of TGF-β on Lung Fibrosis: From Targeting to Biomarkers. Proc Am Thorac Soc 2012;9:111-16. doi:10.1513/PATS.201203-023AW.
19. Mora AL, Rojas M, Pardo A, Selman M. Emerging Therapies for Idiopathic Pulmonary Fibrosis, a Progressive Age-Related Disease. Nat Rev Drug Discov 2017;16:755-72. doi:10.1038/nrd.2017.170.
20. McAnulty RJ, Laurent GJ. Pathogenesis of Lung Fibrosis and Potential New Therapeutic Strategies. Exp Nephrol 1995;2:96-107.
21. Meier-Sydow J, Rust M, Kronenberger H, Thiel C, Amthor M, Riemann H. [Long-Term Follow-up of Lung Function Parameters in Patients with Idiopathic Pulmonary Fibrosis Treated with Prednisone and Azathioprin or d-Penicillamine (Author's Transl)]. Prax Klin Pneumol 1979;33(Suppl 1):680-88.
22. Meier-Sydow J, Weiss SM, Buhl R, Rust M, Raghu G. Idiopathic Pulmonary Fibrosis: Current Clinical Concepts and Challenges in Management. Semin Respir Crit Care Med 1994;15:77-96. doi:10.1055/S-2007-1006351/BIB.
23. Raghu G, Depaso WJ, Cain K, Hammar SP, Wetzel CE, Dreis DF, et al. Azathioprine Combined with Prednisone in the Treatment of Idiopathic Pulmonary Fibrosis: A Prospective Double-Blind, Randomized, Placebo-Controlled Clinical Trial. Am Rev Respir Dis 1991;144:291-96. doi:10.1164/AJRCCM/144.2.291.
24. Johnson MA, Kwan S, Snell NJC, Nunn AJ, Darbyshire JH, Turner-Warwick, et al. Randomised Controlled Trial Comparing Prednisolone Alone with Cyclophosphamide and Low Dose Prednisolone in Combination in Cryptogenic Fibrosing Alveolitis. Thorax 1989;44:280-88. doi:10.1136/THX.44.4.280.
25. Douglas WW, Ryu JH, Swensen SJ, Offord KP, Schroeder DR, Caron GM, et al. Colchicine versus Prednisone in the Treatment of Idiopathic Pulmonary Fibrosis. A Randomized Prospective Study. Members of the Lung Study Group. Am J Respir Crit Care Med 1998;158:220-25. doi:10.1164/AJRCCM.158.1.9709089.
26. Peters SG, McDougall JC, Douglas WW, Coles DT, DeRemee RA. Colchicine in the Treatment of Pulmonary Fibrosis. Chest 1993;103:101-4: doi:10.1378/CHEST.103.1.101.
27. Rennard SI, Bitterman PB, Ozaki T, Rom WN, Crystal RG. Colchicine Suppresses the Release of Fibroblast Growth Factors from Alveolar Macrophages in Vitro. The Basis of a Possible Therapeutic Approach Ot the Fibrotic Disorders. Am Rev Respir Dis 1988;137:181-5. doi:10.1164/AJRCCM/137.1.181.
28. King J, Costabel U, Cordier JF, DoPico GA, DuBois RM, Lynch D, et al. American Thoracic Society. Idiopathic Pulmonary Fibrosis: Diagnosis and Treatment. International Consensus Statement. American Thoracic Society (ATS), and the European Respiratory Society (ERS). Am J Respir Crit Care Med 2000;161:646-64. doi:10.1164/AJRCCM.161.2.ATS3-00.
29. Demedts M, Behr J, Buhl R, Costabel U, Dekhuijzen R, Jansen HM, et al. High-Dose Acetylcysteine in Idiopathic Pulmonary Fibrosis. N Engl J Med 2005;353:2229-42. doi:10.1056/NEJMOA042976.
30. Idiopathic Pulmonary Fibrosis Clinical Research Network; Raghu G, Anstrom KJ, King TE, Lasky JA, Martinez FJ. Prednisone, Azathioprine, and N-Acetylcysteine for Pulmonary Fibrosis. N Engl J Med 2012;366:1968-77. doi:10.1056/NEJMoa1113354.
31. Wen FQ, Liu XD, Terasaki Y, Fang QH, Kobayashi T, Abe S, et al. Interferon-γ Reduces Interleukin-4- and Interleukin-13-Augmented Transforming Growth Factor-B2 Production in Human Bronchial Epithelial Cells by Targeting Smads. Chest 2003;123:372S-373S. doi:10.1016/S0012-3692(15)35217-X.
32. Ziesche R, Hofbauer E, Wittmann K, Petkov V, Block LH. A Preliminary Study of Long-Term Treatment with Interferon Gamma-1b and Low-Dose Prednisolone in Patients with Idiopathic Pulmonary Fibrosis. N Engl J Med 1999;341:1264-9. doi:10.1056/NEJM199910213411703.
33. Raghu G, Brown KK, Bradford WZ, Starko K, Noble PW, Schwartz DA, et al. A Placebo-Controlled Trial of Interferon Gamma-1b in Patients with Idiopathic Pulmonary Fibrosis. https://doi.org/10.1056/NEJMoa030511 2004, 350, 125–133, doi:10.1056/NEJMOA030511.
34. King TE, Albera C, Bradford WZ, Costabel U, Hormel P, Lancaster L, et al. Effect of Interferon Gamma-1b on Survival in Patients with Idiopathic Pulmonary Fibrosis (INSPIRE): A Multicentre, Randomised, Placebo-Controlled Trial. Lancet 2009;374:222-8. doi:10.1016/S0140-6736(09)60551-1.
35. Shi-Wen X, Denton CP, Dashwood MR, Holmes AM, Bou-Gharios G, Pearson JD, et al. Fibroblast Matrix Gene Expression and Connective Tissue Remodeling: Role of Endothelin-1. J Investig Derm 2001;116:417-25. doi:10.1046/J.1523-1747.2001.01256.X.
36. Park SH, Saleh D, Giaid A, Michel RP. Increased Endothelin-1 in Bleomycin-Induced Pulmonary Fibrosis and the Effect of an Endothelin Receptor Antagonist. Am J Respir Crit Care Med 1997;156:600-8. doi:10.1164/AJRCCM.156.2.9607123.
37. Ross B, D'Orléans-Juste P, Giaid A. Potential Role of Endothelin-1 in Pulmonary Fibrosis. https://doi.org/10.1165/rcmb.2009-0175TR2012,42,16–20,doi:10.1165/RCMB.2009-0175TR.
38. Fonseca C, Abraham D, Renzoni EA. Endothelin in Pulmonary Fibrosis. Am J Respir Cell Mol Biol 2011;44:1-10. doi:10.1165/RCMB.2009-0388TR.
39. King TE, Behr J, Brown KK, Du Bois RM, Lancaster L, De Andrade J.A, et al. BUILD-1: A Randomized Placebo-Controlled Trial of Bosentan in Idiopathic Pulmonary Fibrosis. https://doi.org/10.1164/rccm.200705-732OC 2012, 177, 75–81, doi:10.1164/RCCM.200705-732OC.

40. King TE, Brown KK, Raghu G, Du Bois RM, Lynch DA, Martinez F, et al. BUILD-3: A Randomized, Controlled Trial of Bosentan in Idiopathic Pulmonary Fibrosis. https://doi.org/10.1164/rccm.201011-1874OC 2012, 184, 92–99, doi:10.1164/RCCM.201011-1874OC.
41. Raghu G, Behr J, Brown KK, Egan JJ, Kawut SM, Flaherty KR, et al. Treatment of Idiopathic Pulmonary Fibrosis with Ambrisentan: A Parallel, Randomized Trial. Ann Intern Med 2013;158:641-9. doi:10.7326/0003-4819-158-9-201305070-00003.
42. Raghu G, Million-Rousseau R, Morganti A, Perchenet L, Behr J, Goh N, et al. Macitentan for the Treatment of Idiopathic Pulmonary Fibrosis: The Randomised Controlled MUSIC Trial. Eur Respir J 2013;42:1622-32. doi:10.1183/09031936.00104612.
43. Ghofrani HA, Wiedemann R, Rose F, Schermuly RT, Olschewski H, Weissmann N, et al. Sildenafil for Treatment of Lung Fibrosis and Pulmonary Hypertension: A Randomised Controlled Trial. Lancet 2002;360:895-900. doi:10.1016/S0140-6736(02)11024-5.
44. Idiopathic Pulmonary Fibrosis Clinical Research Network; Zisman DA, Schwarz M, Anstrom KJ, Collard HR, Flaherty KR, Hunninghake GW. A Controlled Trial of Sildenafil in Advanced Idiopathic Pulmonary Fibrosis. N Engl J Med 2010;363:620-8. doi:10.1056/NEJMoa1002110.
45. Iyer SN, Margolin SB, Hyde DM, Giri SN. Lung Fibrosis Is Ameliorated by Pirfenidone Fed in Diet after the Second Dose in a Three-Dose Bleomycin-Hamster Model. Exp Lung Res 1998;24:119-33. doi:10.3109/01902149809046058.
46. Molina-Molina M, Machahua-Huamani C, Vicens-Zygmunt V, Llatjós R, Escobar I, Sala-Llinas E, et al. Anti-Fibrotic Effects of Pirfenidone and Rapamycin in Primary IPF Fibroblasts and Human Alveolar Epithelial Cells. BMC Pulm Med 2018;18. doi:10.1186/S12890-018-0626-4.
47. Jin J, Togo S, Kadoya K, Tulafu M, Namba Y, Iwai M, et al. Pirfenidone Attenuates Lung Fibrotic Fibroblast Responses to Transforming Growth Factor-B1. Respir Res 2019;20. doi:10.1186/S12931-019-1093-Z.
48. Raghu G, Johnson, WC, Lockhart D, Mageto Y. Treatment of Idiopathic Pulmonary Fibrosis with a New Antifibrotic Agent, Pirfenidone: Results of a Prospective, Open-Label Phase II Study. Am J Respir Crit Care Med 1999;159:1061-9. doi:10.1164/AJRCCM.159.4.9805017.
49. Nagai S, Hamada K, Shigematsu M, Taniyama M, Yamauchi S, Izumi T. Open-Label Compassionate Use One Year-Treatment with Pirfenidone to Patients with Chronic Pulmonary Fibrosis. Internal Med 2002;41:1118-23. doi:10.2169/INTERNALMEDICINE.41.1118.
50. Azuma A, Nukiwa T, Tsuboi E, Suga M, Abe S, Nakata K, et al. Double-Blind, Placebo-Controlled Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis. Am J Respir Crit Care Med 2005;171:1040-7. doi:10.1164/RCCM.200404-571OC.
51. Taniguchi H, Ebina M, Kondoh Y, Ogura T, Azuma A, Suga MT, et al. Pirfenidone in Idiopathic Pulmonary Fibrosis. Eur Respir J 2010;35:821-9. doi:10.1183/09031936.00005209.
52. Noble PW, Albera C, Bradford WZ, Costabel U, Glassberg MK, Kardatzke D, et al. Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis (CAPACITY): Two Randomised Trials. Lancet 2011;377:1760-9. doi:10.1016/S0140-6736(11)60405-4.
53. King TE, Bradford WZ, Castro-Bernardini S, Fagan EA, Glaspole I, Glassberg MK, et al. A Phase 3 Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis. New England J Med 2014;370:2083-92. doi:10.1056/NEJMOA1402582.
54. Noble PW, Albera C, Bradford WZ, Costabel U, Bois RMD, Fagan EA, et al. Pirfenidone for Idiopathic Pulmonary Fibrosis: Analysis of Pooled Data from Three Multinational Phase 3 Trials. Eur Respir J 2016;47:243-53. doi:10.1183/13993003.00026-2015.
55. Cottin V, Maher T. Long-Term Clinical and Real-World Experience with Pirfenidone in the Treatment of Idiopathic Pulmonary Fibrosis. Eur Respir Rev 2015;24:58-64. doi:10.1183/09059180.00011514.
56. Gulati S, Luckhardt TR. Updated Evaluation of the Safety, Efficacy and Tolerability of Pirfenidone in the Treatment of Idiopathic Pulmonary Fibrosis. Drug Healthc Patient Saf 2020;12:85-94. doi:10.2147/DHPS.S224007.
57. Lancaster LH, de Andrade JA, Zibrak JD, Padilla ML, Albera C, Nathan SD, et al. Pirfenidone Safety and Adverse Event Management in Idiopathic Pulmonary Fibrosis. Eur Respir Rev 2017;26. doi:10.1183/16000617.0057-2017.
58. Garneau-Tsodikova S, Thannickal V. Protein Kinase Inhibitors in the Treatment of Pulmonary Fibrosis. Curr Med Chem 2008;15:2632-40. doi:10.2174/092986708785908969.
59. Buchdunger E, O'Reilly T, Wood J. Pharmacology of Imatinib (STI571). Eur J Cancer 2002;38:S28–S36. doi:10.1016/S0959-8049(02)80600-1.
60. Daniels CE, Lasky JA, Limper AH, Mieras K, Gabor E, Schroeder DR, et al. Imatinib Treatment for Idiopathic Pulmonary Fibrosis: Randomized Placebo-Controlled Trial Results. Am J Respir Crit Care Med 2010;181:604-10. doi:10.1164/RCCM.200906-0964OC.
61. Chaudhary NI, Roth GJ, Hilberg F, Müller-Quernheim J, Prasse A, Zissel G, et al. Inhibition of PDGF, VEGF and FGF Signalling Attenuates Fibrosis. Eur Respir J 2007;29:976-85. doi:10.1183/09031936.00152106.
62. Wollin L, Maillet I, Quesniaux V, Holweg A, Ryffel B. Antifibrotic and Anti-Inflammatory Activity of the Tyrosine Kinase Inhibitor Nintedanib in Experimental Models of Lung Fibrosis. J Pharmac Exper Ther 2014;349:209-20. doi:10.1124/JPET.113.208223.
63. Hilberg F, Roth GJ, Krssak M, Kautschitsch S, Sommergruber W, Tontsch-Grunt U, et al. BIBF 1120: Triple Angiokinase Inhibitor with Sustained

Receptor Blockade and Good Antitumor Efficacy. Cancer Res 2008;68:4774-82. doi:10.1158/0008-5472.CAN-07-6307.
64. Richeldi L, Costabel U, Selman M, Kim DS, Hansell DM, Nicholson AG, et al. Efficacy of a Tyrosine Kinase Inhibitor in Idiopathic Pulmonary Fibrosis. N Engl J Med 2011;365:1079-87. doi:10.1056/NEJMOA1103690.
65. Vancheri C, Kreuter M, Richeldi L, Ryerson CJ, Valeyre D, Grutters JC, et al. Nintedanib with Add-on Pirfenidone in Idiopathic Pulmonary Fibrosis: Results of the INJOURNEY Trial. Am J Respir Crit Care Med 2018;197:356-63. doi:10.1164/RCCM.201706-1301OC.
66. Https://Www.Clinicaltrials.Gov/.
67. Raghu G, Remy-Jardin M, Richeldi L, Thomson CC, Inoue, Y Johkoh T, et al. Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults: An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med 2022;205:e18-e47. doi:10.1164/rccm.202202-0399ST.
68. Zulfikar S, Mulholland,S, Adamali H, Barratt SL. Inhibitors of the Autotaxin-Lysophosphatidic Acid Axis and Their Potential in the Treatment of Interstitial Lung Disease: Current Perspectives. Clin Pharmacol 2020;2:97-108. doi:10.2147/CPAA.S228362.
69. Tager AM, LaCamera P, Shea BS, Campanella GS, Selman M, Zhao Z, et al. The Lysophosphatidic Acid Receptor LPA1 Links Pulmonary Fibrosis to Lung Injury by Mediating Fibroblast Recruitment and Vascular Leak. Nat Med 2008;14:45-54. doi:10.1038/nm1685.
70. Oikonomou N, Mouratis MA, Tzouvelekis A, Kaffe E, Valavanis C, Vilaras G, et al. Pulmonary Autotaxin Expression Contributes to the Pathogenesis of Pulmonary Fibrosis. Am J Respir Cell Mol Biol 2012;47:566-74. doi:10.1165/rcmb.2012-0004OC.
71. Ninou I, Magkrioti C, Aidinis V. Autotaxin in Pathophysiology and Pulmonary Fibrosis. Front Med (Lausanne) 2018;5. doi:10.3389/fmed.2018.00180.
72. Maher TM, van der Aar EM, Van de Steen O, Allamassey L, Desrivot J, Dupont S, et al. Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of GLPG1690, a Novel Autotaxin Inhibitor, to Treat Idiopathic Pulmonary Fibrosis (FLORA): A Phase 2a Randomised Placebo-Controlled Trial. Lancet Respir Med 2018;6:627-35. doi:10.1016/S2213-2600(18)30181-4.
73. Maher TM, Ford P, Brown KK, Costabel U, Cottin V, Danoff SK, et al. Ziritaxestat, a Novel Autotaxin Inhibitor, and Lung Function in Idiopathic Pulmonary Fibrosis. JAMA 2023;329:1567. doi:10.1001/jama.2023.5355.
74. Gill MW, Lakshmi S, Cheng PTW, Murphy BJ, Chadwick K, Lehman-McKeeman L, et al. BMS-986278, an LPA1 Receptor Antagonist for Idiopathic Pulmonary Fibrosis: Preclinical Assessments of Potential Hepatobiliary Toxicity, American Thoracic Society 2019; A5882-A5882.
75. Corte TJ, Lancaster L, Swigris JJ, Maher TM, Goldin JG, Palmer SM, et al. Phase 2 Trial Design of BMS-986278, a Lysophosphatidic Acid Receptor 1 (LPA_1) Antagonist, in Patients with Idiopathic Pulmonary Fibrosis (IPF) or Progressive Fibrotic Interstitial Lung Disease (PF-ILD). BMJ Open Respir Res 2021;8:e001026. doi:10.1136/bmjresp-2021-001026.
76. Corte TJ, Cottin V, Glassberg MK, Kreuter M, Ogura T, Suda T, et al. BMS-986278, an Oral Lysophosphatidic Acid Receptor 1 (LPA1) Antagonist, for Patients With Idiopathic Pulmonary Fibrosis: Results From a Phase 2 Randomized Trial, American Thoracic Society 2023;A2785-A2785.
77. Pelaia C, Crimi C, Vatrella A, Tinello C, Terracciano R, Pelaia G. Molecular Targets for Biological Therapies of Severe Asthma. Front Immunol 2020;11. doi:10.3389/fimmu.2020.603312.
78. Singh S, Kumar NK, Dwiwedi P, Charan J, Kaur R, Sidhu P, et al. Monoclonal Antibodies: A Review. Curr Clin Pharmacol 2018;13:85-99. doi:10.2174/1574884712666170809124728.
79. Lipson KE, Wong C, Teng Y, Spong S. CTGF Is a Central Mediator of Tissue Remodeling and Fibrosis and Its Inhibition Can Reverse the Process of Fibrosis. Fibrogenesis Tissue Repair 2012;5:S24. doi:10.1186/1755-1536-5-S1-S24.
80. Richeldi L, Fernández Pérez ER, Costabel U, Albera C, Lederer DJ, Flaherty KR, et al. Pamrevlumab, an Anti-Connective Tissue Growth Factor Therapy, for Idiopathic Pulmonary Fibrosis (PRAISE): A Phase 2, Randomised, Double-Blind, Placebo-Controlled Trial. Lancet Respir Med 2020;8:25-33. doi:10.1016/S2213-2600(19)30262-0.
81. FibroGen, I. FibroGen Announces Topline Results from Phase 3 ZEPHYRUS-1 Study of Pamrevlumab for the Treatment of Idiopathic Pulmonary Fibrosis.
82. Pilling D, Galvis-Carvajal E, Karhadkar TR, Cox N, Gomer RH. Monocyte Differentiation and Macrophage Priming Are Regulated Differentially by Pentraxins and Their Ligands. BMC Immunol 2017;18:30. doi:10.1186/s12865-017-0214-z.
83. Castaño AP, Lin SL, Surowy T, Nowlin BT, Turlapati SA, Patel T, et al. Serum Amyloid P Inhibits Fibrosis Through FcγR-Dependent Monocyte-Macrophage Regulation in Vivo. Sci Transl Med 2009;1. doi:10.1126/scitranslmed.3000111.
84. Raghu G, van den Blink, B, Hamblin, M.J, Brown, A.W, Golden, J.A, Ho, et al. Effect of Recombinant Human Pentraxin 2 vs Placebo on Change in Forced Vital Capacity in Patients With Idiopathic Pulmonary Fibrosis. JAMA 2018;319:2299. doi:10.1001/jama.2018.6129.
85. Podolanczuk AJ, Richeldi L, Martinez FJ. The Future of Clinical Trials in Idiopathic Pulmonary Fibrosis. JAMA 2023;329:1554. doi:10.1001/jama.2022.23955.
86. Martinez FJ, Yow E, Flaherty KR, Snyder LD, Durheim MT, Wisniewski SR, et al. Effect of Antimicrobial Therapy on Respiratory Hospitalization or Death in Adults With Idiopathic Pulmonary Fibrosis. JAMA 2021;325:1841. doi:10.1001/jama.2021.4956.

87. Raghu G, Ghazipura M, Fleming TR, Aronson KI, Behr J, Brown KK, et al. Meaningful Endpoints for Idiopathic Pulmonary Fibrosis (IPF) Clinical Trials: Emphasis on "Feels, Functions, Survives." Am J Respir Crit Care Med 2024;209(6):647-69. doi:10.1164/rccm.202312-2213SO.
88. Worndl E, Hunt EB, Kennedy MP, Henry MT, Plant BJ, Murphy DM. Roflumilast in COPD. Chest 2015;148:e31. doi:10.1378/CHEST.15-0664.
89. Gooderham M, Papp K. Selective Phosphodiesterase Inhibitors for Psoriasis: Focus on Apremilast. BioDrugs 2015;29:327-39. doi:10.1007/S40259-015-0144-3.
90. McDowell L, Olin B. Crisaborole: A Novel Nonsteroidal Topical Treatment for Atopic Dermatitis. J Pharm Technol 2019;35:172-78. doi:10.1177/8755122519844507.
91. Azevedo MF, Faucz FR, Bimpaki E, Horvath A, Levy I, de Alexandre RB, et al. Clinical and Molecular Genetics of the Phosphodiesterases (PDEs). Endocr Rev 2014;35:195-233. doi:10.1210/er.2013-1053.
92. Pan JB, Hou YH, Zhang GJ. Rolipram Attenuates Bleomycin A5-induced Pulmonary Fibrosis in Rats. Respirology 2009;14:975-82. doi:10.1111/j.1440-1843.2009.01606.x.
93. Cortijo J, Iranzo A, Milara X, Mata M, Cerdá-Nicolás M, Ruiz-Saurí A, et al. Roflumilast, a Phosphodiesterase 4 Inhibitor, Alleviates Bleomycin-induced Lung Injury. Br J Pharmacol 2009;156:534-44. doi:10.1111/j.1476-5381.2008.00041.x.
94. Kohyama T, Liu X, Wen FQ, Kobayashi T, Fang Q, Abe S, et al. Cytokines Modulate Cilomilast Response in Lung Fibroblasts. Clinical Immunology 2004;111:297-302. doi:10.1016/j.clim.2004.01.007.
95. Herrmann FE, Hesslinger C, Wollin L, Nickolaus P. BI 1015550 Is a PDE4B Inhibitor and a Clinical Drug Candidate for the Oral Treatment of Idiopathic Pulmonary Fibrosis. Front Pharmacol 2022;13. doi:10.3389/fphar.2022.838449.
96. Richeldi L, Azuma A, Cottin V, Kreuter M, Maher TM, Martinez FJ, et al. Design of a Phase III, Double-Blind, Randomised, Placebo-Controlled Trial of BI 1015550 in Patients with Idiopathic Pulmonary Fibrosis (FIBRONEER-IPF). BMJ Open Respir Res 2023;10:e001563. doi:10.1136/bmjresp-2022-001563.
97. Richeldi L, Azuma A, Cottin V, Hesslinger C, Stowasser S, Valenzuela C, et al. Trial of a Preferential Phosphodiesterase 4B Inhibitor for Idiopathic Pulmonary Fibrosis. New England J Med 2022;386:2178-87. doi:10.1056/NEJMoa2201737.
98. Richeldi L, Azuma A, Cottin V, Hesslinger C, Stowasser S, Valenzuela C, et al. Additive Effect of BI 1015550 and Nintedanib in Patients with IPF. In Proceedings of the 12.01 - Idiopathic interstitial pneumonias; European Respiratory Society, September 4 2022;4606.
99. Cazzola M, Calzetta L, Rogliani P, Matera MG. The Discovery of Roflumilast for the Treatment of Chronic Obstructive Pulmonary Disease. Expert Opin Drug Discov 2016;11:733-44. doi:10.1080/17460441.2016.1184642.
100. Lee YJ, Choi SM, Lee YJ, Cho YJ, Yoon H Il; Lee JH, et al. Clinical Impact of Depression and Anxiety in Patients with Idiopathic Pulmonary Fibrosis. PLoS One 2017;12. doi:10.1371/JOURNAL.PONE.0184300.
101. Edwards GD, Polgar O, Patel S, Barker RE, Walsh JA, Harvey J, et al. Mood Disorder in Idiopathic Pulmonary Fibrosis: Response to Pulmonary Rehabilitation. ERJ Open Res 2023;9. doi:10.1183/23120541.00585-2022.
102. Torrisi SE, Vancheri A, Pavone M, Sambataro G, Palmucci S, Vancheri C. Comorbidities of IPF: How Do They Impact on Prognosis. Pulm Pharmacol Ther 2018;53:6-11. doi:10.1016/J.PUPT.2018.09.003.
103. Nathan SD, King CS. Treatment of Pulmonary Hypertension in Idiopathic Pulmonary Fibrosis: Shortfall in Efficacy or Trial Design? Drug Des Devel Ther 2014;8:875. doi:10.2147/DDDT.S64907.
104. Lettieri CJ, Nathan SD, Barnett SD, Ahmad S, Shorr AF. Prevalence and Outcomes of Pulmonary Arterial Hypertension in Advanced Idiopathic Pulmonary Fibrosis. Chest 2006;129:746-52. doi:10.1378/CHEST.129.3.746.
105. Nikkho SM, Richter MJ, Shen E, Abman SH, Antoniou K, Chung J, et al. Clinical Significance of Pulmonary Hypertension in Interstitial Lung Disease: A Consensus Statement from the Pulmonary Vascular Research Institute's Innovative Drug Development Initiative-Group 3 Pulmonary Hypertension. Pulm Circ 2022;12. doi:10.1002/PUL2.12127.
106. Behr J, Nathan SD, Wuyts WA, Mogulkoc Bishop N, Bouros DE, Antoniou K, et al. Efficacy and Safety of Sildenafil Added to Pirfenidone in Patients with Advanced Idiopathic Pulmonary Fibrosis and Risk of Pulmonary Hypertension: A Double-Blind, Randomised, Placebo-Controlled, Phase 2b Trial. Lancet Respir Med 2021;9:85-95. doi:10.1016/S2213-2600(20)30356-8.
107. Nathan SD, Flaherty KR, Glassberg MK, Raghu G, Swigris J, Alvarez R, et al. A Randomized, Double-Blind, Placebo-Controlled Study of Pulsed, Inhaled Nitric Oxide in Subjects at Risk of Pulmonary Hypertension Associated With Pulmonary Fibrosis. Chest 2020;158:637-45. doi:10.1016/J.CHEST.2020.02.016.
108. Nathan SD, Behr J, Collard HR, Cottin V, Hoeper MM, Martinez FJ, et al. Riociguat for Idiopathic Interstitial Pneumonia-Associated Pulmonary Hypertension (RISE-IIP): A Randomised, Placebo-Controlled Phase 2b Study. Lancet Respir Med 2019;7:780-90. doi:10.1016/S2213-2600(19)30250-4.
109. Waxman A, Restrepo-Jaramillo R, Thenappan T, Ravichandran A, Engel P, Bajwa A, et al. Inhaled Treprostinil in Pulmonary Hypertension Due to Interstitial Lung Disease. N Engl J Med 2021;384:325-34. doi:10.1056/NEJMOA2008470.
110. Whittle BJ, Silverstein AM, Mottola DM, Clapp LH. Binding and Activity of the Prostacyclin Receptor (IP) Agonists, Treprostinil and Iloprost, at Human Prostanoid Receptors: Treprostinil Is a Potent DP1 and EP2 Agonist. Biochem Pharmacol 2012;84:68-75. doi:10.1016/J.BCP.2012.03.012.

111. Nathan SD, Waxman A, Rajagopal S, Case A, Johri S, DuBrock H, et al. Inhaled Treprostinil and Forced Vital Capacity in Patients with Interstitial Lung Disease and Associated Pulmonary Hypertension: A Post-Hoc Analysis of the INCREASE Study. Lancet Respir Med 2021;9:1266-74. doi:10.1016/S2213-2600(21)00165-X.
112. Nathan SD, Behr J, Cottin V, Lancaster L, Smith P, Deng CQ, et al. Study Design and Rationale for the TETON Phase 3, Randomised, Controlled Clinical Trials of Inhaled Treprostinil in the Treatment of Idiopathic Pulmonary Fibrosis. BMJ Open Respir Res 2022;9. doi:10.1136/BMJRESP-2022-001310.
113. Müller S, Zeidler C, Ständer S. Chronic Prurigo Including Prurigo Nodularis: New Insights and Treatments. Am J Clin Dermatol 2023;25(1):15-33. doi:10.1007/S40257-023-00818-Z.
114. Kitko CL, Arora M, Defilipp Z, Zaid MA, Di Stasi A, Radojcic V, et al. Axatilimab for Chronic Graft-Versus-Host Disease After Failure of at Least Two Prior Systemic Therapies: Results of a Phase I/II Study. J Clin Oncol 2023;41:1864-75. doi:10.1200/JCO.22.00958.
115. Oldham JM, Ma SF, Martinez FJ, Anstrom KJ, Raghu G, Schwartz DA, et al. TOLLIP, MUC5B, and the Response to N-Acetylcysteine among Individuals with Idiopathic Pulmonary Fibrosis. Am J Respir Crit Care Med 2015;192:1475-82. doi:10.1164/RCCM.201505-1010OC.
116. Noth I, Zhang Y, Ma SF, Flores C, Barber M, Huang Y, et al. Genetic Variants Associated with Idiopathic Pulmonary Fibrosis Susceptibility and Mortality: A Genome-Wide Association Study. Lancet Respir Med 2013;1:309-17. doi:10.1016/S2213-2600(13)70045-6.
117. Trujillo G, Meneghin A, Flaherty KR, Sholl LM, Myers JL, Kazerooni EA, et al. TLR9 Differentiates Rapidly from Slowly Progressing Forms of Idiopathic Pulmonary Fibrosis. Sci Transl Med 2010;2. doi:10.1126/SCITRANSLMED.3001510.
118. Russell AM, Adamali H, Molyneaux PL, Lukey PT, Marshall RP, Renzoni EA, et al. Daily Home Spirometry: An Effective Tool for Detecting Progression in Idiopathic Pulmonary Fibrosis. Am J Respir Crit Care Med 2016;194:989-97. doi:10.1164/RCCM.201511-2152OC.
119. Zhao C, Yin Y, Zhu C, Zhu M, Ji T, Li Z, et al. Drug Therapies for Treatment of Idiopathic Pulmonary Fibrosis: A Systematic Review, Bayesian Network Meta-Analysis, and Cost-Effectiveness Analysis. EClinical Medicine 2023;61. doi:10.1016/J.ECLINM.2023.102071.
120. Raghu G, Rochwerg B, Zhang Y, Garcia CAC, Azuma A, Behr J, et al. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline: Treatment of Idiopathic Pulmonary Fibrosis. An Update of the 2011 Clinical Practice Guideline. Am J Respir Crit Care Med 2015;192:e3-e19. doi:10.1164/RCCM.201506-1063ST.
121. Lancaster LH, de Andrade JA, Zibrak JD, Padilla ML, Albera C, Nathan SD, et al. Pirfenidone Safety and Adverse Event Management in Idiopathic Pulmonary Fibrosis. Eur Respir Rev 2017;26. doi:10.1183/16000617.0057-2017.
122. West A, Chaudhuri N, Barczyk A, Wilsher ML, Hopkins P, Glaspole I, et al. Inhaled Pirfenidone Solution (AP01) for IPF: A Randomised, Open-Label, Dose-Response Trial. Thorax 2023;78(9):882-9. doi:10.1136/thorax-2022-219391.
123. Vigeland CL, Hughes AH, Horton MR. Etiology and Treatment of Cough in Idiopathic Pulmonary Fibrosis. Respir Med 2017;123:98-104. doi:10.1016/j.rmed.2016.12.016.
124. Biondini D, Balestro E, Sverzellati N, Cocconcelli E, Bernardinello N, Ryerson CJ, et al. Acute Exacerbations of Idiopathic Pulmonary Fibrosis (AE-IPF): An Overview of Current and Future Therapeutic Strategies. Expert Rev Respir Med 2020;14:405-14. doi:10.1080/17476348.2020.1724096.
125. Janowiak P, Szymanowska-Narloch A, Siemi-ska A. IPF Respiratory Symptoms Management — Current Evidence. Front Med (Lausanne) 2022;9. doi:10.3389/fmed.2022.917973.
126. Kondoh Y, Cottin V, Brown KK. Recent Lessons Learned in the Management of Acute Exacerbation of Idiopathic Pulmonary Fibrosis. Eur Respir Rev 2017;26:170050. doi:10.1183/16000617.0050-2017.
127. Key AL, Holt K, Hamilton A, Smith JA, Earis JE. Objective Cough Frequency in Idiopathic Pulmonary Fibrosis. Cough 2010;6. doi:10.1186/1745-9974-6-4.
128. Hope-Gill BDM, Hilldrup S, Davies C, Newton RP, Harrison NK. A Study of the Cough Reflex in Idiopathic Pulmonary Fibrosis. Am J Respir Crit Care Med 2003;168:995-1002. doi:10.1164/RCCM.200304-597OC.
129. Martinez FJ, Afzal AS, Smith JA, Ford AP, Li JJ, Li Y, et al. Treatment of Persistent Cough in Subjects with Idiopathic Pulmonary Fibrosis (IPF) with Gefapixant, a P2X3 Antagonist, in a Randomized, Placebo-Controlled Clinical Trial. Pulm Ther 2021;7:471. doi:10.1007/S41030-021-00162-9.
130. Visca D, Beghè B, Fabbri LM, Papi A, Spanevello A. Management of Chronic Refractory Cough in Adults. Eur J Intern Med 2020;81. doi:10.1016/J.EJIM.2020.09.008.
131. Maher TM, Forbes W, Bortey E, Sciascia T. An Interim Analysis of a Phase 2 Trial Evaluating Oral Nalbuphine Extended Release for Treating Chronic Cough in Idiopathic Pulmonary Fibrosis. Eur Respir J 2022;60:4404. doi:10.1183/13993003.CONGRESS-2022.4404.
132. Churg A, Müller NL, Silva CIS, Wright JL. Acute Exacerbation (Acute Lung Injury of Unknown Cause) in UIP and Other Forms of Fibrotic Interstitial Pneumonias. Am J Surg Pathol 2007;31:277-84. doi:10.1097/01.PAS.0000213341.70852.9D.

133. Naccache JM, Jouneau S, Didier M, Borie R, Cachanado M, Bourdin A, et al. Cyclophosphamide Added to Glucocorticoids in Acute Exacerbation of Idiopathic Pulmonary Fibrosis (EXAFIP): A Randomised, Double-Blind, Placebo-Controlled, Phase 3 Trial. Lancet Respir Med 2022;10:26-34. doi:10.1016/S2213-2600(21)00354-4.

134. Kulkarni T, Valentine VG, Fei, F, Tran-Nguyen TK, Quesada-Arias LD, Mkorombindo T, et al. Correlates of Survival after Autoantibody Reduction Therapy for Acute IPF Exacerbations. PLoS One 2021;16. doi:10.1371/JOURNAL.PONE.0260345.

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Case Report

OPEN ACCESS

Effective treatment with oral Salbutamol on late onset respiratory impairment in a DOK7 Congenital Myasthenia Syndrome: a case report

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ABSTRACT

Introduction: DOK7 gene deficiency is a neuromuscular disease with an alteration in post-synaptic neuromuscular junction, leading to progressive respiratory impairment. Although, the therapy is not standardized, adrenergic agonists are suggested as first-line treatment.

Case presentation: Our patient had an ambiguous late childhood-onset and had a generalized muscle weakness free of respiratory symptoms during the early phase of the disease. Subsequently, when the respiratory muscle and the diaphragm involvement was impaired, a substantial loss of respiratory function with hypopneas and severe desaturation was detected. It was noteworthy the striking respiratory beneficial impact of oral salbutamol in the resolution of symptoms and functional impairments, leading to a remarkable respiratory improvement and a better quality of life.

Conclusion: Oral salbutamol treatment combined to a timely clinical recognition led to an outstanding respiratory improvement

Key words: Congenital Myasthenia Syndrome, *f*dl, myopathy, DOK7, respiratory insufficiency

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Introduction

Congenital myasthenic syndromes (CMSs) are a genotypically and phenotypically heterogeneous group of neuromuscular disorders, which have in common an impaired neuromuscular transmission. Specifically, CMS in DOK7 gene deficiency is a neuromuscular disease with an alteration in post-synaptic neuromuscular junction. The typical disease onset is in the second year of life, displaying ptosis, limb-girdle weakness, frequent falls or gait waddling and progressive respiratory dysfunction [1]. Actually, the therapy prescribed is oral salbutamol, which has been associated to an improvement of DOK7 CMS [2]. We describe a tricky case of CMS with an adulthood-onset respiratory impairment, which is a rare condition, completely solved by oral salbutamol administration.

Case presentation

In 2018, a 22-year-old man referred to our pulmonary clinic for evaluation of recent onset of dyspnea on exertion, night loud snoring, sudden arousal during sleep, morning headache, daytime sleepiness. He reported, also, a late childhood-onset (around seven years old) of remarkable history of fatigue, muscle contractures, fasciculations, general weakness and difficulty in climbing stairs with a diagnosis of unspecific dystrophy, never investigated. The symptoms were not fluctuating. He never had the ability to run. During the visit the general examination showed bilateral ptosis without ophthalmoplegia or dysmorphic characteristics, nasal speech, dysphonia, upper and lower limb-girdle muscular weakness, diffuse hypotonia and hypotrophy. Body Mass Index (BMI) was normal 21,0 kg/m². On the other hand, Epworth sleepiness scale (ESS): 11/24 and STOP-Bang Questionnaire: 4/8 underlined a high risk for sleep apnoea. Blood tests were normal except for Creatine phosphokinasi (CPK) 474 U/L, Mioglobine 80.440 μg/L. The pulmonary function tests (PFTs) measured Total Lung Capacity (TLC) 84%, Forced Vital Capacity (FVC) 73% and no significant volume reduction in lying 30° position was recorded. Diffusing Capacity of Carbon Monoxide (DL_{CO}) 86% and the Krogh factor 121% were normal. On the contrary, the maximal inspiratory (MIP) and expiratory pressure (MEP) were remarkable lower, respectively 60 cmH_2O e 53 cmH_2O. The blood gas analysis, performed in room air, highlighted a compensated metabolic alkalosis with normoxaemia. Overnight home respiratory polygraphy showed a hypoventilation pattern with severe desaturation. The cardiopulmonary exercise test assessed a reduced exercise tolerance with muscle exhaustion at workloads reduced than predicted, although normal ventilatory efficiency and lactate threshold within age limits. Finally, the diaphragmatic ultrasound, performed with a convex probe in lying 30° position, assessed a reduced excursion (2 cm). After the clinical evaluation he was labeled as myopathy, non-invasive ventilation (NIV) was prescribed and settled, in order to improve his nocturnal respiratory pattern and a neurological consultation was required. In the meantime, muscle biopsy revealed nonspecific myopathic changes and the neurologist started a pharmacological therapy with Pyridostigmine 30 mg three times daily. By this time, oral Pyridostigmine was administered for six months and, during our second evaluation, was reported worsening of all systemic and respiratory symptoms. The patients presented frequent falls, gait difficulties, impossibility in daily activities and a critical respiratory deterioration. Meanwhile, the genetic sequencing revealed a Congenital Myasthenia Syndrome (CMS) with DOK7 (downstream of tyrosine kinase 7) gene mutation. With this scenario, the multidisciplinary team (pulmonologist, neurologist and pharmacologist) decided to stop Pyridostigmine, in line with literature, and start a therapy with oral salbutamol 4 mg three times daily as add-on therapy with NIV. Oral salbutamol administered for at least one-month improved all symptoms. At six months of administration get better muscle weakness, daytime sleepiness, snoring, headache and dyspnea on exertion without remarkable adverse effects. The blood gas analysis showed a normal acid-basic balance with normoxaemia. Moreover, respiratory muscle strength tests were normalized, respectively MIP 90 cmH_2O and MEP 91 cmH_2O. No more nocturnal hypoventilation pattern was seen at overnight respiratory polygraphy and, finally, the cardiopulmonary exercise test showed normal oxygen cost of work ($\Delta V'O2/\Delta power$: 11.06 ml/min/W), with linear growth pattern.

Discussion

Congenital Myasthenia Syndromes (CMSs) [1, 3, 4, 9, 11] includes a group of rare neuromuscular inherited disorders, genotypically and phenotypically heterogeneous, resulting in altered encoding for presynaptic, synaptic, and postsynaptic proteins with impaired neuromuscular junction signal transmission. Due to genetic heterogeneity alterations, the therapy is not standardized, but includes cholinergic agonists (pyridostigmine and 3,4-diaminopyridine), adrenergic agonists (salbutamol/albuterol and ephedrine) and long-lived open-channel blockers of acetylcholine receptor ion channel (fluoxetine and quinidine). A genetic diagnosis is highly recommended before starting a pharmacologic treatment, because a medication could be beneficial in one syndrome and detrimental in another genetic mutation. In fact, if anticholinesterase therapy is effective in most syndromes, it is contraindicated in endplate (EP) acetylcholinesterase (AChE) deficiency, the slow-channel syndrome, DOK7 myasthenia, and β2-laminin deficiency, that respond favorably to salbutamol, a selective β2-adrenergic agonist [2,9]. Although, the precise mechanism of action of β2-adrenergic agonists at the neuromuscular junction (NMJ) is not fully understood, their effect on the postsynaptic stabilisation of the membrane of the NMJ was demonstrated on mice models with DOK7 CMS, showing an improved both neurotransmission and structural integrity of the NMJ and therefore an increased number of active NMJs after administration of salbutamol [9,10]. An increase in the number of detectable NMJs following treatment suggests there is enhanced stability of the synaptic structure [9, 10].

Specifically, our patient was diagnosed with CMS DOK7 gene mutation [5,6], which is involved in normal development and maintenance of the neuromuscular junction [1,7] and clinically deteriorate with cholinesterase inhibitors (Figure 1). In particular, our patient had an ambiguous late childhood-onset and had a generalized muscle weakness free of respiratory symptoms during the early phase of the disease. Subsequently, when the respiratory muscle and the diaphragm involvement was impaired, a substantial loss of respiratory function was detected. The respiratory muscle strength dysfunction was accompanied by significant hypopneas with severe desaturation, revealed during sleep study. Treatment of this patient was started, firstly, with a Pyridostigmine, with no improvement and even a worsening trend. After the genetic diagnosis was made, it was switched to oral salbutamol [8], resulting in a striking clinical and functional improvement. The combination therapy NIV and oral salbutamol achieved an early success since the first month of administration. In particularly, the respiratory muscle strength tests, MIP and MEP, which

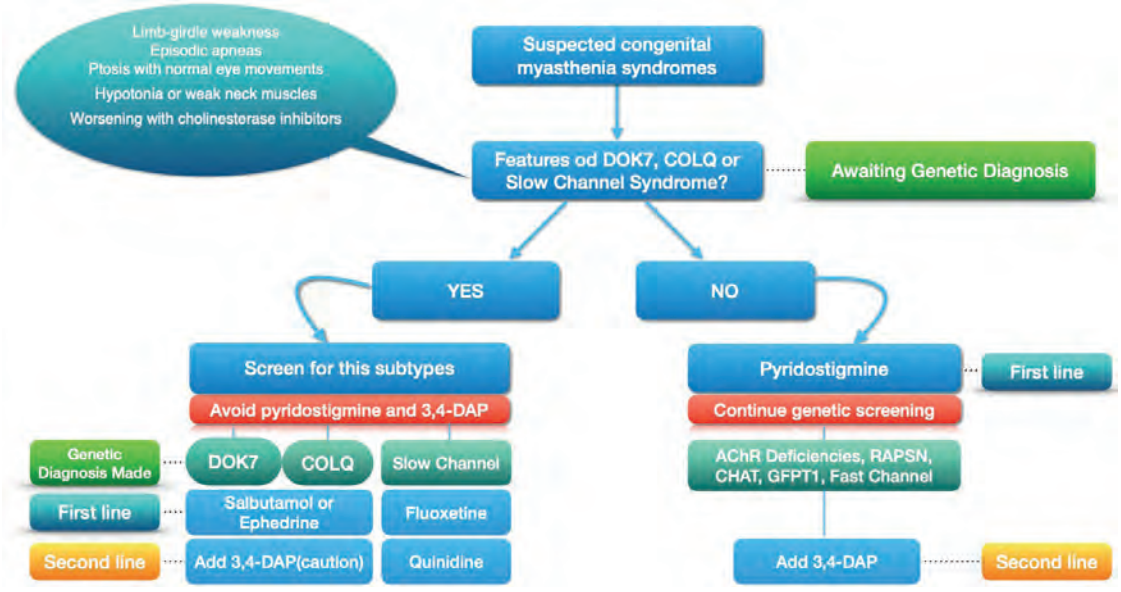

Figure 1. A systematic clinical approach and treatment strategies in different types of congenital myasthenia syndromes.

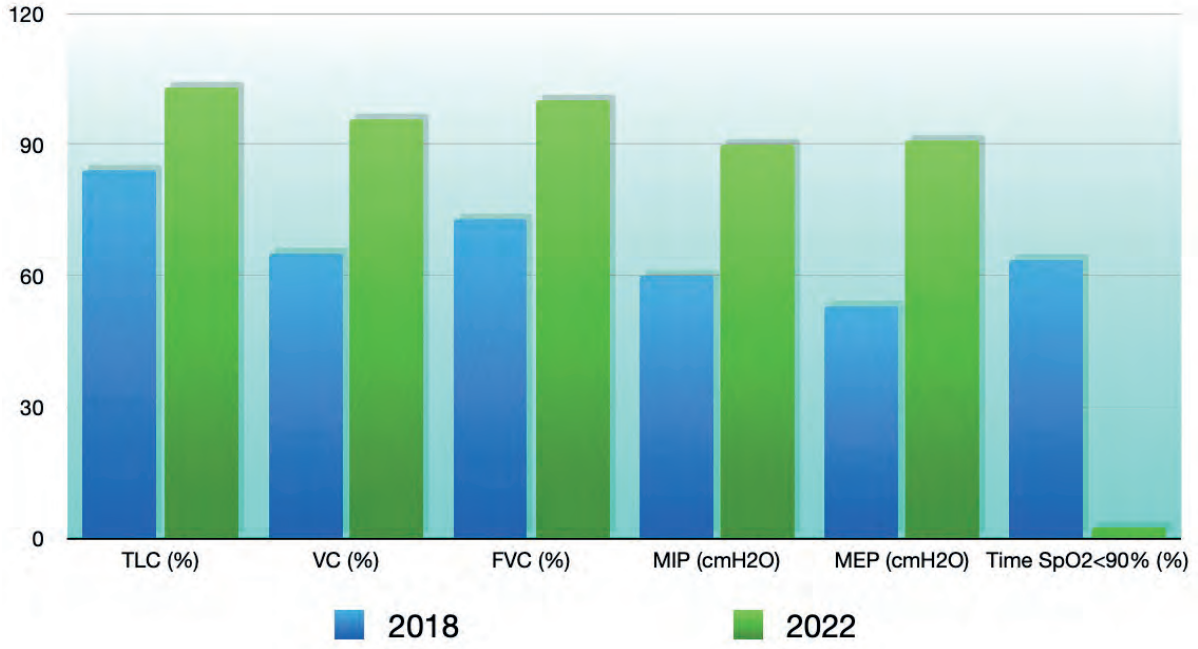

Figure 2. Comparison of the pulmonary function changes before the precise diagnosis (2018) and after constant treatment with oral salbutamol (2022).

allow a simple assessment of global respiratory muscle strength, were significantly improved demonstrating the promptly therapeutic efficacy of salbutamol. Furthermore, although the spirometric values were within normal range at baseline, we noticed a significant boost in the respiratory function testing.

At six months of follow up, pulmonary function tests (PFTs), respiratory muscle strength tests and sleep study assessed the respiratory improvement, as shown in Figure 2. After that, also the cardiopulmonary study confirmed the remarkable respiratory beneficial impact of oral salbutamol in the resolution of symptoms and functional impairments.

Conclusion

In conclusion:

- genetic diagnosis is highly recommended before starting a pharmacologic treatment, because a medication could be beneficial in one syndrome and detrimental in another;
- oral salbutamol treatment combined to a timely clinical recognition led to an outstanding respiratory improvement and a better quality of life.

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Abbreviations

BMI: Body Mass Index
CMS: Congenital myasthenic syndrome
CPK: Creatine phosphokinasi
DL_{CO}: Diffusing Capacity of Carbon Monoxide
ESS: Epworth sleepiness scale
FVC: Forced Vital Capacity
MEP: Maximal Expiratory Pressure
MIP: Maximal Inspiratory Pressure
MuSK: Muscle-Specific tyrosine Kinase
NIV: Non-invasive ventilation
NMJ: Neuromuscular junction
PFTs: Pulmonary Function Tests
TLC: Total Lung Capacity

References

1. Engel AG, Shen XM, Selcen D, Sine SM. Congenital myasthenic syndromes: pathogenesis, diagnosis, and treatment. The Lancet Neurology 2015;14(4):420–34.
2. Lorenzoni PJ, Scola RH, Kay CSK, Filla L, Miranda APP, Pinheiro JMR, et al. Salbutamol therapy in congenital my-

asthenic syndrome due to DOK7 mutation. J Neurol Sci 2013;331(1–2):155–7.
3. Finsterer J. Congenital myasthenic syndromes. Orphanet J Rare Dis 2019;14(1):57.
4. Engel AG. Congenital Myasthenic Syndromes in 2018. Curr Neurol Neurosci Rep 2018;18(8):46.
5. Johnson A, Subramony SH, Chuquilin M. Delayed diagnosis of DOK7 congenital myasthenic syndrome: Case report and literature review. Neurol Clin Pract 2018;8(6):e40–2.
6. Burke G, Hiscock A, Klein A, Niks EH, Main M, Manzur AY, et al. Salbutamol benefits children with congenital myasthenic syndrome due to DOK7 mutations. Neuromuscular Disorders 2013;23(2):170–5.
7. Klein A, Pitt MC, McHugh JC, Niks EH, Sewry CA, Phadke R, et al. DOK7 congenital myasthenic syndrome in childhood: Early diagnostic clues in 23 children. Neuromuscular Disorders 2013;23(11):883–91.
8. Lee M, Beeson D, Palace J. Therapeutic strategies for congenital myasthenic syndromes: Congenital myasthenia: therapeutic strategies. Ann NY Acad Sci 2018;1412(1):129–36.
9. Alsallum MS, Alshareef A, Abuzinadah AR, Bamaga AK, Dallol A. A novel DOK7 mutation causing congenital myasthenic syndrome with limb-girdle weakness: case series of three family members. Heliyon 2021;7(5): e06869. doi: 10.1016/j.heliyon.2021.e06869. PMID: 34027146; PMCID: PMC8120944.
10. Webster RG, Vanhaesebrouck AE, Maxwell SE, Cossins JA, Liu W, Ueta R, et al. Effect of salbutamol on neuromuscular junction function and structure in a mouse model of DOK7 congenital myasthenia. Hum Mol Genet 2020;29(14):2325-2336. doi: 10.1093/hmg/ddaa116. PMID: 32543656; PMCID: PMC7424765.
11. Ohno K, Ohkawara B, Shen XM, Selcen D, Engel AG. Clinical and Pathologic Features of Congenital Myasthenic Syndromes Caused by 35 Genes - A Comprehensive Review. Int J Mol Sci 2023; 24(4):3730.

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L'angolo della Cultura (non solo Medicina…)

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Nell'era della tecnomedicina il dottore sia più umanista

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"Penso che si debba prendere il proprio lavoro molto seriamente, senza prendere seriamente se stessi. Questa è la combinazione migliore".
Judi Dench, attrice inglese.

Come risulta da uno studio del John Hopkins Hospital negli Stati Uniti, i giovani medici dedicano a ciascun ammalato, ogni giorno, otto minuti soltanto e passano la maggior parte del tempo a compilare cartelle cliniche elettroniche, ordinare esami di laboratorio e radiologici, nonché a svolgere tutta una serie di altre attività che li tengono di fatto lontani dagli ammalati. Inoltre, stanno nella stanza di chi è ricoverato appena il 10% del loro tempo di lavoro. Davvero poco anche per gli ammalati che vedono il medico per pochissimi minuti al giorno e passano il resto della giornata a pensare a quando lo vedranno ancora. Pertanto, i medici se stanno vicino agli ammalati per così poco tempo, alla fine non avranno mai l'esperienza che serve per saper ascoltare i pazienti e discutere dei loro problemi; cose queste che aiutano moltissimo ad arrivare alla diagnosi giusta e a trovare la cura.

Ogni medico esperto sa che più tempo si passa con gli ammalati, più li si ascolta, più si parla con loro e meno si sbaglia. A riprova di ciò, ricordiamo che uno pneumologo (ma con una visione olistica della medicina), solo dopo un'attenta visita, diagnosticò ad una "asmatica" che lamentava forte dispnea, oltre l'evidente sindrome anemica grave, una marcata massa ipogastrica che si rivelò all'intervento chirurgico una neoplasia dell'utero.

I giovani medici oggi sono certamente molto più preparati di quanto non fosse chi si è laureato decine di anni fa. Qualcuno di loro ha addirittura tutta la medicina nell'iPhone e là dentro ci sono più informazioni di quante ce ne possano stare nel cervello di mille bravi dottori. Non c'è più bisogno di passare ore in biblioteca per documentarsi, e uno potrebbe pensare che adesso c'è più tempo per gli ammalati. Non è così. Anche nei nostri ospedali i giovani medici passano con ciascun ammalato al massimo otto minuti al giorno (talvolta addirittura meno); per il resto del tempo stanno seduti davanti al computer.

Altro paradosso. Mentre un tempo tutto quello che ruotava intorno al malato - dalla cartella clinica alle prescrizioni di esami e di farmaci - si faceva sulla carta, oggi i medici devono fare i conti con l'informatica senza però che ci sia, con poche eccezioni, un'organizzazione che consenta di farlo in modo efficace e in tempi ragionevoli. Il fatto è che i nostri malati vorrebbero chiederci tante cose, ma non c'è tempo e c'è l'emozione (un po' come per il sarto dei *Promessi sposi* che, troppo emozionato a vedersi davanti il cardinale Borromeo in persona, alla fine riesce a dire solo "*si figuri*"). Qualcosa però l'abbiamo guadagnato, ad esempio il "patient empowerment" (la responsabilizzazione del malato): i pazienti si informano, scelgono, possono conoscere le proprie malattie, questo

realizza una corresponsabilità positiva che permette al malato di partecipare alle scelte che lo riguardano. Un altro esempio sono i programmi per i pazienti cronici, spesso gestiti in team con la partecipazione di infermieri oltre che medici, che spostano la relazione dal singolo professionista all'équipe di riferimento, diventando così un fondamentale presidio di assistenza. La cultura, dall'arte alla letteratura, al cinema, può essere lo strumento attraverso il quale rimodulare un nuovo rapporto tra cittadini, medici e salute e ridare forza a quell'alleanza terapeutica da sempre alla base di qualsiasi cura, restituendo la dimensione umana a una vecchia arte diventata quasi scienza.

Un editoriale di qualche anno fa sul *British Medical Journal* si chiedeva se la forza dell'effetto placebo e di una buona relazione medico-paziente non fossero di per sé un trattamento tanto efficace che negarlo sarebbe non etico, così come lo sarebbe negare un antibiotico a un paziente con la polmonite. La medicina in questi ultimi decenni è sembrata prendere una strada fatta di tecnica e razionalità, ma la mancanza di tempo e di contatto umano ha fatto perdere la consapevolezza della forza della relazione medico-paziente. D'altra parte gli ospedali non prevedono relazioni, spesso gli studi dei medici sono costruiti lontano, anche a due piani di distanza dai reparti di degenza: la cura è ormai concentrata in un asettico tecnicismo. Il tempo per parlare con i pazienti, ascoltarli, capirli e assisterli non è previsto né dalla medicina basata sull'evidenza né dai moderni amministratori della sanità. Ma fare diagnosi, curare e assistere sono qualcosa di diverso. La più umanistica delle scienze ha perso per strada il patrimonio culturale dal quale nasceva, per restare schiacciata tra aziendalismi esasperati e tecnologie ultramoderne.

La professione medica è un arte dove tecnica e umanità devono coesistere, dove il rapporto medico-paziente rappresenta la relazione dinamica tra due persone in cui l'esperto soccorre chi sta male e chi sta male dà il suo consenso alle scelte curative, cui si sottopone con spirito collaborante. Dal momento che tutte le terapie poggiano su due pilastri, la competenza scientifica professionale e il rispetto per la persona, il medico è tenuto a mettere a disposizione del paziente il proprio sapere e la propria abilità sotto forma di decisioni operative e di comprensione umana. Non ci si stancherà mai di ribadire che questa non è medicina romantica, è semplicemente fare una "buona medicina" che allontanerebbe gli scandali, le tentazioni e le speculazioni di alcuni medici che spesso compaiono nelle cronache e nei tribunali del nostro Paese.

Giusto e saggio è anche scegliere un medico bravo anche se antipatico, rispetto a uno meno bravo ma simpatico, o, meglio, empatico, cioè capace di capire il malato e di stabilire un rapporto con lui. Eppure non di rado accade il contrario. Molti preferiscono affidarsi a un curante che si prenda, appunto, cura di loro anche con le parole, i gesti, la disponibilità ad ascoltare, pur sapendo che altrove, magari a poca distanza, c'è un professionista indicato da tutti come più aggiornato o più esperto, ma brusco nei modi, freddo, distaccato. Non può e non deve sorprendere. Ognuno di noi che si occupa di medicina pratica e specialistica sa benissimo che spesso è bastato arrivare in casa per una visita domiciliare e constatare che il malato (ma soprattutto i familiari, *ndr*) era già molto meno agitato per la sola presenza rassicurante del medico. Nostalgia della medicina paternalistica? No. Scivolosa concessione all'irrazionalità? Neppure, visto che uno studio italiano su 21mila diabetici ha rivelato che quelli che avevano un medico empatico hanno seguito meglio le terapie e sono stati ricoverati ben tre volte meno in ospedale per complicanze legate alla loro malattia. Il motivo è che questi malati, secondo lo studio, hanno aderito meglio alle prescrizioni perché sono state spiegate loro con chiarezza e pazienza e da qualcuno che aveva ottenuto la loro fiducia. E l'empatia dei medici non è stata valutata con approssimazione, ma attraverso un questionario specifico e "validato" sottoposto ai loro assistiti. Preparazione, esperienza ed aggiornamento devono rimanere - questo deve essere ben chiaro - le prime qualità da ricercare in professionisti nelle mani dei quali si mette la propria salute; tuttavia, in un periodo in cui la medicina viene sempre più percepita dagli stessi medici come fin troppo informata da algidi algoritmi, tecnologia e obblighi amministrativi, l'importanza di stabilire una sintonia emotiva con i pazienti forse dovrebbe essere riscoperta e valorizzata, anche per rivendicare alla professione medica la sua titolarità di "arte". Un collega mi confidò che una signora, entrando nel suo studio, gli intimò: "*Lei va bene per il fegato?*" "*Non l'ho dimenticato*" fu la garbata risposta. "*Sono ancora un medico*".

Spesso si afferma che il dottore è scomparso. Che cosa ci manca, in realtà? Di medici ne abbiamo, e la loro schiera si è evoluta in una miriade di sottospecie, ciascuna capace di sapere quasi tutto su poco, tanto ristretto è ormai il raggio di azione di ogni specialità. Forse il dottore non c'è più non solo o non tanto perché l'Università non lo forma; l'organizzazione del servizio sanitario lo contempla nella figura del medico di medicina generale, ma non lo valorizza; ma perché lo strapotere delle specialità, in ospedale e fuori, gli tolgono spazio e credibilità. Tutto vero. Però al fondo il "nostro" dottore è scomparso perché noi abbiamo rinunciato a sceglierlo e a costruirlo nel tempo, come rapporto solido di confidenza e comunicazione. Soprattutto le ultime generazioni, che un dottore non lo hanno mai conosciuto e non possono averne nostalgia, è bene che sappiano che un tempo è esistito e potrebbe esserci ancora, per non cadere vittime, anche quando è in gioco la salute, di un consumismo che tutto divora.

A partire dalla "rivoluzione terapeutica", innescata dall'avvento degli antibiotici e proseguita a tutt'oggi con le innumerevoli conquiste vantaggiose della tecno medicina, il rapporto tra curanti e curati si è fatto via via sempre più tecnologico tendendo a sovrapporsi o addirittura a sostituire l'accostamento umano del medico al paziente.

Si è aperta una nuova stagione, che è quella odierna. Le malattie non sono più quelle infettive, che i farmaci potevano guarire; sono quelle metabolico-involutive legate in gran parte al protrarsi della vita media. La tecnomedicina ha molto contribuito a questa maggior quantità di vita e al miglioramento della sua qualità, ma le malattie con cui essa fa i conti sono oggi quelle cardiovascolari e tumorali, infarto, ictus, cancro, leucemie, e quelle neurodegenerative, morbo di Parkinson, sclerosi multipla, Alzheimer, che talvolta non si possono (ancora) guarire, ma che si debbono (sempre) curare.

Il medico d'oggi è certamente un tecnico; guai se non lo fosse. Però non può essere solo tale. La competenza tecnica è necessaria, ma non sufficiente. Egli può usare bene il computer, osservare protocolli e linee guida, fare buon uso di farmaci ed esami, ma non può pensare che tutto ciò possa compensare l'eventuale mancanza del buon metodo clinico, basato anche sulla relazione di cura, sul rapporto interumano, interpersonale, tra la propria persona e la persona del malato. Il malato ha bisogno del medico della persona, tanto competente quanto disponibile, come lo era una volta, salvo eccezioni, "il dottore".

In conclusione, nessun intervento terapeutico può essere efficace e vero se non viene instaurata quella che il Maestro e filosofo Aldo Masullo ha definito "relazione personale", in virtù della quale il medico, alla richiesta di aiuto, risponde con la "cura" che deve significare "prendere a cuore" l'altrui vita.

Meeting Calendar

WHEN	WHERE	WHAT	WHO TO CONTACT
		2024	
September 7-10	San Diego, CA (USA)	2024 Lung Conference on Lung Cancer	https://wclc2024.iaslc.org/
September 7-11	Vienna (Austria)	ERS Congress 2024	www.ersnet.org
September 30- October 2	Naples (Italy)	Skills course: Paediatric bronchoscopy	www.ersnet.org
October 3-6	Sibenik (Croatia)	54th Annual Professional and Scientific Meeting of the Croatian Pulmonology Society HLZ	hpd.hlz.hr
October 6-9	Boston, MA (USA)	CHEST 2024 Annual Meeting	Chestnet.org
October 6-7	Rotterdam (Netherlands)	Course: Academy of paediatric chest imaging	www.ersnet.org
October 16-19	Marseille (France)	Skills course: Thoracoscopy and pleural techniques	www.ersnet.org
October 17-20	Vienna (Austria)	10th Congress of EAPS (European Academy of Paediatric Societies Congress)	https://eaps2024.kenes.com/
Novembre 7-9	Taormina, ME (Italy)	Pneumomeeting 2024	www.pneumomeeting.it
November 7-10	Hong Kong (Hong Khong)	APSR 2024- 28th Congress of the Asian Pacific Society of Respirology	https://www.apsr2024.hk/#
November 12-16	Bali (Indonesia)	The Union World Conference on Lung Health 2024	https://conf2024.theunion.org/
November 14-16	Lisbon (Portugal)	40th Pulmonology Congress – 2024	https://www.sppneumologia.pt/
November 16-18	Milan (Italy)	XXV Congresso Nazionale della Pneumologia SIP 2024	www.sip2024.it
November 19-21	Heidelberg (Germany)	Skills course: Interventional bronchoscopy	www.ersnet.org

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1. Troy NM, et al. J Allergy Clin Immunol 2022;S0091-6749(22)00040-9.
2. BRONCHO MUNAL, Riassunto delle caratteristiche del prodotto.

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