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Systematic Review

Post COVID-19 Pulmonary Fibrosis Management: A Systematic Review

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Abstract

Introduction

Post-COVID-19 Pulmonary Fibrosis (PC-19-PF) is among the complications following COVID-19. It is the complication that is associated with the most amount of long-term impact on the respiratory system. Different physicians approach management in different ways; therefore, we conduct a study to neatly summarize all the different management and their possible outcomes.

Methods

The databases that were searched included CINAHL, PubMed/MEDLINE, Cochrane Library, Web of Science, and EMBASE to identify English language studies published up to October 5th, 2023.

Results

Initially, the systematic search conducted brought 150 papers. Out of the 150, 13 of them were included in this study. A total of 662 patients were included in the study, all with different managements for COVID-19-induced pulmonary fibrosis. The mean age was 61.8 years. Many comorbidities were observed in patients with COVID-19-induced pulmonary fibrosis. Different treatment regimens were picked based on the different conditions of the patients but as far as antifibrotics go, Pirfenidone and Nintedanib were the most commonly used ones.

Conclusion

Both antifibrotics and steroids seemed to yield justifiable outcomes when used separately as well as when used in combination.

1. Introduction

A large family of viruses referred to as the coronaviruses can cause mild to moderate upper respiratory tract diseases in humans. Among the family, the SARS-CoV-2 virus is responsible for the coronavirus disease 2019 (COVID-19) [1]. The "SARS" stands for severe acute respiratory syndrome and the virus can result in pneumonia [2]. The COVID-19 infection was first isolated in individuals who had exposure to the seafood market of Wuhan City in China in December 2019 [3]. The spread was so vigorous that by January 30th, 2020, the World Health Organization (WHO) declared it an outbreak in Public Health Emergency of International Concern (PHEIC) and it was considered a pandemic by March 11th, 2020 [4,5]. As of the instant of writing this manuscript, there have been 770,875,433 cumulative cases of COVID-19 and 6,959,316 cumulative deaths worldwide [6]. According to a review by Mehraeen et al., the infection mostly spreads through either droplet transmission or contact with a contaminated surface. Furthermore, environmental contamination, fecal excretion and fluid pollution are among the other modes of transmission [7]. As far as symptoms go, fever is considered the most frequent, occurring in 81.2% of the cases. This is followed by other symptoms such as cough, fatigue, dyspnea and presence of sputum [8]. One factor that largely contributed to the rapid spread COVID-19 had is the fact that 80% of the patients had either mild symptoms or were asymptomatic making symptom control ineffective. The mortality rate varied largely according to the geographical distribution, with countries such as Singapore and Qatar having rates as low as 0.2% and 0.17%, respectively. On the contrary, countries such as Algeria with a 15% mortality rate and Belgium with a 13.95% mortality rate were amongst the countries on the other end of the mortality spectrum [9]. Apart from the immediate complications and presentations of the COVID-19 virus, long term delayed complications are being recognized and are seen to bring about many morbidities. Post-acute COVID-19 is a term used to describe the morbidities following the recovery of COVID-19 infection. Following recovery, the infection can even leave multi organ consequences apart from the typical clinical symptoms such as tiredness, dyspnea, fatigue, autonomic dysfunction, depression and persistent change in taste and smell, among many others [10]. Post-COVID-19 pulmonary fibrosis (PC-19-PF) is considered to have the most significant impact on respiratory health in the long term. Both pneumonia and acute respiratory distress syndrome (ARDS) due to COVID-19 have been suggested to subsequently result in PC-19-PF. Factors like chronic comorbidities, female sex, older age and the use of mechanical ventilation have all been associated with an increased risk [11]. The treatment of pulmonary fibrosis nowadays is corticosteroids; however, this is for non-COVID-19 ARDS patients [12]. Many different managements have been tried for the purpose of treating PC-19-PF.

Since PC-19-PF is a long-term complication of COVID-19 and it has been almost 4 years since the emergence of COVID-19, we aim to conduct a systematic review regarding the treatment of PC-19-PF in an effort to shed light on different ways the disease can be managed.

2. Methods

2.1. Study design

The guideline that was chosen in this systematic review was the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.

2.2. Data sources and search strategy

Through the CINAHL, PubMed/MEDLINE, Cochrane Library, Web of Science, and EMBASE databases, a systematic search was conducted to identify studies published up to October 5, 2023. The search was done using these keywords: (SARS-CoV-2 OR COVID-19 OR Coronavirus-2019 OR 2019-nCoV) (management OR treatment OR therapeutic OR therapy) AND (fibrotic OR fibrosis OR interstitial-lung OR lung-scarring OR lung-injury). Article titles containing the words "cystic fibrosis" were filtered out of the search to easily exclude a large portion of irrelevant studies. The search was limited to humans and the English language.

2.3. Eligibility criteria

Only studies that met these inclusion criteria were included in this systematic review: 1) Studies where either one or more patients diagnosed with some sort of lung scarring or fibrosis following COVID-19. 2) The patients received some sort of management (Surgical or conservative). 3) Outcome of the management revealed. Studies published in predatory journals (not properly peer-reviewed) were excluded in this systematic review to minimize bias and to elevate credibility of the study.

2.4. Study selection process

Several authors initially screened the titles and abstracts of the identified studies. Subsequently, they conducted a full-text screening to assess whether the studies met the inclusion criteria. In case of any discrepancies, a third author intervened to resolve them.

The variables extracted from the studies included the study design, number of cases, demographics, histological subtypes of mesothelioma, treatment lines, and modes, previous treatment, doses, and modes of administration, adverse events, treatment interruption due to adverse events, death due to adverse events, objective response (OR), progression-free survival (PFS), stable disease (SD), and overall survival (OS).

2.5. Data items

Multiple data were collected from the included articles, including the year of publication, first author, country, study design, sex, age, comorbidities, presenting symptoms and type, dose, duration and outcome of management.

2.6. Data analysis and synthesis

The extracted data were used in qualitative synthesis. They were re-analyzed using the Statistical Package for Social Sciences (SPSS) 26.0 software for quantitative synthesis. Summary tables with relevant variables were designed which were presented as frequency, mean and percentage. The statistical test of choice used in this systematic review was the chi-square test. The

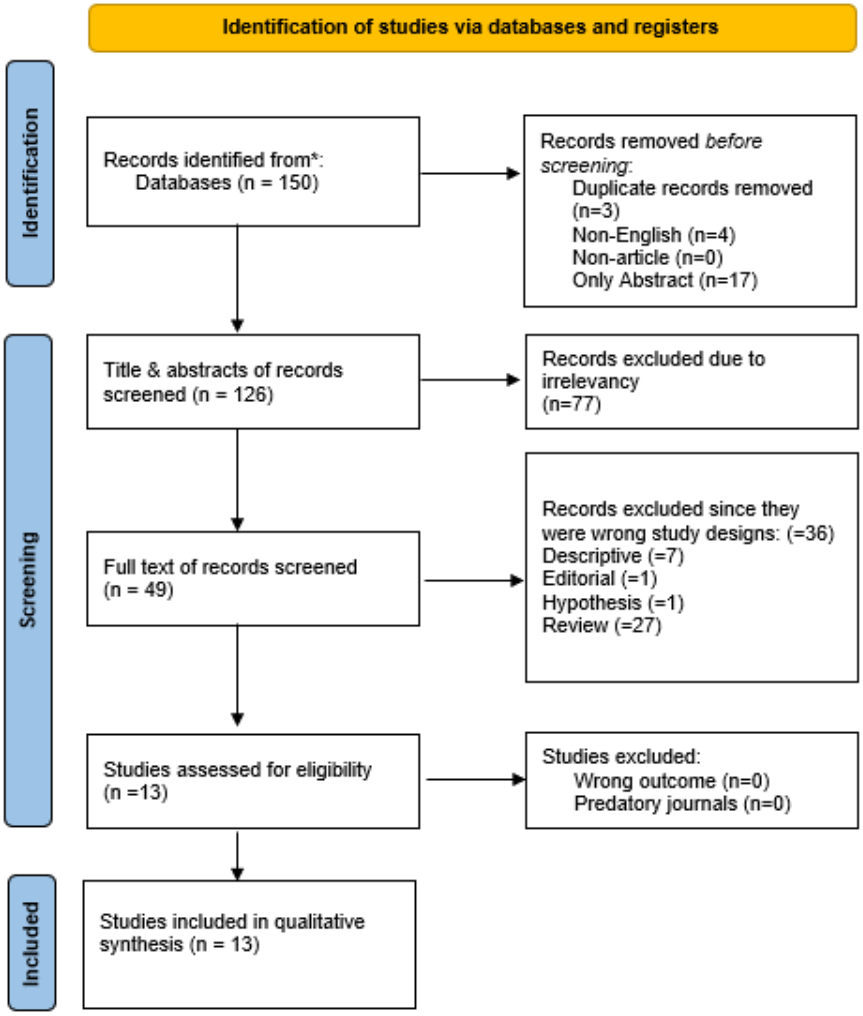

Figure 1. Study selection PRISMA flow chart.

statistical level of significance was set at 0.05 making a p-value of 0.05 or less a significant statistical difference.

3. Results

3.1. Study selection

The systematic search initially revealed a total of 150 articles. Before further screening, 3 duplicates, 4 non-English and 17 only abstract articles were removed. The titles and abstracts of the remaining 126 articles were screened, of which 77 were excluded due to irrelevancy. Out of the remaining 49 articles that were screened, 36 of them were excluded since they were the wrong study design. This left 13 articles that were screened for possible wrong outcome or predatory journals; However, none were found. Finally, the 13 articles remaining were deemed eligible and were included in the systematic review. The detailed PRISMA flow chart is shown in Figure 1.

3.2. Characteristics of the included studies

All of the studies included were either a case report, case series, clinical trials or cohort studies. China had the most number of research with 4 different studies, followed closely by India and Turkey with 2 studies. Other countries such as Poland, Japan, Philippines and Netherlands were all included. More details regarding the studies included in this systematic review is shown below in Table 1.

3.3. Participants

In total, 662 patients were included in the study with different levels of pulmonary fibrosis and interstitial lung diseases following COVID-19. The mean age of the patients was 61.8 years. Out of the 13 studies included in this systematic review, patients from 7 of them were already suffering from comorbidities. Smoking, diabetes, cardiac diseases and hypertension were among the most frequently occurring comorbidities in patients with COVID-19 induced pulmonary fibrosis.

3.4. Assessment time

Table 1: Characteristics of the included studies.

Author	Country	Study Design	Publication date	N. of patients with pulmonary fibrosis	Gender		Age
					Male	Female	
Kooistra et al. (12)	Netherlands	Cohort Study	2023	50	Not Specified	Not Specified	65
Zhou et al. (13)	China	Case Report	2022	1	0	1	66
Singh et al. (14)	India	Case Control	2022	56	44	12	52.5
Lomanta et al. (15)	Philippines	Case Report	2022	1	0	1	51
Uemasu et al. (16)	Japan	Case Report	2022	3	3	0	65.7
Günay et al. (17)	Turkey	Cohort Study	2023	391	259	132	63.03
Wu et al. (18)	China	Case Series	2020	27	19	8	66.5
Vitug et al. (19)	Philippines	Case Report	2021	1	0	1	67
Udwadia et al. (20)	India	Case Report	2022	1	1	0	53
He at al. (21)	China	Randomized Control Trials	2022	78	39	39	61.25
Uyar et al. (22)	Turkey	Case Report	2022	1	1	0	64
Kotfis et al. (23)	Poland	Randomized Control Trials	2022	49	26	23	62.7
Chen et al. (24)	China	Case Report	2021	3	3	0	65.7

The assessment time varied immensely and even continued after patients were discharged from the hospital. As far as treatment duration goes, some patients were prescribed treatments for 3 days and in some patients, the duration went up to 96 weeks.

3.5. Main findings

China was the country with the most studies included in our systematic review as shown in Table 1. Out of the 13 studies included, 7 (53.8%) of them were case reports making it the most frequent study design. The frequencies of the other studies and their percentages is mentioned in Table 3. along with the frequencies of other necessary variables. A total of 662 patients were included in the study and they had a mean age of 61.8. Since comorbidity is a factor very highly correlated to severity in COVID-19 patients, they are all mentioned in the frequency table. Hypertension and smoking were present in 201 and 199 patients, respectively. Diabetes, asthma, COPD, cardiac diseases and renal diseases were all occurring less frequently. The same table also gives provides information regarding the different symptoms the patients presented with. As shown in Table 3, fever, cough and breathing disorder are among the most common presentation with nausea, vomiting, diarrhea and fatigue being less frequent.

Each underwent different treatment regimen based on the severity of their condition and the study they took part in. Majority of the patients recovered and were discharged from the hospital after certain improvements in their general health. Among the few exceptions was one of the patients that underwent lung transplantation as the last management possible but did not survive. In that study, the two other patients who underwent lung transplantation both survived and joined rehabilitation programs. The other 12 studies chose conservative managements instead of surgical approach and majority had pleasing outcomes as shown on Table 2. Antifibrotic agents such as pirfenidone and nintedanib were used and showed promising outcomes in the patients. As far as immunosupressive medications go, both steroids and anticytokines were used. Within the steroid medications, methylprednisolone was the most frequently prescribed medications

4. Discussion

Coronavirus is a large family of enveloped positive sense single-stranded RNA virus that belongs to the Coronavirdae family [25]. The virus causes an illness with a varying range of clinical presentation ranging from mild respiratory symptoms to severe respiratory, gastrointestinal, hepatic and even neurological symptoms [26]. Although many factors are considered to be associated with the level of severity of the illness, age is found to be the most determinant factor associated with COVID-19 hospital mortality and pre-existing comorbidities [27]. As much as 81% of deaths from the disease occurred in patients that were 65 years or older [28]. With this being said, the age of the patients was averaged at 61.8 years in our study. According to WHO, the symptoms generally begin around 5-6 days after exposure and can last from 1 up to 14 days [29]. Based on the meta-analysis conducted by Alimohamadi et al., Fever, which occurs in 81.2% of the patients, is the most commonly occurring symptom in patients presenting with COVID-19. Other common symptoms included the likes of cough, fatigue and dyspnea presenting in 58.5%, 38.5% and 26.1% of the patients, respectively [8]. Similar findings were observed in the systematic review we conducted. Fever turned out to be the most repeated symptoms followed by cough and breathing disorders. Our study also revealed other symptoms such as diarrhea,

Table 2: Different management for pulmonary fibrosis induced by Covid-19 along with their doses, duration and outcome.

Variables	Number of patients (662)	References
Mean Age	61.8 (SD=5.74)	[12-24]
Gender (612 is specified)	395 (64.54%)	[12-24]
Male	217 (35.46%)	
Female		
Comorbidities (518 patients)		[16,17,23]
Smoking	199 (38.42%)	[16-18,22-24]
Hypertension	201 (38.80%)	[16-18,23,24]
Diabetes Mellites	128 (24.71%)	[15,17,24]
Asthma	20 (3.86%)	[12,17,22,24]
COPD	38 (7.34%)	[16,17,23,24]
Cardiac Disease	98 (18.92%)	[17,24]
Renal Disease	9 (1.74%)	[16,17,23,24]
Others	113 (21.81%)	[12,13,14,19-21]
No comorbidities mentioned	144 (27.80%)	
Presenting Symptoms (509 patients)		[15-18,20-22]
Fever	487 (95.68%)	[15-18,21,22]
Cough	470 (92.34%)	[15-18,20,21]
Breathing Disorder	458 (90.98%)	[13]
Nausea or Vomiting	1 (0.20%)	[13,18,21] [21]
Diarrhea	17 (3.34%)	[17,18,21]
Fatigue	66 (12.97%)	[13,18,20,21]
Muscle or Joint pain	399 (78.39%)	[12,14,19,23,24]
Others	17 (3.34%)	
Not mentioned	153 (30.06%)	
Management (447 patients)		[12,14,16,17,21]
Steroid	351 (78.50%)	[13,19,20]
Antifibrotic	3 (0.67%)	[14,15,22]
Mixed	39 (8.71%)	[18,23,24]
Others	54 (12.11%)	
Outcome (447 patients)		
Effective Treatment	390 (87.02%)	[13-19,21,22,24] [12,20,23,24]
Non-Effective Treatment	57 (12.76%)	

fatigue, nausea or vomiting and muscle or joint pain, among others.

Apart from age, other factors considered a risk in COVID-19 patients is pre-existing comorbidities [30]. This correlation is so severe that almost 75% of the patients hospitalized with COVID-19 were seen to have at least one comorbidity [31]. This correlation between comorbidities and its impact on respiratory diseases is not unique to COVID-19 since similar effects have been observed with Middle Eastern Respiratory Syndromes (MERS) [32]. Djaharuddin et al. showed that hypertension was the most frequent comorbidity occurring in 42.31% of the patients. Other comorbidities such as cardiovascular diseases with 30.77%, diabetes with 28.21% and chronic kidney disease with 23.08% were also observed [33]. Our study further emphasizes on this significant correlation between COVID-19 patients and their comorbidities. Out of the 662 patients involved in the study, only 144 (17.2%) of the patients were without any mentioned comorbidities. Among the patients with comorbidities, hypertension was the most common, followed by smoking and diabetes. Others such as cardiac diseases, asthma, COPD, renal diseases and many more were also observed.

Apart from the high number of mortalities the disease possesses, it is also essential to focus on the many complications arising from COVID-19 that do not end up in death. The most commonly affected systems in COVID-19 patients are the kidneys, respiratory, cardiovascular, neurological and gastrointestinal systems, in that order [34]. Jakubec et al. conducted a study to find out the impact of COVID-19 on the pulmonary system and figure out the most commonly occurring complications after the illness. Out of the 98 total individuals included in the study, they stated that infection was the most common post COVID-19 respiratory complication occurring in 55 of the patients. Interstitial lung disease occurred in 22 of the patients, followed by pulmonary embolism in 8, sarcoidosis in 6 and non-infective COPD exacerbation in 5 patients [35]. Another commonly occurring severe complication following COVID-19 is pulmonary fibrosis. Groff et al. performed a systematic review regarding both the short- and long-term sequelae of SARS-CoV-2 infection and revealed that 7% of the patients developed PC-19-PF [36]. The exact prevalence of the disease requires more time and research to be apparent.

The term post-covid-19 pulmonary fibrosis refers to the existence of persistent fibrotic tomographic sequelae associated also with functional impairment observed during follow-up [37]. Amin et al. conducted a meta-analysis on post COVID-19 pulmonary fibrosis and found out that the mean age of patients suffering from fibrosis was 59 years. This was in contrast to the non-fibrotic patients included in the study who had a mean age of 48.5 years. They also observed that the fibrotic patients mostly suffered from symptoms such as dyspnea, cough, chest pain, myalgia and fatigue [38]. As for the pathophysiology of pulmonary fibrosis occurring after COVID, the underlying mechanism is similar to fibrosis in other pulmonary diseases. The pathways leading to formation of fibrous tissue formation in pulmonary fibrosis is very complex in itself since it involves many other fibrotic factors. With this being said, the primary mechanism is considered to be through the activation of a signaling pathway, referred to as the TGF-β1 signaling pathway. TGF-β has many roles but as far as fibrosis goes, it does this mainly through the activation of myofibroblasts which subsequently leads to deposition of extracellular matrix [39].

There are hypothesis suggesting that patients with PC-19-PF can benefit from treatments that are usually given for idiopathic pulmonary fibrosis. This is mostly due to similarities in the pathophysiology of fibrosis in both COVID-19 and idiopathic pulmonary fibrosis [40]. For this reason, antifibrotic agents such as Pirfenidone and Nintedanib have been suggested despite the uncertainty in their role. Apart from interrupting signaling pathways associated with PC-19-PF, pirfenidone also suppresses the accumulation and recruitment of inflammatory cells and fibroblast proliferation as well as extracellular matrix deposition [41]. Nintedanib on the other hand is another

Table 3: Frequency and percentages of different variables such as gender, mean age, symptoms, comorbidities, management and outcome

Author	N. of patients with pulmonary fibrosis	Management	Dose, if mentioned	Duration of treatment	Outcome or Conclusion
Kooistra et al. [12]	50	IV Dexamethasone given to 31 of the 50 patients with Pulmonary Fibrosis (PF)	6 mg/day	10 days	IV Dexamethasone made no significant difference when given to 31 of the patients with PF.
Zhou et al. [13]	1	Oral pirfenidone	1,800mg/day	96 weeks	Patients dyspnea and pulmonary fibrosis improved and was then discharged.
Singh et al. [14]	56	-Steroids (19) -Steroids & Pirfenidone (16) -Steroids & Nintedanib (21)	1mg/kgBW(steroid) & 3x600mg(pirfenidone)/day & 2x150mg/day (Nintedanib)	12 weeks	Nintedanib with steroid showed less severe CT score of 3.67 at 12 weeks when compared to pirfenidone with 9.07 and is hence deemed superior.
Lomanta et al. [15]	1	Hydrocortisone, Methylprednisolone & Nintedanib	2x 150mg/day (Nintedanib)	7 days, 5 days, 4 weeks	After a short course of Nintedanib, Steroid and Rehabilitation, patient's symptoms, pulmonary function and CT scan findings all improved.
Uemasu et al. [16]	3	1. MP & prednisolone & O2 therapy 2.Betamethasone & O2 therapy 3.MP & prednisolone	1.2x500mg/day,1.0mg/kg/d 2.4.0 mg/day 3. 2x 500mg/day, 1.0mg/kg/d	1- 3 days 2- 11 days 3- 3 days	Patient 1 was discharged at day 59 and weaned off O2 at day 69. Patient 2 was discharged at day 62 and started tapering steroid. Patients 3 had improvement in hypoxemia and radiological finding and started tapering steroids.
Günay et al. [17]	391	Corticosteroid was given to 273 patients with parenchymal involvement	Not mentioned	3 Months	After 3 month of the corticosteroid treatment, there was a statistically significant improvement in the pulmonary function test results and the distance in the 6MWT, except FEV1/FVC
Wu et al. [18]	27	IV Human embryonic stem cell derived immunity and matrix-regulatory cells	3 x 10^6 cells/kgBW	Up to 84 days	All 27 patients displayed clinical improvements within 84 days after treatment with our hESC-IMRC therapy with no one experiencing adverse effects.
Vitug et al. [19]	1	Nintedanib	Not mentioned	3 months	Improved lung function was observed with a serial 6 Minute Walk Test (6MWT), pre and post treatment High Resolution Chest CT Scan, and Spirometry.
Udwadia et al. [20]	1	Pirfenidone	3x 600mg/day	2 Years	Persistent restriction observed in PFT with desaturation to 83% on 6MWT and remaining fibrosis with traction bronchiectasis.

Table 3: Continued...

He at al. [21]	78	IV MP was given to 25 patients	1-1.5mg/kg every 12 hours	5 days	Steroid significantly promotes recovery since after 4 cycles, volume reduction percentage of fibrosis dropped by 59.79% and 41.92% in those with severe illness and significant-severe illness, respectively.
Uyar et al. [22]	1	IV MP,Pirfenidone	1000 mg, max 2400mg/day	3 days, 90 days	Radiological and clinical improvement was observed
Kotfis et al. [23]	49	IV potassium Canrenoate dissolved in 100 mL of 0.9% Sodium Chloride was given to 24 patients allocated in the intervention group, the other 25 was placebo	200 mg	7 Days	CT scans showed that after 90 days the percentages of fibrotic changes occurrence in lungs did not differ between the intervention and placebo groups at the time of examination
Chen et al. [24]	3	Lung Transplant	N/A	N/A	2 out of the 3 patients survived and started rehab programs while one passed away.

MP: Methylprednisolone, LMWH: Low Molecular Weight Heparin, IV Dexa: IV Dexamethasone, 6MWT: 6-minute walking test

antifibrotic medication which inhibits tyrosine kinase leading to the suppression of fibroblast and myofibroblast cascades. Both Pirfenidone and Nintedanib, which make up the antifibrotic group in our study, were used for 42 patients and yielded excellent response. Out of the 42 patients, only 1 patient did not benefit from the treatment and had persistent traction bronchiectasis. Even though the United State Food and Drug Administration has approved both drugs, it still does not mean it is useful in all cases [40]. Immunosupression seems to be another way of targeting PC-19-PF. Since corticosteroids can decrease inflammation in the lungs, it can be used to improve the symptoms of post-COVID-19 pulmonary fibrosis. Agents such as prednisolone have been used in many studies to show clinical improvement in patients without having major side effects [42].

5. Conclusion

In our study, apart from prednisolone, agents such as methylprednisolone, dexamethasone, and other steroids were also used for the management of patients suffering from PC-19-PF. Furthermore, most of the studies using them showed different levels of improvement in patients with different levels of severity. Since there are many other agents considered in the management of pulmonary fibrosis in COVID-19 patients, our systematic review also included the likes of IV potassium Canrenoate, Human Embryonic Stem Cell Derived Immunity Matrix-Regulatory Cells, and O_2 therapy. The outcome of all of them is mentioned along with a study where a lung transplant was chosen as the management of choice.

Declarations

Conflicts of interest: The author(s) have no conflicts of interest to disclose.

Ethical approval: Not applicable, as systematic reviews do not require ethical approval.

Patient consent (participation and publication)**:** Not applicable.

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