Effects of pharmacotherapy on post-COVID-19 pulmonary fibrosis: systemic review

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Abstract: Pulmonary fibrosis is one of serious consequences of COVID-19. Its prevalence and risk factors including disease severity, length of mechanical ventilation and hospitalization were studied, but the effect of pharmacotherapy was not widely assessed. This systematic review is aimed to investigate potential effects of drugs used before and during COVID-19 on lung damage possibly leading to pulmonary fibrosis, and effects of post-COVID-19 therapy used to fight formed pulmonary fibrosis. PubMed database was searched to identify studies published in English up to February 10, 2024. The systematic search revealed a total of 580 full-text articles, of which 23 (results of clinical trials) were finally included in the analysis. Most works considering COVID-19 treatment highlighted antibiotics and corticosteroids as groups with the highest frequency of use in patients with negative clinical outcomes and respiratory function decline, suggesting possible negative effects on pulmonary fibrosis development. Pre-COVID-19 treatment revealed rituximab and chemotherapy as main drug factors associated with pulmonary fibrosis development, and post-COVID-19 therapy with antifibrotic drugs revealed discussible results. Our systematic review was an attempt to highlight possible effects of pharmacotherapy on the lung damage leading to the pulmonary fibrosis formation.

1 Introduction

SARS-CoV-2 affects almost all organs and systems in the human organism, and the highest rates of injury are seen in the lungs. Alveolar damage may transform with time into fibrotic tissue progression. Post-COVID-19 pulmonary fibrosis (PF) is one of serious consequences, markedly affecting morbidity and mortality of patients. We know about the role of SARS-CoV-2 in PF development, but little is known about effects of drugs on its incidence. Pandemic is considered to be finished now, and our systemic review is an attempt to assess relations between pharmacotherapy used before, during and after COVID-19 and such outcome, as PF, using published clinical trials data.

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**Objective:** To perform a systematic review of publications in the National Library of Medicine (National Centre for Biotechnology Information, NCBI, https://pubmed.ncbi.nlm.nih.gov)

### 2 Materials and Methods

1. Eligibility Criteria for Inclusion of Clinical Trials
   - We included clinical trials of COVID-19 patients published between March 2020 and January 2024.

2. Search Methods for Identification of Clinical Trials
   - We searched for all clinical trials of patients with COVID-19. We searched the following database:
     - National Library of Medicine (National Centre for Biotechnology Information, NCBI, https://pubmed.ncbi.nlm.nih.gov; from 2020 to 2024; accessed on 10 February 2024);
   - Description of the Database and Website Used for Search, Selection and Analysis of Clinical Trials
     - National Library of Medicine (National Centre for Biotechnology Information, NCBI, https://pubmed.ncbi.nlm.nih.gov); accessed on 10 February 2024. We searched by the search terms of our research interest (post-COVID-19 PF, pharmacotherapy).
     - Search strategy for the following database: PubMed.gov search strategy was based on traditional Cochrane search method by combination of terms and Boolean operators OR and AND:
       - #2. "pulmonary fibrosis" AND
       - #3. "anti-bacterial agents" OR "antibiotics" OR “corticosteroids” OR “glucocorticoids” OR “drugs” OR "pharmacotherapy" AND Filter:
         - #4. #1 AND #2 AND #3
     - The time interval of search was from 1 January 2020 to 10 February 2024 (filter for all searched database results).
   - Four review authors (OIB, EAB, SKZ, YOK) independently examined titles and abstracts of records from the electronic searches and excluded those studies that were obviously irrelevant. Additionally, we used Microsoft Word auto-search and sorting program, EndNote’s duplicate program, which allowed for duplicate removal. We analyzed the full texts of the remaining papers, and the same four review authors independently selected studies for inclusion based on the inclusion criteria. Disagreements were resolved by discussion within the author team. We excluded articles that did not meet the inclusion criteria. Search date was 10th of February 2024 (See Figure 1).

![Fig. 1. PRISMA flow diagram.](image-url)
3 Results and Discussion

We included 23 studies with 458,371 participants. Risk factors of post-COVID-19 PF include severity of disease, prolonged intensive care unit stay, mechanical ventilation duration, use of oxygen support, development of acute respiratory distress syndrome, degree of systemic inflammation [1-3]. So, we included in our analysis works assessing effects of pharmacotherapy on the mentioned above factors (indirect effects), as well, as on pulmonary COVID-19 sequelae (direct effects).

The total number of publications included in the final analysis was 23. Figure 2 demonstrates the structure of analyzed publications.

Among clinical trials evaluating effects of COVID-19 pharmacotherapy on pulmonary sequelae Salem AM et al (2021) [4] demonstrated no effect of drugs (hydroxychloroquine, antibiotics, corticosteroids, antivirals, enoxaparin) on the pattern of lung damage in COVID-19 patients. Estimation of predictors of pulmonary sequelae after COVID-19 pneumonia (1-year follow up) revealed that for non-recovered patients compared with recovered use of other antibiotics (except azithromycin and ceftriaxone) (62% vs. 31%; p = 0.003) and corticosteroids (87% vs. 67%; p = 0.04) was more specific [5]. Another clinical study assessed prognostic factors of PF after COVID-19 and revealed no significant relationship between COVID-19 pharmacotherapy and PF development, though non-recovered patients were more frequently treated with hydroxychloroquine (n = 37, 82 vs. 111, 63%; p = 0.01), antibiotics other than ceftriaxone and azithromycin (n = 25, 56 vs. 44, 25%; p < 0.0001), remdesevir (n = 7, 16 vs. 10, 6%, p = 0.02), tocilizumab (n = 8, 18 vs. 12, 7%; p = 0.02), and steroids (n = 27, 60 vs. 74, 42%; p = 0.03) compared to recovered ones [6].

Next work [7] was aimed on estimation of risk predictors for COVID-19 sequelae and didn’t reveal any drug use among risk factors for pulmonary consequences, though for psychiatric and neurologic sequelae steroids and remdesivir use were reported. Absence of pharmacotherapy effects on the DLCO (carbon monoxide diffusing capacity) tertiles was shown in the work by García-Hidalgo MC et al (2022) [8].

There were 2 clinical trials proving positive effects of corticosteroids use on the pulmonary function [9, 10] and 4 publications reporting their possible negative effects [11-14]. [15] compared effects of methylprednisolone (80 mg, a continuous daily infusion for 8 days) with dexamethasone (6 mg once daily for up to 10 days) in adult patients with COVID-19 pneumonia requiring oxygen or noninvasive respiratory support. It revealed absence of significant differences between drugs by day 28 in mortality and respiratory function, though survivors in the methylprednisolone group required a longer median hospitalization [15]. Results suggest that methylprednisolone may have less beneficial effects considering
respiratory function in COVID-19 patients compared with dexamethasone, which may contribute to a higher rate of pulmonary sequelae, including PF.

Another work reported association of antibiotics (including beta-lactams) consumption with the higher risk of death in critical patients (beta-lactam: RR = 17.49, 95% CI: 4.49–68.12, p < 0.001; other antibiotics: RR = 1.84, 95% CI: 1.39–2.44, p < 0.001) suggesting worsening of respiratory function and possible risks of pulmonary sequelae [16]. One clinical trial reported significant (<0.05) improvement of COVID-19 symptoms and reduction of inflammatory markers (lactate dehydrogenase (LDH), ferritin, and C-reactive protein (CRP) - LF predictors) in case of use of a combination of aspirin, promethazine, vitamin D3, C, and B3 along with zinc and selenium supplementation compared to the control group [17].

There were two publications revealing beneficial effects of mesenchymal stem cells (MSC) in COVID-19 patients. First demonstrated results of phase 1, single-centre open label, prospective clinical trial. MSC use (100 million cells) resulted in marked reduction of inflammatory biomarkers levels (neutrophil-Lymphocyte ratio, CRP, IL6, ferritin and D-dimer), improvement of oxygenation (improvement in the SpO2/FiO2 ratio and PaO2/FiO2 ratio) and resolution signs in chest x-ray and chest CT scan at day 7 in most patients. These changes were accompanied by no progression to severe stage, and early discharge of patients. The most important was absence of post-COVID-19 PF development demonstrated on chest CT 28 days after intervention and chest X ray after 6 months of the intervention [18]. Second work revealed results of 1-year follow-up after human umbilical cord (hUC) MSC administration for patients with severe COVID-19. Pulmonary function parameters were significantly improved at 1-year follow-up in both the hUC-MSCs group, and the control group compared with 3 months after discharge, but laboratory parameters (markers of interstitial lung disease) were better in hUC-MSCs group [19].

Retrospective observational 6-month follow-up study conducted in Spain was aimed on assessment of long-term effects of COVID-19 during 6 months after discharge of patients from hospitals [20]. The most frequent group of COVID-19 sequelae was respiratory (42.0%). In population with sequelae-associated return to emergency services after 6 months the frequency of azithromycin use was higher than in total population (65.7% vs. 73.1%), corticosteroids boluses were also more frequent (35.8% vs. 37.5%), as well as other antibiotics (59.8% vs. 61.9%) and tocilizumab (10.3% vs. 11.3%), though the difference was not significant. In patients with readmission to hospital after 6 months compared with total population higher frequency of next drugs was reported: tocilizumab (10.3% vs. 17.1%), angiotensin-converting enzyme inhibitors/angiotensin receptors antagonists (27.7% vs. 34.3%), azithromycin (65.7% vs. 68.6%). Considering pharmacotherapy features among patients with lethal outcome in 6 months after discharge marked increase in frequency of angiotensin-converting enzyme inhibitors/angiotensin receptors antagonists was seen (27.7% vs. 50.0%), and small increase in frequency of corticosteroids (35.8% vs. 37.5%) [20]. Statistical significance was not proved in this trial for pharmacotherapy, only some tendencies may be considered, of course, not fully reflecting the real relationships between drugs and COVID-19 sequelae.

In the phase 2, prospective, randomized, open-label study possible benefits of zilucoplan (macrocyclic peptide inhibitor of the terminal complement protein C5 that prevents both the formation of active C5a and the membrane attack complex C5b-9) were demonstrated for COVID-19 patients. The improvement in PaO2/FiO2 from baseline to day 6 was shown both for zilucoplan and control groups without statistical significance, though difference in favor to zilucoplan was 35.8 mmHg; at 15 day not significant difference between groups was 39.8% in favor to zilucoplan. Measurements of oxygenation also revealed nonsignificant favor to zilucoplan. Authors proved that a posterior probability that zilucoplan led to an improvement in oxygenation compared with the control group was > 89% for each of analyzed parameters at day 6 and day. At day 28 after randomization 9% in the zilucoplan group died against 21%
in the control (odds ratio, OR, of 0.4 (95% confidence interval (CI) 0.1 to 1.5). At 12–22 weeks follow-up 13% in the zilucoplan group died against 21% in the control group (OR 0.6 (95% CI 0.2 to 2.0), and the posterior probability of survival in the zilucoplan group being superior to the survival in the control group (91% at day 28 and 81% at 12–22 weeks follow-up) [21]. Reported benefits of zilucoplan in follow-up period may indirectly indicate improvement of respiratory function, and authors reported no evidence of PF formation.

A retrospective observational study of 468 symptomatic patients with confirmed diagnosis of COVID-19 treated with early administration of antihistamines and azithromycin revealed reduced odds of hospitalization (OR: 0.49, 95% CI: 0.313–0.767, p = 0.001). Authors also stated that none of survived patients required medical attention for sequelae or symptoms of long COVID, suggesting absence of PF progression [22].

Among publications highlighting effects of pre-COVID-19 pharmacotherapy on the pulmonary sequelae the only one was by Adegunsoye A et al (2023) [23]. A prospective nationwide cohort study in the United States was aimed to estimate influence of drugs used before COVID-19 on PF incidence. It reported the highest post-COVID-19 PF incidence rate ratio (IRR) for rituximab (2.5, 95% CI: 1.2–5.1, p = 0.01) and chemotherapy (1.6, 95% CI: 1.3–2.0, p < 0.0001). Amiodarone exposure was not associated PF (IRR: 0.8, 95% CI: 0.6–1.1, p = 0.24), as well as pre-COVID-19 corticosteroid use (results of sensitivity analyses) [23].

Publications dedicated to the estimation of post-COVID-19 treatment used to fight developed PF revealed 3 clinical trials with antifibrotic drugs. First assessed the role of nintedanib. It demonstrated absence of differences between the study and control groups in terms of oxygen improvement and chest X-ray improvement. The nintedanib group had more improvement in SpO2/FiO2 ratio than the control group (144.38 ± 118.05 vs 55.67 ± 75.09, p= 0.006), but higher 60-day mortality rate (38.1% vs 23.8%, p = 0.317) [24]. Second was a multicenter, retrospective survey study of subjects administered pirfenidone or nintedanib for post-COVID-19 interstitial lung abnormalities. Radiologic improvement in lungs structure was reported in 35.6% in the pirfenidone group and in 34.2% in the nintedanib group, and radiologic response was not different between the outpatients and inpatients (p ≥ 0.08) [25]. 12-month outcome data from a multicentre observational study demonstrated significant benefits of nintedanib regarding pulmonary parameters. 12 months after nintedanib initiation, lung function decline was significantly lower than in the preceding 12 months [26].

Post-COVID-19 PF is an important factor limiting patients recovery and decreasing quality of life. Published data indicate that PF is associated with COVID-19 severity, invasive/non-invasive mechanical ventilation, longer hospitalization period, and steroid, antibiotic and immunoglobulin treatments (p-value < 0.05) [27]. Our work revealed 23 publications with different level of evidence regarding pharmacotherapy effects on post-COVID-19 PF. Three of them demonstrated absence of any effect directly or indirectly [4, 7, 8]. Most of published clinical trials indicated higher frequency of certain drug groups use in patients with severe COVID-19 with negative outcomes, including respiratory function decline and possible relation with future PF development risks [6, 16, 17, 20 - 22]. Among these works higher frequency of antibiotics and corticosteroids use was seen in patients with negative prognosis. Corticosteroids in most of works were considered as negative predictive factors [11-14]. Two works described some nonsignificant benefits of MSC regarding post-COVID-19 pulmonary sequelae [18, 19]. The most obvious results were derived from the work estimated pre-COVID-19 pharmacotherapy [23], which revealed the highest post-COVID-19 PF IRR for rituximab and chemotherapy, but not for amiodarone exposure and corticosteroids use. Post-COVID-19 treatment effects were assessed in 3 publications included antifibrotic drugs nintedanib and pirfenidone, and only one of them demonstrated significant improvement of respiratory parameters with nintedanib [26].
4 Conclusion

With our work we’ve tried to assess possible relationships between drugs used before, during and after COVID-19, and such outcome, as PF. There were no previously published systemic reviews highlighting such complex issue. The results of our systematic review indicate possible negative role of antibiotics and corticosteroids use in COVID-19 patients regarding decline in respiratory function and possible PF development, though high frequency of their use may be secondary to severity of disease mediated by other factors. Pre-COVID-19 pharmacotherapy analysis revealed statistically significant association between PF formation and previous use of rituximab and chemotherapeutic agents. Post-COVID-19 pharmacotherapy is presented with nintedanib and pirfenidone, but there is a need for further study to assess their possible benefits.

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