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RESEARCH ARTICLE

A CRITICALLY APPRAISED TOPIC: IS THERE AN EFFECTIVE POST-COVID PULMONARY FIBROSIS TREATMENT?

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Abstract

Background: the COVID-19 infection induces interstitial lung remodeling after the development of restrictive respiratory distress syndrome, which endures the affected individuals a higher risk for hospitalization and intensive care unit admission from the developed pulmonary fibrosis. Thus, we reviewed the literature for an effective post-covid pulmonary fibrosis treatment.

Methods: PubMed, MEDLINE, and ClinicalKey databases were searched using Medical Subject Headings [MeSH] from November 2019 to Jun 2022 to include human-only studies on confirmed COVID-19 patients via PCR with radiological evidence of interstitial fibrosis. We excluded studies that have pre-existing pulmonary fibrosis patients.

Results: We identified a total of 137 studies. Continuing the title and abstract screening later, we included eight papers for analysis in our review. We found efficacious medication for post-covid pulmonary fibrosis, such as Anakinra, Nintedanib, and human embryonic stem cell-derived immunity- and matrix-regulatory cells (hESC- IMRCs). Moreover, it was tested on a small sample of participants, and the results are promising and safe that can be tested on more extensive randomized trials.

Recommendation: interventional pre-and-post randomized controlled trials shall be conducted to inform further action to reduce morbidity and mortality for such a population.

Introduction:-

We need to investigate the most effective treatment for post-COVID-19 pulmonary fibrosis. As it was observed from the observational studies conducted on such patients, the severity of the COVID-19 infection, which endure them at a higher risk for hospitalization and intensive care unit admission. The development of restrictive respiratory distress syndrome leads to interstitial tissue remodeling that impair exercise tolerance among those patient and leads to poor quality of life (Gentile et al., 2020)

SARS-COV-2 is a novel virus that little is known about and the sequela of its illness. At the same time, the research is accelerated to reach cutting-edge interventions to prevent morbidity and mortality. Some well-known medications are used in therapeutic interventions for fibrosis-related illnesses, such as those used in Idiopathic Pulmonary

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Fibrosis (IPF). The antifibrotic medications such as Pirfenidone and Nintedanib are traditionally used in IPF, while other medicines that target different fibrosis pathways (Wigén et al., 2020) are still under investigation to ensure their safety and efficacy. IdentifyingcoursesassociatedwithCovid-19severitythatresultinpulmonary fibrosis may enable early diagnosis and individualized treatment for these patients to prevent or reduce irreversible fibrotic lung damage.

Intervention: antifibrotic
Outcome: effective treatment

Methodsofliteraturesearch:-

PubMed, MEDLINE, and ClinicalKey databases were searched using Medical Subject Headings[MeSH] and Babylon connectors, as elaborated in [Table:2]. We set inclusion criteria for full text, human only studies conducted since November 2019 up to date with no study design or language restriction while excluding biological laboratory and animal studies. BMJ, SUMSearch, Trip, and Google scholar also checked for a comprehensive search.

Specific criteria were applied for study illegibility, including:

1. Population: COVID-19 patient confirmed by PCR with radiological evidence of interstitial fibrosis. We excluded studies that have pre- existing pulmonary fibrosis patients.
2. Investigations: Patients must have a laboratory and radiographic evaluation pre and post antifibrotic treatment.

After a rigorous search in the literature, title screening and abstract was commenced for study relevance. Animal and biological studies were excluded and then proceeded for full text screening [figure 1] elaborate the search strategy for exclusion reasons.

Table1:- PICOelement.

PICOformat question	Patients	Intervention	Comparator	Outcome
InCOVID-19 pulmonary fibrosis-affected patients, is antifibrotic treatment effective?	COVID-19 pulmonary fibrosisaffected patient	Antifibrotic	N/A	Efficacy

Table2:- Theusedkeywordsandthesearchstrategy.

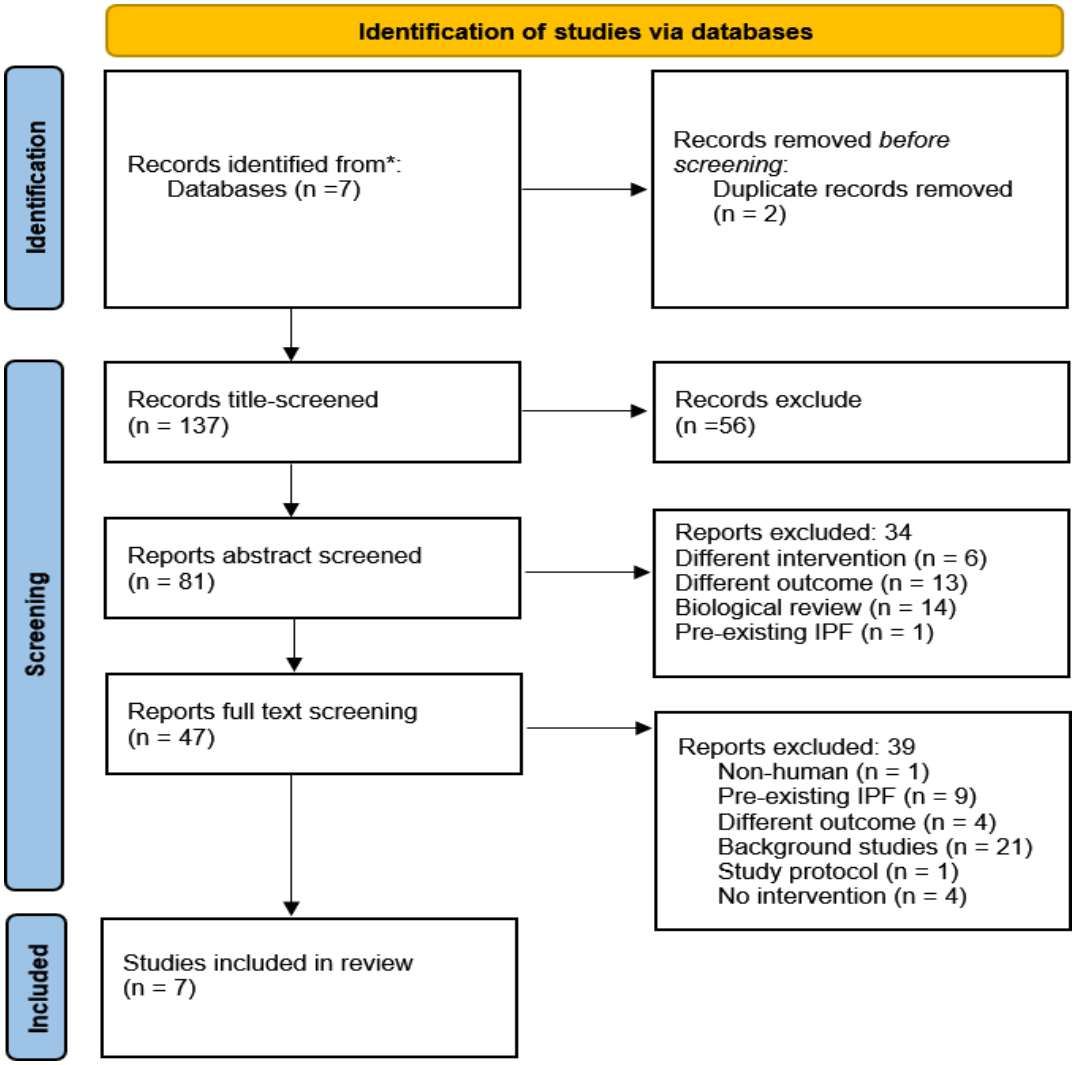
1	COVID-19:	("COVID-19"OR"COVID-19"[MeSH Terms]OR"COVID-19 Vaccines"OR"COVID-19Vaccines"[MeSH Terms]OR"COVID-19 serotherapy" OR "COVID-19 serotherapy"[Supplementary Concept] OR "COVID-19 Nucleic Acid Testing" OR "covid-19 nucleic acid testing"[MeSH Terms] OR "COVID-19 Serological Testing" OR "covid-19 serological testing"[MeSH Terms] OR "COVID-19 Testing" OR "covid-19 testing"[MeSH Terms] OR "SARS-CoV-2" OR "sars-cov-2"[MeSH Terms] OR "Severe Acute Respiratory Syndrome Coronavirus 2" OR "NCOV" OR "2019 NCOV" OR (("coronavirus"[MeSH Terms] OR "coronavirus" OR "COV")
2	Pulmonary fibrosis:	"pulmonary fibrosis"[MeSH Terms]OR("pulmonary"[All Fields] AND "fibrosis"[All Fields]) OR "pulmonary fibrosis"[All Fields]
3	Antifibrotic:	"antifibrotic"[All Fields] OR "antifibrotics"[All Fields]
4	Efficacy:	"efficacies"[All Fields] OR "efficacious"[All Fields] OR "efficaciously"[All Fields] OR "efficaciousness"[All Fields]OR "efficacy"[All Fields]
Strategy:		1 AND 2 AND 3 AND 4

Analysis of the evidence-Internal validity(Quality of the studies):

We identified a total of 137 studies. Continuing the title and abstract screening later, we included eight papers for analysis in our review[Figure:1]. A full-text appraisal was conducted using the JBI Manual for Evidence Synthesis

tool for case report, case series, and non-randomized clinical trials (Moola S, Munn Z, Tufanaru C, Aromataris E, Sears K, Sfetcu R, Currie M, QureshiR,MattisP,LisyK,2020;Munnetal.,2020).The evidence was graded following the Center for Evidence-Based Management according to the hierarchy of evidence for each research category (cause and effect studies). The grading is based on alphabetical ranking; the earlier alphabet, the greater the grade and its strength in the hierarchy of evidence(Barendsetal.,2017). Nonetheless, we included case reports and case series, which have a low level of evidence, yet, they are the up-to-date available literature.

The included studies are categorized in [Table: 3] according to study type, population, limitation, or comment if available. We had three case reports, two case series, and two non-randomized interventional trials pre- and post-evaluation. There are some limitations in most of the studies first: they have no clear selection criteria, which increases the likelihood of selection bias. Second, there is no accounting for the presence of possible confounders. Third, no reporting of unexpected/ adverse events if available, except in Japan's study.



[Figure1]:- PRISMA Flow diagram of critically appraised topic.

Above all, with this low number of cases in the included studies, it is hard to investigate the medication effector its full potential in an unbiased statistical manner. In all included cases, the researched medications effectively treated the post-COVID pulmonary fibrosis regardless of pre-existing chronic illnesses. However, we noticed a measurable adverse event with Nintedanib as it increases liver enzymes. And that could be due to the effect of the antiviral treatment because the adverse event was not statistically significant between cases and controls, and both groups had the antiviral therapy. Finally, we cannot make a recommendation based on a case report or case series; however, it is a

good starting point for the clinicians to conduct trials on a larger sample size with a more explicit description of the possible confounders and adverse events. The appendix includes tables for quality evaluation of each included paper with their specific limitations.

During the collective analysis, all the investigated medications, namely: hESC- IMRCs, Pirfenidone, Nintedanib, Anakinra, Longidaza, and Wobenzym produced a good result in improving the inflammatory markers, resting or /and reducing pulmonary fibrosis in CT scans, reduction/ eliminating of oxygen demand by the patient, reduced hospitalization and returning of the participant to their everyday life. The variation will depend upon drug availability and further testing. Moreover, most antifibrotic drugs are in different stages of clinical testing. They are not yet approved by the national or/and international Drug and Food administration to be used in such patient categories (Sgalla et al., 2021).

Table3:- Study results included study design, country, population, and level of evidence.

Author	Studydesign	Country	Population	Medication	Limitation/ comments	Level of evidence
(Wuetal., 2020)	Phase 1 Non-randomized clinical trail	China	27 participant s	hESC-IMRCs	It might have a selection bias	C
Intervention: Intravenous human embryonic stem cell-derived immunity- and matrix-regulatory cells (hESC- IMRCs) at a dose of 3 × 106 cells/kg of body weight. 25 out of the 27 received two doses, while the remaining had one and three doses, respectively.				Outcome: Nonexhibit adverse event and the drug was well tolerated till the last follow up at 84 days post- treatment.		
(Udwadia et al., 2021)	Case report	India	1	Pirfenidone	Thereareno description of adverse event and no clear description of the intervention's outcome.	E
Intervention: Tocilizumab 400mg single dose. Methylprednisolone120mgdaily Nasal oxygen 4-5 L/min				Outcome: On 30thday: The patient could not perform a pulmonary function test as she was still breathless.		
30thday of admission developed fibrotic interstitial lung disease and was given: Steroid continued. Started Pirfenidone				40 days from admission, discharged on: Home oxygen 2L/min. Steroid, Anti-fibrotic: Pirfenidone No report on the patient after the pirfenidone.		
(Marwah et al., 2021)	Case series	India	4	Nintedanib	No clear inclusion criteria, with no consecutive inclusion of the participant	C
Intervention: Dexamethasone 6 mg injection once daily for ten days IV antibiotics Subcutaneous LMWH Oxygen therapy through NRBM @ 15L/min. Two doses of injection tocilizumab Nintedanib 150 mg oral tablets twice daily for four weeks.				Outcome: Objective: Improvement in oxygenation. On follow up: CT: remarkable clearance of fibrotic opacities		

				Dischargedonminimaldomiciliary oxygen supplement.		
(Umemura et al., 2021)	Non-randomize d controlled before-after- study	Japan	60(30 cases,30 controls)	Nintedanib	Unmeasured confounders	B
Intervention: Nintedanib150 mg twice daily				Outcome: Objective: Ventilator free days within 28-days (17/12) case to control: P-value 0.038 PaO2/FiO2 (PF) ratio was higher in cases relative to controls during all times of measurement after treatment P-value 0.005 CT volumetry significantly lower of high-attenuation areas at cessation of ventilator in cases vs. controls (38.7% vs 25.7%, P = 0.027)		
(Nanetal., 2021)	Case report	Spain	1	Anakinra	No reporting of an unexpected event, if any	E
Intervention: • Standard treatment initiated first: Azithromycin Hydroxychloroquine Lopinavir/ ritonavir Low-molecular-weight heparin (LMWH) Low-flow oxygen therapy with nasal cannula • After six days, symptoms worsened and started on corticosteroid (methylprednisolone) Tocilizumab 600mg(IL-6142mg/ml) single dose				Outcome: Subjective: No respiratory symptoms at 4 and 8 months after discharge. Objective: Hypoxemia correction (PaO2/FiO2 was 252 then 314 mmHg and discharged on 413mmHg) without need for home oxygen therapy. Inflammatory parameters improvement: Before and After Ferritin:1115µg/l 500µg/l		
• 15days from admission with CT findings of diffuse alveolar damage Anakinra 600 mg cumulative dose in three days period. 200 mg twice for the first day, then 100 mg once daily for the next two days.				D-dimers:1999 ng/ml 650ng/ml Decreased pulmonary fibrosis in CT scan		
(Nanetal., 2021)	Case series	Spain	5	Anakinra	No reporting of adverse event	C
Intervention: Anakinra (loading dose of 200 mg twice for one day then 100 mg for two days) cumulative dose 600 mg. one patient had 48 hrs. gap- adjustment between the two 100 mg (adjustment made for his impaired renal function). Corticosteroids Tocilizumab except for one patient. Oxygen.				Hypoxemia correction after 48hrs. of last administration of Anakinra (mean PaO2/FiO2 of 180.2 mmHg (range 128–252)) and at hospital discharge (mean 346.2 mmHg, range 291–413). Inflammatory parameters improvement. Regression of pulmonary fibrosis in CT scan for three patients after eight months. And not available for the rest two. Adverse events were noted in two patients: both had neutropenia, and one also had a		

				three-fold increase in liver enzymes. All patients were discharged without oxygen supplements, except for one, who had a low oxygen therapy.		
(Bontsevich et al., 2020)	Case report	Russia	1	Longidaza and Wobenzym	No reporting of adverse event	E
Intervention: Longidaza 3000 IUI.M.One time in 5-daysfor 5- days Wobenzym 3 tablets 3 times a day for 1month Eliquis 5 mg twice a day for 1 month Atorvastatin 20 mg once a day for 1 month Ascorutin (ascorbic acid+ rutoside) 0.05+0.053 tablets 3 times a day for 2 weeks Aevit (vitaminA+ vitE)100,000 IU/0.01one tablet 3 times a day for 2 weeks Zinc 25mg1tablet per day for 2 weeks Omacor (omega-3fattyacids)1.0g one time per day for one month Vitamin D 5000 IU per day for one month ArifAM (amlodipine+ indapamide) 5/1.5mg one tablet a.m. Prestilol (bisoprolol+ perindopril) 5/5mg1/2 tablet evening Ten sessions of chest massage Breathing exercises Contrast shower Cold training Continue gout treatment. Follow up after two weeks				Outcome: Subjective: no respiratory symptoms with improvement in general condition. Objective: Normalization of the laboratory markers:(before and after) in two weeks of treatment WBC:3.4x 10^9/L 4.1x 10^9/L CRP:15.5 mg/L 2.8 mg/L APTT: 37.3s 31.3s Fibrinogen:4.1g/L 2.85g/L In the spiral CT scan: there was a positive trend with no pathological changes in 3 weeks. In the pulmonary function test: There is an improvement of FVC by 25%, FEV1 by 19%, and PEF by 7% On three weeks of treatment.		

Conclusion:-

We found that there is an efficacious medication for post-covid pulmonary fibrosis. And it was tested on a small sample of participants, and the results are promising and safe that can be tested on more extensive randomized trials. Though we did not specify the efficacy precisely in our searched question, it seems reasonable to consider fibrotic tissue regression and near- normal pulmonary function as targets for medication efficacy proxies.

We recommend that antifibrotic medication be supplemented for COVID-19 patients, especially those hospitalized or who suffered symptomatic respiratory involvement, as they might develop fibrotic tissue lung remodeling, as seen in the included papers from Russa, India, Spain, and China. Furthermore, interventional pre-and-post randomized controlled trials shall be conducted to inform further action to reduce morbidity and mortality for such a population. The result of this review would benefit the local and global population during the current COVID-19 pandemic.

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