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PULMONARY FIBROSIS SECONDARY TO COVID-19 INFECTION IN ADULTS: MECHANISMS OF PATHOGENICITY, IMPACTS AND PREVALENCE

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ABSTRACT

Pulmonary fibrosis is characterized by the stiffening of the lung tissue affecting patient life quality. The shortness breathing and constant coughing are part of these people's daily lives. COVID-19 pandemic emerged in 2020 and had a profound impact on the world and had significant consequences, where many victims of this disease had symptoms that persist even with the end of the Sars-Cov-2 infection, in which the Pulmonary fibrosis appears as one of the most prevalent complications in these cases. However, despite its severity and relevance, many of its pathogenicity mechanisms are still unknown. In this way, this review aims to relate and present the most recent research aimed at the scope of disease related to COVID-19 and pulmonary fibrosis, thus aiming at improving the standards of diagnosis, prevention and treatment of this set of symptoms and pathologies, associated with the post-acute syndrome COVID-19

KEY-WORDS: COVID-19, Complications, Pulmonary fibrosis and Sequelae

1. INTRODUCTION

Coronavirus disease (COVID-19) is an infectious disease caused by the SARS-CoV-2 virus, which is a positive single-stranded RNA virus, these characteristics facilitate the exacerbated proliferation of the vírus, as it causes severe respiratory syndrome in humans. The Coronavirus disease 2019 (COVID-19) has emerged as a serious pandemic since the year 2020. Generally, coronaviruses affect a variety of body systems, and can cause respiratory, gastrointestinal and central nervous system diseases in humans and animals, threatening the human life. These viruses prove to be constant and long-term threats, since they have the ability to adapt to a new environment through mutations and are programmed to modify the host tropism (YESUDAS; SRIVASTAVA; GROMIHA, 2020).

Pulmonary fibrosis is a disease that affects the tissue around the air sacs, or alveoli, in the lungs. This condition develops when the lung tissue becomes thick and stiff from collagen buildup. Over time, these changes can cause permanent scarring of the lungs called fibrosis, which makes breathing progressively more difficult and more prone to respiratory failure.

The pathological mechanism of COVID-19 occurs from the cytokine storm, with uncontrolled and high secretion of pro-inflammatory cytokines such as IL-6 and TNF-a (HU; HUANG; YIN, 2020). This characteristic of the disease affects many organs and raises the fear of major sequelae in patients who have experienced severe forms of the disease. Thus, over time, it was often observed that survivors had persistent neurological, respiratory or cardiovascular symptoms, constituting what has been described as "post-acute COVID-19 syndrome" or "post-COVID-19" that potentially lasts weeks or months (MONTANI et al., 2022).

In this sense, studies indicate that patients who have suffered severe infections of the COVID-19 disease are at increased risk of developing pulmonary fibrosis, in which it is described that the inflammatory process generated could lead to lasting structural changes in the lung, which is mainly seen in patients with chronic comorbidities (MOHAMMADI et al., 2022).

Therefore, this work aims to answer the following guiding question: How do the pathological aspects of pulmonary fibrosis after COVID-19 infection behave in adult patients?

2. MATERIALS AND METHODS

The present study has a quantitative and descriptive approach.

Studies were selected from the following databases: National Library of Medicine (PUBMED) and Virtual Health Library (BVS). To carry out the search, the following descriptors were used: "covid-19"; "complications"; "pulmonary fibrosis", combined with the Boolean operator "AND" to create search strategies. The following strategy was used on both search platforms: (Covid-19) AND (Complications) AND (Pulmonary fibrosis) with a filter from 2019 to 2022.

Inclusion factors were articles that relate the development of pulmonary fibrosis and its mechanisms after COVID-19 infection, published in the last 5 years, in Portuguese, English and Spanish, and with human models.

In PUBMED, 5 articles were selected for analysis in full and, in BVS, 8, totaling 13 (corresponding to 1.73% of the total number of articles initially chosen) which made up the systematic review. In total, 737 papers were excluded from PUBMED and BVS. The steps are detailed in Table 1.

In evaluating the evidence regarding the types of studies used, the 13 articles used were based on 9 types of selected studies: 4 systematic reviews (30% of the types of studies), 1 systematic review with meta-analysis (7.6% of the types of studies), 1 bibliometric analysis (7.6% of types of studies), 1 prospective longitudinal study (7.6% of types of studies), 1 meta-analysis (7.6% of types of studies), 1 case-control study (7.6% of study types), 1 cohort study (7.6% of study types), 1 retrospective cohort study (7.6% of study types) and 1 randomized controlled trial (7.6% of study types).

TABLE 1. Results of search strategies and selection of scientific evidence

Search estrategy (Descriptors combined with Boolean operator)	**Search Platform**	**Resulto f seaccrh (Nº of articles)**		**Selected Articles**	
			After reading the title	**After Reading the abstract**	**After Reading the full text**
((covid-19) AND (complications)) AND (pulmonary fibrosis)	PubMed	368	8	7	5
(pulmonary fibrosis) AND (covid-19) AND (complications)	BVS	382	20	15	8
TOTAL		750	28	22	13

Source: own authorship (2023)

3. RESULTS AND DISCUSSION

The systematic review by d'Ettorre et al. (2021) states that although most patients recover completely within a few weeks after infection with the SARS-CoV-2 virus, some people, including those who had mild versions of the disease, after initial recovery continue to experience symptoms, called these "long haul" symptoms of Covid-19 or post-Covid syndrome. In agreement, Carfi et al. (2020) reports in his cohort study carried out with Italian patients who were discharged from hospitals with COVID-19 that of the 143 patients with Covid confirmed - after the end of the most severe symptoms - more than half of the patients, 60 days after the onset of their illness, continued to have multiple bothersome symptoms, and 41% reported a worse quality of life. In their bibliometric analysis, Zhong et al., 2022 reiterates that

post-COVID-19 fibrosis (PCF) plays a significant role in this scenario of worsening quality of life, since this sequel deteriorates lung function and that people with pulmonary fibrosis may have a greater financial burden, lower income and worse quality of life.

Zhong et al., 2022 mentions that acute respiratory distress syndrome (ARDS) secondary to COVID-19 is reported as the biggest contributor to PCF and that in the course of ARDS, pulmonary fibrosis occurred in less than 1 week. Its underlying pathogenesis is said to be complex, but it is related to the fact that excessive release of the cytokine tumor necrosis factor-a (TNF-a) initiates fibrosis and lung remodeling. Thus, LEUNG et al., 2020 reports that it is believed that SARS-CoV-2 induces many of its pathologies through processes mediated by the immune system, in which the most discussed theoretical explanation for such an association between virus infection and the Adverse immunological outcomes is suggested by molecular mimicry, the epitope cross-talking between host and virus that favors activation of self-reactive or cell-mediated humoral immunity. Other potential mechanisms for disrupting self-tolerance include bystander activation and damage, epitope shedding, and ineffective clearance of persistent viruses. Accordingly, in more detail, Yu et al. (2020) reports that increased inflammatory markers CRP and leucomyin-6 cytokine factor indicated inflammatory damage caused by the COVID-19 virus and generated a series of immune responses, similar to the immunopathogenesis seen in SARS. Furthermore, considering the higher level of CRP and IL-6 in patients with fibrosis ($p < 0.050$), an increased inflammatory reaction can lead to the formation of pulmonary fibrosis during recovery. In this perspective, ISIDORI et al., 2020 corroborates what was mentioned by portraying that when developing a new therapeutic strategy, it is reasonable to try to increase the immune response during the first immune-mediated phase while suppressing the final phase mediated by cytokines, preventing progression from mild to severe and mitigating fibrosis in patients who overcome the acute phase.

In their prospective longitudinal study, Fernández-Plata et al. (2022) addresses that according to the 2015 consensus diagnostic guidelines for PF of the American Thoracic Society (ATS), pulmonary fibrosis was defined as a combination of CT findings, including parenchymal bands, irregular interfaces, thick reticular pattern, and bronchiectasis, which was confirmed by the clinical evaluation of a pulmonologist. Based on these characteristics, pulmonary fibrosis was diagnosed in 31/149 (21%) patients after six months of follow-up from initial SARS-CoV-2 infection. Complementing this, POLAK et al., 2020 demonstrate that the histopathological picture of pneumonitis related to COVID-19 seems to encompass epithelial, vascular and fibrotic patterns of lung injury. When we analyzed these patterns in patients at different stages of the disease in relation to the onset of symptoms, we identified a relatively clear timeline, as fibrotic changes, for example, interstitial fibrous changes, usually appear 3 weeks after the onset of symptoms. Associated with

these data, (LEE; YIM; PARK, 2022) deal with the existence of concern that pulmonary fibrosis develops as a predominant sequel, since the evaluation of the prevalence of this fibrosis that was grouped in 18 studies through analysis of results of follow-up chest CT, indicated that the combined prevalence of pulmonary fibrosis was 32%, which appears as the second most common radiological sequelae of CT follow-up, only behind ground-glass opacification (GGO).

Farghaly et al. (2022) explains that pulmonary fibrosis has been associated with viral pneumonia, such as coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), COVID-19 can cause atypical pneumonia that progresses to acute lung injury and acute respiratory distress syndrome (ARDS). Accordingly, Fernández-Plata et al. (2022) cites that univariate Cox regression analysis (cyclooxygenase) showed that patients with pneumonia had a significantly higher risk of developing post-COVID-19 pulmonary fibrosis than those without pneumonia (hazard ratio (HR) 2.2, 95%CI: 1.4–3.5, p = 0.0007). Likewise, patients with a positive PCR test > 4 weeks were at significantly higher risk than patients without pneumonia (HR 4.4, 95% CI: 2.1–8.7, p < 0.001). In continuity, Oatis et al. (2022) also presents as risk factors for the development of pulmonary fibrosis in COVID-19, advanced age, comorbidities such as hypertension and diabetes, or prolonged stay in the Intensive Care Unit and duration of mechanical ventilation, a particular host response at a level (LEE; YIM; PARK, 2022), likewise exposes patient demographic factors, including age and smoking, that have been associated with the prevalence of pulmonary fibrosis

In harmony with what Yu et al. (2020) had already presented, Fernández-Plata et al. (2022) explains that, like complications in other organs or systems, cellular damage and a robust innate immune response associated with the production of inflammatory cytokines may contribute to the development of this persistence and that the risk of persistent symptoms in the post-acute phase of COVID-19 is likely related to the duration and severity of a hyperinflammatory state, although how long it persists is unknown.

Oatis et al. (2022) further explains that lung injury appears to be directly related to viral rupture of alveolar epithelial cells and a large number of infected and uninfected macrophages. Monocyte-derived macrophages migrate into lung tissue where they become infected resident macrophages and can produce large amounts of pro-inflammatory cytokines and chemokines, which contribute to local tissue inflammation and a harmful systemic inflammatory response called a cytokine storm. Endothelial dysfunctions are claimed to play a crucial role in the pathology of SARS-CoV-2 and have recently been shown to be related to immune cell recruitment and hyperinflammation and alveolar thrombus formation by platelets and fibrin. Through this context, it can be assumed that there is a very high probability of a transition from acute cases of COVID-19 to cases of patients with post-COVID sequelae, which may be associated with the development of pulmonary fibrosis.

In Oatis et al. (2022) explains the role of galectins, which are responsible for promoting post-COVID-19 lung tissue remodeling and fibrosis, in detail it is stated that galectin-1 (Gal-1) is a key player in different biological functions , including growth, cell proliferation, inflammation/immune response, and carcinogenesis. Recently, the involvement of Gal-1 in the progression of idiopathic pulmonary fibrosis was demonstrated. Under hypoxemic conditions, Gal-1 interacts with focal adhesion kinase-1 (FAK 1) in pulmonary epithelial cells and contributes to the transdifferentiation of fibroblasts into myofibroblasts, while its inhibition reduces FAK 1 activity and alleviates the progression of fibrogenesis.

Gal-3 is another important β-galactoside binding lectin and the most studied in terms of involvement in the pathology of COVID-19 and a possible therapeutic target for this disease. Gal-3 modulates the inflammatory response and tissue repair after lung injury and is highly expressed in fibroblasts, endothelial cells and alveolar macrophages. Furthermore, Gal-3 is involved in the immune response, modulating cytokine secretion and leading to a cytokine storm syndrome, so it makes sense that higher blood levels of Gal-3 were found in severe cases. of COVID-19. Ultimately, it was concluded that fibrosis may be further promoted by Gal-3 through regulation of the endothelial-mesenchymal transition, a key event in the progression of idiopathic pulmonary fibrosis.

Gal-9 is another lectin involved in the pathogenesis of SARS-CoV-2. First, it was found that a baseline of 2.042 pg/mL of plasma Gal-9 can differentiate SARS-CoV-2 infected from uninfected patients with 95% specificity, while a strong correlation with pro-inflammatory mediators was observed. First, the role of Gal-9 in viral binding and entry into alveolar epithelial cells in a dependent manner was demonstrated, increasing the binding affinity of the viral spike protein to type 2 alveolar cells. Interestingly, pro-inflammatory mediators interact with Gal-1, -3 and -8, which act in concert through the N- and O-linked glycans located on the viral S protein, and assuming the formation of a galectin-glycan network on the surface of the virus and endothelial cells, generated by the angiotensin-converting receptor (ACE 2), β1 integrin and CD44. However, Gal-1 and -8 have been shown to induce conformational changes in a IIb β3-integrin surface receptors on platelets and lead to fibrinogen binding and platelet activation and aggregation.

Lastly, Farghaly et al. (2022), also exposes that the risk of mortality in patients with COVID-19 with pulmonary fibrosis increases, as pulmonary fibrosis is a progressive disease that leads to respiratory failure and is associated with a poor prognosis; Lung transplantation is the only treatment shown to improve outcomes.

CONCLUSION

Post-COVID-19 pulmonary fibrosis is a serious complication that leads to permanent lung damage or death. With the emerging spread of COVID-19, long-term sequelae involving pulmonary fibrosis become a major health threat.

The great possibility of developing this disease after becoming infected with SARS-Cov-2 highlights the importance of monitoring patients diagnosed with

COVID-19 regardless of their clinical evolution.

Likewise, the importance of inflammatory components, independent of the severity of the disease, but associated with an increased relative risk of developing alterations similar to pulmonary fibrosis, was reported. This last item is an element to consider as a risk factor in post-COVID-19 patients, regardless of the clinical condition of the patients. However, it is safe to say that early detection of this pathology can help prevent or at least delay its development.

Therefore, it is appropriate to focus on the medium and long-term consequences in recovered patients, as this condition is becoming a public health problem, which will require current and future multidisciplinary efforts to treat these patients.

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REFERENCES

YESUDHAS, D. SRIVASTAVA, A.; GROMIHA, M. M. COVID-19 outbreak: history, mechanism, transmission, structural studies and therapeutics**. Infection**, v. 49, n. 2, 4 set. 2020.

Chanda D, Otoupalova E, Smith SR, Volckaert T, De Langhe SP, Thannickal VJ.. Developmental pathways in the pathogenesis of lung fibrosis. **Molecular Aspects of Medicine**, v. 65, p. 56–69, fev. 2019.

HU, B.; HUANG, S.; YIN, L. The Cytokine Storm and COVID-19. **Journal of Medical Virology**, v. 93, n. 1, 27 jun. 2020.

Montani D, Savale L, Noel N, Meyrignac O, Colle R, Gasnier M, Corruble E, Beurnier A, Jutant EM, Pham T, Lecoq AL, Papon JF, Figueiredo S, Harrois A, Humbert M, Monnet X; COMEBAC Study Group. Post-acute COVID-19 syndrome. **European Respiratory Review**, v. 31, n. 163, p. 210185, 9 mar. 2022.

Mohammadi A, Balan I, Yadav S, Matos WF, Kharawala A, Gaddam M, Sarabia N, Koneru SC, Suddapalli SK, Marzban S. Post-COVID-19 Pulmonary Fibrosis. **Cureus**, 2 mar. 2022.

d'Ettorre G, Gentilini Cacciola E, Santinelli L, De Girolamo G, Spagnolello O, Russo A, Tarsitani L, Ciccozzi M, Mastroianni CM, d'Ettorre G, Ceccarelli G. Covid-19 sequelae in working age patients: A systematic review. **Journal of Medical Virology**, v. 94, n. 3, p. 858–868, 22 out. 2021.

Zhong H, Zhou Y, Mei SY, Tang R, Feng JH, He ZY, Xu QY, Xing SP. Scars of COVID-19: A bibliometric analysis of post-COVID-19 fibrosis. **Frontiers in Public Health**, v. 10, 20 set. 2022.

Fernández-Plata R, Higuera-Iglesias AL, Torres-Espíndola LM, Aquino-Gálvez A, Velázquez Cruz R, Camarena Á, Chávez Alderete J, Romo García J, Alvarado-Vásquez N, Martínez Briseño D, Castillejos-López M, Group RW. Risk of Pulmonary Fibrosis and Persistent Symptoms Post-COVID-19 in a Cohort of Outpatient

Health Workers. **Viruses**, v. 14, n. 9, p. 1843, 23 ago. 2022.

Oatis D, Simon-Repolski E, Balta C, Mihu A, Pieretti G, Alfano R, Peluso L, Trotta MC, D'Amico M, Hermenean A. Cellular and Molecular Mechanism of Pulmonary Fibrosis Post-COVID-19: Focus on Galectin-1, -3, -8, -9. **International Journal of Molecular Sciences**, v. 23, n. 15, p. 8210, 26 jul. 2022.

Farghaly S, Badedi M, Ibrahim R, Sadhan MH, Alamoudi A, Alnami A, Muhajir A. Clinical characteristics and outcomes of post-COVID-19 pulmonary fibrosis. **Medicine**, v. 101, n. 3, p. e28639, 21 jan. 2022.

CARFÌ, A.; BERNABEI, R.; LANDI, F. Persistent symptoms in patients after acute COVID-19. **JAMA**, v. 324, n. 6, p. 603–605, 9 jul. 2020.

Yu M, Liu Y, Xu D, Zhang R, Lan L, Xu H. Prediction of the Development of Pulmonary Fibrosis Using Serial Thin-Section CT and Clinical Features in Patients Discharged after Treatment for COVID-19 Pneumonia. **Korean Journal of Radiology**, v. 21, n. 6, p. 746, 2020.

LEE, J. H.; YIM, J.-J.; PARK, J. Pulmonary function and chest computed tomography abnormalities 6–12 months after recovery from COVID-19: a systematic review and meta-analysis. **Respiratory Research**, v. 23, n. 1, 6 set. 2022.

Polak SB, Van Gool IC, Cohen D, von der Thüsen JH, van Paassen J. A systematic review of pathological findings in COVID-19: a pathophysiological timeline and possible mechanisms of disease progression. **Modern Pathology**, p. 1–11, 22 jun. 2020.

Leung TYM, Chan AYL, Chan EW, Chan VKY, Chui CSL, Cowling BJ, Gao L, Ge MQ, Hung IFN, Ip MSM, Ip P, Lau KK, Lau CS, Lau LKW, Leung WK, Li X, Luo H, Man KKC, Ng VWS, Siu CW, Wan EYF, Wing YK, Wong CSM, Wong KHT, Wong ICK. Short- and potential long-term adverse health outcomes of COVID-19: a rapid review. **Emerging Microbes & Infections**, v. 9, n. 1, p. 2190–2199, 1 jan. 2020.

Isidori AM, Giannetta E, Pofi R, Venneri MA, Gianfrilli D, Campolo F, Mastroianni CM, Lenzi A, d'Ettorre G. Targeting the NO-cGMP-PDE5 pathway in COVID-19 infection. The DEDALO project. **Andrology,** v. 9, n. 1, p. 33–38, 3 jul. 2020.