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Respiratory complications following SARS-CoV-2 infection

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DOCTORAL THESIS

Respiratory complications following SARS-CoV-2 infection

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“A lo que partió antes de tiempo

y, aunque fugaz,

sigue acompañándome en mi voluntad

de seguir construyendo”

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LIST OF ABBREVIATIONS

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6MWT - 6-minute walk test

95% CI - 95% confidence interval

ACE2 - Angiotensin-converting enzyme 2

AEs - Adverse events

ARDS - Acute respiratory distress syndrome

AW - Prevalence of airway

BAL - Bronchoalveolar lavage

BMI - Body Mass Index

CO - Carbon monoxide

COP - Cryptogenic organizing pneumonia

COPD - Chronic obstructive pulmonary disease

COVID-19 - Coronavirus 2019

CRP - C-reactive protein

CT - Computed tomography

DLCO - Diffusing capacity of the lung for carbon monoxide

DPP9 - Dipeptidyl peptidase 9

ECMO - Extracorporeal membrane oxygenation

eCRF - Electronic case report form

FEV1 - Forced expiratory volume in 1 second

FVC - Forced vital capacity

GINA - Global Initiative for Asthma

GLI - Global Lung Function Initiative

HFNC - High-flow nasal cannula

HIV - Human immunodeficiency virus

HRCT- Chest high-resolution computed tomography

HRQoL - Health-related quality of life

ICU - Intensive care unit

IgE - Immunoglobulin E

IL - Interleukin

ILD - Interstitial lung diseases

IMV - Invasive mechanical ventilation

IPF - Idiopathic pulmonary fibrosis

LIST OF ABBREVIATIONS

IQR - Interquartile range

JAK - Janus Kinase

LDH - Lactate dehydrogenase

MAR - Missing at random

MERS-CoV - Middle East Respiratory Syndrome Coronavirus

mFAS - Modified full analysis set

mMRC - Modified Medical Research Council

MMRM - Mixed model for repeated measures

NIV - Non-invasive ventilation

OP - Organizing pneumonia

OR - Odds ratio

OSAS - Obstructive sleep apnea syndrome

PP - Per-protocol

SARS-CoV - Severe acute respiratory syndrome Coronavirus

SARS-CoV-2 - Severe acute respiratory syndrome Coronavirus 2

SD - Standard deviation

TMPRSS2 - Transmembrane serine protease 2

WHO - World Health Organization

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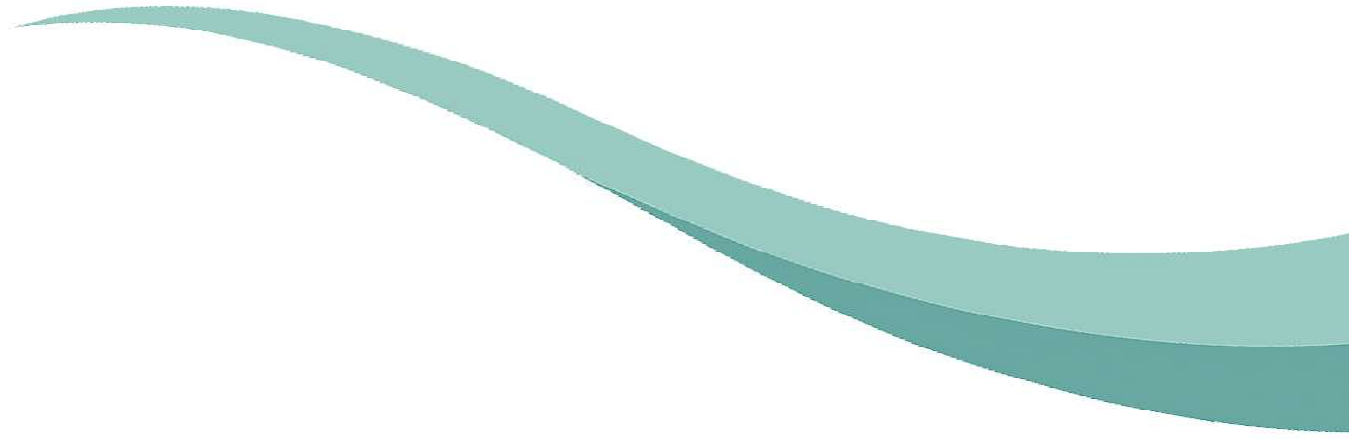

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SUMMARY

Since its emergence in late 2019 in Wuhan, the zoonotic disease caused by the coronavirus-19 (COVID-19) has rapidly spread worldwide. Although many cases are mild or asymptomatic, a proportion of patients develop Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) pneumonia, which can lead to various long-term pulmonary complications, affecting both the lung parenchyma and the airways. Characterizing these complications is essential, as some cases may require treatment to prevent permanent sequelae. In this context, adequate follow-up after hospital discharge is crucial for these patients.

This doctoral thesis aimed to study the presence of respiratory complications following SARS-CoV-2 pneumonia based on the viral involvement itself, the acute treatment administered, and the presence of comorbidities (such as bronchial asthma), as well as to evaluate the need for additional medical interventions for these complications.

Five studies were conducted. First, the impact of dexamethasone during SARS-CoV-2 pneumonia on respiratory complications was assessed, revealing that patients treated with dexamethasone experienced less dyspnea, improved pulmonary function, and fewer signs of fibrosis in follow-up assessments. Second, the prevalence and characteristics of airway involvement were analyzed, revealing that it was common among patients hospitalized with COVID-19 and associated with older age, a history of smoking, lower body mass index (BMI), and cardiometabolic comorbidities. Third, the prevalence of tracheomalacia following hospitalization for SARS-CoV-2 pneumonia was examined, with findings indicating that 0.8% of patients exhibited this complication. Fourth, the incidence and severity of respiratory sequelae were compared between asthmatic and non-asthmatic patients; no significant differences were found in the frequency of sequelae between the two groups. However, asthmatic patients exhibited greater bronchial thickening and/or tracheomalacia, whereas bronchiectasis was more common among non-asthmatic individuals.

Finally, a fifth study involved the design of a clinical trial to determine the optimal dosage of oral corticosteroids for one of the most common complications of COVID-19: organizing pneumonia. The study demonstrated that a descending regimen of 0.5 mg/kg/day over three months was equally effective but associated with fewer adverse effects compared to the conventional treatment regimens, which involve higher doses and an unrestricted duration of six months.

RESUMEN

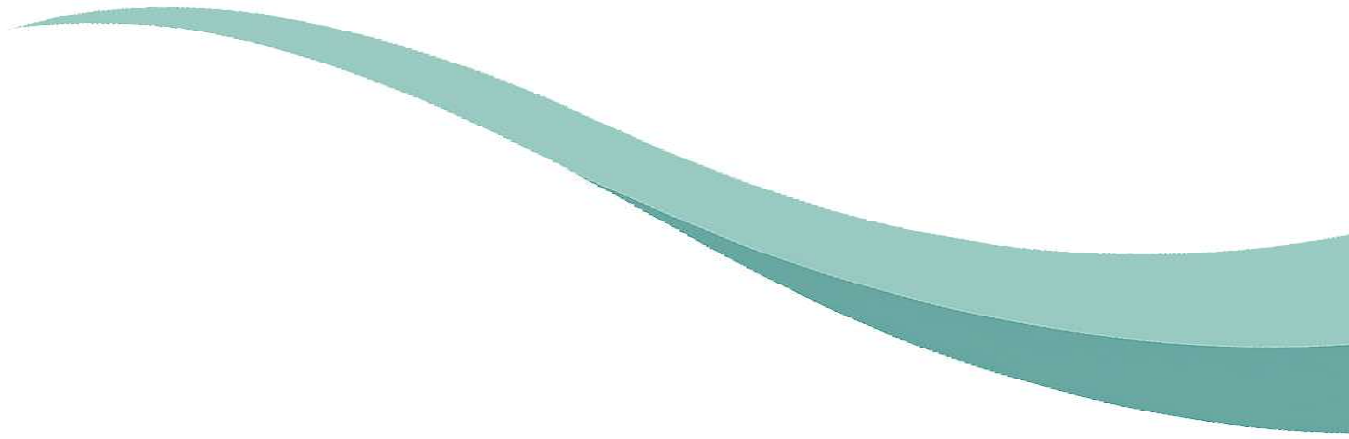
Desde su aparición a finales de 2019 en Wuhan, la enfermedad zoonótica causada por el COVID-19 se ha diseminado rápidamente por todo el mundo. Aunque muchos casos son leves o asintomáticos, una proporción de pacientes desarrolla neumonía por SARS-CoV-2, lo que puede derivar a largo plazo a diversas complicaciones pulmonares, tanto a nivel parenquimatoso como en la vía aérea. Caracterizar estas complicaciones es fundamental, ya que en algunos casos pueden requerir tratamiento para prevenir secuelas permanentes. En este contexto, resulta crucial realizar un seguimiento adecuado tras el alta hospitalaria de estos pacientes.

Esta tesis doctoral tuvo como objetivo estudiar la presencia de complicaciones respiratorias después de una neumonía por SARS-CoV-2 en base a la propia afectación viral, al tratamiento agudo administrado y la presencia de comorbilidades (asma bronquial) y evaluar la necesidad de intervenciones médicas adicionales para estas complicaciones.

Se plantearon cinco estudios. En primer lugar, se evaluó el impacto de la dexametasona durante la neumonía por SARs-CoV-2 en las complicaciones respiratoria en los pacientes tratados con dexametasona tuvieron menos disnea, mejor función pulmonar y menos signos de fibrosis en el seguimiento evolutivo. En segundo lugar, se analizó la prevalencia y las características de afectación de las vías aérea y se demostró que afectación de las vías respiratorias fue común entre los pacientes hospitalizados con COVID-19 y se asoció con mayor edad, antecedentes de tabaquismo, menor índice de masa corporal (IMC) y comorbilidades cardiometabólicas. En tercer lugar, se analizó la prevalencia de traqueomalacia tras la hospitalización por neumonía por SARS-CoV-2; el 0,8% de los pacientes presentaban esta complicación. En cuarto lugar, se comparó la incidencia y gravedad de secuelas respiratorias en pacientes asmáticos y no asmáticos; no se hallaron diferencias en la frecuencia de secuelas entre ambos grupos. Sin embargo, los pacientes asmáticos mostraron mayor engrosamiento bronquial y/o traqueomalacia, mientras que las bronquiectasias fueron más comunes en no asmáticos.

Finalmente se diseñó, en un quinto estudio, un ensayo clínico para determinar que dosis de corticoides orales podría ser más útil para una de las complicaciones más frecuentes de la COVID-19 como es la neumonía organizada. Se demostró que una dosis de 0.5 mg/Kg/día en pauta descendiente durante tres meses es igual de efectiva y con menos efectos adversos que los esquemas clásicos de tratamiento de esta entidad con dosis superiores y una duración libre de seis meses.

1. INTRODUCTION



1.1. SARS-COV-2 INFECTION

1.1.1. Definition and Epidemiology

COVID-19 belongs to the group of betacoronaviruses, which are viruses that infect a wide range of animals and can cause respiratory infections ranging from mild to severe in humans. By the end of 2019, the first cases of the disease, officially named SARS-CoV-2, were identified in Wuhan (1). The disease caused by COVID-19 spread worldwide, and on March 11, 2020, the World Health Organization (WHO) declared it a global pandemic. As of December 31, 2024, the virus has resulted in more than 777 million confirmed cases and over 7.08 million deaths worldwide (2).

Highly pathogenic coronaviruses of zoonotic origin had previously affected humans, causing severe respiratory diseases. Specifically, in 2002, the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) emerged, and in 2012, the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) was identified (3,4).

Determining the incidence at the national level and in Catalonia during the pandemic is highly challenging, as testing was not always conducted to confirm cases, and in some instances, the infection was pauci-symptomatic. Figure 1 presents the recorded hospitalizations due to COVID-19 in our setting, as well as intensive care unit (ICU) admissions from 2020 to 2023 and mortality rates over the same period.

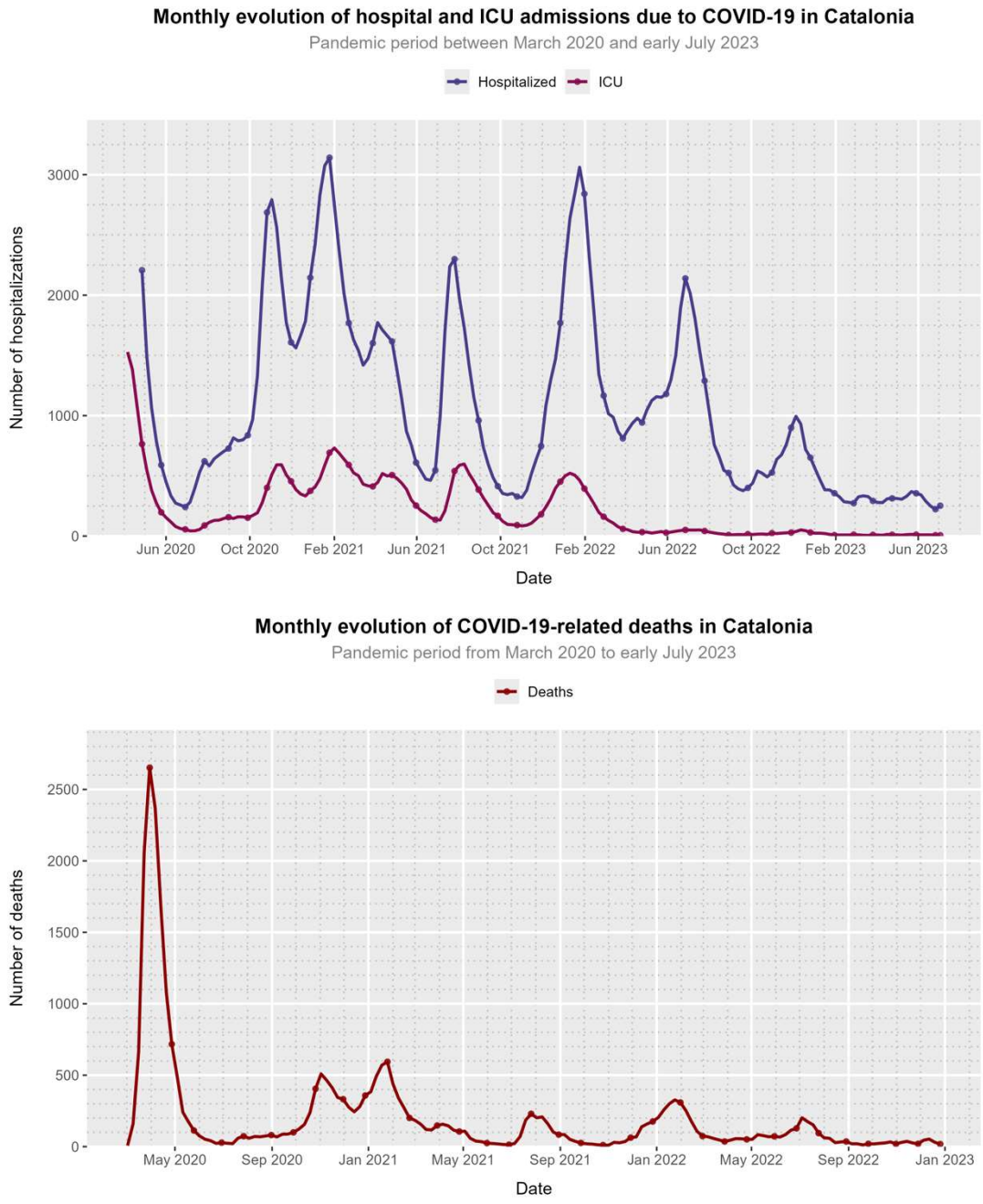


Figure 1: Representation of the waves in Catalonia, adapted from Institut d'Estadística de Catalunya (Idescat)

1.1.2. Pathogenesis

The virus enters the human body through the upper respiratory tract and primarily binds to the cells of the nasal cavity, where it initiates its replication (5). The interaction occurs between the spike (S) protein of the virus and the angiotensin-converting enzyme 2 (ACE2), which is a receptor widely expressed in the epithelial cells of the respiratory tract. The

transmembrane serine protease 2 (TMPRSS2) facilitates this interaction by enabling the fusion of the virus with the cell membrane and its entry into the cytoplasm (6).

In the cytoplasm of the host cell, the virus utilizes the cellular machinery for replication, transcription, and translation of new viral particles (7). During this process, the host activates its innate immune response; however, SARS-CoV-2 has developed mechanisms to evade this response by blocking interferon production and reducing the activation of macrophages and dendritic cells. Consequently, uncontrolled viral replication occurs, leading to an increase in viral load within the organism (8,9).

In the alveoli, type II alveolar cells express a high number of ACE2 receptors, leading to an inflammatory response that triggers diffuse alveolar damage, characterized by macrophage activation and the infiltration of neutrophils and lymphocytes into pulmonary tissue. This process results in the disruption of the alveolar-capillary barrier, pulmonary edema, and the formation of hyaline membranes. In severe cases, this condition can progress to acute respiratory distress syndrome (ARDS) (10). In some patients, the activation of the immune system becomes dysregulated, resulting in a cytokine storm due to the massive release of proinflammatory mediators, which amplify inflammation and cause multi-organ tissue damage (11). In Figure 2, the pathophysiology of SARS-CoV-2 infection is summarized.

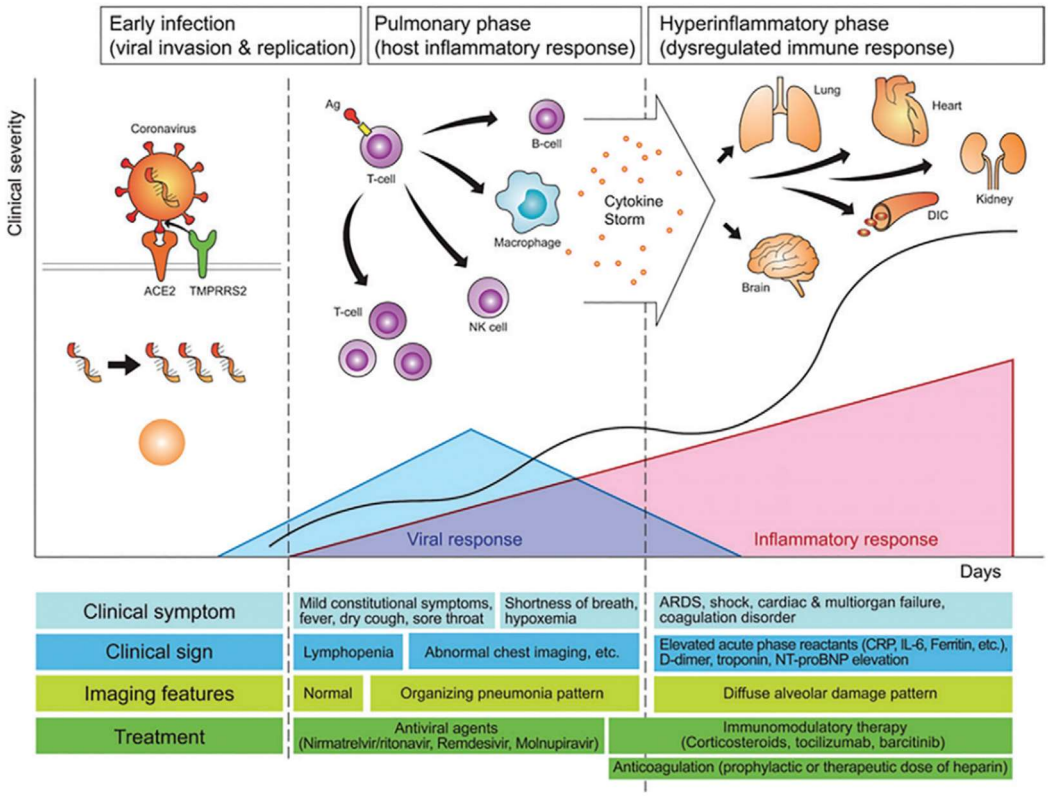


Figure 2: Pathophysiology of SARS-CoV-2 infection according to Jeong et al. (12)

1.1.3. Clinical presentation

Around 80% of patients with SARS-CoV-2 infection present with mild symptoms or an almost pauci-symptomatic clinical course. The main symptoms include fever, fatigue, dry cough, anosmia, ageusia, and muscle pain, while less common symptoms include pharyngolaryngotracheitis, diarrhea, conjunctivitis, or headache (13).

However, in the remaining 20% of patients, alveolar inflammation progresses due to viral replication, leading to pulmonary infiltrates in the form of viral pneumonia associated with hypoxemic respiratory failure. Within this group, approximately 5% of patients develop an excessive proinflammatory response characterized by a cytokine storm, resulting in diffuse alveolar damage and ARDS. This excessive inflammation not only affects the lungs but can also lead to dysfunction in other organs and multi-organ failure (12,13).

It is important to note that the clinical progression described above was observed during the initial phases of the pandemic. As the virus has evolved and vaccination campaigns have been implemented, the clinical presentation has progressively shifted toward less severe forms (14,15).

1.1.4. Treatment

Initially, various treatment modalities were applied, many of which were based on expert recommendations or prior experience in treating similar diseases. Antimalarial drugs such as hydroxychloroquine were used; however, subsequent studies did not demonstrate significant clinical benefits and identified potential cardiac risks associated with their use. As a result, the administration of hydroxychloroquine was discouraged in patients with COVID-19 (16). Other treatments initially used included antiretroviral drugs used for human immunodeficiency virus (HIV), such as Lopinavir/Ritonavir. However, subsequent studies demonstrated that they did not provide significant benefits and were associated with a high incidence of adverse effects (17). Azithromycin, a macrolide antibiotic with broad antibacterial, anti-inflammatory, and antiviral properties, was also routinely used at the beginning of the pandemic. However, studies demonstrated that this treatment did not reduce recovery time, the risk of hospitalization, or mortality (18,19).

As the pandemic progressed, scientific evidence supporting the use of certain medications became available. Among antiviral drugs, Remdesivir was found to reduce recovery time in hospitalized patients with moderate COVID-19, particularly when administered in the early stages of the disease. However, it did not demonstrate a significant impact on reducing mortality, the need for mechanical ventilation, or the duration of hospitalization. (20,21).

Secondly, the administration of dexamethasone at a daily dose of 6 mg for up to 10 days was shown to reduce 28-day mortality by one-third in patients requiring mechanical ventilation and by one-fifth in those receiving supplemental oxygen. This underscores its effectiveness in patients with severe SARS-CoV-2 infection requiring oxygen therapy. (22).

Furthermore, studies demonstrated that in patients with moderate to severe ARDS, intravenous dexamethasone, when combined with standard treatment, significantly increased the number of ventilator-free days over a 28-day period compared to standard treatment alone (23). These findings establish dexamethasone as a key advancement in COVID-19 management, particularly for its role in modulating the inflammatory response in severe cases. A dosage of 6 mg per day for 10 days has been identified as effective, with no clear evidence supporting higher doses or alternative treatment durations (24–26).

Thirdly, a monoclonal antibody targeting interleukin-6, known as Tocilizumab, has demonstrated efficacy in reducing mortality and has been used to treat the 'cytokine storm' in patients with severe COVID-19 (27–29).

These three treatments have been the most widely used for managing COVID-19 patients. Other treatments, such as Janus Kinase (JAK) inhibitors like Baricitinib and Ruxolitinib or convalescent plasma, have been employed in the context of clinical trials but have not been routinely used in our setting. (30–32).

Alongside treatments for managing acute-phase COVID-19, the development of vaccines was crucial in mitigating the spread of SARS-CoV-2 and reducing disease severity and mortality (33). The first mRNA vaccines, such as BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna), emerged in late 2020 and demonstrated high efficacy in preventing severe symptomatic infection, hospitalization, and death (34,35). Subsequently, various COVID-19 vaccines have been developed, providing improved protection for the general population, particularly for the most vulnerable individuals.

1.2. RESPIRATORY COMORBIDITIES AND SARS-COV-2 INFECTION

SARS-CoV-2 infection directly affects the respiratory system, which is why it was initially hypothesized that the presence of chronic respiratory diseases could represent a significant risk factor for disease progression (36). The following section will address the main

respiratory comorbidities in relation to SARS-CoV-2 infection and their impact on the clinical progression of patients.

1.2.1. Chronic obstructive pulmonary disease

Patients with Chronic obstructive pulmonary disease (COPD) have a higher risk of severe COVID-19 compared to the general population. The hospitalization rate for COVID-19 in COPD patients is significantly higher, and there is an increase in mortality (37–39). Currently, there is no evidence that standard COPD treatment, including inhaled corticosteroids when indicated, affects the prognosis of SARS-CoV-2 infection. Therefore, it is recommended to maintain the treatment without modifications in patients with COPD and SARS-CoV-2 infection (38).

1.2.2. Interstitial lung diseases

The COVID-19 pandemic has significantly affected patients with interstitial lung diseases (ILD), increasing the risk of severe infection, hospitalization, and mortality (40,41). SARS-CoV-2 infection has been observed to exacerbate or accelerate the progression of pulmonary fibrosis in these patients, although its long-term effects remain unclear (40).

1.2.3. Obstructive sleep apnea syndrome

Obstructive sleep apnea syndrome (OSAS) has been identified as a risk factor for COVID-19 infection and is associated with increased disease severity (42). Untreated OSAS increases the likelihood of ARDS, ICU admission, invasive mechanical ventilation, and mortality (43,44).

1.2.4. Bronchiectasis and cystic fibrosis

Although studies are limited, patients with bronchiectasis have been observed to have a higher risk of severe disease, hospitalization, and a probable increase in mortality (45). In patients with cystic fibrosis, the impact of SARS-CoV-2 infection was lower than expected, likely due to the protective measures implemented. However, it was observed that in

patients with poorer pulmonary function or other associated comorbidities, such as diabetes mellitus, the infection tended to be more severe (36).

1.2.5. Asthma

Asthmatic patients have an increased susceptibility to viral respiratory infections, which tend to be more severe compared to the general population (46). This vulnerability could be explained by an alteration in the production and release of interferons (α, β, γ) in these patients (47). It is estimated that up to 80% of asthma exacerbations are associated with various viruses, including certain types of coronaviruses (48). This led to the initial assumption during the pandemic that individuals with asthma might be particularly susceptible to SARS-CoV-2 infection.

Numerous studies have been published to assess whether asthma genuinely increases the risk of contracting COVID-19, and current evidence suggests that it does not significantly elevate the risk (49,50). It has also been demonstrated that having asthma does not increase the severity of SARS-CoV-2 infection, the risk of hospitalization, the need for ICU admission, or mechanical ventilation compared to the non-asthmatic population (51,52). Having asthma and contracting COVID-19 does not increase the mortality risk of the disease. Some studies even suggest that it may reduce the risk (53).

Several factors and mechanisms have been proposed to explain why asthma may not increase the risk or could even offer protection against SARS-CoV-2 infection (Figure 3). It has been suggested that the T2 response may confer lower susceptibility compared to asthma with a non-T2 response. In this regard, our group demonstrated in a study conducted during the first wave, involving 2,226 patients, that the prevalence of asthma was 3.2%. The study involved 71 patients, of whom 40% exhibited a T2 response, compared to 59% with a non-T2 response (54).

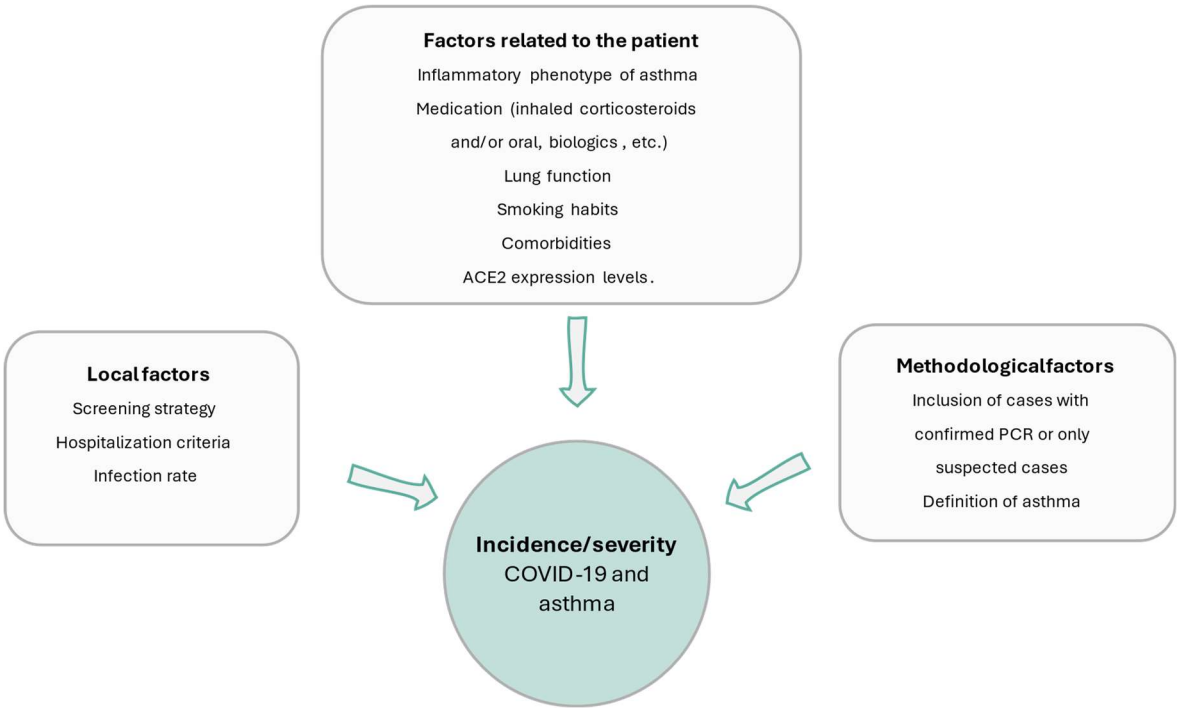


Figure 3: Factors and mechanisms by which asthma could influence the incidence and severity of SARS-CoV-2 infection (adapted from Eger et al.) (55)

To explain this occurrence, several hypotheses have been proposed. Firstly, the T2 response is characterized by eosinophilic inflammation, and it has been demonstrated that having eosinophil counts above 200 cells/mm³ decreases the risk of COVID-19 mortality (56). Secondly, studies have shown that allergic asthma is associated with reduced levels of ACE2 and TMPRSS2, thereby decreasing viral entry into cells (57). Indeed, it has been demonstrated that interleukin-13 (IL-13) and immunoglobulin E (IgE) reduce the expression of the ACE2 receptor (58). Thirdly, the deficiency in interferon production, particularly observed in asthmatic patients with a T2-Th2 response, may prevent the proinflammatory state associated with severe COVID-19 (59). Finally, regarding treatment with inhaled corticosteroids, evidence suggests that they do not increase the severity of COVID-19, and some authors have even proposed them as a protective factor (60). In this regard, several clinical trials were conducted to evaluate the use of inhaled corticosteroids in COVID-19 treatment to prevent disease progression. The findings suggest that the addition of inhaled corticosteroids to standard care in hospitalized patients with COVID-19 pneumonia is safe and may reduce the risk of disease progression (61).

Focusing on the severity of COVID-19 in asthmatic patients, the T2 response is associated with lower disease severity. In our study, patients with a T2 response had a higher proportion of mild cases compared to those with a non-T2 response (45% vs 12%). No significant differences were found between the two groups in terms of age, sex, smoking status, comorbidities, asthma severity, or administered treatments (54). When analyzing the relationship between asthma severity there does not appear to be an increase in the severity of viral infection. In a study by Rial et al., which analyzed a cohort of 545 patients with severe asthma treated with biological therapies, 35 were diagnosed with COVID-19, and only 8 required hospitalization. When comparing these data with asthmatic patients hospitalized for COVID-19 without biological treatment in Spain, no significant differences were found in disease severity, presence of comorbidities, ICU admissions, or mortality (62).

Therefore, we can conclude that bronchial asthma does not significantly increase the risk of COVID-19 infection or disease severity, with this effect being particularly evident in patients with a T2 response (49–51,53,54).

1.3. RESPIRATORY COMPLICATIONS AFTER SARS-COV-2 PNEUMONIA

Respiratory complications are among the most common conditions following COVID-19, particularly in patients who developed severe pneumonia, ARDS, or had pre-existing pulmonary diseases (63). Since the onset of the pandemic, various persistent respiratory symptoms have been described, including dyspnea, cough, and sputum production, among others, following SARS-CoV-2 pneumonia. In many cases, these symptoms are associated with abnormalities in pulmonary function tests or findings on chest computed tomography (CT) scans (64). Among the findings on chest CT scans, parenchymal abnormalities have been the most extensively studied; however, airway abnormalities have also been described (63).

These respiratory complications can significantly impact patients' quality of life by limiting their ability to engage in physical activities and increasing the risk of long-term

complications. Therefore, monitoring patients following SARS-CoV-2 pneumonia is crucial for identifying respiratory complications and assessing the need for therapeutic interventions to prevent permanent respiratory sequelae.

1.3.1. Parenchymal respiratory complications

Since the onset of the COVID-19 pandemic, increasing concern has emerged regarding potential parenchymal complications following SARS-CoV-2 infection. Similar viruses, such as SARS-CoV and MERS-CoV, had previously demonstrated persistent pulmonary abnormalities on CT scans, even years post-infection, including fibrotic changes (65). This suspicion was confirmed following the first publications on the follow-up of patients with SARS-CoV-2 pneumonia in China. At six months, approximately 22-56% of patients exhibited ground-glass opacities and irregular lines on chest CT, along with impaired pulmonary diffusion capacity (64). Subsequent studies have confirmed similar findings. For instance, a meta-analysis including over 70 studies revealed that half of the patients exhibited inflammatory sequelae on chest CT. In 38% of cases, these findings were associated with impaired diffusion capacity, and in 17%, with a restrictive ventilatory defect (66).

Regarding inflammatory complications, the most frequently observed parenchymal disease has been organizing pneumonia (67). However, other entities have also been reported, including nonspecific lymphocytic pneumonia, hypersensitivity pneumonitis, and eosinophilic pneumonia (5,63,68,69). In some cases, reticular patterns or ground-glass opacities have been observed without a definitive diagnosis being established.

When these respiratory complications progress over time, particularly when targeted treatment is required but not initiated early, irreversible fibrotic changes may develop. In fact, it is estimated that fibrotic sequelae are present in approximately 29% of patients (66). For this reason, it is important to conduct a targeted assessment of these complications and to initiate treatment if necessary.

1.3.1.1. Organizing pneumonia

Organizing pneumonia (OP) is an ILD characterized by a pattern of lung tissue repair following injury. The pathogenesis of OP involves inflammation in which the bronchioles and alveoli are filled with granulation tissue, disrupting the normal lung architecture(70,71).

This inflammatory response is a nonspecific lung reaction to damage, though it may also occur without a known cause, in which case it is termed "cryptogenic". Cryptogenic organizing pneumonia (COP) is a rare condition with an undetermined incidence and prevalence. While it was previously estimated that approximately 50% of OP cases were COPs, the majority are now considered secondary. Indeed, fewer than 15% are classified as cryptogenic, probably due to advances in the diagnosis of secondary causes (72,73). Secondary causes of OP include infectious diseases, rheumatologic diseases, radiotherapy, drugs, organ transplantation, hematologic cancer and inflammatory bowel disease, with post infectious etiologies being the most prevalent (70,71). Although it is well known that certain viral or bacterial infections can cause OP, the prevalence in these conditions is not well established and depends on the type of infection and its severity. In the context of SARS-CoV-2 infection, some studies emphasize that OP is one of the most significant complications (74,75) with an estimated prevalence of between 12% and 32% (76,77).

Clinically, it presents with symptoms of subacute onset. The most common symptoms include dyspnea, which worsens particularly with physical activity, and a dry cough. In some cases, patients may also exhibit flu-like symptoms, including fever (70,78–80).

The diagnosis requires a multidisciplinary approach that integrates clinical and radiological evaluation, and in some cases, histopathological sampling (70). Laboratory tests are nonspecific, although inflammatory markers may be elevated (78,80). Pulmonary function tests can be normal in some cases or reveal a restrictive ventilatory disorder and/or a decreased diffusing capacity for carbon monoxide (DLCO) (70,79).

Radiologically, chest X-rays reveal bilateral pulmonary opacities that may appear patchy or diffuse with areas of consolidation. On chest CT, a predominant pattern of ground-glass opacities or multifocal peripheral consolidations can be observed, which may present with or without an air bronchogram. These lesions can be unilateral or bilateral and are distributed throughout all pulmonary zones, although they tend to be slightly more predominant in the subpleural region and the lower lung zones. A linear or band-like pattern with subpleural opacities parallel or perpendicular to the pleura is another possible manifestation. A characteristic finding that may appear is migratory opacities, showing spontaneous regression in some areas while new consolidations emerge in others. A specific but uncommon sign (found in less than 5% of cases) of organizing pneumonia is the reversed halo sign (also known as the atoll sign) (70,78,81,82).

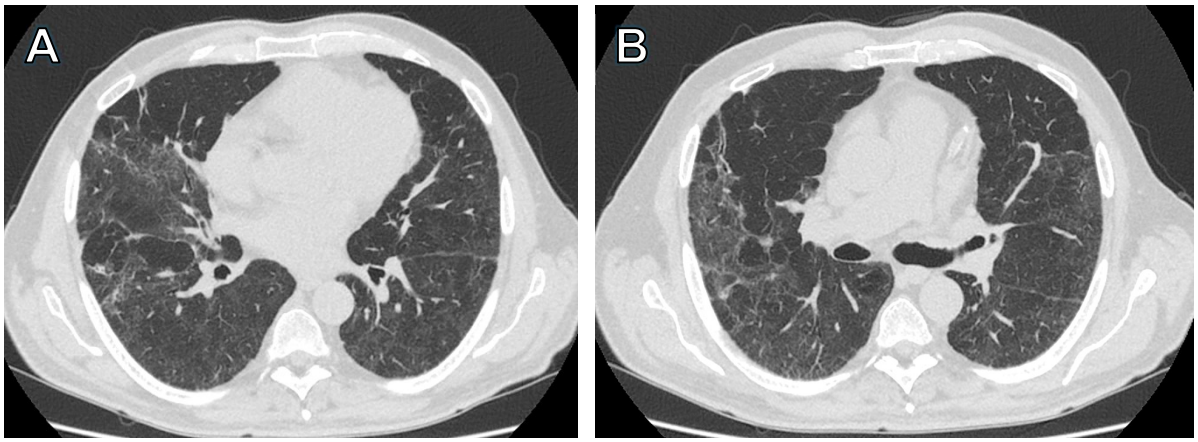


Figure 4: CT performed six months after COVID-19 infection showing radiological features consistent with organizing pneumonia. The patient is a 71-year-old male who was previously admitted to the ICU with SARS-CoV-2 pneumonia, requiring ventilatory support with high-flow nasal cannula (HFNC).

In some cases, bronchoscopy is required to establish a definitive diagnosis. Bronchoalveolar lavage (BAL) analysis is recommended to rule out infections or other pathologies, such as eosinophilic pneumonia or alveolar hemorrhage (78,79,83). Characteristic findings in biopsy samples of OP include granulation tissue buds composed of fibroblasts and myofibroblasts embedded in connective tissue, preserved pulmonary

architecture, mild chronic interstitial inflammation, and a patchy distribution (81,84). In figure 5 shows a biopsy from a patient diagnosed with OP after SARS-CoV-2 pneumonia.

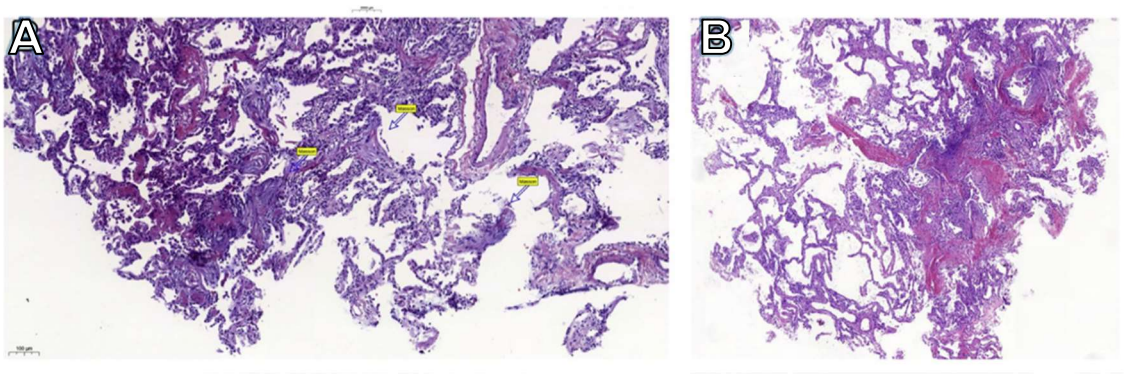


Figure 5: Biopsy consistent with organizing pneumonia, adapted from Culebras et al. (76) **A.** Hematoxylin and eosin-stained section showing expanded interstitium with chronic inflammation and fibroblastic plugs within the alveolar spaces (arrows). **B.** Low-magnification hematoxylin and eosin-stained section demonstrating partially collagenized Masson bodies.

To date, no randomized controlled trials evaluating potential therapies for OP have been published. Spontaneous remission is uncommon. Systemic glucocorticoid therapy is the preferred treatment for symptomatic patients (70,84). The typical initial dosage of prednisone is 0.5 to 1 mg per kilogram of ideal body weight per day, up to 60 mg, given once daily. This dose is maintained for 2 to 4 weeks, then gradually reduced to 0.25 mg per kilogram per day over 4 to 6 months. If the patient improves, the dose is tapered to zero over the next 6 to 12 months (70). Alternative treatment options, though supported by limited evidence, include macrolides, due to their anti-inflammatory properties, as well as immunosuppressive therapies such as cyclophosphamide, azathioprine, mycophenolate, and rituximab (70).

1.3.1.2. Permanent fibrotic sequelae

As previously mentioned, fibrotic changes following SARS-CoV-2 pneumonia may represent an irreversible respiratory sequelae. Several risk factors for the development of fibrotic changes have been described. First, the severity of COVID-19, as patients with severe disease are at higher risk of developing diffuse alveolar damage secondary to ARDS

(85). This damage may result from direct viral infection or, more commonly, from the immune response, leading to severe inflammation and fibrotic remodeling of the lung tissue (86).

Male sex, older age, and preexisting conditions such as obesity, type 2 diabetes, and hypertension have also been associated with a higher incidence of fibrotic changes (63,75). Moreover, certain genes associated with idiopathic pulmonary fibrosis (IPF), such as dipeptidyl peptidase 9 (DPP9), have also been linked to increased severity of COVID-19 (87). These risk factors had already been associated with IPF, which has led some authors to highlight similarities between the two conditions (Figure 6).

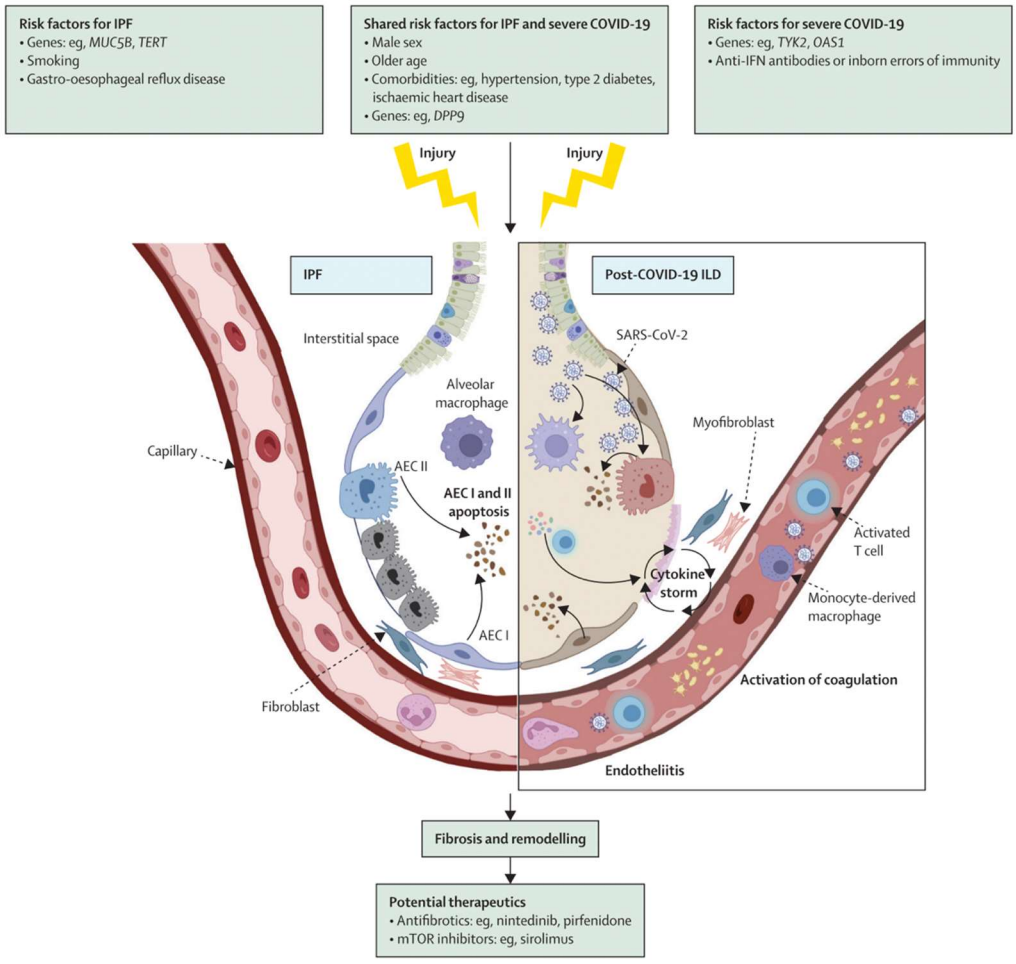


Figure 6: Similarities between IPF and post-COVID fibrosis. Adapted from Singh et al. (63)

Fortunately, although some initial similarities were observed and there was concern that many patients might experience unfavorable progression, our clinical experience indicates

that the progression of fibrotic changes is not common. In most cases, we have observed that these changes remain as a permanent sequela without progressive evolution.

Nevertheless, multiple treatments and clinical trials have been developed for the management of post-COVID-19 fibrosis. Firstly, some therapies used during the acute phase may play a role in reducing fibrotic changes. As previously mentioned, corticosteroids such as dexamethasone have been shown to reduce mortality in severe cases of COVID-19 and may help limit fibrosis progression by reducing pulmonary inflammation (22,88,89). However, their efficacy in post-COVID-19 interstitial lung disease has yet to be confirmed. Secondly, clinical trials have been proposed to evaluate the potential benefit of antifibrotic therapies in patients with established fibrotic abnormalities (90). In particular, studies were designed to assess the efficacy of pirfenidone (FIBRO-COVID, NCT04607928) and nintedanib (NINTECOR, NCT04541680). To date, no results have been published. However, an abstract has been released reporting the findings of the FIBRO-COVID study, indicating that most patients with fibrotic changes following severe COVID-19 showed improvement or stability regardless of whether they received the pirfenidone or the placebo (91).

Despite advances in the treatment of severe COVID-19 pneumonia, the possibility of persistent pulmonary fibrosis remains a concern, and ongoing studies will help clarify the behavior of fibrotic changes (90). For now, we can state that in most cases these changes do not progress over time. Even in cases where progression is observed, it is worth establishing an accurate diagnosis of the underlying condition, as in some instances other preexisting interstitial diseases have been identified, with COVID-19 acting as a trigger (90).

1.3.1.3. Other parenchymal complications

Other less common presentations have been described in the literature. Post-COVID-19 interstitial lung disease may occasionally present with histological findings resembling hypersensitivity pneumonitis. Recent reports have described granulomatous inflammation and Th1-mediated responses, indicating an uncommon presentation that should be taken

into consideration (68). Additionally, isolated cases of acute eosinophilic pneumonia associated with SARS-CoV-2 infection have also been reported, further expanding the spectrum of post-COVID-19 parenchymal involvement (69).

1.3.2. Respiratory complications at the airway

Airway involvement has been less studied compared to parenchymal-origin respiratory complications, despite its potential role in persistent respiratory symptoms. It is well established that, following a respiratory infection, whether bacterial or viral, airway alterations may occur, such as bronchial thickening, tracheomalacia, or bronchiectasis (92). Regarding active SARS-CoV-2 infection, it has been reported that the virus can infect the ciliated epithelium of the airways, which may lead to long-term bronchial wall thickening, bronchiectasis, and small airway disease (93,94). Additionally, beyond the infection itself, another risk factor that may lead to airway involvement is the requirement for mechanical ventilation in patients with severe COVID-19 (95).

The most commonly reported post-COVID-19 airway alterations are bronchiectasis. An incidence of bronchiectasis ranging from 11-24% has been described on chest CT during the follow-up of post-COVID-19 patients (96,97). It has also been observed that some patients exhibit an air-trapping pattern in post-COVID-19 follow-up, which may suggest the presence of bronchiolitis (98). Another airway involvement, such as tracheomalacia, has not been evaluated, although acquired tracheomalacia secondary to airway infections and prolonged mechanical ventilation following intubation or tracheostomy has been described (99). Therefore, it would not be surprising to consider that post-COVID-19 patients may present tracheomalacia secondary to the viral infection itself.

To date, there are no specific studies that investigate this involvement in depth. Given the potential impact of these sequelae on symptomatology and clinical recovery, it is essential to conduct studies aimed at evaluating airway involvement in post-COVID-19 follow-up, enabling a better understanding of its progression and its impact on quality of life.

1.3.3. Effect of acute treatment on respiratory sequelae

Previously, the effects of treatments in the acute phase of COVID-19 and which of them have shown efficacy have been described. However, how these treatments may affect respiratory complications has not been as thoroughly investigated. Specifically, in the case of dexamethasone, the only study published to date in the United Kingdom included adults hospitalized between February 2020 and March 2021 for COVID-19, who met the current recommendations for dexamethasone treatment. Patients were divided into two groups based on whether or not they had received the treatment. Health-related quality of life (HRQoL) was evaluated before hospital admission and one year after discharge, and the reduction in HRQoL was found to be similar in both groups at the one-year follow-up. Thus, the authors concluded that dexamethasone, as an acute-phase treatment, does not appear to influence post-COVID-19 quality of life (100). However, further evidence is needed to determine the impact of dexamethasone on respiratory complications.

1.3.4. Effect of bronchial asthma on respiratory sequelae

Numerous studies have assessed the risk of COVID-19 infection and disease severity in asthmatic patients. However, there is limited evidence on whether these patients have a significantly higher risk of developing respiratory complications after SARS-CoV-2 pneumonia. The only study that directly evaluated whether asthmatic patients experience more persistent respiratory symptoms found no significant differences compared to non-asthmatic individuals (101). However, two large population-based cohorts from the United Kingdom and the United States have reported that asthma may be associated with a higher risk of persistent respiratory symptoms (102,103). Nonetheless, uncertainty remains regarding the impact of asthma on post-COVID-19 respiratory sequelae.

1.4. PURPOSE OF THE DOCTORAL THESIS

Since many patients develop pulmonary complications following SARS-CoV-2 pneumonia, the objective of this doctoral thesis was to determine the presence of respiratory complications after SARS-CoV-2 pneumonia based on the viral involvement itself, the acute treatment administered, and the presence of comorbidities (bronchial asthma). Additionally, it aimed to assess the need for further medical interventions for these complications.

The first part evaluates respiratory complications according to different conditions. The first study aims to determine whether the use of dexamethasone during the acute phase improves clinical outcomes during follow-up. Subsequently, two studies focus on determining the prevalence of airway involvement after hospitalization for COVID-19 pneumonia and identifying and assessing associated risk factors. Finally, a study was conducted to compare whether there are differences in the number and/or severity of respiratory sequelae between asthmatic and non-asthmatic patients who have suffered from SARS-CoV-2 pneumonia.

The second part, which focuses on evaluating the need for additional medical interventions for these complications, includes a clinical trial involving patients who developed OP during post-COVID-19 follow-up. The objective was to assess the efficacy of oral corticosteroid therapy in this condition and determine whether a less intensive corticosteroid regimen provides a therapeutic effect that is not inferior to the standard recommended regimen.

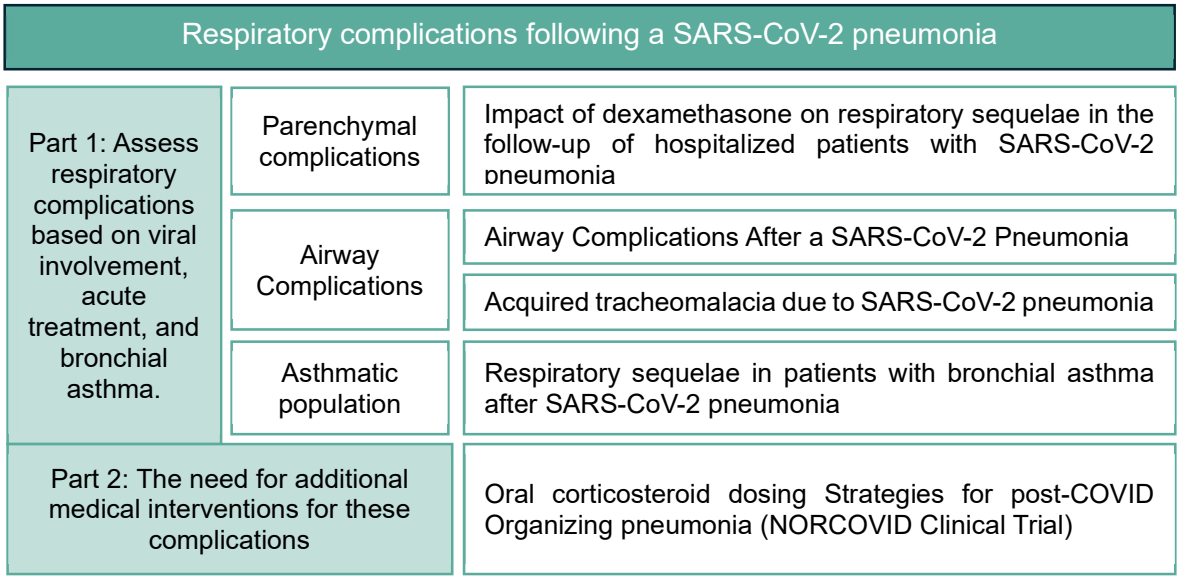


Figure 7: Overview diagram of the studies included in this thesis

2. HYPOTHESIS

HYPOTHESIS

Patients recovering from SARS-CoV-2 pneumonia may experience respiratory complications that vary depending on the initial treatment and may require additional medical interventions. Moreover, asthmatic patients experience fewer complications compared to other hospitalized patients.

3. OBJECTIVES

3.1. MAIN OBJECTIVE

Determine the presence of respiratory complications after SARS-CoV-2 pneumonia based on the extent of viral involvement, the acute treatment administered, and the presence of comorbidities, particularly bronchial asthma. Additionally, the study aims to evaluate the need for further medical interventions resulting from these complications

3.2. SECONDARY OBJECTIVES

1) To compare the clinical outcomes of patients with severe COVID-19 pneumonia who were treated with dexamethasone versus those who received alternative treatments, in order to determine whether dexamethasone leads to improved outcomes during follow-up.
2) Determine the prevalence of airway (AW) involvement and of tracheomalacia following hospitalization for COVID-19 pneumonia and describe and assess risk factors for this condition.
3) To determine whether there are differences in the number and/or severity of respiratory sequelae between patients with and without asthma who have experienced SARS-CoV-2 pneumonia.
4) Evaluate the efficacy of oral corticosteroid therapy in treating OP secondary to SARS-CoV-2 infection and determine whether a less intensive corticosteroid regimen yields a therapeutic effect that is non-inferior to the standard recommended regimen for this condition.

4. METHODS

4.1. PART 1: ASSESS RESPIRATORY COMPLICATIONS

Patient cohort and baseline data

All patients included in the various studies were selected from the cohort of individuals seen at a specialized post-COVID-19 respiratory sequelae clinic, who had required hospitalization for SARS-CoV-2 pneumonia between March 2020 and December 2021. The patients were evaluated between three and nine months after hospital discharge. Each patient underwent a clinical interview, physical examination, chest high-resolution computed tomography (HRCT), spirometry, carbon monoxide (CO) transfer test and 6-min walking test (6MWT).

Demographic data (sex, age, BMI and smoking status), comorbidities, and hospital admission information were collected. This included data on ventilatory support, laboratory parameters (leukocyte count, platelet count, D-dimer, lactate dehydrogenase [LDH], C-reactive protein [CRP], and interleukin-6 [IL-6]), radiographic findings at admission, ICU admission requirements, secondary complications, and treatments administered during hospitalization. Disease was defined as severe if the patient needed FiO_2 < 40%, very severe if they needed FiO_2 > 40%, and critical if they needed ventilatory support.

The study was approved by the local ethics committee (Hospital Vall d'Hebron Ethics Committee approval (PR [AG]222/2020), and all subjects signed an informed consent document prior to their participation.

Follow-up

Clinical evaluation included the degree of dyspnea using the modified Medical Research Council (mMRC) scale and the presence of other respiratory symptoms. A comprehensive physical examination was performed. Additionally, a complete pulmonary function study, including forced spirometry and DLCO, was conducted for all participants. The tests were carried out using an ultrasonic spirometer incorporated into a complete Viasys pulmonary function system (VYaire-Vyntus Body) according to the guidelines of the European

Respiratory Society and the American Thoracic Society (104). All data were expressed as percentages of the predicted values published by the Global Lung Function Initiative (GLI) (105,106). For forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), and DLCO, values below 80% were considered low, while for the FEV1/FVC ratio, values below 70% were considered low. The 6MWT was performed according to the 2014 ERS/ATS Statement guidelines (107).

A HRCT scan of the chest with 1 mm slices at 10 mm intervals during maximum inspiration was performed during follow-up. All imaging features were independently interpreted by a radiologist and a pulmonologist. For controversial images, another radiologist was consulted. The HRCT scans were evaluated for the following features: location (unilateral or bilateral) and distribution (central, peripheral, or both) of the lesion, type of lesion (single, multiple, or diffuse), presence of ground-glass opacity, consolidation, linear opacities, reticulation, and/or mixed pattern, and interstitial changes (septal thickening, crazy paving and fibrosis). Airway involvement was also assessed, and if present, the characteristics of the airway (bronchial wall thickening, bronchiectasis, tracheomalacia, and bronchiolitis) were evaluated. The chest CT scans were evaluated following the descriptions provided in the Fleischner Society guidelines for Radiology (108).

DLCO and presence of fibrosis at the HRCT scan were defined as main follow-up outcome variables.

Different design study

a) Impact of dexamethasone on respiratory sequelae in the follow-up of hospitalized patients with SARS-CoV-2 pneumonia

A longitudinal retrospective study was designed involving all patients seen at a specialized post-COVID-19 respiratory sequelae clinic who had required hospitalization for SARS-CoV-2 pneumonia between March 2020 and April 2021. The patients were divided into two groups: those who were admitted from July 2020 onwards and received dexamethasone

treatment, and those who were admitted between March and June 2020, prior to the use of dexamethasone as a treatment for SARS-CoV-2 pneumonia. Patients who did not require oxygen were excluded, as they were not candidates for dexamethasone treatment. During the study period, the strains included were the wild-type strain or Wuhan strain, the Alpha variant (B.1.1.7), which reached Spain in late 2020, and the Beta (B.1.351) and Gamma (P.1) variants, which were less widespread in this country (109).

b) Airway sequelae in post-acute COVID-19 syndrome

A retrospective longitudinal study was conducted, involving all patients who attended a specialized post-COVID-19 respiratory sequelae clinic following hospitalization for SARS-CoV-2 pneumonia between March 2020 and September 2021. The patients were categorized into two groups based on the presence or absence of airway involvement, and these groups were compared to assess differences and associated factors.

c) Acquired tracheomalacia due to SARS-CoV-2 pneumonia

A retrospective study was conducted, including all patients with tracheomalacia who attended a specialized post-COVID-19 respiratory sequelae clinic after hospitalization for SARS-CoV-2 pneumonia between February 2020 and August 2021. Tracheomalacia was diagnosed using expiratory HRCT imaging. The clinical characteristics of patients diagnosed with tracheomalacia on expiratory HRCT imaging were analyzed (110).

d) Respiratory sequelae in patients with bronchial asthma after SARS-CoV-2 pneumonia

A retrospective case-control study was designed that included all asthma patients treated for SARS-CoV-2 pneumonia at our unit for post-COVID-19 respiratory sequelae from May to December 2020. For each asthma patient, two control patients were matched after adjustment for the date of hospital admission, sex, age and severity of SARS-CoV-2 pneumonia. The severity of asthma was graded according to GINA (Global Initiative for Asthma) guidelines (111). Patients were considered to have a T2-Th2 phenotype when they presented allergic symptoms with sensitization to pneumoallergens, a T2-ILC2 phenotype

when there was eosinophilia in blood or sputum without the presence of allergy, and a non-T2 phenotype when no sensitization or allergic symptoms were found, nor eosinophilia in blood or sputum (109).

Statistical Analysis

A descriptive analysis of the demographic, clinical, and functional characteristics of all patients was conducted, with stratification based on different groups according to various studies, such as dexamethasone treatment, airway sequelae, and asthma patients. Absolute frequencies and corresponding percentages were calculated for qualitative variables. Quantitative variables with a normal distribution were described using the mean and ± standard deviation (SD), while those that did not follow a normal distribution were described using the median and 25^{th}-75^{th} percentiles.

Demographic, clinical, and functional characteristics of patients were compared with another group using the Student's t-test for normally distributed quantitative variables and the Mann-Whitney U test for non-normally distributed variables. For qualitative variables, the Chi-square test or Fisher's exact test was applied as appropriate.

Multivariate linear and logistic regression models were employed to assess the association between dexamethasone treatment and alveolar-capillary diffusion and the presence of fibrosis on follow-up CT scans respectively. Potential confounding factors were tested and included in the final models if (i) they were related to both the exposure and the outcome, (ii) they were modified (>10% change in the regression coefficient) the estimates of the remaining variables, or (iii) there was documented evidence in the literature supporting an association with the outcome variables analyzed.

Results were considered statistically significant if p-value < 0.05. Analyses were performed using the STATA 18.0 statistical software package (StataCorp, College Station, TX, USA).

4.2. PART 2: ORAL CORTICOSTEROID DOSING STRATEGIES FOR POST-COVID ORGANIZING PNEUMONIA (NORCOVID CLINICAL TRIAL)

Trial Design

A randomized, open-label, assessor-blinded, parallel-group, single-center, non-inferiority clinical trial with an active control group comparing two oral prednisone regimens. The control group received prednisone 0.75 mg/kg/day for 4 weeks, followed by 0.5 mg/kg/day for 4 weeks, 20 mg/day for 4 weeks, 10 mg/day for 6 weeks, and 5 mg/day for 6 weeks (total treatment duration: 6 months). The experimental group received prednisone 0.5 mg/kg/day for 3 weeks, followed by 20 mg/day for 3 weeks, 15 mg/day for 2 weeks, 10 mg/day for 2 weeks, and 5 mg/day for 2 weeks (total treatment duration: 3 months). Upon diagnosing OP, the patients were randomized to one of the two treatment arms. Subsequent visits were held at 1, 3, 6, and 12 months. Study outcome variables were assessed by trained hospital nurses and a radiologist who were blinded to the patient's treatment allocation (Figure 8).

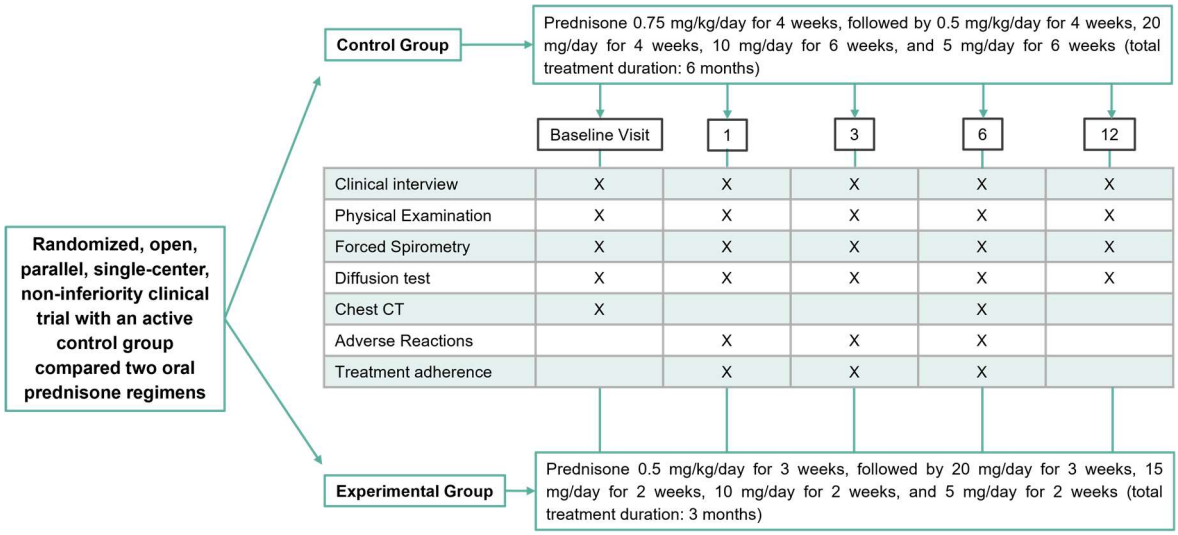


Figure 8: Diagram of the treatment groups in the clinical trial

The trial was conducted in compliance with the principles of the Declaration of Helsinki (112) and the Harmonised Tripartite Guideline for Good Clinical Practice from the International Conference on Harmonisation (113). It was approved by local authorities and trial.gov

number NCT04534478 and it is reported in accordance with the CONSORT statement (114). All patients provided written informed consent before trial entry.

Participants and Randomization

All patients over 18 years of age who had been diagnosed with OP at a post-COVID respiratory sequelae outpatient clinic at Vall d'Hebron Hospital were assessed. This clinic systematically reviewed all patients who had required hospitalization for SARS-CoV-2 pneumonia between March 2020 and December 2021. The diagnosis of OP was established by a multidisciplinary committee based on clinical and radiological data, pulmonary function, and anatomopathological evaluations (see Table 1). All patients included met the inclusion criteria, and none met the exclusion criteria. A complete list of the inclusion and exclusion criteria is provided in Table 2.

Table 1: Criteria used for the diagnosis of organizing pneumonia in the multidisciplinary committee

Criteria **	
The definitive diagnosis of organizing pneumonia was established after discussion in the multidisciplinary committee, considering: a compatible clinical context, HRCT findings, and compatible histology in cases where it was available:	
Clinical symptoms +/- abnormal pulmonary function tests + compatible HRCT + compatible biopsy + discussion in a multidisciplinary committee	55 (69.6%)
Clinical symptoms +/- abnormal pulmonary function tests + compatible HRCT + discussion in a multidisciplinary committee	24 (30,4%)
Compatible clinical context+/- abnormal pulmonary function tests	
Previous hospitalization for SARS-CoV-2 pneumonia, with persistent symptoms such as dyspnea, cough, and chest pain +/- abnormal pulmonary function tests during post-COVID-19 follow-up	
Radiological criteria	
Typical pattern (most common): Patchy alveolar opacities peripheral and peribronchial	
Other Criteria: progressive fibrosis with reticulation and areas of consolidation, predominant nodule solitary/multiple nodules, bronchocentric consolidation, Irregular lines or subpleural bands, ground-glass opacity	
Histopathological criteria	
Buds of granulation tissue consisting of fibroblasts and myofibroblasts embedded in connective tissue, preserved lung architecture, mild interstitial chronic inflammation; patchy distribution	

*** The criteria were adapted from: Cordier JF. Cryptogenic Organising Pneumonia. Eur Respir J. 2006 Aug;28(2):422-46 and Cottin V, Cordier JF. Cryptogenic Organizing Pneumonia. Semin Respir Crit Care Med. 2012 Oct;33(5):462-75.*

Table 2: Inclusion and exclusion criteria of the study

Criteria
Inclusion Criteria
Patients aged 18 years or older
Diagnosis of COVID-19 pneumonia that required hospitalization
Multidisciplinary diagnosis of organizing pneumonia post COVID-19
No contraindications to the study drug
After being properly informed, voluntarily agree to participate in the study after understanding its objectives and risks and provide consent.
Exclusion Criteria
Do not authorize their participation
Patients with contraindications to receiving corticosteroid treatment
Inability to understand the study requirements, in the investigator's opinion
Expected survival less than the study duration, in the investigator's opinion
Clinical evidence of active infection, including but not limited to bronchitis, pneumonia, sinusitis, urinary tract infection, and/or cellulitis
Patient scheduled to receive a lung transplant during the study period
Inability to undergo pulmonary function tests
Poorly controlled diabetes mellitus (HbA1c >10%)
Pregnancy or lactation
Are participating in another interventional study

Patients were randomized in a 1:1 ratio to the two treatment arms. Randomization codes were generated using the PROC PLAN of the SAS system. The randomization of patients was managed through the electronic case report form (eCRF) and was concealed until the confirmation of the randomization for each patient. To minimize missing data, patients who withdrew from the trial regimen prematurely were asked to attend all visits and undergo all examinations as originally planned. For patients who did not attend all visits, vital status at the end of the study was determined.

Interventions

Patients received oral prednisone in the morning with breakfast, adjusted for weight and based on the treatment arm assigned. All patients were also treated with omeprazole 20 mg/day while taking prednisone and trimethoprim/sulfamethoxazole 80/400mg/day to

prevent opportunistic infections as long as the prednisone dose exceeded 10 mg/day. Additionally, calcium and alendronic acid were given to prevent bone-related complications. At the end of the prednisone treatment, before discontinuation, plasma cortisol levels were determined to prevent adrenal insufficiency.

Procedures and assessments

For all patients included, demographic data were collected along with information obtained from the clinical interview, physical examination, blood tests, pulmonary function tests (spirometry and CO transfer test), the 6MWT, and chest CT (Figure 8).

All these procedures are described in Table 3. Moreover, all initial visit variables are described in Table 4.

Table 3: Description procedures

Procedure	Description
Spirometry	It was performed using an ultrasonic spirometer incorporated into a complete Viasys pulmonary function system (VYaire-Vyntus Body) according to the 2005 ERS/ATS standards (115), using the theoretical values proposed by the GLI (105)
CO transfer test	It was conducted with the same equipment using the single-breath method, following the 2019 ERS/ATS standards (104) and using the values proposed by the GLI (106).
6MWT	It was performed according to the guidelines of ERS/ATS Statement in 2014 (107).
Chest CT	It was performed on all patients with 1 mm slices at 10 mm intervals during maximum inspiration, and expiratory slices. The parenchymal involvement was evaluated and categorized into ground-glass opacity, reticulation, linear opacities, condensation or a mixed pattern, which included at least two of the abnormalities. The readings were independently performed by a radiologist and a pulmonologist. In case of disagreement, a second radiologist provided the tie-breaking opinion. In chest CT, improvement was defined as a 25% reduction in overall involvement compared to the previous chest CT. Stability was defined as no significant changes, and worsening was defined as a 25% increase in overall involvement compared to the previous chest CT.

Table 4: Variables collected during the baseline visit

Variables collected during the baseline visit	
Met the inclusion criteria and none of the exclusion criteria	
Signature of informed consent	
Randomization	
Datos demographics	
Age	
Sex	
Height	
Weight	
Exposure to tobacco	Smoker, former smoker and non-smoker
Year packages	
Comorbidities	
Previous treatment	
SARS-CoV-2 admission	
Date of test	
Type of test	
Result	
Record symptoms of this episode	
COVID-19 severity	No oxygen required, Oxygen therapy FiO_2 <40%, NIV or HFNC and IMV or ECMO
Organizing pneumonia diagnosis	
Pathology report	
Committee diagnosis	
Date of test	
WHO Scale- the ordinal clinical improvement (the clinical variable recommended by the WHO R&D Blueprint expert group)	
1. Not hospitalized, no limitations on activities	
2. Not hospitalized, limitation on activities	
3. Hospitalized, not requiring supplemental oxygen	
4. Hospitalized, requiring supplemental oxygen	
5. Hospitalized, on NIV or high flow oxygen devices	
6. Hospitalized, on IMV or ECMO	
7. Death	
Vital Signs	
Heart rate	
Systolic blood pressure	
Diastolic blood pressure	
Respiratory rate	
Body temperature	
Physical examination	
Blood test	
Complete blood count (total leukocytes, % neutrophils, % lymphocytes, % eosinophils, % basophils, % monocytes), electrolytes (Na, K), liver function (AST, ALT, total bilirubin, ALP, GGT), renal function (creatinine, urea), and inflammatory markers (CRP, LDH)	
Spirometry	
FVC (absolute value)	
FVC (% of theoretical value)	
FEV1 (absolute value)	

FEV1 (% of theoretical value)	
FEV1/FVC (% of theoretical value)	
DLCO (absolute value)	
DLCO (% of theoretical value)	
KCO (% of theoretical value)	
6MWT	
Meters travelled	
Initial oxygen saturation	
Mean oxygen saturation	
Maximum desaturation	
Initial heart rate	
Final heart rate	
Chest CT	
Localization	Unilateral and bilateral
Distribution	Central, peripheral, central + peripherical
Injuries	Simple, multiple, diffuse
Main Characteristics	Ground glass opacity, consolidation, linear opacities, reticulation, mixed type, nothing.

During follow-up, clinical progress, pulmonary function test, chest CT scans, adverse events (AEs), and treatment adherence were assessed. Variables and definitions are detailed in Table 5.

Table 5: Variables collected during the follow-up visits

Variables collected during the follow-up visits	
Study treatment	
The patient taken the medication correctly	Yes or no
Fulfilment	
Reason	
Concomitant medication	
Who Scale- the ordinal clinical improvement (the clinical variable recommended by the WHO R&D Blueprint expert group)	
1. Not hospitalized, no limitations on activities	
2. Not hospitalized, limitation on activities	
3. Hospitalized, not requiring supplemental oxygen	
4. Hospitalized, requiring supplemental oxygen	
5. Hospitalized, on NIV or high flow oxygen devices	
6. Hospitalized, on IMV or ECMO	
7. Death	
Vital Signs	
Heart rate	
Systolic blood pressure	
Diastolic blood pressure	
Respiratory rate	
Body temperature	

Physical examination	
Blood test *	
Complete blood count (total leukocytes, % neutrophils, % lymphocytes, % eosinophils, % basophils, % monocytes), electrolytes (Na, K), liver function (AST, ALT, total bilirubin, ALP, GGT), renal function (creatinine, urea), and inflammatory markers (CRP, LDH), cortisol	
Spirometry	
FVC (absolute value)	
FVC (% of theoretical value)	
FEV1 (absolute value)	
FEV1 (% of theoretical value)	
FEV1/FVC (% of theoretical value)	
DLCO (absolute value)	
DLCO (% of theoretical value)	
KCO (% of theoretical value)	
6MWT	
Meters traveled	
Initial oxygen saturation	
Mean oxygen saturation	
Maximum desaturation	
Initial heart rate	
Final heart rate	
Chest CT *	
Localization	Unilateral and bilateral
Distribution	Central, peripheral, central + peripherical
Injuries	Simple, multiple, diffuse
Main Characteristics	Ground glass opacity, consolidation, linear opacities, reticulation, mixed type, nothing.
Comparison with the baseline CT	Improvement was defined as a 25% reduction in overall involvement compared to the previous chest CT. Stability was defined as no significant changes, and worsening was defined as a 25% increase in overall involvement compared to the previous chest CT
Adverse Effects	
Description	It was any harmful health incident, regardless of its causal relationship with the study drug. AEs were recorded throughout the study and up to 30 days after the administration of the last dose of prednisone.
Started time	
End date	
Intensity	Mild, moderate, intense, very intense
Serious	Yes or no
Have the patient received any concomitant treatment	
Causality	They were classified as related AEs when there was a temporal relationship with the administration of the medication indicating a possible causal relationship that could not be explained by other factors, or as unrelated AEs when the relationship with the study drug was unlikely or due to other factors such as the clinical condition or other therapeutic interventions.
Outcome	Recovered, recovered with residual effects, not yet recovered, death, unknow

** In this case, it was only repeated at the 6-month visit.*

End points

The primary efficacy endpoint was the between-treatment comparison of the change in pulmonary diffusion capacity as measured by the baseline-adjusted predicted DLCO (%) from baseline to 6 months, in terms of non-inferiority using a non-inferiority margin of 10%.

The secondary variables analysed included: the percentage of patients with DLCO values <80% predicted, FVC, FEV1, and FEV1/FVC% from forced spirometry, the distance covered in the 6MWT, the need to increase the oral corticosteroid dose or to start a new treatment period, parenchymal involvement on the chest CT, complications related to prednisone treatment (both severe and non-severe), complications of any type (both severe and non-severe), all-cause mortality, and the ordinal clinical improvement (the clinical variable recommended by the WHO R&D Blueprint expert group for the acute phase). This variable was assessed at each visit, and the worst score obtained during the study was recorded as a summary measure.

Sample size

Sixty patients per group were planned to be randomized to ensure an 80% statistical power for demonstrating the non-inferiority of the less intensive prednisone regimen compared to the established regimen for the predicted DLCO. This calculation was based on a non-inferiority margin of 10% and a SD of 14.3% and accounted for a potential imbalance of up to 2.5% against the experimental treatment, with a one-sided alpha value of 2.5%.

Statistical analysis

Two efficacy populations were predefined: the modified full analysis set (mFAS) based on the intention-to-treat principle and the per-protocol (PP) population. For the primary efficacy endpoint of non-inferiority, both mFAS and PP were co-primary, while mFAS was primary for the remaining endpoints.

Categorical variables were summarized using frequencies and percentages, and continuous variables were reported as mean ± SD, or median with interquartile range (IQR), as appropriate.

The primary efficacy variable and Gaussian longitudinal continuous variables were analysed using a mixed model for repeated measures (MMRM), which deals appropriately with observations missing at random (MAR). The MMRM model included treatment, visit, treatment-by-visit interaction, and a continuous baseline variable, with a common unstructured covariance structure to model within-patient errors. Other variables were analysed using Fisher's exact test for categorical data, Student's t-test for Gaussian variables, and the Mann-Whitney test for non-Gaussian continuous and ordinal variables.

Analyses were performed using SAS 9.2 software (SAS Institute Inc., Cary, NC, USA), with a significance level of 0.05 (two-sided).

5. RESULTS

5.1. PART 1: ASSESS RESPIRATORY COMPLICATIONS

5.1.1. Impact of dexamethasone on respiratory sequelae in the follow-up of hospitalized patients with SARS-CoV-2 pneumonia

A total of 1,448 patients who had been hospitalized for SARS-CoV-2 pneumonia between March 2020 and April 2021 were evaluated at the post-COVID medical unit. All patients were diagnosed with pneumonia based on radiological findings on chest X-rays and a positive SARS-CoV-2 test. Patients who did not require oxygen therapy during hospitalization and those not treated with dexamethasone during the second and third waves were excluded, resulting in a final analysis of 1,011 patients. The patients were divided into two groups: 348 patients who were not treated with dexamethasone (first wave) and 663 patients who were treated with dexamethasone, further subdivided into 311 patients from the second wave and 352 patients from the third wave (Figure 9).

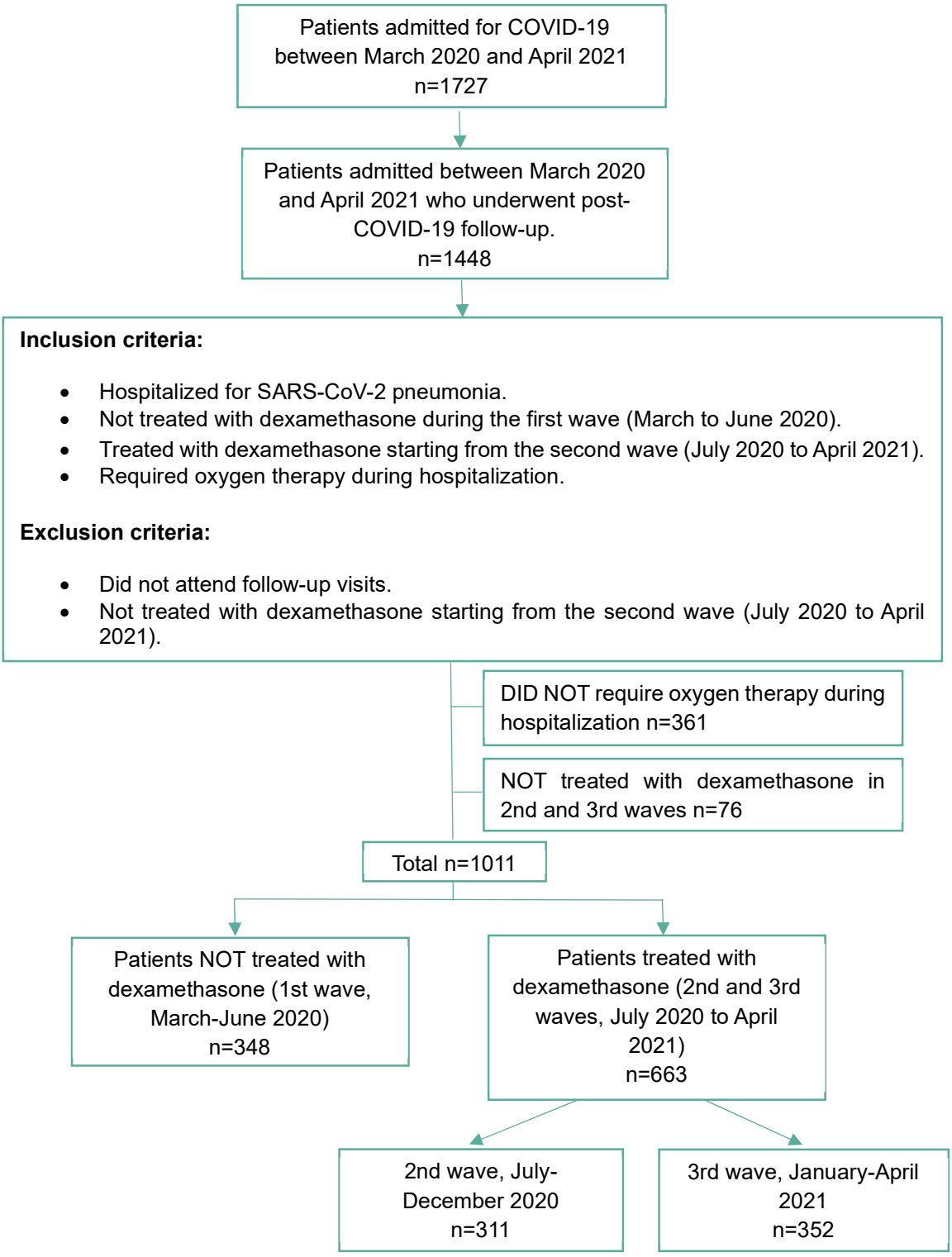


Figure 9: Patient Flowchart according to dexamethasone treatment

The mean age at admission was 58.9 years (± 12.7), and 387 patients (38.3%) were female. Patients treated with dexamethasone were older, with a mean age of 59.5 years (± 12.5), compared to those not treated with dexamethasone, whose mean age was 57.8 years (±

13.1; p = 0.044). Smokers in the treated group had a higher pack-year history, 30 (18-50) vs. 25 (11-40) in the no treatment group (p = 0.016). Regarding comorbidities, patients treated with dexamethasone had a higher prevalence of obesity, with 309 patients (46.6%), and gastroesophageal reflux disease, with 32 patients (4.8%), compared to those not treated with dexamethasone, among whom 139 patients (39.9%) had obesity and three (0.9%) had gastroesophageal reflux disease, indicating a significant difference between the two groups (p = 0.043 and p = 0.001 respectively). No other significant differences were observed in baseline demographic characteristics or comorbidities between the two groups (Table 6).

Table 6: Baseline demographic characteristics of the study population according to dexamethasone treatment

	Total (n=1011)	No dexamethasone treatment (n=348)	Dexamethasone treatment (n=663)	p-value
Age at admission (years), mean (SD)	58.9 (12.7)	57.8 (13.1)	59.5 (12.5)	**0.044**
Sex, female, n (%)	387 (38.3)	138 (39.7)	249 (37.6)	0.514
BMI (kg/m²), mean (SD)	29.5 (5.0)	29.1 (5.0)	29.7 (4.9)	0.073
Race, n (%)				
White	729 (72.1)	254 (73.0)	475 (71.6)	0.547
Asian	10 (1.0)	5 (1.4)	5 (0.8)	
Black	11 (1.1)	5 (1.4)	6 (0.9)	
Hispanic/Latino	247 (24.4)	81 (23.2)	166 (25.0)	
Other	14 (1.4)	3 (1.0)	11 (1.7)	
Smoking status, n (%)				
Active smokers	44 (4.4)	15 (4.3)	29 (4.4)	0.790
Former smokers	351 (34.7)	116 (33.3)	235 (35.4)	
Non-smokers	616 (60.9)	217 (62.4)	399 (60.2)	
Pack-years, median (IQR)	32.2 (22.8)	25 (11-40)	30 (18-50)	**0.016**
Comorbidities, n (%)				
Hypertension	423 (41.8)	147 (42.2)	276 (41.6)	0.851
Obesity	448 (44.3)	139 (39.9)	309 (46.6)	**0.043**
Diabetes	219 (21.7)	69 (19.8)	150 (22.6)	0.305
Renal insufficiency	73 (7.2)	26 (7.5)	47 (7.1)	0.823
Immunosuppression	50 (5.0)	20 (5.6)	30 (4.5)	0.394
Ischemic heart disease	53 (5.2)	12 (3.5)	41 (6.2)	0.064
Heart failure	28 (2.8)	11 (3.2)	17 (2.6)	0.583
Atrial fibrillation	42 (4.2)	15 (4.3)	27 (4.1)	0.857
Solid cancer	91 (9.0)	34 (9.8)	57 (8.6)	0.536
Leukemia	18 (1.8)	8 (2.3)	10 (1.5)	0.366

Psychiatric disorder	129 (12.8)	43 (12.4)	86 (13.0)	0.781
Gastroesophageal reflux	35 (3.5)	3 (0.9)	32 (4.8)	**0.001**
Respiratory comorbidities, n (%)				
Asthma	45 (4.5)	13 (3.7)	32 (4.8)	0.424
Obstructive sleep apnea (OSA)	78 (7.7)	24 (6.9)	54 (8.1)	0.503
Chronic obstructive pulmonary disease (COPD)	51 (5.0)	14 (4.0)	37 (5.6)	0.282
Bronchiectasis	12 (1.2)	3 (0.9)	9 (1.4)	0.490
Cystic fibrosis	1 (0.1)	0 (0.0)	1 (0.2)	0.999
Pulmonary arterial hypertension	9 (0.9)	5 (1.4)	4 (0.6)	0.288
Pulmonary fibrosis	2 (0.2)	2 (0.6)	0 (0.0)	0.118
Other interstitial lung disease	11 (1.1)	5 (1.4)	6 (0.9)	0.526
Scoliosis/kyphosis	9 (0.9)	1 (0.3)	8 (1.2)	0.176
Thoracic trauma	8 (0.8)	2 (0.6)	6 (0.9)	0.722

Patients treated with dexamethasone had a shorter hospital stay than those not treated, with median values of 10 days (6-16) vs. 17 days (10-34) respectively ($p < 0.001$). Additionally, 259 (39.1%) of the patients treated with dexamethasone were admitted to the ICU, compared to 200 (57.5%) of those not treated ($p < 0.001$). ICU stay was also shorter for the treated group, with a median of 8 days (5-16) compared to 12 days (6-24) for the untreated group ($p = 0.007$). Patients treated with dexamethasone required a lower FiO_2, and fewer needed ventilatory support during hospitalization; they presented lower rates of acute respiratory distress, and fewer secondary infections, septic shock, and deep vein thrombosis. Table 7 presents the remaining hospitalization variables according to dexamethasone treatment.

Table 7: Hospitalization Variables According to Dexamethasone Treatment and subanalysis of the treated group according to the pandemic wave.

	Total (n=1011)	Without DEX treatment 1st wave (n=348)	With DEX treatment (n=663)	p-value	With DEX treatment subanalysis (n=663)		
					2nd wave (n=311)	3rd wave (n=352)	p-value
Duration of hospital stay (days), median (p25-p75)	12 (7-21)	17 (10-34)	10 (6-16)	**<0.001**	10 (6-17)	9 (6-15)	**0.046**
ICU admission, n (%)	45 (45.4)	200 (57.5)	259 (39.1)	**<0.001**	122 (39.2)	137 (38.9)	0.935
Duration of ICU stay (days), median (p25-p75)	10 (5-20)	12 (6-24)	8 (5-16)	**0.007**	11 (5-21)	7 (5-14)	**0.008**
Oxygen therapy, n (%)							
Yes	1011 (100)	348 (100)	663 (100)	--	311 (100)	352 (100)	--
FiO_2<40	487 (48.2)	109 (31.3)	378 (57.0)	**<0.001**	177 (56.9)	201 (57.1)	0.961
FiO_2>40	524 (51.8)	239 (68.7)	285 (43.0)		134 (43.1)	151 (42.9)	
Ventilatory support, n (%)							
None	509 (50.3)	112 (32.2)	397 (59.9)	**<0.001**	185 (59.5)	212 (60.2)	0.846
HFNC	448 (44.3)	182 (52.3)	266 (40.1)	**<0.001**	127 (40.8)	139 (39.5)	0.724
NIV	43 (4.3)	29 (8.3)	14 (2.1)	**<0.001**	9 (2.9)	5 (1.4)	0.188
IMV	241 (23.8)	138 (39.7)	103 (15.5)	**<0.001**	55 (17.7)	48 (13.6)	0.151
ECMO	7 (0.7)	6 (1.7)	1 (0.1)	**0.008**	0 (0.0)	1 (0.3)	0.999
Type Rx of lung involvement at **hospital admission,** n (%)							
Alveolar infiltrate	929 (91.9)	308 (88.5)	621 (93.7)	**0.004**	282 (90.7)	339 (96.3)	**0.003**
Pleural effusion	2 (0.3)	2 (0.6)	0 (0.0)	0.118	0 (0.0)	0 (0.0)	--
Interstitial pattern	117 (11.6)	68 (19.5)	49 (7.4)	**<0.001**	38 (12.2)	11 (3.1)	**<0.001**
Atelectasis	5 (0.5)	2 (0.6)	3 (0.5)	0.999	1 (0.3)	2 (0.6)	0.999
Other	5 (0.5)	1 (0.3)	4 (0.6)	0.665	4 (1.3)	0 (0.0)	**0.048**
Laterality							
Unilateral	97 (9.6)	37 (10.6	60 (9.1)	0.421	32 (10.3)	28 (7.9)	0.290
Bilateral	913 (90.4)	311 (89.4)	602 (90.9)		278 (89.7)	324 (92.1)	
Extent of lung involvement							
<33%	311 (32.8)	81 (23.3)	250 (37.8)	**<0.001**	115 (37.1)	135 (38.4)	0.180
33-66%	470 (46.5)	166 (47.7)	304 (45.9)		152 (49.0)	152 (43.2)	
>66%	209 (20.7)	101 (29.0)	108 (16.3)		43 (13.9)	65 (18.5)	

Secondary complications, n (%)							
Acute respiratory distress	440 (43.5)	179 (51.4)	261 (39.4)	**<0.001**	122 (39.2)	139 (39.5)	0.945
Heart failure	18 (1.8)	5 (1.4)	13 (1.9)	0.626	7 (2.3)	6 (1.7)	0.613
Septic shock	28 (2.8)	19 (5.5)	9 (1.4)	**<0.001**	6 (1.9)	3 (0.9)	0.230
Acute cardiac injury	8 (0.8)	4 (1.2)	4 (0.6)	0.465	1 (0.3)	3 (0.9)	0.627
Acute kidney injury	79 (7.8)	31 (8.9)	48 (7.3)	0.355	20 (6.5)	28 (7.9)	0.451
Secondary infection	24 (24.5)	107 (30.8)	141 (21.3)	**0.001**	63 (20.3)	78 (22.2)	0.550
Pneumothorax	15 (1.5)	5 (1.4)	10 (1.5)	0.924	5 (1.6)	5 (1.4)	0.851
Cerebrovascular accident	8 (0.8)	4 (1.2)	4 (0.6)	0.353	1 (0.3)	3 (0.9)	0.380
Pulmonary embolism	47 (4.7)	15 (4.3)	32 (4.8)	0.771	18 (5.8)	14 (3.9)	0.278
Deep vein thrombosis	42 (4.2)	24 (7.0)	18 (2.7)	**0.001**	9 (2.9)	9 (2.6)	0.790
Corticosteroid treatment, n (%)							
Corticosteroids (yes)	756 (74.8)	93 (26.7)	663 (100)	**<0.001**	311 (100)	352 (100)	NA
Type of corticosteroids							
Prednisone	30 (4.0)	19 (20.4)	11 (1.7)	**<0.001**	2 (0.6)	9 (2.6)	0.054
Methylprednisolone	105 (13.9)	80 (86.0)	25 (3.8)	**<0.001**	11 (3.5)	14 (4.0)	0.766
Dexamethasone	663 (87.7)	0 (0.0)	663 (100)	**<0.001**	311 (100)	352 (100)	NA
Hydrocortisone	7 (0.9)	7 (7.5)	0 (0.0)	**<0.001**	0 (0.0)	0 (0.0)	NA
Cumulative dose of corticosteroids, median (p25-p75)	375 (375-375)	577 (356-1125)	375 (375-375)	**<0.001**	375 (375-375)	375 (375-375)	0.561
Other treatments, n (%)							
Hydroxychloroquine	328 (32.4)	327 (93.7)	1 (0.2)	**<0.001**	1 (0.3)	0 (0.0)	0.469
Lopinavir/ritonavir	257 (25.4)	257 (73.9)	0 (0.0)	**<0.001**	--	--	--
Darunavir/cobicistat	26 (2.6)	26 (7.5)	0 (0.0)	**<0.001**	--	--	--
Antibiotics	585 (57.9)	335 (96.3)	250 (37.7)	**<0.001**	133 (42.8)	117 (33.2)	**0.012**
Baricitinib	1 (0.10)	0 (0.0)	1 (0.15)	0.999	0 (0.0)	1 (0.3)	0.999
Remdesivir	56 (5.5)	6 (1.7)	50 (7.5)	**<0.001**	50 (16.1)	0 (0.0)	**<0.001**
Tocilizumab	179 (17.7)	156 (44.8)	23 (3.5)	**<0.001**	19 (6.1)	4 (1.1)	**<0.001**
Convalescent plasma	7 (0.7)	0 (0.0)	7 (1.1)	0.103	6 (1.9)	1 (0.3)	0.055

Regarding post-COVID-19 follow-up, patients treated with dexamethasone were seen later, after a median of 180 days (109-262) compared to 92 days (61-182) for those not treated (p < 0.001). Clinically, patients treated with dexamethasone experienced proportionally lower levels of dyspnea, recorded in 188 patients (28.4%) compared to 131 patients (37.6%)

in the non-dexamethasone group (p = 0.003). Comparing patients treated with dexamethasone between the second and third waves, those from the later wave reported significantly less dyspnea. There were no significant differences in the other symptoms reported during the follow-up consultations. In pulmonary function tests, the DLCO of patients treated with dexamethasone was better at 76.9% (± 15.6), compared to 69.9% (± 20.7); similarly, patients from the third wave had better DLCO values than those from the second wave. There were no differences in the other spirometry values. Regarding the 6MWT, patients treated with dexamethasone walked a greater distance and had a better average oxygen saturation (Table 8).

Table 8: Clinical and functional data during post-COVID-19 follow-up according to dexamethasone treatment and subanalysis of the treated group according to the pandemic wave.

	Total (n=1011)	Without DEX treatment 1st wave (n=348)	With DEX treatment (n=663)	p-value	With DEX treatment subanalysis (n=663)		
					2nd wave (n=311)	3rd wave (n=352)	p-value
Time from discharge to post-COVID consultation (days), median (p25-p75)	144 (92-251)	92 (61-182)	180 (109-262)	**<0.001**	138 (103-261)	238 (123-262)	**<0.001**
Symptoms, n (%)							
Cough	71 (7.0)	23 (6.6)	48 (7.2)	0.709	19 (6.1)	29 (8.2)	0.291
Expectoration	17 (1.7)	6 (1.7)	11 (1.7)	0.939	5 (1.6)	6 (1.7)	0.922
Dyspnea	319 (31.6)	131 (37.6)	188 (28.4)	**0.003**	105 (33.8)	83 (23.6)	**0.004**
Chest pain	35 (3.5)	14 (4.0)	21 (3.2)	0.480	12 (3.9)	9 (2.6)	0.340
Dyspnea (mMRC; 0-4), median (p25-p75)	1 (1-2)	1 (1-2)	1 (1-2)	0.989	1 (1-2)	1 (1-2)	0.174
Pulmonary function, mean (SD)							
FVC (% predicted)	90.4 (17.8)	91.2 (19.1)	90.0 (17.0)	0.477	88.3 (17.2)	91.5 (16.6)	**0.026**
FEV1 (% predicted)	92.7 (19.3)	94.3 (21.4)	91.9 (18.0)	0.075	90.5 (18.3)	93.1 (17.7)	0.091
FEV1/FVC (%)	80.7 (7.6)	81.6 (8.1)	80.2 (7.2)	**0.005**	80.3 (7.2)	80.1 (7.3)	0.724
DLCO (% predicted)	74.4 (20.2)	69.9 (20.7)	76.9 (15.6)	**<0.001**	74.9 (19.0)	78.8 (19.9)	**0.013**
KCO (% predicted)	85.1 (17.6)	81.1 (16.8)	87.4 (17.7)	**<0.001**	85.0 (15.7)	89.7 (19.1)	**<0.001**

6-minute walk test, mean (SD)							
Distance (m), median (p25-p75)	420 (360-480)	405 (360-465)	435 (360-480)	**0.002**	435 (360-480)	435 (375-484)	0.233
Baseline SpO2 (%)	96.9 (1.7)	96.3 (1.8)	97.3 (1.9)	**<0.001**	96.8 (1.9)	98.0 (1.7)	**<0.001**
Lowest SpO2 (%)	93.2 (4.1)	92.6 (4.2)	93.7 (3.8)	**<0.001**	93.2 (3.5)	94.3 (4.2)	**<0.002**
Mean SpO2 (%)	94.9 (3.1)	94.2 (3.1)	95.4 (3.0)	**<0.001**	94.9 (2.9)	96.0 (3.1)	**<0.001**

Radiologically, there were no differences in the number of pathological chest CT scans across the different groups. However, there were differences in the type of parenchymal involvement, with a notable decrease in reticulation observed in the dexamethasone-treated group (23 [4.4%]) compared to the non-dexamethasone group (28 [9.5%]). As for interstitial changes, there were clear differences between the groups: patients treated with dexamethasone had significantly fewer septal thickenings (30 [5.8%]) and less fibrosis (18 [3.5%]) compared to those not treated with dexamethasone, who presented 31 (10.5%) cases of septal thickening and 46 (15.6%) cases of fibrosis. It is important to note that in this case, there were no differences between patients in the second and third waves, during which time both groups received dexamethasone. In the thoracic CT scans, no clear differences were observed in the percentage of bronchial involvement between the two groups. However, differences were noted in the type of bronchial involvement; patients treated with dexamethasone exhibited fewer cases of bronchiolitis 37 cases (10.3%) compared to 61 cases (33.3%) in the untreated group ($p < 0.001$). Additionally, patients treated with dexamethasone showed a higher prevalence of bronchiectasis, which was recorded in 269 cases (74.9%) compared to 117 cases (63.9%) in the non-treated group ($p = 0.007$), and greater bronchial thickening, recorded in 227 cases (63.2%) compared to 70 cases (38.3%) among those not treated ($p < 0.001$) (Table 9).

Table 9: Description of chest CT findings during post-COVID-19 follow-up according to dexamethasone treatment and subanalysis of the treated group according to the pandemic wave.

	Total (n=1011)	Without DEX treatment 1st wave (n=348)	With DEX treatment (n=663)	p-value	With DEX treatment subanalysis (n=663)		
					2nd wave (n=311)	3rd wave (n=352)	p-value
Pathological, n (%)	816 (81.9)	294 (84.7)	522 (80.4)	0.093	251 (81.5)	271 (79.5)	0.517
Parenchymal Involvement, n (%)							
Ground-glass opacity	209 (25.6)	73 (24.8)	136 (26.1)	**0.009**	65 (25.9)	71 (26.2)	0.449
Consolidation	6 (0.7)	5 (1.7)	1 (0.2)		1 (0.4)	0 (0.0)	
Linear opacities	54 (6.6)	21 (7.1)	33 (6.3)		11 (4.4)	22 (8.1)	
Reticulation	51 (6.3)	28 (9.5)	23 (4.4)		13 (5.2)	10 (3.7)	
Mixed type *	373 (45.7)	122 (41.5)	251 (48.1)		123 (49.0)	128 (47.2)	
None	123 (15.1)	45 (15.3)	78 (14.9)		38 (15.1)	40 (14.8)	
Interstitial, n (%)							
Septal thickening	61 (7.5)	31 (10.5)	30 (5.8)	**0.012**	11 (4.4)	19 (7.0)	0.197
Crazy paving	4 (0.5)	2 (0.7)	2 (0.4)	0.622	0 (0.0)	2 (0.7)	0.500
Fibrosis	64 (7.8)	46 (15.6)	18 (3.5)	**<0.001**	8 (3.2)	10 (3.7)	0.753
No	690 (84.6)	223 (75.9)	467 (89.5)	**<0.001**	224 (89.2)	243 (89.7)	0.874
Bronchial Involvement, n (%)							
Bronchial Involvement	542 (66.4)	183 (62.2)	359 (68.8)	0.058	175 (69.7)	184 (67.9)	0.653
Type of bronchial involvement, n (%)							
Bronchiectasis	386 (71.2)	117 (63.9)	269 (74.9)	**0.007**	121 (69.1)	148 (80.4)	**0.014**
Bronchial thickening	297 (54.8)	70 (38.3)	227 (63.2)	**<0.001**	109 (62.3)	118 (64.1)	0.717
Bronchiolitis	98 (18.1)	61 (33.3)	37 (10.3)	**<0.001**	29 (16.6)	8 (4.4)	**<0.001**
Tracheomalacia	18 (3.3)	7 (3.8)	11 (3.1)	0.640	2 (1.1)	9 (4.9)	0.062

**Mixed type: patient presents two of the other conditions*

In the multivariate analysis, a linear regression model was created to evaluate the association between dexamethasone treatment and alveolar-capillary diffusion, adjusted for potential confounding factors such as age, sex, severity during hospitalization, and time from discharge to post-COVID visit. The model showed a mean DLCO of 81.24% (95% confidence interval [CI]: 71.22, 91.26) with a significant improvement of 9.25% (95% CI: 0.50, 18.00; p = 0.038) among patients treated with dexamethasone, even after adjustment

for confounding variables. In the logistic regression model assessing the association between dexamethasone treatment and the presence of fibrosis on follow-up CT scans, adjusted for confounding factors, it was found that patients treated with dexamethasone had a lower likelihood of fibrosis on follow-up, with an Odds Ratio (OR) of 0.24 (95% CI: 0.12, 0.49; $p < 0.001$) (Table 10).

Table 10: Adjusted analysis using a multiple linear regression model of the relationship between dexamethasone treatment during hospital admission and the value of DLCO assessed at follow-up, and adjusted analysis using a logistic regression model of the relationship between dexamethasone treatment and the presence of fibrosis in follow-up CT.

DLCO (% predicted)		
	Coefficient † (95% CI)	**p-value**
Constant *	81.24 (71.22-91.26)	**<0.001**
Dexamethasone treatment	9.25 (0.50-18.00)	**0.038**
Age at admission (years)	-0.25 (-0.34- -0.15)	**<0.001**
Sex (male)	3.54 (1.01-6.00)	**0.005**
BMI (kg/m²)	0.92 (0.67-1.71)	**<0.001**
Fibrosis on admission X-ray	-1.27 (-5.01-2.47)	0.506
Lung transplant patient	-27.16 (-44.76- -9.56)	**0.003**
FiO_2 >40%	-5.71 (-8.66- -2.76)	**<0.001**
Non-invasive ventilation (NIV)	-6.32 (-9.76- -2.88)	**<0.001**
Invasive mechanical ventilation (IMV)	-10.27 (-16.55- -4.01)	**0.001**
Hydroxychloroquine on admission	10.22 (1.52-18.91)	**0.021**
Tocilizumab on admission	-1.97 (-5.64-1.70)	0.292
Duration of hospital stay (days)	-0.06 (-0.11- -0.01)	**0.025**
Time from discharge to post-COVID consultation	0.03 (0.02-0.05)	**0.021**
Presence of fibrosis on follow-up CT scan		
	OR (95% CI)	**p-value**
Dexamethasone treatment	0.24 (0.12-0.49)	**<0.001**
Age at admission (years)	1.04 (1.02-1.07)	**0.001**
Sex (Male)	1.35 (0.74-2.45)	0.330
BMI (kg/m²)	0.93 (0.87-0.99)	**0.032**
Fibrosis on admission X-ray	0.71 (0.31-1.01)	0.409
FiO_2 >40%	2.45 (1.07-5.61)	**0.034**
Non-invasive ventilation (NIV)	2.62 (1.38-4.99)	**0.003**
Tocilizumab on admission	0.77 (0.39-1.51)	0.452
Time from discharge to post-COVID consultation	0.98 (0.99-1.00)	0.467

**: Adjusted mean value based on the multiple linear regression equation corresponding to the mean DLCO (% predicted) in a subject with average values for continuous variables and the reference category for categorical variables.*

†: The coefficients represent an increase or decrease in percentage units of DLCO for (i) each unit of the continuous variables, or (ii) the difference relative to the reference category in the categorical variables.

5.1.2. Airway sequelae in post-acute COVID-19 syndrome

Among the 2,027 patients admitted for SARS-CoV-2 pneumonia between March 2020 and December 2021, 1,652 had post-COVID-19 follow-up visit with an available chest CT scan. Of these 1,652 patients, 199 were excluded due to pre-existing respiratory diseases, specifically: 80 with asthma, 71 with COPD, 13 with bronchiectasis, 2 with cystic fibrosis, 8 with pulmonary hypertension, 20 with ILD, 5 with a history of lung transplantation, 13 with kyphoscoliosis, and 10 with prior thoracic trauma (note: some patients had multiple comorbidities).

The remaining patients were divided into two groups based on the presence or absence of airway involvement on chest CT: 758 patients exhibited airway abnormalities, while 695 did not. Among those with airway involvement: 527 patients (69.5%) had bronchiectasis, 435 (57.4%) had bronchial wall thickening, 122 (16.1%) had bronchiolitis, and 22 (2.9%) had tracheomalacia. Notably, a single patient could present with more than one airway abnormality (Figure 10).

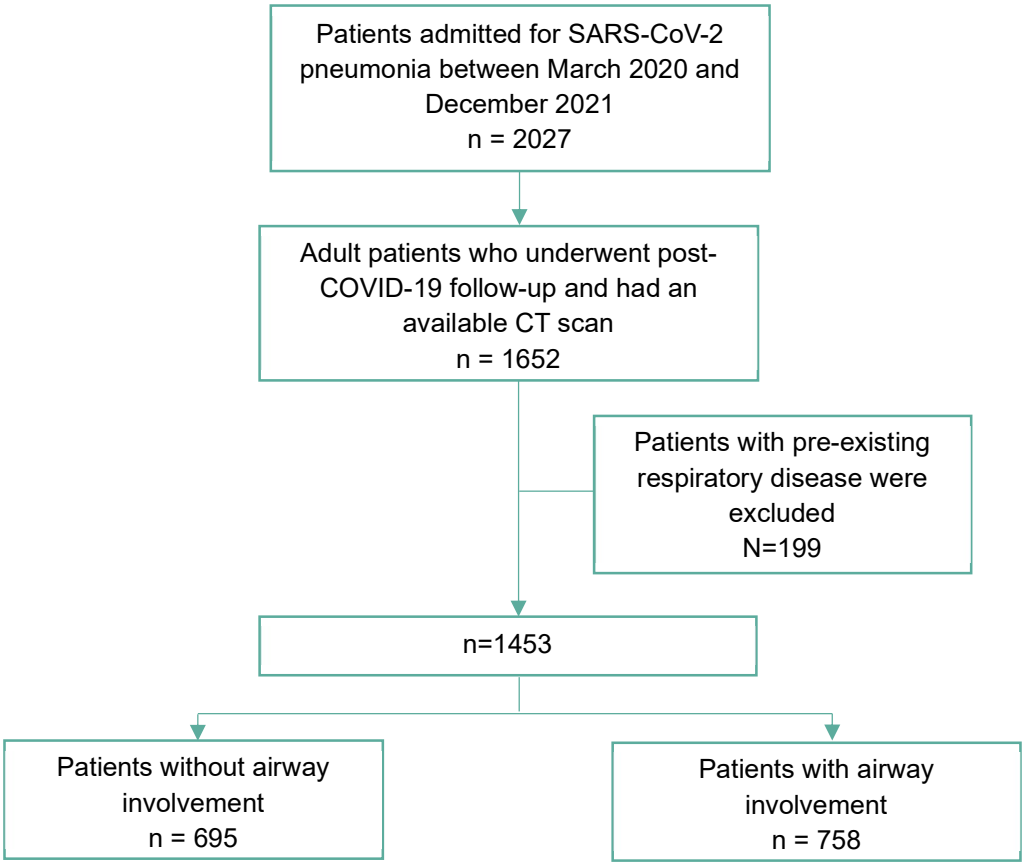


Figure 10. Patient flowchart according to airway involvement

The mean age at admission was 56.8 years (± 13.3). Patients with airway involvement were older, with a mean age of 60.1 years (± 12.2), compared to those without airway involvement, whose mean age was 53.2 years (± 13.5; $p < 0.001$). In patients with airway involvement, there was a predominance of males, comprising 63.1%, compared to 55.5% in those without airway involvement ($p = 0.004$). Additionally, these patients had a slightly lower BMI, with a mean of 29 kg/m² (± 4.8) compared to 29.9 (± 5.3) in those without airway involvement ($p = 0.016$). Regarding race, there was a higher proportion of White patients among those with airway involvement, 73.5%, compared to 65.1% of those without airway involvement ($p = 0.005$). Smoking or ex-smoking status was more prevalent in patients with airway involvement compared to non-smokers ($p < 0.001$). Furthermore, a positive correlation was found with the pack-year history, as patients with a higher pack-year history had a greater likelihood of airway involvement ($p = 0.036$).

Regarding comorbidities, patients with airway involvement had a higher prevalence of hypertension, with 314 patients (41.4%) compared to 213 (30.7%) in those without airway involvement ($p < 0.001$). Diabetes was present in 165 patients (21.8%) vs. 109 (15.7%) ($p = 0.003$), ischemic heart disease in 45 (5.9%) vs. 18 (2.6%) ($p = 0.002$), heart failure in 17 (2.2%) vs. 5 (0.7%) ($p = 0.018$), and other heart diseases in 70 (9.2%) vs. 42 (6%) ($p = 0.024$) in patients with and without airway involvement, respectively (Table 11).

Table 11: Baseline demographic characteristics of the study population according to airway involvement

	Total (n=1453)	Not airway involvement (n=695)	With airway involvement (n=758)	p-value
Age at admission (years), mean (SD)	56.8 (13.3)	53.2 (13.5)	60.1 (12.2)	**<0.001**
BMI (kg/m²), mean (SD)	29.5 (5.1)	29.9 (5.3)	29 (4.8)	**0.016**
Sex, n (%)				
Male	864 (59.5)	386 (55.5)	478 (63.1)	**0.004**
Female	589 (40.5)	309 (44.5)	280 (36.9)	
Race, n (%)				
White	1008 (69.5)	452 (65.1)	656 (73.5)	**0.005**
Asian	32 (2.2)	20 (2.9)	12 (1.6)	
Black	17 (1.2)	10 (1.4)	7 (0.9)	
Hispanic/Latino	394 (27.2)	212 (30.6)	182 (24)	
Smoking status, n (%)				
Active smokers	60 (4.1)	21 (3)	39 (5.2)	**<0.001**
Former smokers	443 (30.5)	184 (26.5)	259 (34.2)	
Non-smokers	950 (65.4)	490 (70.5)	460 (60.7)	
Pack-years, median (p25-p75)	26 (15-40)	20 (10-30)	30 (16-40)	**0.036**
Comorbidities, n (%)				
Hypertension	527 (36.3)	213 (30.7)	314 (41.4)	**<0.001**
Obesity	623 (42.9)	315 (45.3)	308 (40.6)	0.071
Diabetes	274 (18.9)	109 (15.7)	165 (21.8)	**0.003**
Renal insufficiency	86 (5.9)	41 (5.9)	45 (5.9)	0.999
Immunosuppression	73 (5.0)	33 (4.8)	40 (5.3)	0.719
Ischemic heart disease	63 (4.3)	18 (2.6)	45 (5.9)	**0.002**
Heart failure	22 (1.5)	5 (0.7)	17 (2.2)	**0.018**
Atrial fibrillation	41 (2.8)	18 (2.6)	23 (3.0)	0.639
Other heart diseases	112 (7.7)	42 (6.0)	70 (9.2)	**0.024**
Solid cancer	107 (7.4)	45 (6.5)	62 (8.2)	0.214
Leukemia	22 (1.5)	10 (1.4)	12 (1.6)	0.834
Psychiatric disorder	176 (12.1)	83 (11.9)	93 (12.3)	0.849
Gastroesophageal reflux	41 (2.8)	16 (2.3)	25 (3.3)	0.252

Patients with airway involvement during hospitalization for SARS-CoV-2 pneumonia had a longer hospital stay, with a median of 11 days (6-23) compared to 8 days (5-15) ($p < 0.001$). A higher proportion of patients with airway involvement required ICU admission (44.2% vs. 35.9%; $p = 0.001$), and their ICU stay was significantly longer (12 days [7-25] vs. 9 days [4-19]; $p = 0.001$).

Patients requiring oxygen therapy, regardless of FiO_2 levels, exhibited higher airway involvement (81.3% vs. 74.2%; $p = 0.001$). Similarly, patients with airway involvement had greater ventilatory support requirements, including invasive mechanical ventilation (25.6% vs. 18.4%, $p = 0.001$) and high-flow nasal cannula therapy (42.7% vs. 34.9%; $p = 0.002$).

Moreover, patients with airway involvement showed significantly elevated inflammatory markers upon admission compared to those without airway involvement. Additionally, a greater extent of lung involvement was observed on admission chest radiographs in these patients. All relevant data is presented in Table 12.

Table 12: Hospitalization Variables According to Airway involvement: clinical, blood test and X-ray

	Total (n=1453)	**Not airway involvement (n=695)**	**With airway involvement (n=758)**	**p-value**
Duration of hospital stay (days), median (p25-p75)	10 (5-19)	8 (5-15)	11 (6-23)	**<0.001**
ICU admission, n (%)	585 (40.3)	250 (35.9)	335 (44.2)	**0.001**
Duration of ICU stay (days), median (p25-p75)	11 (5-22)	9 (4-19)	12 (7-25)	**<0.001**
Oxygen therapy, n (%)				
Yes	1132 (77.9)	516 (74.2)	616 (81.3)	**0.001**
FiO_2 <40	495 (43.7)	238 (46.1)	257 (41.7)	0.137
FiO_2 >40	637 (56.3)	278 (53.9)	359 (58.3)	
Ventilatory support, n (%)				
None	829 (57.1)	427 (61.4)	402 (53.0)	**0.001**
HFNC	567 (39.0)	243 (34.9)	324 (42.7)	**0.002**
NIV	38 (2.6)	13 (1.9)	25 (3.3)	0.088
IMV	322 (22.2)	128 (18.4)	194 (25.6)	**0.001**
ECMO	11 (0.8)	5 (0.7)	6 (0.8)	0.874

Blood test on admission, median (p25-p75)				
Leukocytes (x 10^9/L)	6.4 (4.9-8.2)	6.3 (4.8-7.9)	6.5 (5.0-8.5)	0.067
Neutrophils (%)	76.8 (68.6-83.2)	75.8 (68.0-82.4)	77.6 (69.6-83.9)	**0.025**
Lymphocytes (%)	15.7 (10.7-22.5)	16.7 (11.8-23.4)	15.0 (9.8-21.6)	**<0.001**
Fibrinogen (g/L)	5.4 (4.7-6.2)	5.3 (4.6-6.1)	5.4 (4.7-6.2)	**0.023**
D-dimer (ng/mL)	233 (160-401)	224 (153-378)	244 (170-423)	**0.008**
PCR (mg/dL)	9.4 (4.5-15.2)	8.8 (4.1-14.6)	10.0 (5.2-15.4)	**0.017**
IL-6 (pg/mL)	45.9 (24.8-83.1)	41.9 (23.2-74.7)	49.5 (26.6-90.0)	**0.001**
Ferritin (ng/mL)	554 (320-989)	493 (261-944)	597 (347-1039)	**0.001**
LDH (UI/L)	335 (276-421)	326 (270-411)	343 (283-428)	**0.006**
Type Rx of lung involvement at hospital admission, n (%)				
Alveolar infiltrate	1336 (91.9)	637 (91.7)	699 (92.2)	0.694
Pleural effusion	1 (0.1)	0 (0.0)	1 (0.1)	0.999
Interstitial pattern	150 (10.3)	79 (11.4)	71 (9.4)	0.211
Atelectasis	9 (0.6)	4 (0.6)	5 (0.7)	0.999
Other	6 (0.4)	3 (0.4)	3 (0.4)	0.999
Laterality				
Unilateral	163 (11.2)	81 (11.7)	82 (10.8)	0.619
Bilateral	1290 (88.8)	614 (88.4)	676 (89.2)	
Extent of lung involvement				
<33%	570 (39.2)	283 (40.7)	287 (37.8)	0.288
33-66%	629 (43.3)	301 (43.3)	328 (43.2)	
>66%	254 (17.5)	111 (15.9)	143 (18.9)	

Regarding secondary complications, patients with airway involvement had a higher incidence of acute respiratory distress, with 42.9% compared to 34.4% in those without airway involvement (p = 0.001). Airway involvement was also associated with a higher rate of heart failure (2.1% vs. 0.6; p = 0.012). Additionally, patients with airway involvement had a higher prevalence of secondary infections (27.4% vs. 16.9%; p < 0.001) and septic shock (3.7% vs. 1.3%; p = 0.004). Furthermore, deep vein thrombosis was more common in patients with airway involvement (5.5% vs. 2.7%; p = 0.012). In terms of acute phase treatment, a significant difference was observed in antibiotic use, with 57.1% of patients with airway involvement requiring antibiotics compared to 48.6% in those without airway involvement (p = 0.001). No other treatment approaches appeared to influence airway involvement (Table 13).

Table 13: Hospitalization Variables According to Airway involvement: secondary complications and treatment

	Total (n=1453)	Not airway involvement (n=695)	With airway involvement (n=758)	p-value
Secondary complications, n (%)				
Acute respiratory distress	564 (38.8)	239 (34.4)	325 (42.9)	**0.001**
Heart failure	20 (1.4)	4 (0.6)	16 (2.1)	**0.012**
Septic shock	37 (2.6)	9 (1.3)	28 (3.7)	**0.004**
Acute cardiac injury	14 (1.0)	5 (0.7)	9 (1.2)	0.286
Acute kidney injury	113 (7.8)	38 (5.5)	75 (9.9)	**0.002**
Secondary infection	325 (22.4)	118 (16.9)	207 (27.4)	**<0.001**
Pneumothorax	19 (1.3)	7 (1.0)	12 (1.6)	0.329
Cerebrovascular accident	10 (0.7)	3 (0.4)	7 (0.9)	0.346
Pulmonary embolism	58 (4.0)	34 (4.9)	24 (3.2)	0.108
Deep vein thrombosis	60 (4.2)	19 (2.7)	41 (5.5)	**0.012**
Treatment, n (%)				
Hydroxychloroquine	381 (26.2)	187 (26.9)	194 (25.6)	0.570
Lopinavir/ritonavir	306 (21.1)	161 (23.2)	145 (19.1)	0.059
Darunavir/cobicistat	31 (2.1)	18 (2.6)	13 (1.7)	0.249
Antibiotics	771 (53.1)	338 (48.6)	433 (57.1)	**0.001**
Baricitinib	2 (0.1)	1 (0.1)	1 (0.1)	0.999
Remdesivir	56 (4.3)	24 (3.8)	32 (4.8)	0.350
Tocilizumab	209 (14.4)	91 (13.1)	118 (15.6)	0.180
Convalescent plasma	8 (0.6)	4 (0.6)	4 (0.6)	0.953
Corticosteroids (yes)	879 (60.5)	407 (58.6)	472 (62.3)	0.149
Type of corticosteroids				
Prednisone	35 (4.0)	16 (3.9)	19 (4.0)	0.943
Methylprednisolone	154 (17.5)	71 (17.4)	83 (17.6)	0.947
Dexamethasone	766 (87.1)	349 (85.8)	417 (88.4)	0.251
Hydrocortisone	10 (1.1)	6 (1.5)	4 (0.85)	0.527

The post-COVID-19 follow-up visit was conducted at 157 days (100-252). There were no significant clinical differences between patients with and without airway involvement. Regarding functional tests, a slight decrease in diffusion capacity was observed, with a mean of 76.5% (± 21.3) in patients with airway involvement, compared to 79.1% (± 20.7) in those without ($p = 0.026$), while no alterations were found in spirometry parameters. In the 6MWT, a minimal difference in the distance walked was found: 420 meters (360-480) for patients with airway involvement vs. 435 meters (375-480) for those without ($p = 0.021$). In terms of chest CT scans, patients with airway involvement generally showed less ground-glass opacification (18.2% vs. 40.7%; $p < 0.001$) and more septal thickening (8.9% vs. 2.7%;

p < 0.001). No significant differences were observed in terms of pulmonary fibrosis between the two groups (Table 14).

Table 14: post-COVID-19 follow-up according to airway involvement

	Total (n=1453)	Not airway involvement (n=695)	With airway involvement (n=758)	p-value
Time from discharge to post-COVID consultation (days), median (p25-p75)	157 (100-252)	169 (101-253)	147 (98-251)	0.313
Symptoms, n (%)				
Cough	100 (6.9)	41 (5.9)	59 (7.8)	0.156
Expectoration	28 (1.9)	12 (1.7)	16 (2.1)	0.595
Dyspnea	440 (30.3)	205 (29.5)	235 (31.0)	0.532
Chest pain	59 (4.1)	24 (3.5)	35 (4.6)	0.261
Dyspnea (mMRC; 0-4), median (p25-p75)	1 (1-2)	1 (1-2)	1 (1-2)	0.947
Pulmonary function, mean (SD)				
FVC (% predicted)	91.3 (16.1)	91.6 (15.8)	91.0 (17.8)	0.454
FEV1 (% predicted)	93.8 (17.8)	93.7 (17.0)	94.0 (18.4)	0.712
FEV1/FVC (%)	81.4 (6.8)	81.4 (6.9)	81.4 (6.8)	0.854
DLCO (% predicted)	77.8 (21.0)	79.1 (20.7)	76.5 (21.3)	**0.026**
KCO (% predicted)	88.1 (17.6)	89.2 (1769)	87.2 (17.6)	**0.039**
6MWT, mean (SD)				
Distance (m), median (p25-p75)	420 (360-480)	435 (375-480)	420 (360-480)	**0.021**
Baseline SpO2 (%)	97.2 (1.9)	97.3 (1.8)	97.0 (1.6)	**0.032**
Lowest SpO2 (%)	93.6 (3.8)	93.7 (3.6)	93.5 (4.0)	0.287
Mean SpO2 (%)	95.3 (2.8)	95.4 (2.7)	95.2 (2.9)	0.222
Parenchymal Involvement Chest TC, n (%)				
Principal characteristic				
Ground-glass opacity	291 (25.7)	154 (40.7)	137 (18.2)	**<0.001**
Consolidation	6 (0.5)	4 (1.1)	2 (0.3)	
Linear opacities	72 (6.4)	31 (8.2)	41 (5.4)	
Reticulation	59 (5.3)	23 (6.1)	36 (4.8)	
Mixed type	488 (43.1)	156 (41.3)	332 (43.8)	
None	217 (19.2)	10 (2.7)	207 (27.4)	
Interstitial				
Septal thickening	78 (6.9)	10 (2.7)	68 (8.9)	**<0.001**
Crazy paving	5 (0.4)	0 (0.0)	5 (0.7)	0.176
Fibrosis	86 (7.6)	26 (6.9)	60 (7.9)	0.533

5.1.3. Acquired tracheomalacia due to SARS-CoV-2 pneumonia

From February 2020 to August 2021, 1,920 patients were included in the cohort. Tracheomalacia was observed in 15 (0.8%) on expiratory HRCT imaging. The median age

of these patients was 65.5 years. The treatment for SARS-CoV-2 infection in these patients was modified in the light of the new information obtained during the different waves of the pandemic. Several treatment protocols were applied including antiviral therapies as well as corticoids and empirical antibiotherapy with cephalosporins and quinolones. In this group, 10 patients received hydroxychloroquine, 9 lopinavir/ritonavir, 2 tocilizumab, 5 dexamethasone and 13 azithromycin (some patients received several treatments at the same time). Regarding the symptoms identified on clinical examination, only 3 (20%) patients were asymptomatic; 10 (67%) had dyspnoea and 2 (13%) had cough. In HRCT, 14 patients were diffuse tracheomalacia, affecting the entire trachea. Of these, in 6 cases, there was clear associated bronchomalacia. In one patient, the malacia was segmental at the level of the upper third of the trachea. No tracheal stenosis was observed. In 9 patients, tracheomalacia affected both at the membranous and cartilaginous level, and in 6 cases, the membranous part was only affected. Ground glass opacities in the CT scan were found in all patients with tracheomalacia. 6 patients (40%) also presented other parenchymatous alterations such as septal thickening and reticulation. 12 patients also had airway sequelae such as bronchiectasis, bronchiolitis or airway bronchial thickening. The baseline characteristics and findings reported at the follow-up visit for pulmonary function and chest CT are summarized in Table 15.

Table 15: Baseline characteristics of 15 patients with tracheomalacia in thoracic HRCT.

Characteristics	
Gender, male n (%)	8 (53)
Age, median (p25-p75)	65.5 (48 – 75)
Smokers n (%)	4 (27)
Respiratory disease n (%)	
Chronic Obstructive Pulmonary Disease	1 (7)
Asthma	2 (13.3)
Obstructive Sleep Apnoea	2 (13.3)
None	10 (67)
Ventilatory support n (%)	
Invasive ventilatory support	5 (33.3)
Non-Invasive ventilatory support	3 (20)
O_2 venturi effect †	2 (13.3)
No oxygen therapy or ventilation support	5 (33.3)

Radiology pattern	
Unilobed pneumonia	5 (33.3)
Multilobe pneumonia	10 (66.6)
Diffuse interstitial disease	0
Severity of SARS-CoV-2 pneumonia n (%)	
Mild	5 (33.3)
Severe	2 (13.3)
Very Severe	0 (0)
Critical	8 (53.3)
Data from follow-up visit	
Pulmonary respiratory function test, median (p25-p75)	
Forced vital capacity (FVC%)	89.2 (66-123)
Forced expiratory volume in the 1st second (FEV1%)	92.3 (38-131)
FVC/FEV1	83.3 (43-99)
Diffusing capacity for carbon monoxide (DLCO%)	64.7 (43-109)
HRCT Tracheomalacia characteristics n (%)	
Membranous part	6 (40)
Membranous and cartilaginous (Both)	9 (60)
Cicatricial stenosis	0
Location	
Segmental (upper third)	1 (6.6)
Diffuse	14 (93.3)
HRCT parenchymal sequelae n (%)	
Ground Glass Opacities	15 (100)
Ground Glass Opacities and reticulation or septal thickening	6 (40)
HRCT airway tract sequelae n (%)	
Bronchiectasis	9 (60)
Bronchial thickening	1 (6.6)
Bronchiolitis	2 (13.3)
Only tracheomalacia	3 (20)
Treatment n (%)	
No treatment	8 (53)
LABA	2 (13)
LAMA	2 (13)
Inhaled corticosteroids	2 (13)
Oral corticosteroids	2 (13)
CPAP	1 (7)
Surgery	0 (0)

† O_2 Venturi effect: Oxygen provided by Venturi system

5.1.4. Respiratory sequelae in patients with bronchial asthma after SARS-CoV-2 pneumonia

A total of 2,457 patients were attended during the study period, 66 of whom had asthma (26 males, 39%), with a median age of 52 years (28-83) and a median BMI of 29 Kg/m^2 (17-48). Patients were adjusted with controls based on the date of hospital admission, sex, age

and severity of COVID-19, as discussed earlier. There were no significant differences were observed between groups regarding the number of days requiring ICU admission or the duration of ventilatory support. Regarding treatment during the acute phase, controls required significantly more tocilizumab compared to asthmatic patients (p = 0.034). However, no differences were observed regarding the rest of the treatment (Table 16).

Table 16: Baseline demographic characteristics and hospitalization variables according to asthma

	Asthma (n = 66)	No asthma (n = 132)	p-value
Age, median (IQR)	52 (17.25)	58 (15.00)	0.14
Sex, male, n (%)	26 (39)	54 (41)	0.48
BMI, median (IQR)	29 (7.50)	30 (7.81)	0.09
Comorbidities, n (%)	53 (80)	89 (67)	0.09
Smoking habit, n (%)			
Non-smoker	45 (68)	78 (59)	0.38
Smoker	1 (2)	5 (4)	
Ex-smoker	20 (30)	49 (37)	
Pack/years, median (p25-p75)	14.5 (2-35)	30 (3-60)	0.24
Data collected during admission, n (%)			
Duration of ventilatory support, median (IQR)	12 (13)	10 (8)	0.31
Days of stay in the ICU, median (IQR)	13 (16)	8 (19.50)	0.81
Severity COVID-19			
Mild FiO_2 <40%	39 (59)	78 (59)	1.00
Moderate FiO_2 >40%	5 (8)	10 (8)	
Severe NIVM or NIV	22 (33)	44 (33)	
COVID-19 treatment			
Kaletra	32 (48)	54 (41)	0.19
Remdesivir	1 (1)	6 (4)	0.26
Tozilizumab	5 (8)	24 (18)	**0.034**
Hydroxychloroquine	35 (53)	70 (53)	0.56
Azithromycin	36 (54)	71 (54)	0.51
Dexametasone	21 (32)	50 (38)	0.25

As for phenotype, 48 patients were T2-Th2, eight T2-ILC2, and 10 non-T2. No differences were found between the phenotypes in asthma severity (only 6% had severe asthma) or asthma treatment. Table 17 presents the characteristics of asthmatic patients according to different phenotypes.

Table 17: Characteristics of asthmatic patients according to different phenotypes

	Asthma (n = 66)	T2-Th2 (n = 48)	T2-ILC2 (n = 8)	Non-T2 (n = 10)	p-value
Atopy, n (%)	48 (73)	48 (100)	0	0	**0.0001**
Rhinitis, n (%)	35 (53)	32 (67)	3 (37)	0	**0.0001**
Rhinosinusitis, n (%)	6 (9)	4 (8)	2 (25)	0	0.17
Rhinopolyposis, n (%)	7 (11)	4 (8)	3 (37)	0	**0.023**
Asthma severity, n (%)					
Intermittent	13 (20)	11 (23)	0	2 (20)	0.73
Mild persistent	19 (29)	14 (29)	2 (25)	3 (30)	
Moderate persistent	30 (45)	21 (44)	5 (62)	4 (40)	
Severe persistent	4 (6)	2 (4)	1 (13)	1 (19)	
Type 2 Inflammatory Markers, median (IQR)					
Eosinophils, x 10^9/L	300 (200)	200 (275)	350 (275)	100 (150)	**0.05**
Total IgE, KU/L	88 (228.50)	118 (243.50)	48 (55)	9 (54.50)	0.67
Asthma medication, n (%)					
SABA on demand	39 (59)	30 (62)	4 (50)	5 (50)	0.65
LABA on demand	4 (6)	4 (8)	0	0	0.45
Inhaled corticosteroids	52 (79)	37 (77)	8 (100)	7 (70)	0.26
LABA	49 (87)	34 (71)	8 (100)	7 (70)	0.21
LAMA	17 (26)	8 (17)	5 (62)	4 (40)	**0.012**
No treatment	3 (4)	2 (4)	0	1 (10)	0.58
Oral corticosteroids	0	0	0	0	1.00
Montelukast	15 (23)	11 (23)	3 (37)	1 (10)	0.38
Azithromycin	2 (3)	0	2 (25)	0	**0.001**
Biological treatment	1 (1)	1 (2)	0	0	0.83

Regarding the different asthma phenotypes, no differences were observed in age, sex, smoking habits, BMI, or comorbidities. The severity of pneumonia was lower in patients with the T2-Th2 phenotype. Regarding treatments among the different phenotypes, no major differences were observed. However, the T2-ILC2 phenotype required more tocilizumab than the others, although the number of patients in each group was very small (Table 18).

Table 18: Baseline demographic characteristics and hospitalization variables according to asthma phenotypes

	T2-Th2 (n = 48)	T2-ILC2 (n = 8)	Non-T2 (n = 10)	p-value
Age, median (IQR)	49 (10.75)	67 (9)	58 (24)	0.07
Sex, male, n (%)	19 (39)	4 (50)	3 (30)	0.45
BMI, median (IQR)	30 (6)	26 (7)	30 (10)	0.19
Comorbidities, n (%)	37 (77)	6 (75)	10 (100)	0.54
Smoking habit, n (%)				
Non-smoker	32 (67)	5 (63)	8 (80)	0.97
Smoker	1 (2)	0	0	
Ex-smoker	15 (31)	3 (37)	2 (20)	
Data collected during admission, n (%)				
Duration of ventilatory support, median (IQR)	12 (12)	11 (10)	14 (23.50)	0.13
Days of stay in the ICU, median (IQR)	13 (17.50)	17 (10)	10 (10)	0.25
Severity COVID-19				
Mild FiO_2 <40%	32 (67)	3 (37)	4 (40)	**0.002**
Moderate FiO_2 >40%	0	3 (37)	2 (20)	
Severe NIVM or NIV	16 (33)	2 (25)	4 (40)	
COVID-19 treatment				
Kaletra	22 (46)	5 (62)	5 (50)	0.68
Remdesivir	1 (2)	0	0	0.82
Tozilizumab	1 (2)	3 (37)	1 (10)	**0.002**
Hydroxychloroquine	24 (50)	5 (62)	6 (60)	0.72
Azithromycin	23 (48)	6 (75)	7 (70)	0.21
Dexametasone	17 (35)	1 (12)	3 (30)	0.43

At the post-COVID-19 follow-up visit, asthma patients exhibited a higher prevalence of cough, fatigue, and wheezing compared to the control population; however, no significant differences in pulmonary function parameters were detected. The chest CT did not reveal differences in terms of parenchymal involvement, with mixed interstitial involvement being the most frequent sequela. Although no differences were found in terms of the incidence of airway involvement, the type of involvement did vary patients with asthma had more tracheomalacia, more bronchial thickening and less bronchiectasis than the control population (Table 19).

Table 19: post-COVID-19 follow-up according to asthma

	Asthma (n = 66)	No asthma (n = 132)	p-value
Symptoms, n (%)			
Dyspnea	30 (45)	58 (44)	0.48
mMRC			
0	32 (48)	75 (57)	0.47
1	24 (36)	35 (26)	
2	10 (16)	22 (17)	
Cough	10 (15)	8 (6)	**0.04**
Fatigue	12 (18)	0	**0.0001**
Expectoration	1 (1)	1 (1)	0.56
Chest pain	4 (6)	5 (4)	0.35
Wheezing	5 (8)	0	**0.004**
Pulmonary function			
FEV1 (%), median (IQR)	83 (20.8)	87 (28.2)	0.20
FEV1 (%) < 80%, n (%)	19 (29)	35 (26)	--
FVC (%), median (IQR)	88 (18)	87 (25.88)	0.10
FVC (%) < 80%, n (%)	14 (21)	36 (27)	--
FEV1 / FVC, median (IQR)	77 (8)	80 (8.4)	0.32
FEV1 / FVC < 70%, n (%)	10 (15)	8 (6)	--
DLCO (%), median (IQR)	76 (20)	79 (22.4)	0.33
DLCO (%) < 80%, n (%)	21 (32)	70 (53)	--
KCO (%), median (IQR)	85 (25.8)	83 (18)	0.26
Chest CT, n (%)			
Pathological, yes	52 (79)	103 (78)	0.98
Principal			
None	38 (57)	51 (39)	0.09
Ground glass	10 (15)	36 (27)	
Consolidation	1 (2)	2 (2)	
Linear opacities	2 (3)	3 (2)	
Reticulation	1 (2)	6 (4)	
Mixed type *	14 (21)	34 (26)	
Interstitial			
None	62 (94)	121 (90)	0,67
Septal thickening	4 (6)	8 (6)	
Crazy paving	0	1 (2)	
Fibrosis	0	2 (2)	
Bronchial involvement, yes	40 (61)	71 (54)	0,24
Bronchial involvement			
Bronchiectasis	11 (17)	40 (30)	**0,007**
Bronchial thickening	22 (33)	25 (19)	
Bronchiolitis	3 (4)	7 (5)	
Tracheobronchomalacia	4 (7)	0	

**Mixed type: patient presents two of the other conditions*

The sequelae in asthma patients were independent of their asthma phenotype. No differences were observed in clinical presentation, pulmonary function, or chest CT findings (Table 20).

Table 20: post-COVID-19 follow-up according to asthma phenotypes

	T2-Th2 (n = 48)	T2-ILC2 (n = 8)	Non-T2 (n = 10)	p-value
Symtomps, n (%)				
Dyspnea	21 (44)	4 (50)	5 (50)	0.90
mMRC				
0	24 (50)	4 (50)	4 (40)	
1	18 (37)	2 (25)	4 (40)	
2	6 (13)	2 (25)	2 (20)	0.59
Cough	8 (17)	1 (12)	1 (10)	0.84
Fatigue	9 (19)	1 (12)	2 (20)	0.90
Expectoration	1 (2)	0	0	0.83
Chest pain	2 (4)	0	2 (20)	0.12
Wheezing, n (%)	4 (8)	1 (12)	0	0.57
Pulmonary function				
FEV1 (%), median (IQR)	83 (19.50)	76 (33)	88 (29)	0.20
FVC (%), median (IQR)	88 (15)	94 (23.50)	93 (34.50)	0.56
FEV1 / FVC, median (IQR)	77 (9.50)	73 (15.75)	76 (8)	0.37
DLCO (%), median (IQR)	79 (20)	72 (28.25)	70 (27)	0.51
KCO (%), median (IQR)	86 (22.50)	84 (21.25)	76 (18.50)	0.62
Chest CT, n (%)				
Pathological, yes	35 (73)	8 (100)	9 (90)	0.14
Principal				
None	30 (62)	3 (37)	5 (50)	
Ground glass	6 (13)	1 (13)	3 (30)	
Consolidation	0	0	1 (10)	0.23
Linear opacities	2 (4)	0	0	
Reticulation	1 (2)	0	0	
Mixed type *	9 (19)	4 (50)	1 (10)	
Interstitial				
None	45 (94)	8 (100)	9 (90)	
Septal thickening	3 (6)	0	1 (10)	0.67
Crazy paving	0	0	0	
Fibrosis	0	0	0	
Bronchial involvement, yes	27 (56)	5 (62)	8 (80)	0.37
Bronchial involvement				
Bronchiectasis	7 (15)	2 (25)	2 (20)	
Bronchial thickening	14 (29)	2 (25)	6 (60)	0.81
Bronchiolitis	3 (6)	0	0	
Tracheobronchomalacia	3 (6)	1 (12)	0	

**Mixed type: patient presents two of the other conditions*

5.2. PART 2: ORAL CORTICOSTEROID DOSING STRATEGIES FOR POST-COVID ORGANIZING PNEUMONIA (NORCOVID CLINICAL TRIAL)

Patients

In this study the intention was to randomize 120 patients, but recruitment was halted after randomization of 82 patients (41 per group) due to a critically slow recruitment rate. Among the patients who were randomized and included in the mFAS population, 79 (96.34%) completed the trial regimen, and 74 (90.24%) finished the trial (Figure 11).

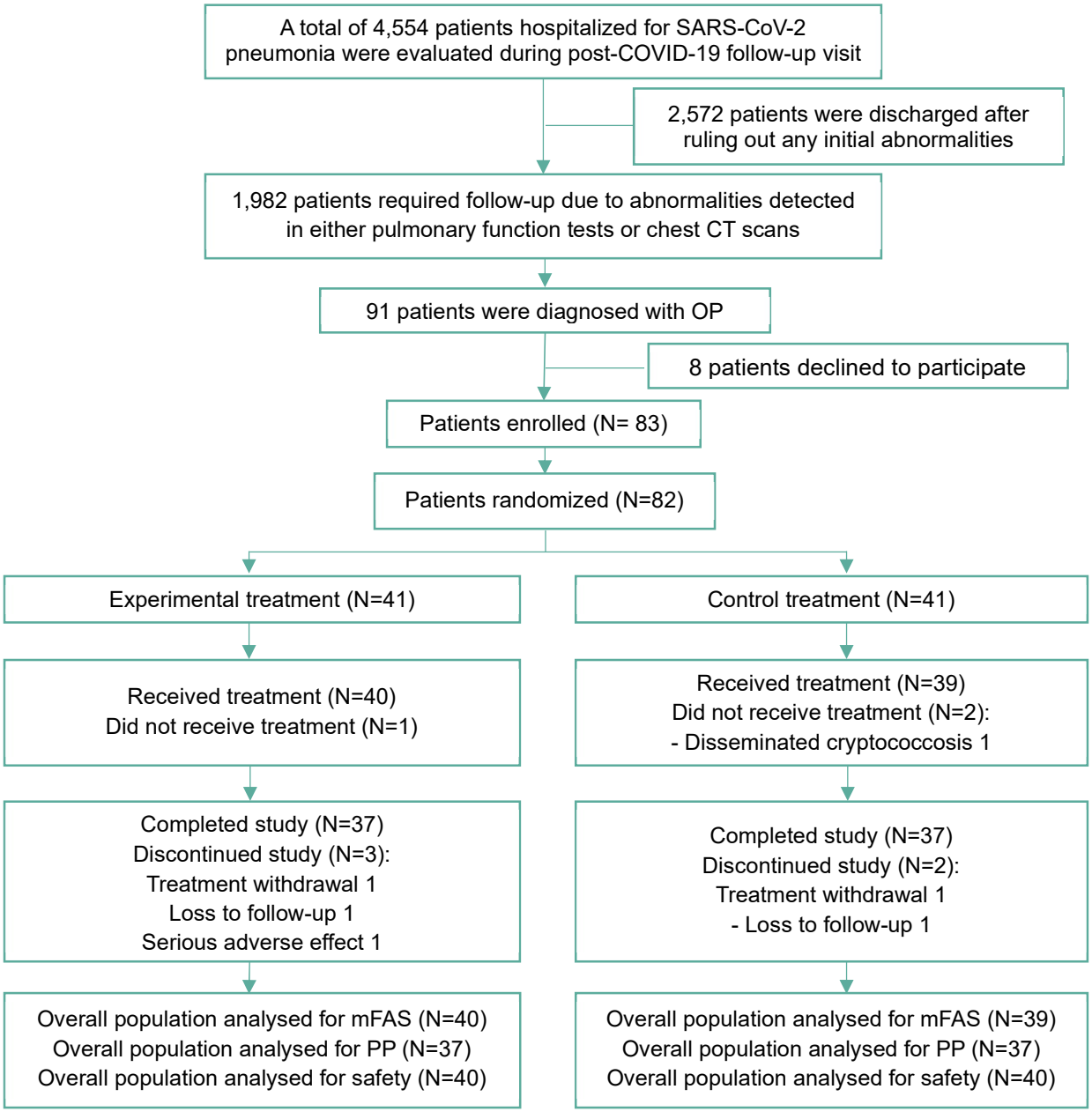


Figure 11: Flowchart of patient enrollment

In the mFAS population, the mean age was 61.5 years (10.9%), and 56 (70.9%) were men. Fifty-five patients (69.6%) had histopathology consistent with OP, while the others were diagnosed based on clinical and radiological criteria. Baseline clinical characteristics of the mFAS population are displayed in Table 21. Comorbidities are outlined in Table 22.

Table 21: Demographic data and clinical characteristics of the mFAS population

		Control (n=39)	Experimental (n=40)	Total (n=79)
Age, mean (SD)		62.7 (11.3)	60.3 (10.6)	61.5 (10.9)
Sex, male, n (%)		29 (74.4)	27 (67.5)	56 (70.9)
BMI, mean (SD)		28.1 (3.6)	28.8(3.8)	28.5 (3.7)
Tobacco exposure, n (%)				
Smoker		0 (0)	2 (5)	2 (2.5)
Former smoker		13 (33.3)	15 (37.5)	28 (35.4)
Non-smoker		26 (66.6)	23 (57.5)	49 (62)
COVID-19 severity, n (%)				
No oxygen required		3 (7.7)	5 (12.5)	8 (10.1)
Oxygen therapy FiO_2 <40%		8 (20.5)	13 (32.5)	21 (26.6)
NIV or HFNC		13 (33.3)	5 (12.5)	18 (22.8)
IMV or ECMO		15 (38.5)	17 (42.5)	32 (40.5)
Post-COVID control, n (%)				
Dx OP with pathological anatomy		27 (69.2)	28 (70)	55 (69.6)
Symptoms, n (%)				
Cough		6 (15)	6 (15)	12 (15)
Expectoration		0 (0)	2 (5)	2 (2.5)
Fever		0 (0)	0 (0)	0 (0)
Dyspnea		37 (95)	39 (98)	76 (96)
mMRC				
0		2 (5.1)	1 (2.5)	3 (3.8)
1		14 (35.9)	11 (27.5)	25 (31.6)
2		21 (53.8)	23 (57.5)	44 (55.7)
3		2 (5.1)	5 (12.5)	7 (8.9)
Chest pain		8 (20.5)	3 (7.5)	11 (13.9)
Respiratory function tests, mean (SD)				
FVC (% of theoretical value)		76.9 (24.7)	78.7 (21.6)	77.8 (2)
FEV1 (% of theoretical value)		80.8 (25.9)	83.2 (22.9)	82 (24.3)
DLCO (% of theoretical value)		55.5 (16.5)	59.31 (16.7)	57.5 (16.6)
DLCO/VA (% of theoretical value)		76.9 (17.5)	79.2 (19.2)	78 (18.3)
Chest CT, n (%)				
Pathological		39 (100)	40 (100)	79 (100)
Parenchymal involvement	Linear opacities	1 (2.6)	0 (0)	1 (1.3)
	Mixed type *	32 (82.1)	30 (75)	62 (78.5)
	Reticulation	2 (5.1)	1 (2.5)	3 (3.8)
	Ground glass opacity	4 (10.3)	9 (22.5)	13 (16.5)

**Mixed type: patient presents two of the other conditions. All patients with consolidations exhibited additional findings and were therefore classified under the mixed pattern*

Table 22: Comorbidities for the modified mFAS population

Comorbidities, n (%)	**Control (n=39)**	**Experimental (n=40)**	**Total (n=79)**
Asthma	3 (7.7)	1 (2.5)	4 (5.1)
Sleep apnea/hypopnea syndrome	3 (7.7)	2 (5.0)	5 (6.3)
Chronic obstructive pulmonary disease	1 (2.6)	0 (0)	1 (1.3)
Arterial hypertension	17 (43.6)	14 (35.0)	31 (39.2)
Diabetes Mellitus	11 (28.2)	7 (17.5)	18 (22.8)
Cancer	3 (7.7)	6 (15.0)	9 (11.4)
Obesity	8 (20.5)	9 (22.5)	17 (21.5)
Dyslipidemia	9 (23.1)	11 (27.5)	20 (25.3)
Cardiovascular	7 (17.9)	5 (12.5)	12 (15.2)
Renal	5 (12.8)	3 (7.5)	8 (10.1)
Digestive	5 (12.8)	4 (10.0)	9 (11.4)
Allergy	0 (0)	4 (10.0)	4 (5.1)
Hyperuricemia	1 (2.6)	2 (5.0)	3 (3.8)
Hyperprolactinemia	1 (2.6)	0 (0)	1 (1.3)
Hypothyroidism	1 (2.6)	7 (17.5)	8 (10.1)
Respiratory	2 (5.1)	2 (5.0)	4 (5.1)
Hearing impairment	2 (5.1)	1 (2.5)	3 (3.8)
Anxiety/Depression	4 (10.3)	5 (12.5)	9 (11.4)
Osteoarthritis/Lumbalgia	8 (20.5)	8 (20.0)	16 (20.3)
Benign Prostatic Hyperplasia	6 (15.4)	2 (5.0)	8 (10.1)
Others	11 (28.2)	17 (42.5)	28 (35.4)

Primary endpoint

The initial mean DLCO was 59.3% (±16.7) in the experimental group and 55.5% (±16.5) in the control group. At 6 months, the mean increases were 11.7% (95% CI: 7.18-16.17) and 12.8% (95% CI: 8.57-17.11), respectively. The difference between groups at 6 months was 1.16 (95% CI: -5.06, 7.38) in the mFAS population and 1.23% (95% CI: -5.13, 7.59) in the protocol population, the experimental regimen being non-inferior to the control group within a margin of 10%. At 12 months, the mean increases were 15.5% (95% CI: 10.28, 20.73) and 22.26% (95% CI: 17.01, 27.51) respectively. The difference between groups at 12 months was 6.75 (-0.66, 14.17) with a p = 0.074. Table 23 shows the evolution of the diffusion test in the mFAS population.

Table 23: Evolution of diffusion test

	Baseline*	Baseline-adjusted changes from Baseline	
		At 6 months *	At 12 months *
DLCO SB (% of the theoretical value)			
Control (n=39)	55.54 (16.48)	12.84 [8.57,17.11]	22.26 [17.01,27.51]
Experimental (n=40)	59.31 (16.65)	11.68 [7.18,16.17]	15.50 [10.28,20.73]
Difference between control and experimental groups	--	1.16 [-5.06,7.38] p = 0.711	6.75 [-0.66,14.17] p = 0.074
Difference between control and experimental groups (PP)	--	1.23 [-5.13,7.59] p = 0.701	7.12 [-0.58,14.82] p = 0.069
Patients with DLCO <80% of predicted			
Control (n=38)	54.66 (15.77)	13.78 [9.52,18.05]	23.09 [17.76,28.42]
Experimental (n=36)	55.87 (13.54)	12.41 [7.68,17,13]	17.01 [11.46,22.56]
Difference between control and experimental groups	--	1.38 [-4.99,7.75] p = 0.668	6.08 [-1.61,13.77] p = 0.120

All analyses are presented for mFAS population, except for the sensitivity analyses of the main per-protocol variable (PP), as noted in the table.
**: Mean (SD) for Baseline Values and Baseline-Adjusted Changes from Baseline [95% CI] for 6- and 12-Month Visits. Inferential results are based on mixed models for repeated measures.*

Exploratory analyses among DLCO tertile levels did not show a differential treatment effect (Figures 12 to 15 p = 0.1450).

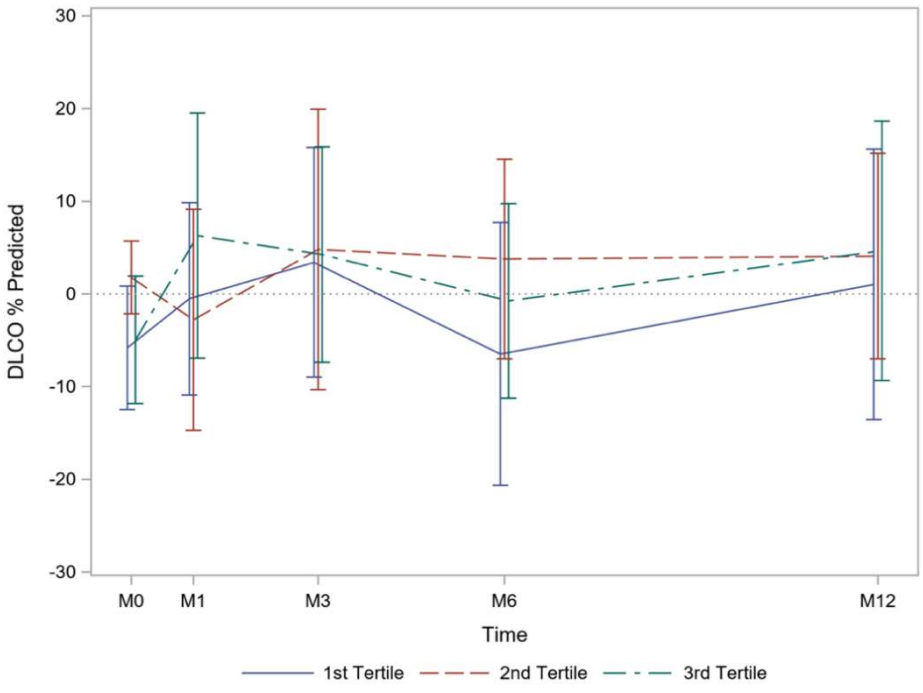


Figure 12: the difference DLCO evolution between group in tertiles

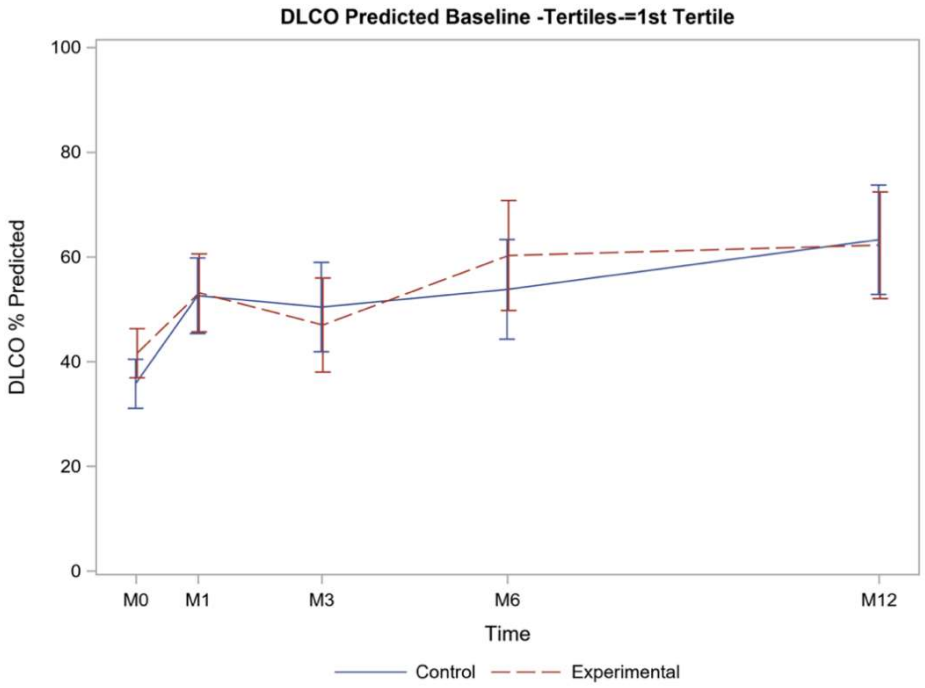


Figure 13: DLCO evolution in 1st tertile

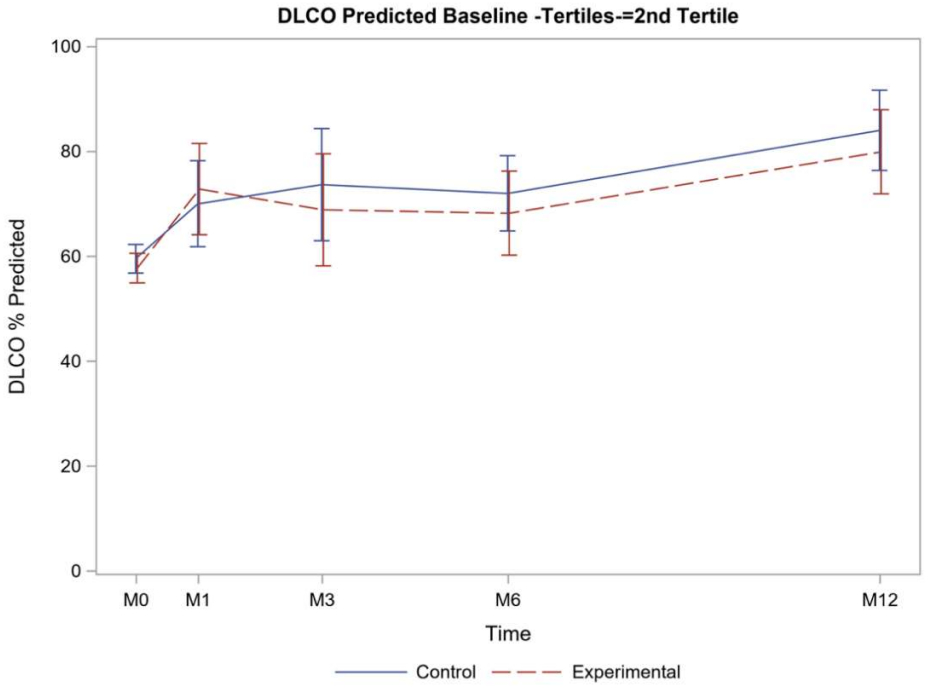


Figure 14: DLCO evolution in 2nd tertile

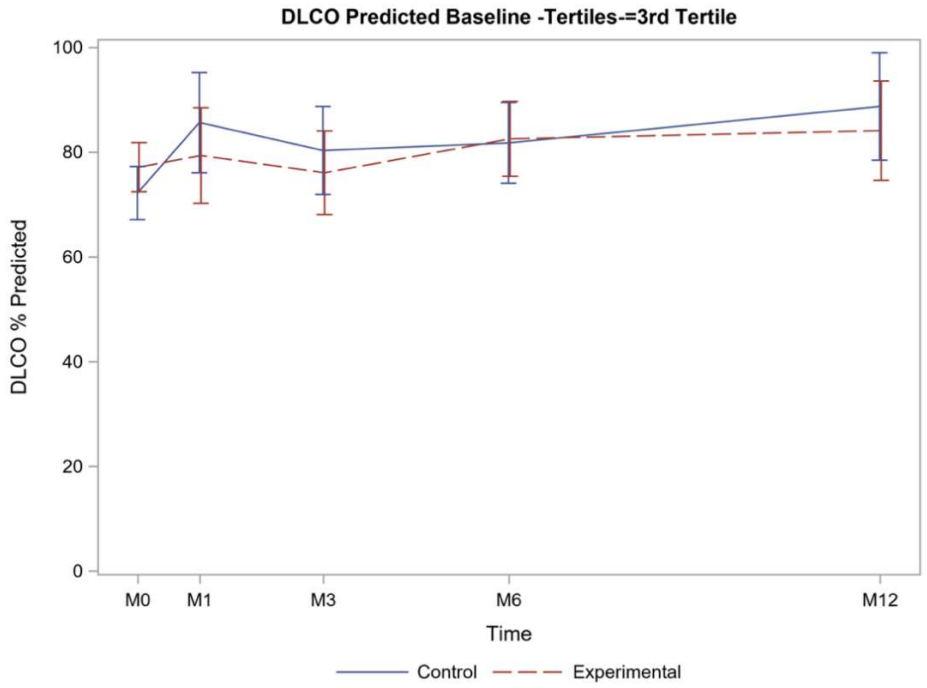


Figure 15: DLCO evolution in 3rd tertile

Secondary endpoints

In the subgroup of patients with an initial DLCO below 80%, the non-inferiority criterion between the two corticosteroid treatment protocols was also met (Table 2). Regarding spirometry, the control group showed greater increases in FVC and FEV1 than the experimental group. The difference in FEV1 between the groups reached statistical significance, with a p = 0.033; however, no significant differences were observed between the groups in the FEV1/FVC ratio (p = 0.607) or in the six-minute walk test results (Table 24).

Chest CT abnormalities were present in all patients, with ground-glass opacity in 13 patients (16.5%), reticulation in 3 (3.8%), linear opacities in 1 (1.3%), and a mixed pattern in 62 (78.5%). All patients with consolidations exhibited additional findings and were therefore classified under the mixed pattern. When comparing the chest CT at 6 months to the baseline CT, no patients in the experimental group showed worsening; 32.5% remained unchanged, 52.5% showed improvement, and 15% achieved resolution of abnormalities. In

the control group, 2.6% worsened, 43.6% remained stable, 46.2% improved, and 7.7% achieved resolution. No significant differences were observed between groups (Table 24).

Baseline symptoms are summarized in Table 21. Clinical progression was assessed using the WHO Clinical Progression Scale. Initially, 23.7% of the control group and 13.2% of the experimental group were not hospitalized and did not present activity limitations. At 12 months, these rates rose to 85.7% and 75.7% respectively, with no significant differences (p = 0.3755) (Table 24).

Of all the patients who completed the treatment regimen, three in the experimental group and two in the control group presented relapses.

Table 24: Progression of Secondary Endpoints

	Baseline *	**Baseline-Adjusted Changes from Baseline at 6 months ***		
FVC (% of theoretical value)				
Control (n=37)	76.88 (24.72)	9.51 [4.93,14.09]		
Experimental (n=38)	78.69 (21.58)	3.69 [-1.00,8.37]		
Difference between control and experimental groups		5.82 [-0.73,12.38] **p = 0.081**		
FEV1 (% of theoretical value)				
Control (n=37)	80,7 (25.9)	9,51 [5,23, 13,79]		
Experimental (n=38)	83,15 (22.9)	2,76 [-1,7, 7,21]		
Difference between control and experimental groups		6,75 [0,57, 12,93] **p = 0.033**		
FEV1/FVC (% of theoretical value)				
Control (n=37)	82.48 (5.67)	82.24 [80.75, 83.72]		
Experimental (n=38)	82.96 (6.37)	81.68 [80.13, 83.23]		
Difference between control and experimental groups		0.56 [-1.59, 2.70] p = 0.607		
WT6 (Meters walked) **&**	**Baseline**	**Changes from Baseline**		
Control (n=27)	375 (316-450)	30 [-9 ,53]		
Experimental (n=27)	405 (346-465)	45 [6 ,104]		
Median difference between control and experimental groups		32.5 [-10, 75] p = 0.148		
Chest CT	**Baseline**	**Change with respect to baseline at 6 months**		
Control (n=39)	39 (100)	Deterioration	1 (2.6)	p = 0.149
		Stability	17 (43.6)	
		Improvement	18 (46.2)	
		Resolution	3 (7.7)	

Experimental (n=40)	40 (100)	Deterioration	0 (0)	
		Stability	13 (32.5)	
		Improvement	21 (52.5)	
		Resolution	6 (15)	
WHO grade scale	**Baseline**		**At 6 months** p = 0.646	
Control (n=38), n (%)				
1. Not hospitalized, no limitations on activities	9 (23.7)		22 (57.9)	
2. Not hospitalized, limitation on activities	26 (68.4)		16 (42.1)	
3. Hospitalized, not requiring supplemental oxygen	2 (5.3)		0	
4. Hospitalized, requiring supplemental oxygen	1 (2.6)		0	
Experimental (n=38) [$], n (%)				
1. Not hospitalized, no limitations on activities	5 (13.2)		19 (51.4)	
2. Not hospitalized, limitation on activities	31 (81.6)		18 (48.6)	
3. Hospitalized, not requiring supplemental oxygen	2 (5.3)		0	
4. Hospitalized, requiring supplemental oxygen	0 (0.0)		0	

**: Mean (SD) for Baseline Values and Baseline-Adjusted Changes from Baseline [95% CI] for 6- and 12-Month Visits. Inferential results are based on mixed models for repeated measures.*

[&]: Median (25^{th} - 75^{th}) percentiles for descriptive data and median difference [95%CI] for inference using the Hodges-Lehmann estimator

[$]: One missing value for one patient.

Safety and side-effect profile

Non-severe complications of any type were more frequent in the control group (22 cases, 56.4%) than in the experimental group (9 cases, 22.5%) (p = 0.003). No differences between the groups were observed in severe complications or in complications of any degree related to prednisone treatment (Table 25). During the trial, one patient in the control group succumbed to disseminated cryptococcosis caused by *C. neoformans*. Additionally, two patients developed pulmonary thromboembolism, one experienced deep vein thrombosis, and another developed adrenal insufficiency. Table 26 details the primary corticosteroid-related adverse effects.

Table 25: Adverse Effects

	Control (n = 39)	Experimental (n = 40)	p-value
	n (%)		
Complications of prednisone treatment (severe)	1 (2.56)	0 (0)	0.494
Complications of prednisone treatment (non-severe)	8 (20.51)	5 (12.5)	0.378
Complications of any type (severe)	1 (2.56)	2 (5)	>0.999
Complications of any type (non-severe)	22 (56.4)	9 (22.5)	0.003

Table 26: Description of adverse effects related to treatment

System Organ Class Preferred Term **	Serious	Control (n=40)	Experimental (n=40)	Total (n=80)
		Occurrences/Subjects(%)		
Endocrine disorders				
Adrenal insufficiency	No	1 / 1 (2.5)	0 / 0 (0)	1 / 1 (1.3)
General disorders				
Swelling	No	2 / 2 (5)	0 / 0 (0)	2 / 2 (2.5)
Investigations				
Cortisol decreased	No	0 / 0 (0)	1 / 1 (2.5)	1 / 1 (1.3)
Weight increased	No	1 / 1 (2.5)	0 / 0 (0)	1 / 1 (1.3)
Metabolism and nutrition disorders				
Hyperglycaemia	No	2 / 2 (5.0)	1 / 1 (2.5)	3 / 3 (3.8)
Dyslipidaemia	No	0 / 0 (0)	1 / 1 (2.5)	1 / 1 (1.3)
Musculoskeletal and connective tissue				
Musculoskeletal pain	No	0 / 0 (0)	1 / 1 (2.5)	1 / 1 (1.3)
Myalgia	No	0 / 0 (0)	1 / 1 (2.5)	1 / 1 (1.3)
Nervous system disorders				
Dizziness	No	0 / 0 (0)	1 / 1 (2.5)	1 / 1 (1.3)
Paraesthesia	No	1 / 1 (2.5)	0 / 0 (0)	1 / 1 (1.3)
Tremor	No	1 / 1 (2.5)	0 / 0 (0)	1 / 1 (1.3)
Psychiatric disorders				
Insomnia	No	1 / 1 (2.5)	0 / 0 (0)	1 / 1 (1.3)
Respiratory, thoracic and mediastinal				
Pulmonary embolism	Yes	0 / 0 (0)	1 / 1 (2.5)	1 / 1 (1.3)
Skin and subcutaneous tissue disorders				
Erythematous rash	No	1 / 1 (2.5)	0 / 0 (0)	1 / 1 (1.3)
Skin lesion	No	1 / 1 (2.5)	0 / 0 (0)	1 / 1 (1.3)
Vascular disorders				
Hypertension	No	1 / 1 (2.5)	0 / 0 (0)	1 / 1 (1.3)

***A patient may be in multiple categories.*

6. DISCUSSION

DISCUSSION

In this doctoral thesis, the respiratory complications arising from SARS-CoV-2 pneumonia have been characterized in greater detail. It was observed that, during the acute phase, dexamethasone plays a pivotal role in the development of subsequent respiratory complications. Furthermore, it was found that over half of the patients seen at the post-COVID clinic (52.2%) present airway abnormalities, associated with a particular clinical phenotype characterized by greater severity, a higher comorbidity burden, and a more complicated hospital course. Nonetheless, among these airway abnormalities, tracheomalacia remains an exceptional complication in SARS-CoV-2 survivors. With respect to asthma, it has not been identified as a risk factor for respiratory complications following SARS-CoV-2 pneumonia. Finally, it has been demonstrated that a less intensive corticosteroid regimen (0.5 mg/kg/day) for organizing pneumonia is just as effective as more prolonged and higher-dose regimens, thereby reducing adverse effects in the management of this common complication.

Dexamethasone plays a role in respiratory sequelae

The patients treated with dexamethasone experienced less dyspnea, had better DLCO, walked a greater distance in the six-minute walk test and had a better average oxygen saturation in post-COVID-19 follow-up. Radiologically, a notable decrease in reticulation, significantly fewer septal thickenings and less fibrosis were observed in the dexamethasone-treated group compared to the non-dexamethasone group. In consonance with previous studies, our results also indicate associations between dexamethasone treatment during hospitalization and shorter hospital and ICU stays, and lower FiO_2 and ventilatory support requirements.

Although it has been demonstrated that dexamethasone represents a major step forward in COVID-19 treatment, many individuals continue to experience symptoms such as shortness of breath, persistent cough, and reduced lung capacity months after their initial infection.

Therefore, the evidence indicates that many patients present respiratory sequelae at both the clinical and imaging levels, as well as in pulmonary function tests (82,116). Since organizing pneumonia has been identified as the most common pulmonary sequela following SARS-CoV-2 pneumonia, it is reasonable to suggest that corticosteroids administered in the acute phase may aid recovery in these patients (67). Organizing pneumonia is a diffuse interstitial lung disease (ILD) characterized by a pattern of lung tissue repair following injury, such as that caused by SARS-CoV-2 pneumonia, that can progress to fibrotic changes observed in chest computed tomography (CT), particularly in cases that advance without treatment. Therefore, administering anti-inflammatory treatment in the acute phase, when an inflammatory response occurs (117), may improve recovery from viral injury, reducing repair defects and subsequent fibrotic changes

In this regard, the present study demonstrated clinical improvement and enhanced lung function in the group treated with dexamethasone during follow-up, suggesting that the anti-inflammatory effects of the drug extend beyond the acute phase and provide long-term respiratory benefits. Radiological assessments further reinforce these clinical findings, as patients treated with dexamethasone exhibited fewer fibrotic changes such as septal thickening and fibrosis than the untreated group. Other studies have suggested that dexamethasone in the acute phase of COVID-19 may be a factor that may reduce post-COVID-19 syndrome by controlling inflammation (118,119). Although it appeared that symptoms were decreasing in these patients, Leavy et al.'s study showed no improvements in quality of life or other secondary outcomes, such as lung function, in patients treated with systemic corticosteroids one year after COVID-19 infection (100). It is worth noting that data on lung function in many patients in that study were incomplete (for example, other diagnostic tests such as chest CT were not always available) which limits the assessment of its impact. Additionally, the baseline quality of life questionnaire prior to hospitalization was assessed retrospectively (100). In the present study, the sequelae following pneumonia

caused by SARS-CoV-2 can be evaluated better, as all patients underwent a clinical evaluation combined with functional respiratory tests and chest CT scans.

Although, as previously mentioned, in the present study we observed differences in parenchymal involvement in patients treated/not treated with dexamethasone, no differences were observed in terms of airway involvement between the two groups. In this regard, in patients with COVID-19 infection, intense and persistent inflammation in the airways can cause tissue damage and deterioration of the epithelial barrier function of the airways, thus producing alterations in the airway (117). The results of the present study suggest that dexamethasone treatment produces a change in the type of alterations in the airway, reducing the degree of bronchiolitis but increasing the bronchiectasis. If these results are confirmed in future studies, the reason why this may happen will have to be studied.

This study has several limitations. First, its retrospective design may introduce bias; the fact that comparison groups were from different time periods may have influenced the results since variations in viral strains may affect disease severity and treatment response. The follow-up period also varied between groups, with dexamethasone-treated patients generally being seen later, a difference that may have influenced the assessment of long-term outcomes. However, multivariate analysis shows that differences in DLCO and fibrosis on chest CT in dexamethasone- treated/non-treated patients remained significant, even after adjusting for the time from discharge to post-COVID consultation. Although these patients received other treatments that might influence disease progression, the use of antivirals, tocilizumab, or convalescent plasma among dexamethasone-treated patients was limited and unlikely to account for the observed outcomes.

In conclusion, this study demonstrates that dexamethasone treatment during hospitalization for severe COVID-19 is associated with improved long-term respiratory outcomes, including reduced dyspnea, better lung function, and fewer radiological signs of pulmonary fibrosis. These findings support the continued use of dexamethasone as a key treatment in

managing severe COVID-19, not only for reducing acute mortality but also for promoting better long-term recovery.

Airway involvement constitutes a distinct clinical phenotype

It has been observed that, following SARS-CoV-2 pneumonia, more than half of patients display airway abnormalities on chest CT, and multiple abnormalities may coexist within the same individual. Among those with airway involvement, the majority presented with bronchiectasis or bronchial wall thickening, suggesting a chronic inflammatory process or a post-infectious response mediated by epithelial damage and alterations in tissue repair (93). These findings contrast with previous studies, which reported a lower proportion of bronchiectasis—approximately 11–24%—although those investigations did not specifically focus on airway assessment (96,97). In addition, bronchiolitis was observed in 16.1% of affected patients, consistent with earlier reports identifying it as a post-COVID-19 complication (98). Finally, tracheomalacia was much less frequent, illustrating the wide range of manifestations associated with this disease.

In patients with airway involvement, significant clinical, functional, and prognostic differences have been identified compared to those without such involvement. These patients were older, predominantly male, had a lower body mass index, and a higher proportion of White individuals. Moreover, they more frequently reported a history of smoking and a markedly greater burden of comorbidities, particularly cardiovascular risk factors such as hypertension and diabetes mellitus, as well as ischemic heart disease and heart failure. These findings are consistent with previous studies linking hypertension, diabetes, and various cardiac comorbidities to increased susceptibility for severe COVID-19 (120–122).

Furthermore, patients with airway involvement exhibited prolonged hospitalization and longer stays in intensive care units, in addition to more frequent requirements for ventilatory support, indicating a more severe clinical presentation during their hospital stay. Moreover,

elevated inflammatory markers and a greater extent of pulmonary involvement were observed in the initial radiological images. Previous studies have already demonstrated that higher COVID-19 severity is associated with a more intense systemic inflammatory response (123,124). This heightened inflammatory reaction likely contributes to increased respiratory complications, including airway involvement (125). Similarly, it has been shown that patients with comorbidities and cardiac complications during hospitalization can exhibit a more pronounced inflammatory response, which may explain the greater degree of airway involvement in this subgroup of patients (126).

It is also important to note that patients with airway involvement experienced more secondary complications, such as secondary infections and septic shock. These complications may be associated with an exacerbated inflammatory process and increased vulnerability due to airway alterations (127). This is further supported by the more frequent use of antibiotics in these patients, likely reflecting a higher burden of associated infections.

Patients who develop deep vein thrombosis (DVT) as a secondary complication often experience more pronounced airway involvement. This occurs because systemic hyperinflammation not only intensifies the prothrombotic state that promotes clot formation in the deep venous system, but also fosters airway edema and inflammation, thereby exacerbating respiratory compromise (128).

During the post-COVID follow-up, conducted approximately five months after hospital discharge, no clinically significant differences were observed between the groups. However, patients with airway involvement showed a slight reduction in pulmonary diffusion capacity, as well as a shorter distance walked in the six-minute walk test, though these findings had limited clinical relevance. On chest CT scans, these patients exhibited fewer ground-glass opacities but a higher degree of septal thickening, with no difference in the prevalence of pulmonary fibrosis. These results suggest that airway alterations and parenchymal abnormalities are not always interrelated, and likely involve different underlying mechanisms.

This study has several limitations that should be considered. First, its retrospective design can introduce selection bias and complicate the establishment of causal relationships. Furthermore, although pre-existing respiratory disorders were excluded, the presence of undiagnosed comorbidities or early disease stages prior to SARS-CoV-2 infection cannot be ruled out. Another point to highlight is the choice of chest CT over bronchoscopy, which may lead to either overestimation or underestimation of certain abnormalities—particularly in the context of the pandemic and among critically ill patients. Additionally, as this is a single-center cohort, the findings may not be fully generalizable to other populations with different resources or clinical characteristics. Finally, long-term follow-up is essential to assess the evolution of these changes and to determine whether they might progress to additional complications, such as fibrosis or stenosis, or instead show improvement.

Focusing now on the study of tracheomalacia, it is an exceptional sequela observed in SARS-CoV-2 survivors and is consistently associated with parenchymal and other airway findings. In our opinion, there are three possible explanations for the appearance of tracheomalacia in the SARS CoV-2 survivor population. The first one is orotracheal intubation. Although the prevalence of primary or secondary tracheomalacia is unknown in the general population, its most common acquired cause is orotracheal intubation or tracheostomy. In these cases, tracheomalacia is related to increases in the respiratory airway pressure, oxygen toxicity and recurrent infections (99). Recently, Guarnieri et al. reported tracheomalacia in 8 of 151 patients with SARS-CoV-2 acute respiratory distress syndrome who required intubation or tracheostomy and mechanical ventilation (129). In the present series, however, intubation was only required in five patients.

Secondly, respiratory infections are a well-known cause of tracheomalacia and were present in 67% of our patients. It should be highlighted that chronic infections are more strongly associated with tracheomalacia tan acute presentations. However, in our experience, tracheomalacia is not an isolated finding, because all patients had parenchymal alterations and 80% had other airway sequelae. Therefore, high levels of inflammation, such

as those related with SARS CoV-2 infection, may be responsible for these alterations. In fact, Borczuk et al. found airway inflammation in the form of chronic diffuse inflammation in 41% of cases in a series of 68 necropsies in the initial stages of the pandemic (128).

The third possible explanation for the tracheomalacia in these patients is the presence of previous respiratory diseases. Five patients were affected by asthma, COPD or OSA. Although seldom described, some authors estimate the incidence of tracheomalacia in adult patients with respiratory airway disease to be approximately 12.6% (99).

The present study has some limitations. Probably, bronchoscopy should be used as a gold-standard diagnostic tool for this disease,5 but CT scan was used in the context of the pandemic, and in severe stages of the disease in which the use of more invasive techniques was not justified. In fact, emerging evidence in pediatric populations suggests that CT scan can effectively diagnose tracheomalacia and should be considered as a less invasive alternative to bronchoscopy (130). Another limitation is that tracheomalacia may also have existed before the SARS-CoV-2 infection, especially since most series established the mean age of presentation at 40 years old (99). However, in the present series of patients, a guided clinical interview did not reveal any respiratory symptoms before the SARS CoV-2 infection that might have been related to a possible tracheomalacia or any predisposing factor that might explain its presence. Finally, we cannot rule out the development of cicatricial stenosis in the long term.

Overall, the findings from these studies underscore the clinical relevance of identifying airway abnormalities in patients following SARS-CoV-2 pneumonia, given that such complications are both common and understudied. The different forms of airway involvement can trigger respiratory symptoms with a substantial impact on patients' quality of life, and they are a well-established predisposing factor for recurrent respiratory infections, potentially leading to serious comorbidities in the future. Further research is needed to elucidate the specific pathophysiology of these abnormalities and to develop

targeted interventions aimed at improving patient outcomes and minimizing long-term pulmonary sequelae.

Asthma does not increase the risk of respiratory complications

The results of the present study demonstrated that patients with asthma (regardless of severity), do not appear to have a higher incidence of respiratory sequelae after experiencing SARS-CoV-2 pneumonia that required hospital admission. However, there were differences in airway involvement: bronchiectasis was more common in non-asthma patients, and bronchial thickening and/or tracheomalacia in asthma patients, regardless of asthma phenotype.

The relationship between asthma and SARS-CoV-2 infection throughout the pandemic has been the subject of multiple studies, which have reached a variety of conclusions. Currently, there seems to be a consensus that SARS-CoV-2 infection in patients with asthma is less common than in the general population (51) and less severe in those who present a T2-TH2 asthma phenotype (53,54). As a result, we might surmise that the appearance of sequelae in patients with SARS-CoV-2 infection could also be influenced by whether they have asthma, and, if they do, whether they present a particular phenotype. In general, approximately 29% of patients severely affected by SARS-CoV-2 present fatigue and 19% dyspnea one year after infection(131). At radiological level, it has been reported that approximately 45% of patients present ground glass opacities on chest CT, 28% fibrosis and approximately 21% reticulations (132). There are hardly any data regarding airway involvement, although the appearance of bronchiectasis seems to be the predominant form (132).

Around 40% of the patients included in this study had dyspnea between three and six months after hospital discharge, regardless of whether or not they had asthma. Asthma patients had more fatigue, cough and wheezing than controls. This finding contrasts with the only related study reported to date, in which no differences were found between patients

with and without asthma in terms of the evolution of symptoms(101). More significant is the fact that no differences were found between the two populations in terms of parenchymal involvement, highlighting that neither the presence of asthma, nor the presence of a particular phenotype, is a risk factor for lung injury in the case of SARS-CoV-2 infection. Another interesting point is the fact that asthma could prevent the appearance of bronchiectasis after SARS-CoV-2 infection. Bronchiectasis is common after severe lung infections, regardless of the causative agent (133), and SARS-CoV-2 infection does not appear to be an exception; Han et al (97) reported bronchiectasis in 7% of patients with SARS-CoV-2 infection at the time of admission, but the rate had risen to 24% in a control CT scan six months after hospital discharge. The administration of inhaled corticosteroids in patients with asthma may prevent the appearance of bronchiectasis due to their anti-inflammatory effect, in the same way as they reduce the severity of SARS-CoV-2 infection (61,134).

We observed that patients with asthma had more bronchial thickening than controls. This finding is difficult to attribute to the viral infection itself, since practically all patients with asthma present this type of alteration (135). The presence of tracheomalacia in these patients may have a different explanation; although it may be due to their asthma, it has also been attributed to the SARS-CoV-2 infection (110).

The present study is not without limitations. It is a single-center, retrospective study in which lung function tests and chest CT were not available prior to SARS-CoV-2 pneumonia. However, the confirmation that there were no differences in respiratory sequelae between asthmatic patients and controls lends support to the notion that asthma is not a risk factor in SARS-CoV-2 pneumonia. Moreover, although patients were adjusted for severity, the percentage of patients treated with tozilizumab was higher in the controls. However, this difference does not seem to affect the respiratory sequelae between both groups.

Oral corticosteroids lasting three months may be recommended in post-COVID OP

This study is the first clinical trial conducted on patients with OP since the first description of this condition in the 1970s (136). It has demonstrated that a 3-month treatment regimen, starting with a dose of 0.5 mg/kg/day, is as effective as longer treatments with higher initial doses and halves the rate of adverse effects.

Systemic glucocorticoids are the preferred treatment for symptomatic patients with respiratory impairment due to OP (70,84). Although they have proven effective, they are not free from side effects, especially when administered at the high doses and extended durations currently proposed for the treatment of this condition (137) Only 23% of patients treated with the experimental regimen experienced corticosteroid-related adverse effects, compared to 56% of those treated with the conventional regimen. For the treatment of patients with any post-COVID-19 respiratory sequelae, a low-dose prednisone regimen can be as effective as one with a higher dose, and also presents fewer adverse effects (138).

Progression to pulmonary fibrosis following post-infectious OP is a significant concern, particularly in patients who experience recurrences (139) The recurrence rate is estimated to be between 20% and 30%, similar to that of COP, which ranges between 9% and 33% according to various studies (139–142). In this study, the recurrence rate was similar in both treatment groups, ranging from 5% to 7.5%. Generally, irrespective of recurrence, it is estimated that between 10% and 15% of patients with post-infectious OP may progress to pulmonary fibrosis (143). In the specific context of post-COVID-19 OP, the incidence of pulmonary fibrosis appears to be more pronounced. Some studies suggest that up to 30% of patients with post-COVID-19 OP may develop fibrotic sequelae (66,144). This high percentage is attributed to the intense inflammatory response triggered by SARS-CoV-2 and the extensive lung damage that can occur during the acute phase of the infection (5). In this context, intensive clinical and radiological follow-up seems crucial to detect early progression to fibrosis and adjust treatment accordingly.

Diffusion is one of the parameters that can be monitored in both the management and follow-up of these patients. Reductions in DLCO are common in patients with diffuse ILD, as in the case of idiopathic pulmonary fibrosis (IPF), and are associated with increased mortality (145). Changes in DLCO values over time may indicate stabilization, improvement, or worsening of the disease and can thus guide therapeutic decisions (146). DLCO has already been analysed in various clinical trials investigating interstitial lung diseases, primarily in the context of assessing the response to antifibrotic drugs, immunosuppressants, or corticosteroids themselves. Thus, in patients with IPF, hypersensitivity pneumonitis, nonspecific interstitial pneumonia, or even in patients with systemic sclerosis with lung involvement, stable increased DLCO was associated with a favourable response to treatment (147–151). In most of these studies, changes greater than 15% were considered significant (151,152). The fact that a change of 10% was established as significant in the present study may reinforce the value of the observed results. It is important to emphasize that, in these trials, DLCO served not only to assess the response to treatment but also the progression of the disease, as a DLCO that remains stable or improves indicates a slowing or reversal of interstitial damage. In this context, when analysing the subgroup of patients with DLCO <80%, similar increases were observed in both treatment groups.

Chest CT is an essential component for both the diagnosis and follow-up of OP. As described in multiple studies the majority of patients included in this clinical trial exhibited a mixed pattern with peripheral consolidations, reticulation, and ground glass opacities (67,75,116). Fewer than 20% of the patients presented any of these alterations in isolation. This variable was analysed as secondary since a significant proportion of patients show only a partial resolution of alveolar opacities, while reticular opacities tend to persist despite treatment (82). Indeed, only 15% and 7.7% of patients in the experimental and control groups respectively showed complete resolution of changes in CT at the end of the study. No differences were observed in the degree of improvement between the treatment

regimens. Nor were there significant differences in other secondary variables such as FVC, the distance walked in the 6MWT, or quality of life.

As recommended by the WHO, particularly in patients with infection and/or post-COVID-19 sequelae, in the study variables we included the WHO Clinical Progression Scale, which reflects patient trajectory and resource use over the course of clinical illness. This scale was created to facilitate data pooling across cohort studies and clinical trials, with the objective of expediting the exchange of knowledge to benefit patients infected with SARS-CoV-2 and to guide optimal resource planning (153). Again, no differences were observed between the groups.

This study is not without limitations. First, it is an open-label, single-center clinical trial, a circumstance that may introduce biases and limit the generalizability of the results to other populations and clinical settings. However, the raters responsible for measuring all the study outcomes were blinded to patient allocation, thereby reducing the risk of this detection bias. Second, the study was prematurely terminated after recruiting 66% (79/120) of the planned sample size due to a critical decline in patient enrollment. Although the reduced sample size may have affected the statistical power for certain secondary outcomes, the 95% confidence intervals calculated from the recruited sample provide adequate precision to support the conclusion of non-inferiority for both mFAS and PP analyses of the primary endpoint. Consequently, this reduction did not compromise the study's primary objectives. Third, the use of clinical interviews with patients to assess treatment adherence, without additional verification methods, may also have introduced a bias. The lack of a placebo group could also be seen as a limitation, as it makes it impossible to determine whether the observed improvements are solely due to corticosteroid treatment or to the natural progression of the disease. However, given that all patients included were symptomatic and had both radiological and pulmonary function abnormalities, it would have been unethical to leave any patients untreated. Finally, the fact that up to 30% of the patients were diagnosed without histological tests to confirm the diagnosis could be considered a

limitation. Nonetheless, it should be stressed that all patients, with or without histology, were diagnosed by consensus in a multidisciplinary committee consisting of clinicians, radiologists, and pathologists. In fact, having access to histopathological studies in up to 70% of the patients is considered extraordinarily valuable, given the challenges of conducting such studies during peak pandemic waves.

Despite these limitations, we believe we can conclude that a three-month treatment of prednisone starting at a dose of 0.5 mg/kg/day in patients with post-COVID-19 organizing pneumonia can be as effective as the longer standard regimen, with the additional advantage of fewer adverse effects. In the absence of clinical trials and given the difficulty of conducting them, we think that this treatment protocol can be extended to all patients with post-infectious organizing pneumonia, regardless of the causative agent. It may be more controversial to generalize these results to other aetiologies of organizing pneumonia, particularly idiopathic or cryptogenic forms, although the results of this study open up this possibility.

7. CONCLUSIONS

CONCLUSIONS

1. The dexamethasone treatment during hospitalization for severe COVID-19 is associated with improved long-term respiratory outcomes, including reduced dyspnea, better lung function, and fewer radiological signs of pulmonary fibrosis.

2. Airway involvement was common among patients hospitalized with COVID-19 and was associated with older age, smoking history, lower BMI, and cardiometabolic comorbidities. This phenotype was linked to more severe in-hospital disease progression but did not result in worse clinical outcomes during post-COVID follow-up.

3. Patients with asthma (regardless of severity), do not appear to have a higher incidence of respiratory sequelae after experiencing SARS-CoV-2 pneumonia that required hospital admission.

4. The three-month treatment of prednisone starting at a dose of 0.5 mg/kg/day in patients with post-COVID-19 organizing pneumonia can be as effective as the longer standard regimen, with the additional advantage of fewer adverse effects.

8. FUTURE LINES OF RESEARCH

FUTURE LINES OF RESEARCH

Although this thesis has focused on respiratory complications following SARS-CoV-2 pneumonia, the findings obtained pave the way for several future research directions:

- **Long-term follow-up of post-COVID fibrotic sequelae.** Extending the follow-up of patients with fibrotic changes identified on chest CT through multicenter studies lasting at least two years would enable a more thorough characterization of these sequelae. Such studies could clarify whether fibrotic patterns stabilize over time or, conversely, show progression warranting specific interventions. Furthermore, investigating genetic or molecular factors potentially influencing disease progression would be highly valuable. This information not only applies to the SARS-CoV-2 context, but could also be extrapolated to other viral pneumonias, thereby advancing our understanding and management of fibrotic sequelae arising from different etiologies.
- **Systematic Evaluation of Airway Involvement**. Implementing advanced protocols for functional assessment and imaging (expiratory chest CT, pulmonary MRI, functional imaging), in conjunction with artificial intelligence tools (machine learning, deep learning), is essential to accurately quantify and compare airway alterations following viral pneumonias of various etiologies (e.g., COVID-19, influenza, or RSV). Automated analysis of radiological patterns and clinical data enables correlation of the severity of airway involvement with symptomatology and quality of life, identification of risk factors, and prioritization of therapeutic interventions (respiratory physiotherapy, anti-inflammatory treatments). This approach ultimately reduces the burden of post-infectious sequelae and optimizes recovery across a broad spectrum of patients.
- **Characterizing viral-induced asthma exacerbations** (e.g., COVID-19, influenza, or RSV) is essential, as these events can accelerate airway dysfunction and heighten the risk of long-term respiratory sequelae. Investigating the frequency, severity, and immunological profile of such exacerbations will facilitate the design of more tailored

therapeutic interventions and support the implementation of preventive strategies aimed at reducing their incidence.

- **Optimization of corticosteroid use in organizing pneumonia.** The evidence gathered from this clinical trial, which focuses on optimizing corticosteroid dosage and treatment duration in post-COVID-19 organizing pneumonia (OP), may lay the groundwork for future research addressing OP secondary to other infectious etiologies or even cryptogenic OP. Should the findings confirm that lower-dose regimens and shorter treatment periods provide efficacy comparable to conventional protocols, this would support the adoption of less aggressive therapies, thereby reducing the risk of adverse effects.
- **Advancing Post-COVID research through AI and omics.** The use of machine learning algorithms to analyze large clinical, imaging, and histopathological datasets, along with omics studies (genomics, transcriptomics, proteomics, metabolomics), enables the identification of predictive patterns of sequelae, progression markers, and novel therapeutic targets. Integrating these tools into personalized medicine platforms will optimize patient follow-up and treatment in the aftermath of COVID-19 infection.

9. BIBLIOGRAPHY

BIBLIOGRAPHY

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10. ANNEXES

10.1. FINANCING AND SCIENTIFIC AWARDS

10.1.1. Financing

PhD student, David Espejo Castellanos has received financial support during his doctoral thesis:

- Rio Hortega programme from Instituto de Salud Carlos III (CM23/00174)

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- Fondo Europeo de Desarrollo Regional (FEDER).

10.1.2. Scientific awards

PhD student, David Espejo Castellanos has received scientific award during his doctoral thesis:

- Winner of the Best Communication in the EPID Area at the SEPAR 2024 Annual Congress. The title of the communication was: "Impacto del uso de corticoides orales en la neumonía organizada post COVID-19 (ensayo clínico NORCOVID)"

10.2. SCIENTIFIC PRODUCTION

10.2.1. Abstract presented at conferences related to this doctoral thesis

10.2.1.1. Abstract 1

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Conference Abstract

Impact of the use of oral corticoids in organizing pneumonia post COVID-19 (the NORCOVID clinical trial)

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Abstract

Introduction: Organizing pneumonia (OP) is one of the most frequent sequelae of Sars-Cov-2 pneumonia. The aim of this study is to establish the optimal dose of oral corticosteroids for the treatment of this complication.

Methods: Randomized, open, parallel, single-center, non-inferiority clinical trial with an active control group comparing two oral prednisone regimens. The control group received prednisone 0.75 mg/Kg/day 4 weeks; 0.5mg/Kg/day 4 weeks; 20mg/day 4 weeks; 10mg/day 6 weeks; 5 mg/day 6 weeks (6 months) and the experimental group prednisone 0.5 mg/Kg/d 3 weeks, 20 mg/day 3 weeks; 15mg/day 2 weeks; 10mg/day 2 weeks, 5mg/day 2 weeks (3 months). Visits were carried out at baseline and at 3, 6 and 12 months with clinical history, physical examination, functional tests and chest CT. The primary outcome was non-inferiority with a margin of 10% in CO transfer (DLCO) at 6 months.

Results: Seventy-nine patients were randomized, 40 in the experimental group and 39 in the control group. Mean baseline DLCO was 59.3% (SD 16.7) in the experimental group and 55.5% (SD 16.5) in the control group, with mean improvements at 6 months of 11.7% (95%CI 7.18 -16.17) and 12.8% (95%CI 8.57-17.11) respectively. The difference between groups at 6 months was 1.23% [(95%CI -5.13-7.59], the experimental regimen being non-inferior to the control group with the margin of 10%. Patients in the experimental group had less than half as many adverse effects as controls: 9 (23%) vs 22 (56%) (p=0.0027).

Conclusions: Treatment with oral corticosteroids lasting three months (initial dose of prednisone 0.5 mg/Kg/d) may be recommended in patients with post-COVID OP.

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Footnotes

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