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LONG-TERM RESPIRATORY CONSEQUENCES AFTER SEVERE COVID-19 PNEUMONIA

A 12-MONTH FOLLOW-UP FROM AN OBSERVATIONAL PROSPECTIVE COHORT STUDY

Final Degree Project

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1. ABSTRACT

Background: The new SARS-CoV-2 virus causes a respiratory syndrome that, although it resolves completely in most of the population, in some patients may evolve to a severe state. Of those, a minor percentage will suffer persistence of symptoms, poor quality of life, impaired lung function and/or worse exercise capacity. Also, CT scan imaging in those patients show some kind of interstitial lesion degree, which may or may not evolve into pulmonary fibrosis. But because the pandemic is too recent and, therefore, follow-up studies are too short, there is not enough evidence to make a clear statement on the long term respiratory consequences of COVID-19.

Objectives: The aim of this project is (i) to find out the incidence of pulmonary fibrosis among patients with post severe COVID-19 pneumonia. As secondary objectives we want (ii) to assess their 12-month evolution regarding quality of life, respiratory function and exercise capacity and (iii) to investigate whether older people have a higher risk of developing interstitial lesion than younger people.

Methodology: This is an observational prospective cohort study conducted in Hospital Universitari Doctor Josep Trueta designed as a 12-month follow-up on 94 subjects that suffered a severe COVID-19 pneumonia. Participants will be selected according to the inclusion and exclusion criteria. The research will assess many parameters that may be affected by post COVID-19: clinical status, quality of life, pulmonary function and exercise function. To answer the main objective, we will perform a series of HRCT scan. This follow-up will be made of four medical visits, at 1 month, 3 months, 6 months and 12 months.

Results: The study included 94 participants, 69 (73.4%) men and 25 (26.6%) women, with a mean (SD) age of 62.93 (13,23) years. The Saint George's Respiratory Questionnaire total score showed an improvement along the 12 months of 3.9 points: 22.8 (18.6) at 3 months vs 18.9 (16.8) at 12 months. Dyspnea was persistent all along the follow-up, but those more severe degrees tended to decrease. The oxygen saturation related to the effort of the walking test had, at all times, rather normal values, with few cases of desaturation. The distance walked also showed appropriate results all the time. DLCO was the only parameter to be initially (at 3 months) under the predicted % value (75.9 [17.0]). However, at the following visits it increased and reached

normal values. Of those 45 out of 94 patients that at 3 months had impaired DLCO, at the end of the 12 months period, only 22 remained under the % predicted value. At the end of the 12-month follow-up, evidence of pulmonary fibrosis was observed in 24 (25.5%). Multivariable analysis identified age as an associated factor to pulmonary fibrosis.

Conclusion: HRCT findings at 12 months show pulmonary fibrosis in 25.5% of those patients who survived severe COVID-19 pneumonia. Along these 12 months there is proof of an improvement tendency regarding quality of life, pulmonary function and exercise capacity. Association between age and higher risk of pulmonary fibrosis has been proven.

Keywords: SARS-CoV-2, COVID-19, severe pneumonia, interstitial lesion, pulmonary fibrosis, follow-up.

2. ABBREVIATIONS

ACE2	Angiotensin-Converting Enzyme 2
ALT	Alanine transaminase
aPTT	Activated partial thromboplastin time
ARDS	Acute Respiratory Distress Syndrome
AST	Aspartate transaminase
BMI	Body Mass Index
CK	Creatine Kinase
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Coronavirus Disease 2019
DAD	Diffuse alveolar damage
DLCO	Diffusion capacity to carbon monoxide
DM	Diabetes Mellitus
DVT	Deep Venous Thrombosis
ECM	Extracellular matrix
ECMO	Extracorporeal Membrane Oxygenation
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GCSF	Granulocyte colony stimulating factor
GGO	Ground-glass opacity
HFNC	High-flow nasal cannula
HT	Hypertension
ICU	Intensive Care Unit
IL	Interleukin
IPF	Idiopathic pulmonary fibrosis
IQR	Interquartile range
IRT	Invasive respiratory therapy
KCO	Carbon monoxide transfer coefficient
LDH	Lactate dehydrogenase
MERS-CoV	Middle East Respiratory Syndrome Coronavirus

NIPPV	Non-invasive positive pressure ventilation
NIRT	Non-invasive respiratory therapy
PFT	Pulmonary Function Tests
Pt	Prothrombin time
PTE	Pulmonary thromboembolism
RAS	Renin-angiotensin System
RCP	Reactive C Protein
RNA	Ribonucleic acid
RV	Residual volume
SARS-CoV	Severe Acute Respiratory Syndrome Coronavirus
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SD	Standard Deviation
SGRQ	Saint George's Respiratory Questionnaire
TLC	Total lung capacity
VOC	Variants of Concern
VOI	Variants of Interest
WHO	World Health Organization
6MWT	6 minute walking test

3. INTRODUCTION

In December 2019, in the Chinese city of Wuhan, several cases of an unexplained viral pneumonia spread rapidly throughout the population. In just a few weeks, many countries around the world started reporting similar cases of pneumonia. Shortly after the outbreak, it was discovered that the responsible for those pneumonias was a new viral pathogen named SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2). This virus caused - and it is still causing - a clinical profile that has been named COVID-19 (Coronavirus disease 2019). The worldwide spreading was so fast and the number of infected people and deaths so high that on March 11th 2020 the World Health Organization (WHO) declared it a global pandemic. As of November 2021, there have been more than 244.000.000 confirmed cases and 4.970.000 deaths globally (1).

All pertinent authorities have recognized the SARS-CoV-2 pandemic as a worldwide emergency for many reasons. Being one of the most relevant the high transmission rate and the high mortality rate. All in all, it has resulted in a public health, economic, social and political problem.

Months after the COVID-19 outbreak, many researches begin to find a vaccine against SARS-CoV-2 as soon as possible. However, of those hundreds of laboratories that initiated the process, just a few have succeeded to achieve commercialization. As of November 2021, more than 6.800.000.000 vaccines doses have been administrated (1). It is believed that vaccinating a big part of the population, and therefore achieving group immunity, will mean being a step closer to the end of the COVID-19 pandemic.

COVID-19 manifestations can range from asymptomatic to a severe disease, and it has been proven that SARS-CoV-2 can cause a disease more deadly than the flu (2). According to WHO, 80% of cases will be mild, 4% severe and 6% critical (3). Another real problem is that of those severe cases, a considerable proportion may develop long-term consequences despite a correct management of the acute infection. For example, cases of pulmonary interstitial lesion development have been reported in severe patients. Several early studies dare to say that about

1/3 of those severe patients may end up with pulmonary fibrosis (4–6). This is an important matter to address because this outcome can happen in any person, even without a previous pulmonary disease background. Moreover, there is not enough up-to-date evidence to predict the progression of the interstitial lesion, whether it will regress or progress to pulmonary fibrosis overtime. Further studies are needed to make more solid statements.

The coronavirus family is composed of 7 different strains, 3 of which have the ability to infect and cause disease in humans (7). These are SARS-CoV, MERS-CoV and the newly SARS-CoV-2. We could say that SARS-CoV-2 has been the 3rd major coronavirus outbreak in the last 20 years after SARS-CoV and MERS-CoV. Furthermore, the three of them cause a predominantly pulmonary syndrome. SARS-CoV outbreak originated in China in 2002, and up-to-date data states that it infected about 8.400 people and caused 916 deaths. While MERS-CoV outbreak started in the Arabian Peninsula in 2012 and caused around 2.500 cases and 866 deaths (8).

Autopsies made to several victims of SARS and MERS revealed the presence of pulmonary fibrosis. Also, some follow-up studies on patients who survived SARS or MERS found abnormal radiologic patterns suggestive of pulmonary fibrosis (3). Many studies took place to know the real incidence of pulmonary fibrosis after the acute infection, and some of them state that more than 50% for SARS and around 30% for MERS (9,10).

This information results of great interest as these three viruses share a considerable proportion of genetic information (80% between SARS-CoV and SARS-CoV-2, and 50% between MERS and SARS-CoV-2) (3). This could mean that since MERS and SARS have the ability to cause pulmonary fibrosis sequelae, SARS-CoV-2 could also result in this outcome and preliminary follow-up studies are already suggesting that.

Thus, with this project we will try to broaden the actual knowledge on pulmonary consequences after severe COVID-19 pneumonia. As previously mentioned, many studies declared that severe patients could suffer lung interstitial lesion or have impaired respiratory function, among other consequences. However, those studies are too preliminary since the pandemic is quite recent,

meaning that this matter needs further investigation. The present research project will attempt to provide new information to the matter.

Note that although most literature talks about “pulmonary fibrosis” after COVID-19, the present project will use the term “interstitial lesion” instead. This is because it has already been seen that some patients experience a radiological improvement, meaning that what was seen on previous CT scans was not established fibrosis, but some degree of interstitial damage. It is possible that many interstitial lesions finally end up in pulmonary fibrotic sequelae, but since we do not know how these cases will evolve, we feel more comfortable using the term “interstitial lesion”.

3.1. THE COVID-19 PANDEMIC EVOLUTION

We have already been through more than a year and a half of pandemic and, although science is advancing fast and we are becoming more aware of things, this situation is far from over. Since the beginning, we have already had 5 waves. *Wave* is a term used to describe a situation where confirmed cases rise above the previous tendency. This rise in the number of cases could be explained by many reasons, for example the climate conditions, the viral new mutations, people not following the recommended measures (wearing a face mask, avoiding gatherings, social distancing, regular hand-washing), among others.

Mutations are not uncommon in the evolution of viruses and, therefore, are an important matter to address. In fact, SARS-CoV-2 has a considerable tendency to genetic evolution (11). This could lead to new variants with different pathogenic characteristics involving virulence, tax of transmissibility, reduced neutralization by antibodies, etc.

As a matter of fact, during this pandemic many new SARS-CoV-2 variants have been identified. The WHO has classified these variants into two groups considering its potential concern: the variants of concern (VOCs) and the variants of interest (VOIs). The VOCs are new variants with a considerable potential to improve transmissibility, virulence or mortality, to be less affected by neutralizing antibodies (natural or from vaccines) or to imply a decrease in therapeutics or

vaccine effectiveness. Whereas the VOIs are variants with specific markers or characteristics that could enhance the pathogenic properties, but not as clear as the VOCs. As of October 2021, 4 new SARS-CoV-2 VOCs have been identified since the beginning of the pandemic. The alpha, beta and delta variants were identified in late 2020, while the gamma variant was identified in early 2021 (11).

This means that, like any other pandemic, this is not a static situation and many outcomes could happen.

3.2. PATHOGENESIS

SARS-CoV-2 is a betacoronavirus that causes a zoonotic disease, with potential to infect both humans and animals (12). The current hypothesis is that the virus came from bats and, through an intermediate animal sold in a sea food market in Wuhan, managed to infect humans.

Evidence suggests that SARS-CoV-2 spreads mainly between people who are in close contact, generally within 1 meter. A person can be infected by inhaling respiratory aerosols or droplets containing the virus or if these vehicles come into direct contact with mucous membranes (eyes, nose, or mouth). Infected people are the source of infection, even during the incubation period, by expelling aerosols when coughing, sneezing or speaking. It is concerning the fact that it can spread asymptomatically. Fecal-oral transmission is also possible.

Once it enters the system, SARS-CoV-2 binds and attacks the cells, especially those that have the **ACE2 receptor** (angiotensin-converting enzyme 2 receptor), abundant in the respiratory tract epithelial cells (among others) found in the upper airway, bronchiolar epithelium and submucosal gland epithelium; but also present in the pneumocytes (type I and II), alveolar macrophages and hyaline membranes (8).

SARS-CoV-2 has four main structural proteins important for infection and replication: spike (s) protein, membrane (m) protein, envelope (e) protein and nucleocapsid (n) protein.

The s protein is especially important because it is necessary for binding to the ACE2 cell receptor and is a major contributor to the immunogenic response. That is why the s protein is currently the target of most vaccines (9). It is also important as the s protein is the main region where mutations occur, generating new SARS-CoV-2 variants.

All in all, the ACE2 receptor represents the point of entry of the virus to the human host, and since we can find it especially in the respiratory tract, that would explain the predominantly respiratory clinic.

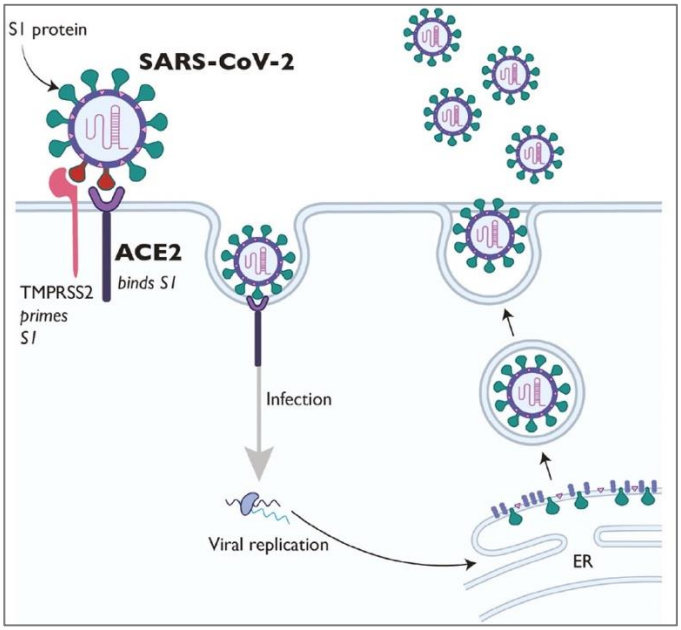

Figure 1. Critical role of ACE2 in the regulation of viral invasion in ACE2 expressing cells (15).

Once SARS-CoV-2 binds to the ACE2 receptor, endocytosis starts, enabling the virus to replicate using the cellular machinery and migrate through the airway cells. Many virus copies leave the cell by exocytosis and infect new cells along the respiratory tract. Eventually, it enters the alveolar epithelial cells in the lungs, with the possibility of causing further damage (8).

Changes that can be seen in COVID-19 patients are diffuse alveolar damage, hyaline membrane formation, desquamation of pneumocytes and fibrine deposits. Occasionally, exudative inflammation (9).

Following the initial viral infection, the first host's response is the activation of the **innate immune system**, which consists in the recognition of the pathogen and the release of proinflammatory cytokines. Then, the **adaptative immune system** follows, involving T cells and B cells. Altogether create the immune response. Although crucial, if these steps are too intense, there may be damage in normal tissue due to an uncontrolled inflammatory response.

Once the virus infection and replication begins, a leukocyte recruitment and interferon transcription starts. Also, T cells are rapidly activated into T helper (Th) cells that engage monocytes (which will start the inflammation process) and stimulate cytokine cascades.

Due to a fast viral replication, a strong immune response takes place, consisting in a "**cytokine storm**", which refers to a high release of cytokines (IL-1ß, IL-2, IL-6, IL-7…, TNF-a…). This cytokine storm is responsible for the clinical deterioration, including acute respiratory distress syndrome (ARDS), respiratory failure, shock, organ failure and eventually death. In non-severe cases, cytokine levels are also elevated but not as much (9,10).

Moreover, SARS-CoV-2 has the ability to disrupt normal immune responses. In severe and critical patients, we may find an impaired immune system and an uncontrolled inflammatory response. This can be seen in the form of lymphopenia (which might be due to sequestration of lymphocytes in tissues), lymphocyte activation and dysfunction, granulocyte and monocyte abnormalities, high cytokine levels and increase in antibodies (IgG, IgA, IgM) (10).

While an adequate T cell response (including CD4+ and CD8+) is associated with a milder disease, if T cell levels are low the odds of developing SARS are higher (9,10).

Nowadays it is known that some characteristics enhance the spike protein and ACE2 binding efficiency, including age and male sex. Moreover, age (≥60 years) and pre-existing diseases represent a greater risk of developing ARDS and death (11).

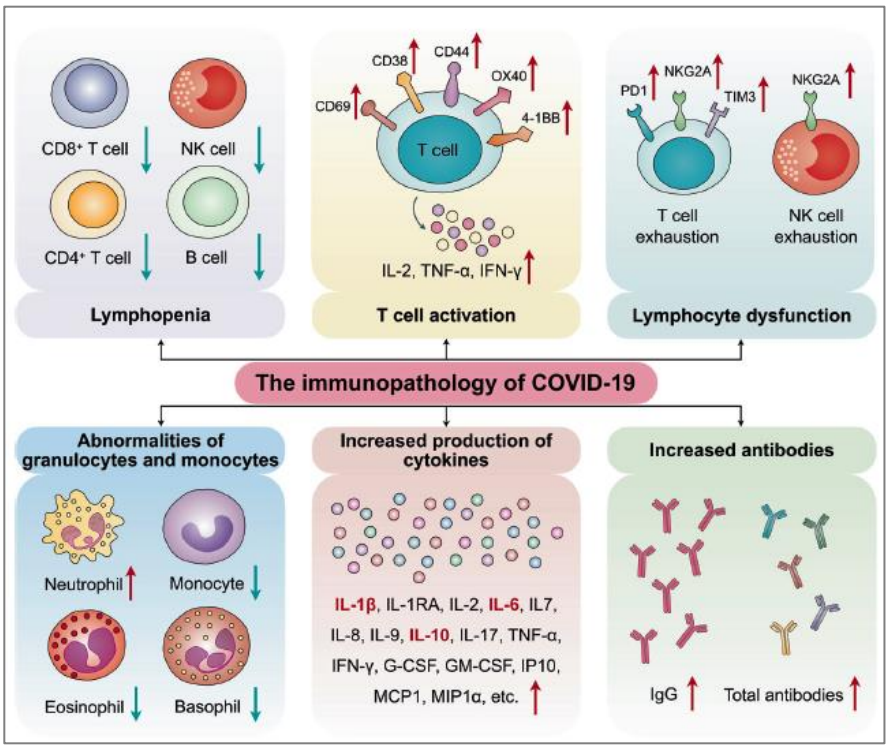

Figure 2. The immunopathology of COVID-19 (16).

3.3. RISK FACTORS FOR COVID-19 SEVERITY

Developing COVID-19 - and the severity of its presentation - differs from one subject to another. These differences among people could be in part explained by the individual characteristics.

That is why many researches have studied possible risk factors for disease severity. However, we cannot just pay attention to the host characteristics, but also to the viral and environmental features (11).

Some **viral** characteristics play a significant role in the outcome of COVID-19, both from a community and individual point of view. These would be (i) the transmissibility (because it is easily spread by aerosols and it remains alive for some time in surfaces), (ii) the viral evolution (leading to mutations) and (iii) the viral load (it has an important role in the clinic course of the disease).

Also, it is important to pay attention to the **environmental** risk factors. This means that there are some situations that favor the spread of the virus, such as crowding or social gatherings,

occupational jobs (health care workers, bus drivers, restaurant staff…), poor ventilation, low education, poor hygiene, animal contact, and many others.

And remarkably important are the **host** risk factors. Since the beginning of the pandemic, many research studies have been going on trying to find out which are the individual characteristics that can actually be risk factors for disease severity (11,12).

Among all of them, the risk factors with more consistency between studies are: **old age** (>60 years old), **male** gender, **diabetes**, **cancer** and other **comorbidities** (hypertension, history of cardiovascular disease, chronic diseases such as COPD, obesity), high body temperature/fever and heavy smoking. Some other risk factors but with less consistency could be ethnicity (black and other minority races), pregnancy, malnutrition, immunodeficiencies, autoimmune diseases, poor diet and poor lifestyle, etc.

In addition to the risk factors mentioned above, some laboratory indicators play an important role as prognostic factors or markers of mortality risk. The most important so far are high **CRP**, leukocytosis, **lymphopenia**, high **LDH**, high ferritin, high D-dimer, low albumin, thrombocytopenia… If these laboratory markers are present, and do not improve, the risk of a bad COVID-19 outcome is possible. Other laboratory prognostic factors with less consistency are high procalcitonin levels, high cardiac tropins, increased prothrombin time and high ALT and AST levels, among others (11).

3.4. CLINICAL AND LABORATORY FINDINGS

3.4.1. CLINICAL PRESENTATION

COVID-19 has a wide clinical spectrum that can range from asymptomatic or just mild symptoms, to pneumonia, severe respiratory failure or even death. And as it is known, the host's immune system has the most important role in the disease pathogenesis and clinical manifestations.

Based on the severity of the presentation, the disease can be classified as mild, moderate, severe and critical presentation (13).

Mild disease accounts for an 80% of all infected people. It presents with “flu like” upper respiratory tract symptoms, including mild fever, dry cough, nasal congestion, sore throat, headache and even muscle pain and malaise.

If it progresses, it can turn into a **moderate presentation** with cough, shortness of breath and tachypnea. Some cases go further, turning into a more **severe disease**, with the possibility of developing severe pneumonia, ARDS, sepsis or even septic shock. Those patients will present severe dyspnea, tachypnea and respiratory distress.

If this situation cannot be reversed, with high probability this severe state will turn into a **critical state**, requiring ICU admission and intubation, and with features of respiratory failure, cardiac injury, septic shock, multiple organ dysfunction and eventually death.

But since more than half of the infected people present a mild disease, the most common symptoms are fever, dry cough, fatigue and diarrhea. Depending on the study the percentage of anosmia differs, but in general it is also a rather common symptom. Less common are sputum, headache, anorexia, chest pain, sore throat, chills, nausea/vomiting and dyspnea.

The incubation period goes from 1 day to 14 days, but the average is 5 days (8).

All ages are susceptible to SARS-CoV-2 infection. However, as age increases more risk of disease severity. That is why we could state that clinical presentation differs with age. Young people are more likely to be asymptomatic or suffer a mild disease, whereas older people have greater risk of moderate to severe disease. Furthermore, if a person has any kind of comorbidity, the risk is higher.

For example, in many comorbidities such as diabetes, hypertension or heart disease, it has been seen that the number of ACE2 receptors of vascular and heart cells is higher. This means that SARS-CoV-2 can cause in these subjects a greater damage. In fact, a recent study from China stated that in an 8% of patients, COVID-19 causes acute cardiac injury manifested by arrhythmias, myocarditis, cardiogenic shock and heart failure (14).

To sum up, as older the age, more risk of disease. Moreover, the highest morbidity has been observed in patients of advanced age (≥65 years) and the highest mortality is in ≥85 years (2).

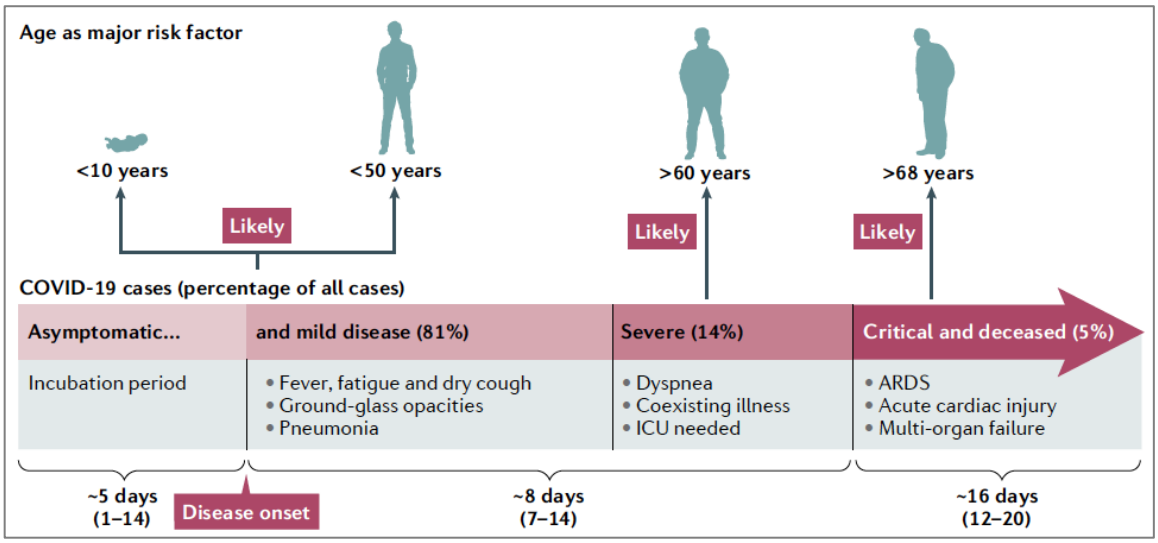

Figure 3. Clinical features of COVID-19 (13).

Non-respiratory symptoms

Although SARS-CoV-2 affects mainly the respiratory tract, it is not rare to find other non-respiratory symptoms (15). This is because ACE2 receptors can also be found in other systems. The most common are **gastrointestinal symptoms** (2-40%), such as diarrhea, and **taste/olfactory disorders** (53%), such as anosmia.

Other less common symptoms might be dizziness, headache, stroke (ischemic or hemorrhagic), musculoskeletal disturbances, altered mental state and Guillain Barré syndrome.

Regarding the cardiovascular system, there have been reported cases of myocardial injury, myocarditis, pericarditis, arrhythmias and heart failure. COVID-19 can also induce a prothrombotic state that can lead to micro-thrombotic disease or macro-thrombotic disease (such as venous thromboembolic events like PTE or DVT).

About the ocular affection (32%), it can be affected as conjunctival hyperemia, chemosis and increased secretions.

3.4.2. LABORATORY FINDINGS

Laboratory abnormalities can be found in many patients, even in mild and moderate ones. However, they will be notably altered in severe patients (16).

Some of these findings are high **LDH**, high **PCR**, low **lymphocyte** count, high **ferritin**, low albumin, high ALT and AST, high CK, elevated coagulation indexes (Pt, APTT, D-dimer), high IL / GCSF / TNF-α, high procalcitonin, etc. (16).

High CRP (an inflammation marker) and procalcitonin levels are correlated with COVID-19 severity and also progression.

In severe cases it can also be found markers of coagulation activation, cellular immune deficiency, heart injury, renal injury and hepatic injury.

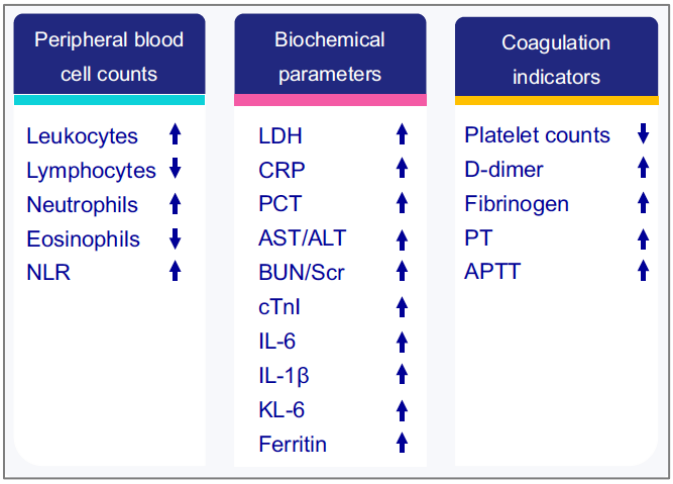

Figure 4. Laboratory indexes associated with severe and critical COVID-19 (17).

3.4.3. COVID-19 COMPLICATIONS

The most frequent complications caused by SARS-CoV-2 are ARDS, acute cardiac injury, acute kidney injury, abnormal coagulopathy, secondary infection and shock (16). It is important to remark that in the high-risk population (elderly, presence of comorbidities) the virus has a higher prevalence of complications.

Acute respiratory distress syndrome (**ARDS**) is presented with respiratory failure and is defined by bilateral alveolar infiltrates, acute hypoxia and pulmonary edema, due to an increase in the alveolocapillary membrane's permeability. ARDS has many causes but, in this case, it can be explained by the pneumonia or sepsis induced by a severe COVID-19 disease.

In ARDS there is a process known as **diffuse alveolar damage** (DAD) characterized by acute inflammation and exudation in the alveoli. There is edema, hyaline membranes formation and interstitial inflammation. This situation is followed by an organizing phase with fibrosis in the alveolar septa, that eventually should resolve to how it was initially.

All in all, in ARDS there is a rapid episode of acute respiratory failure with an increase in the respiratory work, that in most cases may require mechanical ventilation temporarily. Those patients may evolve either positively or eventually die. And of those who survive, some will develop interstitial lesion that could lead to pulmonary fibrosis.

Available data from some cohorts state that approximately a 40% of those severe COVID-19 patients will develop ARDS, and of them, 20% will suffer a severe ARDS (18).

The most critical patients are those who suffer from **sepsis**. The infection causes an alteration of the host response that can end up in multiorgan dysfunction. This situation can be manifested with dyspnea, low oxygen saturation, decreased urine output, tachycardia, hypotension, cold extremities and skin mottling among others. Laboratory results show acidosis, high lactate, high bilirubinemia and thrombocytopenia.

3.5. CT SCAN FINDINGS

Chest CT scan is a highly important tool in the diagnostic and follow-up of COVID-19 pneumonia thanks to its high sensibility in the detection of lung alterations.

COVID-19 pneumonia can present itself with different features, ranging from a normal appearance to diffuse changes. Despite these differences, there is some consistency among studies. According to a meta-analysis including 40 studies and 4598 patients (20), an 80% of patients with COVID-19 pneumonia presented **bilateral lung involvement**. The predominant pattern was **ground-glass opacities** (**GGO**) (64,9%) followed by mixed pattern (GGO with consolidation or reticulation) (59,2%), consolidation (30,3%), reticulation (17%) and nodular pattern (16,6%).

More findings were **interlobular septal thickening** (63,6%) and **vascular enlargement** (61,4%). Other findings with less consistency were air bronchogram signs, crazy-paving pattern, bronchiectasis, pleural effusion, subpleural bands and lymphadenopathy.

The lesion distribution was mainly **peripheral** (70%), while central and mixed distribution was less common. The most affected lung regions were the **lower lobes**: right lower lobe (86,5%), left lower lobe (81%), right upper lobe (58,4%), right middle lobe (49,7%), left upper lobe (64,5%).

Finally, regarding the number of lobes involved, the most frequent was just **1 lobe** (58,4%) or all **5 lobes** (43,2%). This difference might be related to the moment the CT scan was done. In early stages there is probably only 1 or few lobes involved, while in more advanced stages, all lobes might be already affected.

The pattern of GGO accounts for diffuse alveolar damage. When the virus replicates in the alveolar epithelium, it causes damage and therefore leaking and filling of the alveolar cavity. That would explain why this pattern is by far the most common.

Findings such as lymphadenopathy or pleural effusion, which account for extrapulmonary manifestations, may indicate progression of the initial pneumonia.

It is important to remark that pulmonary patterns and other findings can change overtime, depending on the time interval from symptoms. For example, the alterations seen during the first week of symptomatic presentation may differ from those in the third week. Initially, the predominant pattern is GGO but within the second week this pattern evolves to a mixed GGO with consolidation, ending with a predominance of consolidation. Generally, CT findings tend to decrease in the third week.

If CT findings show a different evolution from the one mentioned above and there are signs of reticulation pattern, bronchiectasis and/or interlobular or septal thickening, it could mean the emergence of interstitial lesions, suggesting the development of pulmonary fibrosis.

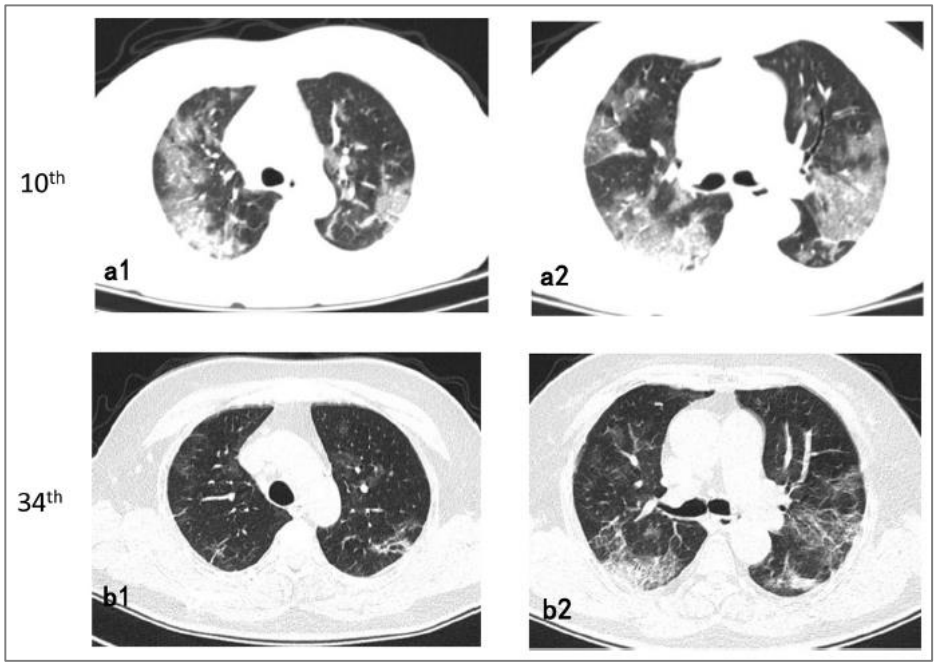

Figure 5. 72-year-old female. Follow-up chest CT images (34th day from onset). Images b1-b2 show a decrease in the extent of GGO than the 10th day images and an increase in fibrotic lesions (a1-a2) (24).

3.6. TREATING OPTIONS

Since the beginning of the pandemic, one of the main objectives has been to find out how to treat a **moderate to severe COVID-19 patient**. Numerous studies and clinical trials are trying to identify or discover the best drug to beat the infection. However, until that happens, patients who are in need of medical intervention are treated with preexisting drugs, known as repurposed drugs (21,22).

Until now the available drugs are:

- Anti-viral therapies
- Anti-SARS-CoV-2 monoclonal antibodies
- Anti-inflammatory drugs
- Immunomodulator agents

Antiviral drugs include **Remdesivir**, Hydroxichloroquine / Chloroquine, Lopinavir-Ritonavir, among others. Remdesivir, the most promising of this group, is an inhibitor of the RNA-dependent polymerase, meaning that it interferes in the virus' RNA replication. The other antiviral drugs are less used because of poorer results or due to a less secure profile.

Anti-SARS-CoV-2 antibodies are mainly obtained through **convalescent plasma**. This means plasma from patients that where infected with SARS-CoV-2. It is a save procedure that if given in an early stage, it can suppress viremia. However, it remains explorative.

Immunomodulator agents include **corticosteroids** (dexamethasone), IL-6 receptor antagonists (Tocilizumab), Sarilumab, JAK inhibitors, Baricitinib, Tofacitinib, etc. They are more effective if used in a late stage.

Apart from these more specific drugs, other important therapies that may be necessary in moderate to severe cases, are:

- Antipyretics
- Thromboprophylaxis and fibrinolysis. The preferred agent is the low molecular weight heparin (enoxaparin).

- Antifibrotic therapy, such as Nintedanib or Pirfenidone. These drugs are currently under trials and in some cases might be used, but for now, they are not an stablished treatment included in the protocols.
- Oxygen therapy; high flow nasal cannula (HFNC) and noninvasive positive pressure ventilation (NIPPV); endotracheal intubation. In mild or moderate ARDS the standard is to use HFNC or NIPPV. In severe ARDS it requires endotracheal intubation and mechanical ventilation.
- Extracorporeal membrane oxygenation (ECMO): Used in critical patients who do not seem to respond to the available treatment options. However, not all patients meet the requirements needed to undergo ECMO.

Suggested management based on severity (22)

- Asymptomatic: Isolation + monitor symptoms + symptomatic treatment.
- Mild disease: Supportive care + isolation + monitor symptoms (especially if elderly or with comorbidities).
- Moderate illness: Hospitalize for close monitoring + oxygen therapy + thromboembolic prophylaxis + antiviral ± corticosteroid.
- Severe / critical illness: Hospitalization + HFNC/NIPPV/intubation + antiviral + prophylactic anticoagulation + corticosteroid ± other immunomodulators.

According to the actual protocols followed at Hospital Universitari Doctor Josep Trueta (27), the standard management of moderate-to-severe pneumonia is as follows: Remdesivir + Corticosteroids (dexamethasone) ± Tocilizumab (if bad evolution). These drugs are the standard, but they are just administrated if patients meet several indications.

Note that these protocols are in constant change depending on the clinical evidence of the moment. For example, in the early 2020, during the first wave, corticosteroids were not protocollary, so not all moderate-to-severe patients did receive them.

3.6.1. VACCINES

Just a few months after the COVID-19 outbreak many researches begin in order to find a vaccine against SARS-CoV-2 as soon as possible. Until now, hundreds of laboratories have initiated the process but just a few have managed to overcome the numerous steps to achieve commercialization.

The mechanism of action of the vaccines can be classified into different categories (22,23):

- Inactivated or attenuated vaccines: This procedure consists of introducing the virus alive but without the capacity to do harm.
- Protein-based vaccines: It consists of injecting viral proteins (protein s) to stimulate an immune response.
- Viral vector-based vaccines: An immunogenic part of the virus (like the s protein) is selected and inserted into a viral vector like an adenovirus.
- RNA-based vaccines: The viral RNA instructs the host's cells to synthetize specific coronavirus proteins. These proteins will trigger an immune response.

The spike (s) protein is one of the main antigen targets of the vaccine. The aim of the vaccines is to trigger the host's immune system in order to produce neutralizing antibodies against SARS-CoV-2. Thus, if the virus enters the system of a previous vaccinated person, the immune response will be faster and more effective thanks to the circulating antibodies.

Finding an effective vaccine is the best long-term answer to the current COVID-19 pandemic.

3.7. INTERSTITIAL LESION. PULMONARY FIBROSIS.

During the first months following the COVID-19 outbreak, some cases of severe pneumonia continued to remain hypoxemic despite what seemed an adequate treatment of the infection.

It has been seen that a complication of COVID-19 and ARDS is **interstitial lesion**, with the risk of developing **pulmonary fibrosis** afterwards. There is no current data on the frequency, but it is estimated to affect a third of the patients hospitalized with SARS-CoV-2 (18,19).

The lung interstitium is a connective tissue layer located between the alveolar basal membrane and the capillary endothelium (see Figure 6). In normal conditions we can find cells (macrophages, fibroblasts, myofibroblasts…) and extracellular membrane (collagen, fibronectin…) altogether (30). When an external aggression occurs to the lung tissue, the inflammatory cells, fibroblasts and alveolar epithelial cells liberate cellular mediators generating alveolar inflammation. It is important to understand that not all alveolar inflammations end up with pulmonary fibrosis (30). Normally the interstitium will heal shortly with minimal or no scaring. In this sense, developing fibrosis depends on several aspects such as the integrity of the basal membrane, a genetic predisposal and immunity disorders. If these features are not present, after the lung aggression there will most probably be a phase of healing and a functional recover (31). The most feared outcome is the formation of irreversible lung scars (fibrosis) because it is usually progressive and originates important abnormalities in the respiratory function and gas exchange (31).

Pulmonary fibrosis is caused by an excess of fibroblasts and excessive deposition of ECM (extracellular matrix) molecules including collagen, laminin and fibronectin, in the parenchymal lung tissue. This leads to an increase in the alveolar wall's thickness, generating a bad gas exchange and, therefore, a decreased lung function and exercise intolerance. These translates into a reduction in the subject's quality of life (3).

It manifests as a flu-like illness, mainly with dry cough, fatigue and progressive dyspnea. It can be accompanied by weight loss, physical deterioration and low quality of life.

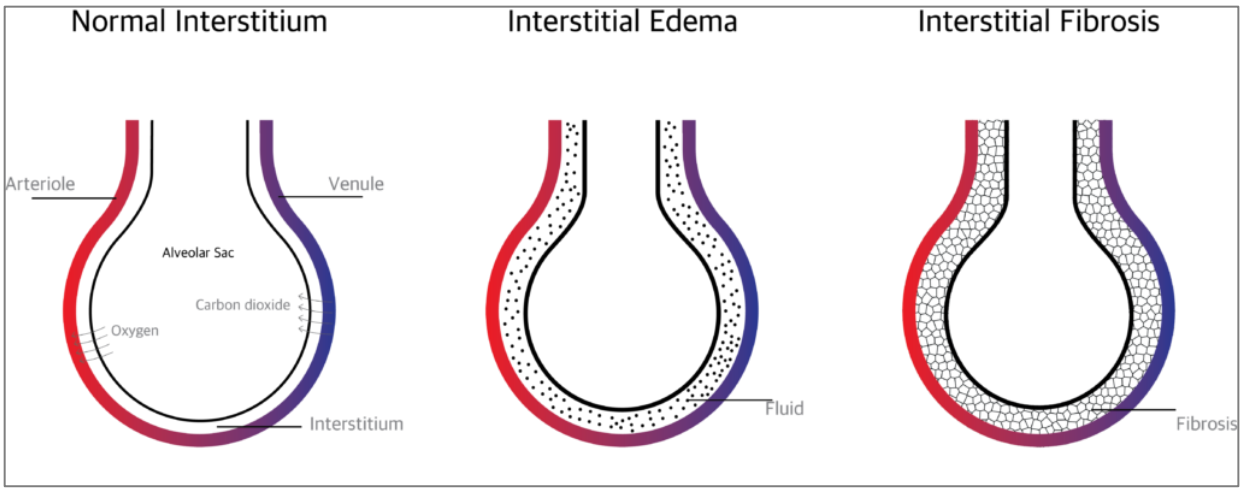

Figure 6. Representation of the lung interstitium in a normal situation, with edema and with fibrosis (32).

Further studies are needed to know the real prevalence of post COVID-19 interstitial lesion. It also needs to be studied the impact of COVID-19 in the progression of pulmonary fibrosis with a preexisting interstitial lung disease.

3.7.1. RISK FACTORS

Advanced age is a risk factor for developing interstitial lesion. The aging lung is more susceptible and it is also associated with ECM dysregulation. Another risk factor is the presence of **comorbidities**. Some well-known comorbidities are hypertension, diabetes and coronary artery disease. Another risk factor is the **length of the disease**, as the disease lasts longer, the risk of pulmonary lesion is higher (3,4,19).

Other important predictors of interstitial changes are **illness severity**, **length of ICU stay**, **mechanical ventilation duration**, **smoking**, **chronic alcoholism**, and **high CPR** at admission (3,4,19)

And most important, **ARDS** is the main predictor of fibrosis since fibrosis is a well-known sequelae of ARDS.

3.7.2. PATHOGENIES

Although unknown, it has been suggested that pulmonary fibrosis could be secondary to many events: the viral infection, the cell host response, an immune-mediated mechanism (cytokine cascade), the mechanical ventilation or a mix of all (2).

a. **Viral infection**. In our system we can find both ACE and ACE2 receptors. These two receptors control the **renin-angiotensin system** (RAS), achieving hemostatic balance and fluid homeostasis. On the one hand, ACE activates signal pathways leading to aldosterone release, bringing the RAS system to induce vasoconstriction and sodium and fluid retention. But most important to this matter is that the ACE pathway also has proinflammatory and profibrotic effects. On the other hand, ACE2 activates protective anti-inflammatory and anti-fibrotic effects. Once SARS-CoV-2 binds to ACE2, the process of endocytosis starts, leading to a decrease in the number of ACE2 receptors. This means that the RAS system is not balanced anymore, in favor of ACE (pro-inflammatory state). Consequently, there is activation of IL-6, TNF-α and many more elements, recruitment of macrophages, neutrophils and collagen gene activation. In this respect, SARS-CoV-2 contributes to activate the host's pro-inflammatory and pro-fibrotic pathways.

   Moreover, when the virus attacks the respiratory cells, cytoskeletal changes occur, generating abnormal mechanical forces. These mechanical stimuli are detected by the integrins in the ECM. This situation can also activate fibroblasts, macrophage and profibrotic pathways, among others.

b. **Cell response**. SARS-CoV-2 attacks many cells, but one of the most significant are alveolar epithelial cell type II (AEC-II), alveolar macrophages and endothelial cells. All these cells, by different routes, can activate the fibrosis pathway.

c. **Inflammation process**. Cytokine and chemokines activate macrophages and other immune cells. Those activated macrophages contribute to neutrophil recruitment. An abundance of neutrophils can contribute to tissue injury, initiating the fibroblast activity and deposition of ECM, with the possibility of ending in fibrosis.

d. **Mechanical ventilation**. Through mechanisms such as barotrauma, mechanical ventilation can cause stretch force injury. This insult can cause oxidative injury that may result in excessive collagen deposition.

Once lung injury has been stablished, a phase of acute inflammation follows, along with an attempt of repair. The repair process consists of fibroblasts located in the alveolar interstitium that transform into myofibroblasts, who are responsible for the deposition of ECM. This situation can evolve into two different situations, the restoration of normal pulmonary architecture or the start of pulmonary fibrosis with architectural distortion and lung dysfunction. In severe lung injuries the fibroblastic activity persists, leading to an excessive deposition of ECM, which will result in a disorganized alveolar architecture.

3.7.3. CT FINDINGS

In patients suffering from interstitial lesions we can find fibrotic changes in the form of traction bronchiectasis, parenchymal bands, architectural distortion, reticular pattern, irregular septal thickening and honeycombing.

3.7.4. TREATMENT

Even if the acute infection is handled as correct as possible, prevention from interstitial lesion development is not guaranteed. Moreover, there is still no data on weather those patients will fully recover, experience stable damage or progress to pulmonary fibrosis (2).

Given this situation and due to a lack of clinical trials, post COVID-19 lung fibrosis management remains unexplored. There are no fully proven options for the treatment. Until now, the most used antifibrotic drugs are **Pirfenidone** and **Nintedinib**. As it has been proven in patients with idiopathic pulmonary fibrosis (IPF), these drugs can attenuate the rate of lung function decline (3). This is why they are starting to be considered a potential treatment for stablished fibrosis in post-COVID-19 patients (33), although it is still experimental.

Moreover, it is believed that prolonged low dose of **corticosteroids** may prevent the development of pulmonary fibrosis in patients with already interstitial lesion (3).

Further, **rehabilitation** in both the acute stage and recovery stage results beneficial as it improves the respiratory function, exercise tolerance, self-care in daily living activities and psychological support (4).

4. JUSTIFICATION

Although everyday we know more about SARS-CoV-2 and the COVID-19 disease, many questions and unknowns still stand and will stand for some time, mostly in relation to once the acute infection phase has been cured. Its importance and concerns lies in the great impact the infection has made on the whole society.

Since the start of the pandemic, there have been rising cases of COVID-19 survivors that continue to suffer symptoms of the illness despite having been tested negative for the disease. And, preliminary results in the early follow-up suggest interesting outcomes. It seems that some patients might be at risk of suffering from persistent symptoms, have abnormal patterns in chest imaging, impaired lung function and/or poor quality of life (6,34).

Some studies have reported that a notably high percentage of discharged patients after COVID-19 pneumonia (especially if it was severe) present persistence of at least one symptom for some moths (4). Of them, the most common are fatigue or muscle weakness, dyspnea, and sleep difficulties. Less common are anxiety and depression (6). Moreover, those more severe patients have an increased risk of pulmonary diffusion abnormality, consistent with the CT scan findings. Restrictive ventilatory defects is the second most common finding (34), that could be explained by neuro-muscular weakness.

Whether radiological or pulmonary diffusion abnormalities completely resolve remains unknown and needs to be investigated in further follow-up studies. But, as it was seen with MERS-CoV and SARS-CoV survivors, the resolution could take months and even years.

And regarding the lung interstitial lesions, which is the target of our research study, although further investigations are needed, up to date analysis suggest that at least one third of those hospitalized patients will develop pulmonary fibrosis (4,5,34). And, considering all those millions of COVID-19 cases worldwide, even a small percentage of pulmonary fibrosis after COVID-19 is a cause for concern.

The actual problem is that there is not enough evidence to make a clear statement about the long term health consequences of COVID-19 regarding interstitial lesions and how they will evolve. The pandemic is too recent and, therefore, follow-up studies too short.

So, the aim of this project is to assess the COVID-19 long-term health consequences, especially regarding the development of interstitial lesions and how this affects the pulmonary function and quality of life. If there is any existence of pulmonary fibrosis after discharge, we will assess the disease's severity and the possibility of progression thanks to the 12-month follow-up.

As said before, it is important to take into consideration that previous studies have been done in a short period of time, which could affect the scientific evidence. Furthermore, they cannot represent the long term impact of the pandemic. And, most probably, neither will do this present research project, but we hope it will help to be a step closer to unmask some of the post COVID-19 uncertainties.

Considering that SARS-CoV-2 infection is one of the biggest health problems science is facing nowadays and that it is causing thousands of death worldwide, it is important to improve the knowledge with the aim of preventing and managing the effects of this virus.

5. HYPOTHESIS

- SARS-CoV-2 infection triggers profibrotic pathways. Therefore, a proportion of patients who suffer severe COVID-19 pneumonia will experience pulmonary interstitial lesion. Of those, some will develop fibrotic sequalae.
- Quality of life, pulmonary function and exercise capacity improves 12 months after suffering severe COVID-19 pneumonia.
- Elderly people have a greater risk of developing pulmonary fibrosis after severe COVID-19 pneumonia than younger people.

6. OBJECTIVES

MAIN OBJECTIVE

- To determine the incidence of pulmonary fibrosis development after suffering severe COVID-19 pneumonia by SARS-CoV-2.

SECONDARY OBJECTIVES

- To investigate the 12-month evolution of quality of life, pulmonary function and exercise capacity in patients who suffered severe COVID-19 pneumonia.
- To evaluate if older patients have a greater risk of developing pulmonary fibrosis than younger patients.

7. METHODOLOGY AND MATERIALS

7.1. STUDY DESIGN

This research is designed as an observational prospective cohort study, with just a single-group. We collected data from patients with laboratory confirmed SARS-CoV-2 infection and related severe COVID-19 pneumonia that required non-invasive respiratory therapy (NIRT) or invasive

respiratory therapy (IRT), and that were discharged from the Pneumology Service between March and June 2020.

This research project consists of a 12-month follow-up period, with check-ups approximately every 3 months, in which we will divide the whole group into 2 cohort subgroups, depending on the presence or not of pulmonary fibrotic findings.

The ethics committee approved this study and granted the informed consent of the participants.

7.2. SETTING

The study will be conducted in the Pneumology Service of Hospital Universitari Doctor Josep Trueta, in Girona.

7.3. STUDY POPULATION

The study population is composed of 94 patients aged 34 to 93 with a history of severe COVID-19 pneumonia hospitalized in Hospital Universitari Doctor Josep Trueta's Pneumology Department, between March and June of 2020 , which accounts for the period of the first wave.

Patients were diagnosed with a positive result int the polymerase chain reaction (PCR) for SARS-CoV-2 nucleic acid, with throat or nasopharyngeal samples.

We defined severe pneumonia as those patients that during hospitalization required either non-invasive respiratory therapies (NIRT; high-flow nasal cannula, continuous positive airway pressure, or non-invasive ventilation) or invasive respiratory therapies (IRT).

7.3.1. INCLUSION CRITERIA

- Patients discharged from Pneumology Service with a diagnosis of severe COVID-19 pneumonia diagnosed by a positive PCR for SARS-CoV-2, and that had required NIRT or IRT.
- Patients over 18 years old.

- Patients who agree to participate in the study by understanding and signing the informed consent.

7.3.2. EXCLUSION CRITERIA

- Patients who are not willing to be included int the study.
- If any pregnant women enters the study, they can be included in the follow-up, but no CT scan or radiography will be performed during pregnancy.

7.4. SAMPLE

7.4.1. SAMPLE SELECTION

Participants will be selected by a pneumologist after being discharged from hospital, so the selection is single-center and following the non-probabilistic consecutive sampling model.

Participants will be chosen applying the inclusion and exclusion criteria. They will be given an information sheet and will be informed of the study objectives (ANNEX 3). After receiving the information, those who want to participate will be given the informed consent (ANNEX 4).

1.1.1. SAMPLE SIZE

A minimum of 94 patients will be included to estimate the incidence of pulmonary fibrotic sequelae after severe pneumonia by SARS-CoV-2 with a Confidence Interval (CI) of 95% and a precision of ±10 %.

1.2. STUDY VARIABLES

Since this is a single-group cohort study, we cannot use the terms *independent variable* and *dependent variable*; we will then use the terms *principal variable* and *secondary variables*.

1.2.1. DEPENDENT VARIABLES

PRINCIPAL VARIABLE

To answer the main objective, the present research project chose the principle dependent variable to be the presence of pulmonary fibrosis in the chest HRCT scan. The information will be

taken from the HRCT scan performed at 12 months after the severe pneumonia. Patients will be divided into two groups: Group A for “pulmonary fibrosis” and Group B for “non-pulmonary fibrosis”.

It will be presented as a qualitative dichotomous variable, expressed as the presence or absence of pulmonary fibrosis seen in the HRCT scan.

According to literature, lung fibrosis can be defined by the presence of: parenchymal bands, distortion and irregular interfaces (bronchovascular, pleural or mediastinal), reticular opacities and traction bronchiectasis with or without honeycombing (35,36). This research will conclude that there are fibrotic changes if any of the following are present: **traction bronchiectasis or bronchiolectasis**, **architectural distortion** and/or **honeycombing**.

A part from these findings, other parenchymal abnormalities that can be suggestive of interstitial lesion are: parenchymal pattern (ground-glass opacity, consolidation) and reticular pattern (fine subpleural reticulation, coarse opacities). We also evaluated the number of lungs involved (one: unilateral; two: bilateral) and the distribution of the interstitial lesions (peripherical, central).

HRCT findings		**Group A**	**Group B**
GGO	Parenchymal pattern		
Consolidation			
Fine subleural reticulation	Reticular (septal) pattern		
Coarse linear or curvilinear opacities			
Traction bronchiectasis	Stablished fibrosis		
Honeycombing			
Architectural distortion			
Other			
Normal			

Table 1. List of HRCT findings that will be looked for, and correlation with pulmonary fibrosis. GGO: ground-glass opacity.

SECONDARY VARIABLES

These secondary dependent variables will help us to give a more complete answer to the proposed objectives.

A. Quality of life

Quality of life after COVID-19 will be assessed by answering the **Saint George's Respiratory Questionnaire** and looking at the following parameters: *symptoms scale*, *activity scale*, *impact scale* and *total scale*. Results will be given as a %, that goes from 0% (best outcome) to 100% (worst outcome). It will be presented as a continuous quantitative variable.

B. Pulmonary Function

Pulmonary function will be assessed by performing the **Pulmonary Function Tests** (PFT) (spirometry, diffusion capacity tests and lung volumes) and analyzing the following parameters: FVC (L), FVC (%), FEV1 (L), FEV1 (%), TLC (%), RV (%), DLCO (%) and KCO (%). They will be presented as continuous quantitative variables.

C. Exercise capacity

Exercise capacity will be assessed with the **6 Minutes Walking Test** (6MWT) and looking at the following parameters: *walked distance* (meters), *mean oxygen saturation* (%) during the test, *basal oxygen saturation* (%) before the test, and *minimal oxygen saturation* (%) during the test. They will be presented as continuous quantitative variables.

1.2.2. COVARIATES

These are characteristics of the patients that could interact as cofounding variables and affect the outcome in the study. The present research has identified the following covariates:

1) CLINICAL FEATURES

COVARIATE	TYPE OF VARIABLE	CATEGORY OF VALUES
Sex	Dichotomous qualitative	Male / Female
Age	Continuous quantitative	Years
BMI	Continuous quantitative or Ordinal qualitative	*

Body mass index (BMI) is a tool invented in the 1970s and that has become since then an easy assessment method to classify people according to their nutritional status. BMI is the result from dividing the weight (kg) with the height (m^2) of a person (BMI = kg / m^2).

* The variable can be presented as a continuous quantitative variable (BMI score number) or as an ordinal qualitative variable: < 18.5 (underweight), 18.5-24.9 (normal), 25-29.9 (overweight), 30-34.5 (obesity class I), 35-39.9 (obesity class II) and > 40 (obesity class III). (37)

2) TOXIC HABITS

COVARIATE	TYPE OF VARIABLE	CATEGORY OF VALUES
Smoking	Nominal qualitative	Yes / Ex-smoker / No

According to WHO's *Smoking and Tobacco Use Policy* (38), a smoker is "someone who smokes any tobacco product, either daily or occasionally". "A daily smoker is someone who smokes any tobacco product at least once a day. And an occasional smoker is someone who smokes, but not every day". An ex-smoker is someone that has given up smoking.

Smoking can clearly affect the lungs. Therefore, HRCT imaging, PFR and 6MWT findings could show cofounding abnormalities that might be previous to the SARS-CoV-2 infection.

3) COMORBIDITIES

COVARIATE	TYPE OF VARIABLE	CATEGORY OF VALUES
Hypertension	Dichotomous qualitative	Yes / No
Diabetes mellitus	Dichotomous qualitative	Yes / No
Dyslipidemia	Dichotomous qualitative	Yes / No
Chronic diseases	Dichotomous qualitative	Yes / No

The information was collected by looking at the patients' medical records.

Hypertension (HT): High blood pressure (or hypertension) is the condition when the force exerted by the circulating blood against the arteries' walls is too high. According to WHO, HTA is diagnosed when the systolic blood pressure is ≥140 mmHg and diastolic blood pressure is ≥90 mmHg.

Diabetes mellitus (DM): DM is a chronic disease in which blood glucose levels are too high. It can be diagnosed when glucose levels are ≥126mg/dl after a period of at least 8h of fasting.

Dyslipidaemia (DLP): It is the condition when blood lipids are above the normal ranges. Normal values are: <200mg/dl for total cholesterol, <150mg/dl for triglycerides and >40mg/dl for HDL.

Chronic diseases: We include here respiratory and cardiovascular chronic diseases. Chronic diseases are long-lasting conditions that suppose the presence of persistent symptoms.

These comorbidities, as explained in the Introduction section, have been declared risk factors for developing severe COVID-19 pneumonia.

4) RESPIRATORY SYMPTOMS

COVARIATE	TYPE OF VARIABLE	CATEGORY OF VALUES
Dyspnea	Ordinal qualitative	0, 1, 2, 3, 4
Cough	Dichotomous qualitative	Yes / No
Pleuritic pain	Dichotomous qualitative	Yes / No

Cough: It is defined as the "air forced out of the lungs through the throat with a short, loud sound, often unwillingly", and that was initiated after the hospitalization for COVID-19 pneumonia.

Pleuritic pain: It is defined as a "sudden and intense sharp pain in the chest when inhaling and exhaling", initiated after the hospitalization for COVID-19 pneumonia.

Dyspnea: It is defined as the subjective perception of lack of breath. It will be assessed following the *modified Medical Research Council (mMRC) Dyspnea Scale*:

Grade	Description of Breathlessness
Grade 0	I only get breathless with strenuous exercise
Grade 1	I get short of breath when hurrying on level ground or walking up a slight hill
Grade 2	On level ground I walk slower than people of the same age because of breathlessness, or I have to stop for breath when walking at my own pace on the level
Grade 3	I stop for breath after walking about 100 yards or after a few minutes on level ground
Grade 4	I am too breathless to leave the house or I am breathless when dressing

We will consider dyspnea those grades higher than 0 (≥1).

1.3. MEASUREMENTS AND INSTRUMENTS

The tests performed to obtain the patients' necessary information will be:

HRCT scan: The CT scan used is the *Siemens Somatom Perspective 64*. It will be performed with the patient in supine position during end-inspiration. Images will be reconstructed at 1mm slice thickness. The scan will cover the entire chest and will provide a detailed look from the thoracic inlet to the costophrenic angle. It will be used the CT's lung window to evaluate the pulmonary parenchyma. The images will be informed by an experienced radiologist. After reading the radiologist's inform and reviewing the CT images by a pneumologist, the most significant lung abnormalities of each subject will be chosen and entered to the study database. The presence, extent and distribution of interstitial findings will be registered using the nomenclature recommended by the Fleischner Society (ANNEX 1).

Pulmonary Function Tests (PFT): The PFT are a group of tests that evaluate how the lungs are functioning. They will be done in the Lung Function Laboratory using the MasterScreen PFT (Jaeger, Germany). The performed tests will be spirometry, diffusion capacity and pulmonary volumes (plethysmography). With each technique we will study different parameters (ANNEX 1).

- **Spirometry**: FEV_1 (forced expiratory volume in 1 second), *FVC* (forced vital capacity).
- **Diffusion capacity tests**: *DLCO* (diffusion capacity to carbon monoxide), *KCO* (carbon monoxide transfer coefficient). DLCO must be corrected with hemoglobin.
- **Pulmonary volumes**: *TLC* (total lung capacity), *RV* (residual volume)

If obstruction was detected, the spirometry measurements will be repeated after the administration of bronchodilators.

All procedures will be done according to the American Thoracic Society (ATS) and European Respiratory Society (ERS) guidelines. Results are expressed as a percentage (%). Since normal values are based on age, sex and height, a value will be considered abnormal if it is lower than its predicted value (39,40).

6 Minutes Walking Test (6MWT): This test evaluates the response of several systems (respiratory, cardiovascular, metabolic, musculoskeletal and neurosensorial) to a stress imposed by the exercise. It consists in measuring the maximum distance that a subject can walk, as fast as possible, during a 6-minute-period. This test is a good tool to evaluate and establish the prognosis of chronic respiratory diseases (41). The assessed parameters are distance (meters), basal oxygen saturation, minimal oxygen saturation and mean oxygen saturation. Oxygen saturation will be measured by pulse oximetry on index fingers. It will be performed according to the ATS/ERS guidelines.

In general, healthy people tend to walk between 400 and 700 meters, depending on age, gender and height. For patients that walk less of what would be expected, this test is a good tool for their prognosis (42). This 6MWT is also useful to assess desaturation during exercise. A drop of 4% (ending below 92%) is considered significant (40) and an important prognostic indicator in patients with interstitial lesion.

Saint George's Respiratory Questionnaire (SGRQ): This questionnaire is used to assess the patients' quality of life. It can be performed individually or in a clinical interview. It is made of 50 items (question with four answers) divided in three scales: symptoms, activity and impact (ANNEX 2). The *symptom scale* assesses the frequency and severity of the respiratory symptoms. The *activity scale* analyzes the limitation in the activities due to dyspnea. The *impact scale* assesses the psychological and social dysfunction on daily life due to the disease (43).

Interpretating these parameters is complicate so it will be used a program that only requires entering the participant's answers.

This questionnaire was originally made for patients with obstructive airways disease, however, it is used as a rutinary quality of life questionnaire and is considered the reference in many pulmonary pathologies including idiopathic pulmonary fibrosis (IPF).

1.4. DATA COLLECTION

This is a prospective clinic research. For data collection it will be used a non-probabilistic consecutive sampling method. The subjects included in the research will be patients with post SARS-CoV-2 infection discharged from the Pneumology Service after suffering severe pneumonia with requirements of non-invasive respiratory therapy (NIRT) and/or invasive respiratory therapy (IRT).

The collected data covers all relevant aspects of clinical history (demographic characteristics, clinical characteristics and comorbidities), quality of life, respiratory functional study and gas exchange associated with post COVID-19. Baseline demographic characteristics (sex, age, height, weight, BMI), history of smoking and comorbidities will be obtained from the electronic medical records system.

There will be four visits, one telematic and three presential. In every follow-up visit participants will be asked to perform and answer several tests in order to obtain the pertinent information needed for the study.

Visit Nº 1. **Time period**: 1 - 1,5 months after discharge. **Mode**: Via telephone.

A part from being the first visit of the study, the radiography is usually included in the protocollary check-up done to all patients that have suffered a severe pneumonia. In this first visit only information related to clinical status will be collected.

× Clinical status and respiratory symptoms (dyspnea, cough, chest pain)

× Chest radiography

Visit Nº 2. **Time period**: 2,5 - 3,5 months after discharge. **Mode**: Presential.

In this visit patients will be informed of the clinical study. If they accept being part of it, once being correctly informed, having read the information sheet, and having signed the informed consent, they will be enrolled in the study.

Then, data collected from visit nº1 will be revised by the investigator.

The following tests will be performed:

- × Clinical status and respiratory symptoms (dyspnea, cough, chest pain)
- × Saint George's Respiratory Questionnaire (SGRQ)
- × Pulmonary Function Tests (PFT)
- × 6-minutes walking test (6MWT)
- × High resolution CT scan (HRCT scan)

Visit Nº 3. **Time period**: 5,5 - 6,5 months after discharge. **Mode**: Presential.

Tests performed in visit nº 2 will be revised and results will be collected.

In this visit just the following tests will be done:

- × Clinical status and respiratory symptoms (dyspnea, cough, chest pain)
- × Saint George's Respiratory Questionnaire (SGRQ)

The other tests (PFT, 6MWT, HRCT scan) will only be done if they were altered at visit nº2.

Visit Nº 4. **Time period**: 11,5 - 12,5 months after discharge. **Mode**: Presential.

Tests performed in visit nº 3 will be revised and results will be collected.

In this visit just the following tests will be done:

- × Clinical status and respiratory symptoms (dyspnea, cough, chest pain)
- × Saint George's Respiratory Questionnaire (SGRQ)

The other tests (PFT, 6MWT, HTCT scan) will only be done if they were altered at visit nº3.

It is important to take into account that the present research project is based on an original study conducted in Hospital Doctor Josep Trueta. In Data collection *section we just mention the tests and examens that we need to develop this research project. However, the real study will perform more tests and will have more variables to analyse.*

So, a part from the mentioned tests (SGRQ, PFT, 6MWT and HRCT), the real study also will perform the following tests: chest radiography, blood tests, sputum culture (if there was expectoration), arterial blood gases (if SatO2 < 92%), lung ultrasound, transthoracic echocardiogram and angio-CT (if PTE or D-dimer >2.500).

2. STATISTICAL ANALYSIS

Data analysis will be performed using the SPSS2 and R statistical softwares. In all the analysis we set the statistical significance level at $p<0.05$.

Univariate analysis

A descriptive analysis will be done to all variables included in the study. Categorical variables will be described as **absolute numbers and percentages**. Quantitative variables will be described as **mean and standard deviation (SD)** if they follow a parametric distribution, or as **median and interquartile range (IQR)** if they follow a non-parametric distribution. To estimate if a variable follows a parametric or non-parametric distribution we will use the Shapiro-Wilk test for those variables with <50 subjects, and Kolmogorov-Smirnov test for those variables with ≥50 subjects.

Bivariate and multivariate analysis

Variables will be analysed controlling the estimation of the precision with a 95% Confidence Interval (95%CI).

Comparison between groups will be made with the following statistical tests:

- **T-test**: It will be used for those numeric variables with a normal distribution. It is used to compare the mean between two independent groups. If there are more than two groups, it will be used **ANOVA test**.
- **Mann-Whitney U test**: It will be used for those numeric variables following a non-normally distribution. It is used to compare the mean between two independent groups. If there are more than two groups, it will be used the **Kruskall-Wallis test**.
- **Wilcoxon Signed-rank test**: It is used as Mann-Whitney test but for paired samples.
- **Chi-square test**: It will be used to compare two categorical variables. It will be used if all expected values are >5. When any expected values are ≤5 it will be used **Fisher's exact test**.
- **Spearman's correlation test**: It will be used to determine any association between two quantitative variables when they are non-normally distributed.

It will be necessary to do a multivariate analysis adjusting the independent covariables with the dependent variables, so we avoid confusion. For qualitative variables it will be used a multiple logistic regression analysis, and for quantitative variables it will be used a multiple linear regression analysis.

Comparisons at baseline between fibrosis and non-fibrosis groups will be done using a comparison of independent proportions for categorical variables and a Welch two sample t-test for quantitative variables. To take into account repeated measures and missing values, comparisons between periods will be done fitting linear mixed-effect models. For categorical variables, the likelihood ratio test will be used to analyse differences between periods. For quantitative variables, the F-test based on the Kenward-Roger approach will be considered.

3. WORK PLAN AND CHRONOGRAM

3.1. TEAM MEMBERS

- **Investigation team**:
    - Main investigator: Saioa Eizaguirre, a pneumologist from Hospital Doctor Josep Trueta. She is responsible for the coordination of the study, doing the bibliographic research, elaborating the protocol, doing the medical visits and collecting the data.
    - Investigation team: Many pneumologists also participated and helped with data collection, medical visits, evaluating data, etc.
    - Cíntia Olivet, the author of these research project, helped with the data collection from visit nº 4 , did the bibliographic research for this research project, analysed the final data and presented results and conclusions.
- **Nursing staff**: Responsible for performing PFR, 6MWT, blood sample extraction and SGRQ.
- **Laboratory staff**: Responsible for analysing blood samples.
- **Radiologist staff**: Responsible for doing the CT scan imaging and interpretation.
- **Expert in statistical analysis**: Responsible for the study's statistical analysis.

3.2. WORKING PLAN

The research study will be organized in different steps, and it has been originally planned to last 12 months. The stages are the following:

STAGE 0: **Protocol elaboration**. From April 2020 to June 2020.

This stage includes:

- Bibliographic research about up-to-date COVID-19 information.
- Elaboration of the study protocol after a wide literature review.
- Prepare all pertinent documents necessary to bring the study forward.

STAGE 1: **Presentation to CEIC**. From May 2020 to June 2020.

- The protocol will be presented to *Comitè Ètic d'Investigació Clínica* (CEIC) for its approval.

- Any modifications to the protocol shall be made if necessary.

STAGE 2: **Data collection**. From June 2020 to July 2021.

- This is the largest phase. It includes visit nº 1, visit nº 2, visit nº 3 and visit nº 4.
- At visit nº 2 patients will be informed and given the possibility to enrol in the study.
- Early in this stage, an Excel database will be created to enter all information collected in the visits (personal information, clinical features, tests and imaging, etc).

STAGE 3: **Statistical analysis**. From August 2021 to October 2021.

- The whole data will be organised and sent to the statistical analyst who will process these data performing a descriptive analysis, bivariate and multivariate analysis.

STAGE 4: **Interpretation and writing of the results**. From October 2021 to November 2021.

- The results of the analysis will be interpretated by the investigators and conclusions will be extracted.
- Afterwards, the results and conclusions will be written in the article.

STAGE 5: **Publication of the results and dissemination**. From November 2021 to March 2021.

- The research team will publish the study to share the results with the scientific community.

3.3. CHRONOGRAM

	CALENDAR																				
	2020									2021											
STAGES	**Ap**	**Ma**	**Ju**	**Ju**	**Au**	**Se**	**Oc**	**No**	**De**	**Ja**	**Fe**	**Ma**	**Ap**	**Ma**	**Ju**	**Ju**	**Au**	**Se**	**Oc**	**No**	**De**
STAGE 0 Protocol elaboration. Bibliographic search.																					
STAGE 1 Presentation to CEIC and acceptance																					
STAGE 2 Visits nº1,2,3,4. Excel database creation.																					
STAGE 3 Statistical analysis																					
STAGE 4 Interpretation and writing of the results																					
STAGE 5 Results' publication and dissemination																					
ORIGINAL STUDY																					

4. BUDGET

PERSONAL EXPENSES			
ITEM	PRICE	HOURS	SUBTOTAL
Investigation team	--	--	0 €
Nurse	12 €/h	70 h	840 €
Statistical analyst	35 €/h	30 h	1.050 €

EXECUTIVE EXPENSES		
ITEM	PRICE	SUBTOTAL
PFR	--	0 €
HRCT scan	--	0 €
6MWT	--	0 €
Paper	0,03 €/paper	200 €

PUBLICATION and DISSEMINATION	
ITEM	SUBTOTAL
Publication in open access	2.000 €

TOTAL	4.090 €

This budget is focused on the expenses that suppose developing this research project. However, the original study has more tests and exams, so the expenses would be higher.

PERSONAL EXPENSES: The team of pneumologists will perform the subjects recruitment, the follow-up visits, the data collection and the results interpretation. The nursing staff will carry out PFR, 6MWT, SGRQ, etc. Since the pneumologists from the investigation team are Hospital Josep Trueta's staff and their time is included in the usual clinical practice, they will not receive monetary compensation for their work. However, a nurse will receive compensation because it will require putting extra hours. He/she will be paid 12 €/h. The only professional that will be hired is the statistical analyst. We have estimated approximately 30 hours of work. He will be paid 35 €/h, so we estimate 1.050 €.

EXECUTIVE EXPENSES: The articles, other bibliography and database used in this research do not suppose any additional cost. Printing material refers to the papers used to print the SGRQ, the information sheet and the informed consent. We estimate a cost of 200€.

The tests performed to carry on this research include a chest HRCT scan (235€/each), pulmonary function tests (320€/each), and a 6-minute walking test (52€/each). However, since performing these tests is included in the usual clinical practice of a severe pneumonia follow-up, these expenses will not be included in the budget.

PUBLICATION AND DISSEMINATION: If the researchers think is appropriate, the study will be published as a journal article.

5. ETHICAL AND LEGAL CONSIDERATIONS

To ensure that no ethical conflict will take place, the present research study will be based on pursuing and meeting the following requirements.

This study will take place according to the ethical principles established by The World Medical Association in the **Declaration of Helsinki**, signed in 1964 and last revised in October 2013. These values account for non-maleficence, beneficence, autonomy and justice.

Moreover, the initial research protocol was presented to the ***Comitè Ètic d'Investigació Clínica*** (CEIC) (Ethical and Clinical Research Committee) of Hospital Universitari Doctor Josep Trueta. This committee must evaluate and ensure that the protocol fits the ethical requirements. Also, any suggested modifications must be applied to the protocol. Once the committee approved it, the study was able to start.

Subjects will be included in the study only after being properly informed, having read the patient's information sheet and signed the **informed consent**. They will also be informed that they are free to abandon the study at any time, and that no detriment shall occur.

Also, according to "**Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y Garantía de Derechos Digitales (LOPD-GDD)**", personal data (name, surname, medical history number, etc.) will only be used, according to the mentioned legal framework, by the research team and anonymity and confidentiality of the participants will be ensured from the beginning. Moreover, each subject will be identified with a number that only the research team will have access to.

The authors of the study declare no conflict of interest.

6. LIMITATIONS AND STRENGTHS

This study has some potential limitations that may interfere with the results, so they should be considered in order to reduce them.

- We do not have a group of patients without COVID-9 pneumonia that acted as control group, meaning we just have one cohort group (a single-group study). That can be a cause of bias because we cannot control all covariates (for example, chronic pulmonary or cardiovascular diseases). Moreover, we cannot stablish causality between variables, but just association.
- We do not have the pulmonary function prior to the COVID-19 infection. Since it could be already impaired (for any other reason), it means that we could assume as newly pathological something that was already there. This could suppose a limitation since we want to make comparisons with measurements done after discharge.
- Some participants did not perform all the tests required. This could affect the validity of the outcome.

- Although the signs we have seen on the HRCT scan are convincing, we did not perform histologic confirmation of fibrosis in any patient.
- This research only recruited patients with severe COVID-19 pneumonia. Meaning that all patients with mild or moderate pneumonia were excluded, dismissing any potential mild-moderate cases who might as well develop fibrosis. This could mean final results are not as representative as we would like to due to a selection bias.
- During the process of data collection, although being as careful as possible in filling the excel database, some error might have happened, with the risk of inducing bias.

A part from all these limitations, we could point out some strengths:

- To our knowledge, few studies have conducted a long follow-up of up to 12 months, to evaluate the consequences of COVID-19.
- Also, this research has evaluated many features and characteristics (quality of life, respiratory function, exercise capacity and pulmonary imaging), instead of focusing in just one parameter. This has given a broader look into the post COVID-19 pneumonia situation and its evolution.
- The research's sample size is quite big considering that COVID-19 is a new disease.

7. IMPACT ON NATIONAL HEALTH SYSTEM

An important issue to consider is the impact SARS-CoV-2 is making on the National Health System. COVID-19 is nowadays a global health emergency with thousands of infected cases and deaths every day. This is causing a huge impact on the system, so much that many countries' public health has collapsed.

Moreover, the long-term health consequences of the SARS-CoV-2 pandemic are too recent to be completely known. However, what we do know for sure – as it happened with SARS-CoV and MERS-CoV – is that it will have some impact on the health system.

So, although its limitations, the aim of this research is to add some new valuable information to the actual knowledge on post COVID-19 interstitial lesion and pulmonary fibrosis.

Patients with post COVID-19 pulmonary fibrosis will most probably suppose a burden to the national health system because it will require more resources (health practitioners, material infrastructures and medicines) to manage them. This will mean adding more pressure on a healthcare system that is already struggling. That is why this research could be useful to help predict how much and for how long this burden to the health system could last.

Moreover, if studies like this could successfully make solid statements, it might help the population to be more conscious of the threat this virus supposes. Because it is not only a "flu-like" syndrome, as some people say. Many people, especially the elderly and those with comorbidities, have a greater risk of suffering a chronic disease such as pulmonary fibrosis, among many other complications.

8. FEASIBILITY

To take this research forward, several equipment will be required: HRCT scan, lung function tests and a 6-minute walking test, which Hospital Doctor Josep Trueta already owns. Moreover, personal including pneumologists, nurses and other qualified technicians will be also required. Thanks to its long experience, this team will result sufficiently qualified for their role. So, Hospital Doctor Josep Trueta has the necessary infrastructures, materials and human resources to conduct this study.

Regarding the budget, although this research is based on a long follow-up study, and they tend to be expensive, it has been adjusted as much as possible.

Therefore, with all the above aspects considered, we have concluded our study to be feasible.

9. RESULTS

To analyse the results we will start by describing the general features of the participants (sex, age, comorbidities…). Next, we will discuss the parameters we assessed (quality of life, pulmonary function, exercise function, and HRCT scan) by describing each visit separately and then comparing between visits. Finally, we will pay attention to the results of pulmonary fibrosis found on the HRCT scan.

The sample size of the study is 94. However, those participants that had a normal result in the PFR, 6MWT and HRCT at 3 months, did not need to repeat the same tests at 6 and 12 months. That is why the *n* at 6 months is smaller, and at 12 months even smaller.

Note that in the following tables there will be two p-value scores: p-value[1] refers to the comparison between 3 and 6 months, while p-value[2] refers to the comparison between 3 and 12 months.

9.1. DESCRIPTION AND COMPARISON OF RESULTS

CLINICAL CHARACTERISTICS

The study is composed of 94 participants. Of them, 25 (26.6%) were women and 69 (73.4%) men. Their mean (SD) age was 62.93 (13.23) years old, the minimal being 34 and the maximum being 93. The mean (SD) BMI was 29.81 (5.23) Kg/m^2, the minimal being 19,2 and the maximum being 47,6.

The most common comorbidity was hypertension, found in 45 (47.87%) subjects, followed by dyslipidaemia in 32 (34.04%) subjects, diabetes mellitus in 23 (24.47%) subjects, respiratory chronic diseases in 23 (24.47%) subjects and chronic cardiac diseases in 20 (21.28%) subjects. Just 4 (4.26%) participants were actual smokers, while 36 (38.3%) were former smokers.

QUALITY OF LIFE

Quality of life was measured with **Saint George's Respiratory Questionnaire**, an instrument designed to assess the impact on overall health, daily life, and perceived well-being. Scores range from 0% to 100%, with higher scores indicating more limitation.

3 MONTHS: All participants answered the SGRQ. Of those, only 3 (3.2%) patients had a *total score* of 0 in the SGQR at three months.

6 MONTHS: There were 10 participants that did not answer the questionnaire. Only 5 (5.3%) patients had a *total score* of 0 in the SGQR at six months.

12 MONTHS: There were 21 participants that did not answer the questionnaire. Only 5 (5.3%) patients had a *total score* of 0 in the SGQR at twelve months.

Table 2 shows results by month and SGRQ scales, expressed as mean (SD). As we can see, the most affected category is *activity score*, followed by *symptoms score*. However, considering that the worst situation is a score of 100, the scores shown at the table are quite low, meaning that the disease's impact is rather small.

A comparison between months was done to see if there is an actual improvement or not in the patients' quality of life. As we can see in the table below, between 3 and 12 months there is a statistically significant improvement in the *impact score* and *total score*. In fact, *total score* considerably decreases 3.9 points between 3 and 12 months.

	3 months	12 months	p-value
Symptoms score	22.3 (16.3)	19.8 (17.2)	0.220
Activity score	35.7 (27.3)	32.4 (27.0)	0.223
Impact score	15.6 (18.6)	11.1 (14.1)	**0.009**
Total score	22.8 (18.6)	18.9 (16.8)	**0.019**

Table 2. Comparison by months of quality of life assessed with SGRQ. Table results are expressed as mean (SD). Comparison between data was done using Wlcoxon Signed-rank test. Statistical significance is set at p<0.05.

Dyspnea was assessed with the *modified Medical Research Council (mMRC) Dyspnea Scale*, which classifies the degree of dyspnea into four categories according to the severity of symptoms (see *Study Variables* section). Data shows that the presence and grade of dyspnea changes between visits (see Figure 7). At 3 months, the predominance is dyspnea GRADE 0 (52.7%), followed by GRADE 1 (25.8%). While just a 2.2% of participants is classified as GRADE 3. No participants were classified as GRADE 4. At 6 months, dyspnea GRADE 0 decreases, becoming the most frequent the GRADE 1 (41.2%). Any participant referred having dyspnea GRADE 3 or GRADE 4. At 12 months, the most frequent remains being dyspnea GRADE 1 (50%), with less people at GRADE 2 (9.5%) and non at GRADE 3 or GRADE 4.

Just a difference statistically significant (p=0.007) was observed in GRADE 1 comparing between 3 and 12 months, but not between 3 and 6 months.

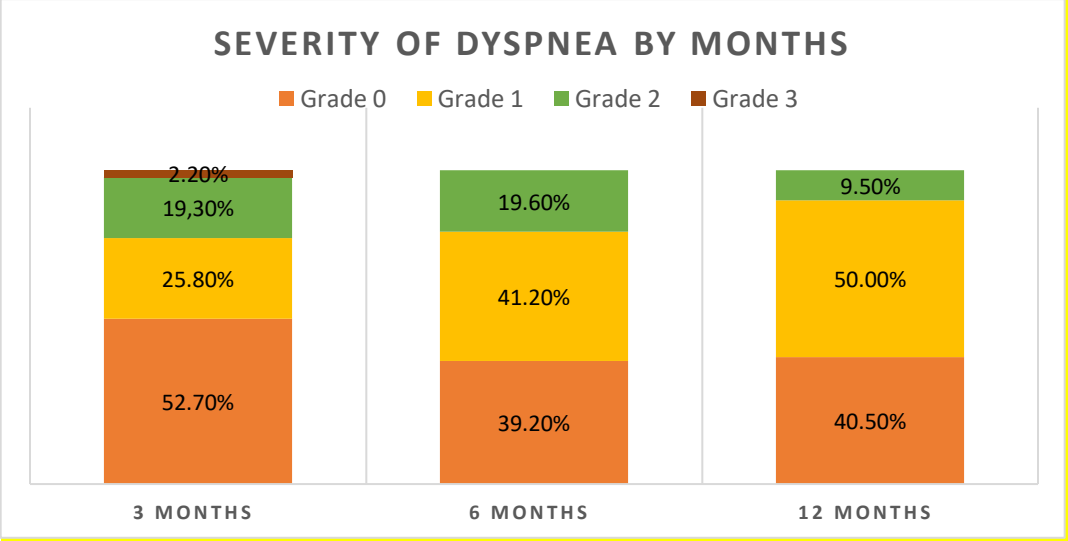

Figure 7. Comparison by month of perception of dyspnea. Results are expressed as proportions (%) of participants. Comparison between data was done using Chi-square test. Comparison of GRADE 1 between 3 and 12 months resulted statistically significant (p=0.007). Statistical significance is set at p<0.05.

If we separate participants between mild dyspnea and severe dyspnea (see Table 3), we can see that 12% of patients that at 3 months are classified as severe, at 12 months join the mild group, most probably because of a clinical status improvement.

	3 months	12 months	p-value
Mild dyspnea (Grade 0 + Grade 1)	52.7 + 25.8 = **78.5%**	40.5 + 50 = **90.5%**	**0.013**
Severe dyspnea (Grade 2 + Grade 3)	19.3 + 2.2 = **21.5%**	9.5 + 0 = **9.5%**	

Table 3. Comparison of dyspnea between 3 and 12 months, and separating by mild and severe dyspnea. Results are expressed as proportions (%) of participants. Statistical significance is set at p<0.05.

PULMONARY FUNCTION

Pulmonary function was assessed performing **pulmonary function tests**, which includes spirometry (FEV_1, FVC), diffusion capacity tests (DLCO, KCO) and pulmonary volumes with plethysmography (TLC, RV). Normal values are based on age, sex and height, thus a value will be considered abnormal if it is lower than its predicted value. Normal values range between 80 and 120% of the predicted value.

3 MONTHS: A total of 7 patients did not perform the PFT at 3 months. At this time, all parameters are inside the normal range, except for the DLCO. The DLCO mean for all the group is 75.9%, meaning that it is slightly under the normal range. Of all participants, 45 (50.6%) of them had a DLCO score lower than the predicted value (<80%).

6 MONTHS: A total of 33 patients performed the PFT at six months. The DLCO % predicted improves and rises to 81.6%, inside normal range. However, as a whole, 19 patients still had the DLCO under the normal range.

12 MONTHS: A total of 35 patients performed PFT at twelve months. The DLCO % predicted mean is 80.6%. In 22 patients the DLCO was under the normal range. These final 22 patients suppose a 23.4% from the whole group of 94 subjects.

	3 months	6 months	12 months	p-value[1]	p-value[2]
FVC	94.8 (16.6)	97.1 (17.0)	101.2 (17.3)	0.271	**0.002**
FEV_1	95.2 (21.0)	98.4 (18.9)	100.0 (20.2)	0.153	**0.026**
TLC	97.2 (17.6)	97.6 (11.7)	92.9 (15.5)	0.875	0.063
RV	100.6 (23.1)	102.6 (19.5)	87.9 (25.4)	0.593	**0.001**
DLCO	75.9 (17.0)	81.6 (18.8)	80.6 (15.7)	**0.021**	0.051
KCO	98.5 (15.5)	106.3 (16.9)	96.2 (15.7)	**0.005**	0.390

Table 4. Comparison by months of pulmonary function. Results (%) are expressed as mean (SD). Comparison was done using paired sample T-test. Statistical significance is set at p<0.05. FVC: Forced vital capacity, FEV1: forced expiratory volume during first second, TLC: total lung capacity, RV: residual volume, DLCO: diffusing capacity for carbon monoxide, KCO: carbon monoxide transfer coefficient.

All parameters show a significant improvement between 3 and 12 months, except for the diffusion capacity parameters (DLCO and KCO). However, DLCO and KCO did improve at 6 months. It is important to remark that DLCO was the only parameter to be initially under the predicted value, although not being excessively low, and rising to normal levels afterwards.

EXERCISE CAPACITY

Exercise capacity was evaluated with the **6-minute walking test** (6MWT) and assessing the basal, the mean and the minimal oxygen saturation ($SatO_2$) related to exercise, and the walked distance within those 6 minutes.

3 MONTHS: Of all participants, 4 of them did not perform the 6MWT. At this time, the mean *basal $SatO_2$* at the beginning of the test is 97.9%. Regarding the mean *minimal $SatO_2$* during the test, which is 95.4%, just 24 patients had a $SatO_2$ <95%, and only 3 patients had a $SatO_2$ ≤90%, the minimum being 88%.

6 MONTHS: Just 13 participants repeated the 6MWT. This is because logistic problems and the second COVID-19 wave made it difficult to program all 6MWT. At the beginning of the test, the mean *basal $SatO_2$* was 97.5%. During the test, the mean *minimal $SatO_2$* was 94.0%. Of those, 7 subjects had a minimal $SatO_2$ <95%, the minimum being 90%.

12 MONTHS: At this time, 36 participants performed the 6MWT. The mean *basal $SatO_2$* was 97.5%. During the test, the mean *minimal $SatO_2$* was 94.2%. Of those, 14 patients had a minimal $SatO_2$ <95%, the minimum desaturating to 86%.

Data along these 12 months shows that oxygen saturations were inside normal ranges, and that there were not many desaturations.

Comparison between months was done. As seen in the table below, at 12 months there are statistically significant differences regarding the *basal $SatO_2$* and in the *minimal $SatO_2$*. A reason why the oxygen saturation's mean at 12 months is slightly lower than at 3 months might be because, since only those patients with poor results repeated the 6MWT at the following visits, the *n* (sample size) is much smaller at 12 months than at 3 months.

	3 months	6 months	12 months	p-value[1]	p-value[2]
Basal $SatO_2$	97.9 (0.6)	97.5 (0.9)	97.5 (1.1)	0.148	**0.008**
Mean $SatO_2$	96.3 (1.7)	95.7 (1.2)	95.8 (1.7)	0.201	0.067
Minimal $SatO_2$	95.4 (2.2)	94.0 (2.0)	94.2 (2.4)	**0.039**	**0.010**
Distance	368.3	414.4	390.7	**0.002**	**0.020**

Table 5. Comparison by months of exercise function. Oxygen saturation results (%) are expressed in mean (SD; Walked distance results (meters) is expressed in mean. Comparison between data was done using T-test. Statistical significance is set at $p<0.05$. $SatO_2$: oxygen saturation.

The walked distance (Table 5), expressed as meters, shows that there was a significant improvement already at 3 months after discharge. Although the distance at 12 months is shorter than at 6 months (probably because of the *n*), both comparisons with data at 3 months show a statistically significant improvement.

RADIOLOGIC IMAGING

To answer the main objective, we performed a multiple series of **chest HRCT scans**. To those people that did not have any alterations, HRCT scan was not repeated in the following visits.

		3 months	6 months	12 months	p-value[1]	p-value[2]
Pathological CT scan	*Parenchymal pattern*	72.5%	15.1%	0.3%	**0.002**	**0.0001**
	- GGO	66.5%	19.7%	0.5%	**0.007**	**0.0001**
	- Consolidation	-	-	-	-	-
	Reticular pattern (septal)	37.0%	51.0%	24.4%	0.425	0.331
	- Fine subpleural reticular	34.6%%	50.5%	17.9%	0.393	0.170
	- Coarse linear or curvilinear opacities	14.6%	15.2%	2.8%	0.941	**0.009**
	Stablished fibrosis	18.6%	25.0%	25.8%	0.546	0.476
	- Traction bronchiectasis	6.9%	13.5%	17.8%	0.222	0.063
	- Honeycombing	-	-	-	-	-
	- Architectural distortion	19.8%	13.3%	3.2%	0.442	**0.004**

Table 6. Comparison by months of pathological HRTC scan findings. Results are expressed as proportions (%). Comparison between data was done using Chi-square test. Statistical significance is set at p<0.05. GGO: ground-glass opacities.

3 MONTHS: 67 out of 94 participants (71.3%) had a pathological CT scan at that time. We identified parenchymal pattern in 72.5% participants, reticular pattern in 37% participants, and an 18.6% of those pathological CT scans already presented stablished fibrosis.

At 3 months, GGO (parenchymal pattern) resulted to be the most common finding, present in 66.5% of participants. If we pay attention to the fibrotic findings, 6.9% participants had traction bronchiectasis, 19.8% participants had architectural distortion and non had honeycombing.

Of those pathological, 82.7% had bilateral affection and in 17.3% it was unilateral. Regarding the distribution, 94.6% participants had peripheral lesion and 5.3% had central lesion.

6 MONTHS: Of those 67 participants that at 3 months had a pathological CT scan, at 6 months 47 still presented pulmonary lesions. At that time, parenchymal pattern decreased considerably to 15.1%, in 51% participants we found reticular pattern, and stablished fibrosis increased to a 25%.

At 6 months fine subpleural reticulation (reticular pattern) was the most common finding, present in 50% of all pathological scans. Regarding the fibrotic findings, both traction bronchiectasis and architectural distortion were the predominant findings, and there was no honeycombing.

12 MONTHS: At that time, 45 of those 67 initial pathological CT scans at 3 months remained as pathological. We identified parenchymal pattern in 0.3% participants, reticular pattern in 24.4% participants and stablished fibrosis remained to 25.8% participants, with traction bronchiectasis

as the most common finding, followed by architectural distortion. There was no honeycombing either at that time.

Comparison by months was made and, first of all, we can state that there is a statistically significant decrease in the number of pathological CT scans overtime. Also significant is the decrease in the reticular pattern, the GGO, the coarse opacities and the architectural distortion.

We can see that early at 6 months, nearly all GGO got reabsorbed (from 66.5% to 19.7%), while at 12 months there was significant reabsorption but it was scarcer (from 19.7% to 0.5%). Therefore, we can conclude that most GGO reabsorption happened before 6 months, and that little GGO (0.5%) remained at the end of the follow-up.

Moreover, the proportion of stablished fibrosis between 6 and 12 months does not change much (25% vs 25.8%), which could mean that most fibrotic lesions where stablished already at 6 months after discharge.

Comparing the HRCT scans at 3 month vs 6 months, we observed that the majority of participants (72%) had radiological improvement and 28% had stabilization, with no one with radiological worsening. Whereas, comparing the HRCT scans at 6 months vs 12 months, only 30,4% of participants had radiological improvement and 69.6% had stabilization. There was not radiological worsening either.

9.2. COMPARISON BETWEEN GROUPS

Once all data was analyzed, 24 (25.5%) participants were designated as group A (with pulmonary fibrosis), and 70 (74.5%) participants as group B (with no pulmonary fibrosis). The demographic and clinical characteristics of the two groups are comparatively presented in Table 9.

After doing a logistic regression analysis and correcting for multiple comparisons, age has been the only parameter to have statistical significant (p=0.0016) association with fibrosis. Patients in

group A are older than those in group B (mean age: 67.86 vs 60.83 years). All the other features (sex, BMI, smoking history and comorbidities) did not result to be statistically significant.

		Total (n=94)	**Fibrosis** (n=24)	**No fibrosis** (n=70)	**p-value**
Sex	*Male* *Female*	69 (73.40%) 25 (26.60%)	19 (79.17%) 5 (20.83%)	50 (71.43%) 20 (28.57%)	0.6364
Age		62.93 (13.23)	69.25 (9.67)	60.76 (13.65)	**0.0016**
BMI		29.81 (5.23)	29.23 (4.59)	30.02 (5.45)	0.4960
Smoking	*Current* *Former* *Never*	4 (4.26%) 36 (38.30%) 54 (57.45%)	0 (0.00%) 11 (45.83%) 16 (54.17%)	4 (5.71%) 25 (35.71%) 41 (58.57%)	1.0000 0.5243 0.8907
Comorbidities	*HT* *DLP* *DM* *Resp. disease* *CV disease*	45 (47.87%) 32 (34.04%) 23 (24.47%) 23 (24.47%) 20 (21.28%)	10 (41.67%) 9 (37.50%) 5 (20.83%) 7 (29.17%) 7 (29.17%)	35 (50.00%) 23 (32.86%) 18 (25.71%) 16 (22.86%) 13 (18.57%)	0.6394 0.8692 0.8377 1.7298 0.4205

Table 7. Patients' characteristics related to pulmonary fibrosis. Age (years), mean (SD); BMI (Kg/m²), mean (SD). The other variables are expressed as proportions (%). Comparison between data was done using Chi-square test, Fisher's exact test, T-test or Mann-Whitney U test. Statistical significance is set at p<0.05. BMI: body mass index, HT: hypertension, DLP: dyslipidemia, DM: diabetes mellitus; CV: cardiovascular.

10. DISCUSSION

The aim of this project research has been to study the scientific community's rising concern on post COVID-19 respiratory sequelae, especially pulmonary fibrosis. Many studies have stated that developing interstitial lesion sequelae is not rare (4,6), and that it must be taken into consideration, especially because it can lead to functional alterations, including respiratory function abnormalities, impaired quality of life and exercise capacity (6,34).

In this 12-month follow-up of a prospective cohort study of patients with a history of severe COVID-19 pneumonia, we have found out the following conclusions.

Among all clinical characteristics studied in this research, only *age* has proven to have a statistically significant correlation with pulmonary fibrosis. The group with pulmonary fibrosis is older (mean: 69,25 years) than the group with no pulmonary fibrosis (mean: 60,76 years). This is consistent with what most bibliography suggest, that the elderly might have a greater risk of developing fibrotic sequelae after COVID-19 pneumonia (4).

In the objective "*To evaluate if older patients have a greater risk of developing pulmonary fibrosis than younger patients*", we did not put a limit age to separate between "old" and "young" because despite the fact that many studies suggest 60 years old as a plausible limit, we did not want to conditionate our study. This way, without having proposed a limit, we have corroborated that the group of pulmonary fibrosis tend to be people of older age compared to the non-pulmonary group, that are younger.

To assess the impact on the patients' daily life after severe COVID-19 pneumonia, we used the *Saint George's Respiratory Questionnaire* and the *mMRC dyspnea scale*.

After analysing the SGRQ data, although some patients still reported ongoing respiratory symptoms at the end of the follow-up, we conclude that there has been a significant improvement along this 12 months. More specifically, the improvement has been in the *impact*

scale (assesses the psychological and social dysfunction on daily life due to the disease) and the *total scale*, though not in the *symptom* and *activity scales*.

We also assessed the impact on daily life with the perception of dyspnea, which is also important to the perceived wellbeing. As seen at *Results* section, in most patients there is a significant improvement in the perception of dyspnea over the 12 months follow-up, meaning that although being present, the severity decreases. However, comparison at 6 months did not show any statistically significant differences. That could be explained because most patients underwent a bigger clinical improvement at 3 months than at 6 months. Therefore, this slower evolution of symptoms at that time might have created a subjective perception bias.

All in all, seeing that the SGRQ and the perception of dyspnea show a significant improvement, results suggest that quality of life improves along this 12 months.

As it was previously seen with MERS and SARS, recovered patients were at risk of suffering persistent impairment of pulmonary function (34). And since the beginning of the COVID-19 pandemic, hypothesis about the post-infection respiratory function sequelae have pointed to this same direction. In this research, comparison between 3 and 12 months has shown that at 12 months nearly all respiratory parameters have had a statistically significant improvement, except for the diffusion capacity parameters (DLCO and KCO) and the TLC. In fact, DLCO at 3 months was under the predicted value, although not extremely low, whereas all other parameters at this time were already within the normal range. This low DLCO at 3 months is consistent with what many early studies had previously pointed out, such as Y. Zhao et al. (44). Hence, results confirm that survivors of severe COVID-19 may be at risk of suffering lung function abnormalities, the most frequent abnormality being reduced DLCO (6,34). In fact, of those 45 out of 94 patients that at 3 months had impaired DLCO, at the end of the 12 months period, only 22 remained under the % predicted value. This supports the general idea of direct pulmonary injury impairing the gas exchange.

Despite this early DLCO alteration, that at 6 months resolves, we could state that the pulmonary function alteration is minimal and that it gets better overtime. It is plausible to think that the

improvement in the quality of life (both SGRQ and dyspnea) mentioned before, might be related to the improvement in the pulmonary function.

Exercise capacity, assessed with the 6MWT, is another feature that can be affected by COVID-19, as seen in many studies. After analysing all data regarding the oxygen saturation during the 6MWT, this research has not found any significant variations in the 12 month follow-up. A possible explanation might be because, since only those patients with poor results repeated the 6MWT at the following visits, the *n* (sample size) is much smaller at 12 months than at 3 months, and therefore results do not correspond to all participants.

On the other side, data shows that there has not been any significant oxygen desaturations during the test and, in general, participants show good levels of oxygen saturation. For this reason, although there is not a significant improvement within the 12 months, patients tend to have good oxygen saturation levels. This could be related to the fact that diffusion parameters (DLCO, KCO) did not result as impaired as it was thought initially, and as we have mentioned before.

Regarding the walked distance, statistics shows that there was a significant improvement already at 3 months after discharge; moreover comparison between each month's data show a statistically significant improvement also at 6 and 12 months.

Chest HRCT scan was used to evaluate the degree and type of pulmonary lesion. At 3 months, 67 participants had a pathological HRCT scan. So, as explained before, those 67 patients should undergo another HRCT scan at 6 months. However, at this time, of those 67 patients only 34 did actually perform the scan. This is because of those 67 participants, many of them had minimal lesions at 3 months, and we thought that although having a slightly interstitial lesion, the balance benefit-risk was more important than repeating de HRCT scan. The same happened between 6 and 12 months, of the 34 pathological scans at 6 months, only 27 repeated the HRCT at 12 months.

After analysing all collected data from the HRCT scans, we can say with quite confidence that most patients experienced radiological improvement at 6 months after discharge, while at 12 months it predominated the radiological stability. And, since we consider “stablished lesion” to all those parenchymal lesions that have not changed or suffered any evolution in 12 months, participants that at 12 months still had any kind of parenchymal alteration, they were most probably catalogued as “chronic lesion”.

Radiologic lesions have mostly followed a bilateral, peripheric distribution, but the predominance of radiologic findings have changed overtime. At 3 months the predominance was parenchymal pattern with ground-glass opacities (GGO), which is consistent with what many studies have also reported (23,45). While at 6 and 12 months, the situation changed, being the predominance a reticular pattern with fine subpleural reticulation. This could be explained because the lung parenchymal inflammation (seen as GGO at the CT scan) after the pneumonia might take some time to be reabsorbed. And as time passes, there is less inflammation (less GGO) while other parenchymal abnormalities remain constant.

Findings suggest that most GGO experience reabsorption and resolve without necessarily developing persistent fibrosis, especially at 6 months. However, some GGO and other interstitial alterations may persist overtime whether or not they end up developing fibrotic sequelae. This research concludes that 47.9% of all participants still present some kind of interstitial lesion at 12 months, although they are just mild lesions and as we have seen without big functional repercussion and few clinic repercussion.

Finally, among all 94 participants, 24 (25.5%) of them has suffered stablished pulmonary fibrosis. This finding seems quite consistent with what many studies declare, that approximately a third of those severe patients will develop fibrotic sequelae. This research defined pulmonary fibrosis when any of the following characteristics was present: traction bronchiectasis, honeycombing or architectural distortion. Of them, the most frequent pattern has been architectural distortion, followed by traction bronchiectasis and honeycombing.

After using multivariable analysis, to see if there is any correlation between pulmonary fibrosis and the clinical characteristics, only age has been statistically significant. This is consistent with what nearly all clinical studies say, that the elderly have higher risk of developing a more severe pneumonia and of suffering fibrotic sequalae after (3). The reason is unknown, but some hypothesis try to explain it from an immunological point of view. Most old people have a less effective immune system compared to younger people, which can involve having a greater risk of severe pneumonia. And, as mentioned before, severe pneumonia and ARDS are risk factors for lung fibrotic sequelae. Another hypothesis is related to the increased resistance of fibroblasts and myofibroblasts to apoptosis in older people (3,46).

Regarding the other clinical characteristics, we did not find any significant correlation with fibrosis. Contrarily, many reports based on studies agree on saying that some comorbidities such as diabetes mellitus, hypertension or chronic diseases, are risk factors for severe COVID-19 pneumonia.

Many years ago, long follow-up studies in patients who suffered SARS and MERS took place to know the real incidence of pulmonary fibrosis after the acute infection. Some of them found around 50% for SARS and 30% for MERS (9,10). Compared with post MERS and SARS lung sequelae, it looks like COVID-19 would have a lower incidence of induced pulmonary fibrosis. However, larger (meaning having a bigger sample size) follow-up studies are needed to compare the incidence of post COVID-19 pulmonary fibrosis with SARS and MERS, to make more clear statements.

Our hypothesis is that those parenchymal lesions that at 12 months are still present, could be catalogued as stablished lesions. However, what happens to the interstitial lesion after those 12 months is unknown. Therefore, whether these lesions remain, diminish, or completely disappear requires further observation.

To sum up, we can conclude that there has been an improvement in most of the parameters analyzed along this 12-month follow-up. In fact, data shows that many patients presented, already at 3 months after discharge, correct pulmonary function and oxygen saturation scores. Also the walking test did not present significant alterations. And, as time passed, they continued experiencing improvement, although in a slower pace. Quality of life also followed a similar evolution, with the greatest improvement happening not later after hospital discharge, rather than at 6 months. In fact, our hypothesis is that because the fastest and biggest improvement was already at 3 months, they were subjectively biased to think that at 6 months non or little improvement was happening. However, at 12 months we can see that a significant improvement occurred.

Additionally, an association with the functional and clinical manifestations can be done to the radiographic findings. Initially, the most common pattern was ground-glass opacities (GGO), which reflects the inflammation and edema of the lung's interstitial space after the severe pneumonia. As time passed, especially before the 6 month, the number of patients with GGO diminished, which is consistent with the clinical and functional improvement registered at that time. After this period, they became more apparent the lesions that did not get reabsorbed, which translates to those patients that still had persistent symptoms. Nevertheless, although the non-negligible number of pathological HRCT scans at 12 months, including the pulmonary fibrotic ones, we can conclude that the clinical repercussion is minimal and that it has improved satisfactorily overtime.

11. SUMMARY AND CONCLUSIONS

We conclude that, at 12 months, interstitial lesion is present in 47.9% of patients and, of those, 25.5% account for pulmonary fibrosis. But, despite the presence of this pathological findings, there is generally just minimal functional impairment.

In addition, along these 12 months after the severe COVID-19 pneumonia, we have observed an improvement tendency regarding quality of life, pulmonary function and exercise capacity.

Already at 3 months after discharge, the majority of subjects had all respiratory function parameters within the normal range, except for the DLCO that was below the % predicted value. However, in the following months it rose to normal levels. Quality of life, assessed with a respiratory questionnaire and the perception of dyspnea, also proved to have a statistically significant improvement. Although half of participants still presented dyspnea at 12 months, the frequency and severity did decrease compared to how it was initially. Exercise capacity showed promising results. Even though there was not a significant improvement in the oxygen saturations, values were always among normal ranges, and no important desaturations occurred. Also, the distance walked was always considered appropriate.

We detected a statistically significant association between older people and having a higher risk of developing pulmonary fibrosis, compared to younger people. Still, we did not find any other significant associations with other characteristic (sex, BMI, comorbidities, etc..).

All in all, this research project has demonstrated that abnormalities, both radiographic and functional, tend to decrease 12 months after having suffered severe COVID-19 pneumonia. Nonetheless, a significant proportion of patients will be at risk of presenting long-term consequences. Therefore, those subjects will require a proper follow-up and control, including early rehabilitation exercises and management of any persistent symptoms.

Finally, even though a 12 month follow-up is enough time to draw reliable conclusions, further observation is needed to find out what really happens to those interstitial lesions after these 12 months, whether they remain, diminish, or completely disappear.

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13. ANNEXES

ANNEX 1. Definitions

LUNG FUNCTION PARAMETERS

SPIROMETRY	
FVC (Forced vital capacity)	The total volume of air that can be exhaled during a maximal forced expiration effort.
FEV_1 (Forced expiratory volume in 1 second)	The volume of air exhaled in the first second under force after a maximal inhalation.
LUNG VOLUMES	
TLC (Total lung capacity)	The volume of air in the lungs at maximal inflation.
RV (Residual volume)	The volume of air remaining in the lungs after a maximal exhalation.
DIFFUSION	
DLCO (Diffusing capacity for carbon monoxide)	It is a measure of the conductance of gas transfer from inspired gas to the red blood cells.
KCO (Carbon monoxide transfer coefficient)	It is an index of the efficiency of alveolar transfer of carbon monoxide.

Information taken from *Manual de Neumología Clínica* (40).

RADIOLOGICAL FINDINGS

Architectural distortion	Distorted appearance of lung anatomy usually associated with pulmonary fibrosis and volume loss.
Atelectasis	Reduced volume accompanied by increased attenuation in the affected part of the lung.
Bronchiectasis	Bronchial dilatation with respect to the accompanying pulmonary artery (ring sign), lack of tapering of bronchi, and identification of bronchi within 1 cm of the pleural surface.
Bronchiolectasis	Dilated bronchioles filled with exudate and with thick walls. They are visible as a tree-in-bud pattern or as centrilobular nodules.
Consolidation	Homogeneous increase in pulmonary parenchymal attenuation that obscures the margins of vessels and airway walls.
Crazy-paving pattern	Thickened interlobular septa and intralobular lines superimposed on a background of GGO, resembling irregularly shaped paving stones.
Ground-glass opacity	Hazy increase opacity of lung, with preservation of bronchial and vascular margins. GGO is less opaque than consolidation, in which broncho-vascular margins are obscured.
Honeycombing	Clustered cystic air spaces, typically of comparable diameters on the order of 3-10 mm. it is usually subpleural and is characterized by well-defined walls.

Infiltrate	Region of pulmonary opacification caused by airspace or interstitial disease.
Parenchymal band	Linear opacity, usually 1-3mm thick and up to 5 cm long that usually extends to the visceral pleura. It reflects pleuroparenchymal fibrosis and is usually associated with distortion of the lung architecture.
Reticulation	Interlobular septal thickening, intralobular lines or cyst walls of honeycombing.
Traction bronchiectasis	Irregular bronchial and bronchiolar dilatation caused by surrounding retractile pulmonary fibrosis.

Information taken from *Fleischner Society: Glossary of Terms for Thoracic Imaging* (47).

ANNEX 2. Saint George's Respiratory Questionnaire (SGRQ)

debido a la influencia del lenguaje y cultura. Una correcta adaptación requiere un diseño amplio que tome en cuenta no sólo el aspecto lingüístico, sino todos los aspectos técnicos y conceptuales que están implícitos en las mediciones relacionadas a la salud [11]. En este sentido consideramos que aplicar el cuestionario en forma supervisada sería suficiente para su contestación. Debido a las dificultades encontradas para su aplicación en los pacientes analfabetas, son necesarios otros estudios con este tipo de población, una propuesta nuestra es adaptar el cuestionario a través de tarjetas de colores respetando la versión original para poder ser administrado específicamente a pacientes que no saben leer ni escribir.

CONCLUSIÓN

No obstante las diferencias culturales y sociales de nuestros pacientes, los resultados obtenidos mostraron que el CRSG adaptado en la población mexicana es un instrumento reproducible y por lo tanto útil para evaluar la calidad de vida en pacientes mexicanos que acuden a la Clínica de EPOC.

INSTITUTO NACIONAL DE ENFERMEDADES RESPIRATORIAS

CUESTIONARIO RESPIRATORIO DE SAINT GEORGE (CRSG)

Instrucciones:

Este cuestionario ha sido diseñado para ayudarnos a saber mucho más sobre sus problemas respiratorios y cómo le afectan a su vida. Usamos el cuestionario para saber qué aspectos de su enfermedad son los que le causan más problemas.

Por favor, lea atentamente las instrucciones y pregunte lo que no entienda. No use demasiado tiempo para decidir las respuestas.

Recuerde que necesitamos que responda a las frases solamente cuando este seguro (a) que lo (a) describen y que se deba a su estado de salud.

NOMBRE DEL PACIENTE:_____

Apellido paterno Apellido materno Nombre (s)

FECHA:_____ EXPEDIENTE No: _____

EDAD:_____ SEXO: Masculino ( ) Femenino ( )

Parte 1

A continuación, algunas preguntas para saber cuántos problemas respiratorios ha tenido durante el último año. **Por favor, marque una sola respuesta en cada pregunta.**

1. Durante el último año, he tenido tos

- ○ La mayor parte de los días de la semana
- ○ Varios días a la semana
- ○ Unos pocos días a la semana
- ○ Sólo cuando tuve infección en los pulmones o bronquios
- ○ Nada en absoluto

2. Durante el último año, he sacado flemas (sacar gargajos)

- ○ La mayor parte de los días de la semana
- ○ Varios días a la semana
- ○ Unos pocos días a la semana
- ○ Sólo cuando tuve infección en los pulmones o bronquios
- ○ Nada en absoluto

3. Durante el último año, he tenido falta de aire

- ○ La mayor parte de los días de la semana
- ○ Varios días a la semana
- ○ Unos pocos días a la semana
- ○ Sólo cuando tuve infección en los pulmones o bronquios
- ○ Nada en absoluto

4. Durante el último año, he tenido ataques de silbidos (ruidos en el pecho).

- ○ La mayor parte de los días de la semana
- ○ Varios días a la semana
- ○ Unos pocos días a la semana
- ○ Sólo cuando tuve infección en los pulmones o bronquios
- ○ Nada en absoluto

5. Durante el último año ¿cuántos ataques por problemas respiratorios tuvo que fueran graves o muy desagradables?

- ◯ Más de tres ataques
- ◯ Tres ataques
- ◯ Dos ataques
- ◯ Un ataque
- ◯ Ningún ataque

6. ¿Cuánto le duró el peor de los ataques que tuvo por problemas respiratorios? (si no tuvo ningún ataque serio vaya directamente a la pregunta No. 7)

- ◯ Una semana o más
- ◯ De tres a seis días
- ◯ Uno o dos días
- ◯ Menos de un día

7. Durante el último año ¿cuántos días a la semana fueron buenos? (con pocos problemas respiratorios)

- ◯ Ningún día fue bueno
- ◯ De tres a seis días
- ◯ Uno o dos días fueron buenos
- ◯ Casi todos los días
- ◯ Todos los días han sido buenos

8. Si tiene silbidos en el pecho (bronquios), ¿son peores por la mañana? (si no tiene silbidos en los pulmones vaya directamente a la pregunta No. 9)

- ◯ No
- ◯ Sí

Parte 2

Sección 1

9. ¿Cómo describiría usted su condición de los pulmones? **Por favor, marque una sola de las siguientes frases:**

- ◯ Es el problema más importante que tengo
- ◯ Me causa bastantes problemas
- ◯ Me causa pocos problemas
- ◯ No me causa ningún problema

10. Si ha tenido un trabajo con sueldo. **Por favor marque una sola de las siguientes frases:** (si no ha tenido un trabajo con sueldo vaya directamente a la pregunta No. 11)

- ◯ Mis problemas respiratorios me obligaron a dejar de trabajar
- ◯ Mis problemas respiratorios me dificultan mi trabajo o me obligaron a cambiar de trabajo
- ◯ Mis problemas respiratorios no afectan (o no afectaron) mi trabajo

Sección 2

11. A continuación, algunas preguntas sobre otras actividades que normalmente le pueden hacer sentir que le falta la respiración. **Por favor, marque todas las respuestas que correspondan a cómo usted está actualmente:**

	Cierto	Falso
Me falta la respiración estando sentado o incluso descansando	☐	☐
Me falta la respiración cuando me lavo o me visto	☐	☐
Me falta la respiración al caminar dentro de la casa	☐	☐
Me falta la respiración al caminar alrededor de la casa, sobre un terreno plano	☐	☐
Me falta la respiración al subir un tramo de escaleras	☐	☐
Me falta la respiración al caminar de subida	☐	☐
Me falta la respiración al hacer deportes o jugar	☐	☐

Sección 3

12. Algunas preguntas más sobre la tos y la falta de respiración. **Por favor, marque todas las respuestas que correspondan a como está usted actualmente:**

	Cierto	Falso
Me duele al toser	☐	☐
Me canso cuando toso	☐	☐
Me falta la respiración cuando hablo	☐	☐
Me falta la espiración cuando me agacho	☐	☐
La tos o la respiración interrumpen mi sueño	☐	☐
Fácilmente me agoto	☐	☐

Sección 4

13. A continuación, algunas preguntas sobre otras consecuencias que sus problemas respiratorios le pueden causar. **Por favor, marque todas las respuestas a cómo está usted en estos días:**

	Cierto	Falso
La tos o la respiración me apenan en público	☐	☐
Mis problemas respiratorios son una molestia para mi familia, mis amigos o mis vecinos	☐	☐
Me asusto o me alarmo cuando no puedo respirar	☐	☐
Siento que no puedo controlar mis problemas respiratorios	☐	☐
No espero que mis problemas respiratorios mejoren	☐	☐
Por causa de mis problemas respiratorios me he convertido en una persona insegura o inválida	☐	☐
Hacer ejercicio no es seguro para mí	☐	☐
Cualquier cosa que hago me parece que es un esfuerzo excesivo	☐	☐

Sección 5

14. A continuación, algunas preguntas sobre su medicación. (Si no está tomando ningún medicamento, vaya directamente a la pregunta No. 15)

	Cierto	Falso
Mis medicamentos no me ayudan mucho	☐	☐
Me apena usar mis medicamentos en público	☐	☐
Mis medicamentos me producen efectos desagradables	☐	☐
Mis medicamentos afectan mucho mi vida	☐	☐

Sección 6

15. Estas preguntas se refieren a cómo sus problemas respiratorios pueden afectar sus actividades. **Por favor, marque cierto sí usted cree que una o más partes de cada frase le describen si no, marque falso:**

	Cierto	Falso
Me tardo mucho tiempo para lavarme o vestirme	☐	☐
No me puedo bañar o, me tardo mucho tiempo	☐	☐
Camino más despacio que los demás o, tengo que parar a descansar	☐	☐
Tardo mucho para hacer trabajos como las tareas domésticas o, tengo que parar a descansar	☐	☐
Para subir un tramo de escaleras, tengo que ir más despacio o parar	☐	☐
Si corro o camino rápido, tengo que parar o ir más despacio	☐	☐

Mis problemas respiratorios me dificultan hacer cosas tales como, caminar de subida, cargar cosas subiendo escaleras, caminar durante un buen rato, arreglar un poco el jardín, bailar o jugar boliche.....	☐	☐
Mis problemas respiratorios me dificultan hacer cosas tales como, llevar cosas pesadas, caminar a unos 7 kilómetros por hora, trotar, nadar, jugar tenis, escarbar en el jardín o en el campo.....	☐	☐
Mis problemas respiratorios me dificultan hacer cosas tales como, un trabajo manual muy pesado, correr, ir en bicicleta, nadar rápido o practicar deportes de competencia.....	☐	☐

Sección 7

16. Nos gustaría saber ahora cómo sus problemas respiratorios afectan normalmente su vida diaria. **Por favor, marque cierto si aplica la frase a usted debido a sus problemas respiratorios:**

	Cierto	**Falso**
No puedo hacer deportes o jugar.....	☐	☐
No puedo salir a distraerme o divertirme.....	☐	☐
No puedo salir de casa para ir de compras.....	☐	☐
No puedo hacer el trabajo de la casa.....	☐	☐
No puedo alejarme mucho de la cama o la silla.....	☐	☐

A continuación, hay una lista de otras actividades que sus problemas respiratorios pueden impedirle hacer (no tiene que marcarlas, sólo son para recordarle la manera cómo sus problemas respiratorios pueden afectarle)

Ir a pasear o sacar al perro
Hacer cosas en la casa o en el jardín
Tener relaciones sexuales
Ir a la iglesia o a un lugar de distracción
Salir cuando hace mal tiempo o estar en habitaciones llenas de humo, visitar a la familia o a los amigos, o jugar con los niños

POR FAVOR, ESCRIBA AQUÍ CUALQUIER OTRA ACTIVIDAD IMPORTANTE QUE SUS PROBLEMAS RESPIRATORIOS LE IMPIDAN HACER:

A continuación ¿Podría marcar sólo una frase que usted crea que describe mejor cómo le afectan sus problemas respiratorios?

- ○
- ○ No me impiden hacer nada de lo que me gustaría hacer
- ○ Me impiden hacer una o dos cosas de las que me gustaría hacer
- ○ Me impiden hacer la mayoría de las cosas que me gustaría hacer

Me impiden hacer todo lo que me gustaría hacer

Gracias por contestar el cuestionario

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ANNEX 3. Sheet of analysed variables

QUADERN DE RECOLLIDA DE DADES:

Utilitat de l'ergometria i la fisioteràpia després d'una pneumònia greu per SARS-CoV-2.

CODI PACIENT: _____

VARIABLES DEMOGRÀFIQUES

Edat..... anys
Sexe..... V/M
Pes..... kg
Talla..... cm
IMC..... Kg/m²
Fumador..... si/no/ex

VARIABLES BASALS

HTA..... S/N
DM..... S/N
DLP..... S/N
M. resp crònica... S/N
M. cardíaca..... S/N

PARÀMETRES AVALUATS A CADA VISITA

Dispnea (MRC)..... 0/1/2/3/4
Tos..... S/N
Expectoració..... S/N
Debilitat EEII..... S/N

Rx de tòrax (normal/patològic)

Si és patològic....

- Tipus d'afectació: (vidre esmerilat/infiltrat/ fibrosi/pèrdua volum/bronquièctasi/altres)
- Localització de la patologia: (unilateral/bilateral/perifèric/central)
- Nº de lòbuls afectats: LSD/LID/LSE/LIE/LSD+LID/LSE+LIE/tots

Qüestionari de qualitat de vida (Qüestionari Saint George)

Proves de funció respiratòria

FVC..... L
FVC..... %
FEV1..... L
FEV1..... %
TLC..... %
VR..... %
DLCO..... %
KCO..... %

PIM..... %
PEM..... %
TC6M..... metres
TC6M..... metres segons valors de referència
TC6M..... Sat O_2 inicial
TC6M..... Sat O_2 mitjà
TC6M..... Sat O_2 mínim

Escala de Borg inicial (0-10)
Escala de Borg final (0-10)
Escala de fatiga EEII inicial (0-10)
Escala de fatiga EEII final (0-10)

$SatO_2$..... %
GSA..... pH
GSA..... pO_2 (mmHg)
GSA..... pCO_2 (mmHg)
GSA..... HCO_3 (mEq/L)

Analítica

Hemoglobina..... g/dl
Hematòcrit..... %
Limfòcits..... K/mcl
LDH..... U/L

Ferritina..... ng/ dL
PCR..... ng/dL
Dímer D..... ng/mL
Fibrinogen..... mg/dL

TCAR (normal/patològic)

Si és patològic....

- Tipus d'afectació: (normal/ vidre esmerilat/infiltrat/reticulació panal/pèrdua volum/atelèctasi/bronquièctasi/altres)
- Localització de la patologia: (unilateral/bilateral/ perifèric/central)
- Nº de lòbuls afectats: LSD/LID/LSE/LIE/LSD+LID/LSE+LIE/tots

ANNEX 4. Information sheet

PROTOCOL COVID-PNEUMO
V2 (02/06/20)

FULL D'INFORMACIÓ AL PACIENT

ESTUDI SEGUIMENT PNEUMO COVID-19

Projecte d'investigació: *Seguiment de pacients amb pneumònia greu per SARS-CoV2*

Servei: Pneumologia

Investigadora principal: Saioa Eizaguirre Anton

Informació general

Ens dirigim a vostè per informar sobre un estudi de recerca (a dalt esmentat) que s'està duent a terme en aquest hospital (Servei Pneumologia) i a què se li convida a participar-hi. L'estudi ja ha estat revisat i aprovat pel Comitè Ètic d'Investigació Clínica (CEIC) d'aquest hospital.

La col·laboració que li demanem és molt senzilla, però abans de fer res, ens cal el seu consentiment lliure i voluntari. Per això volem proporcionar-li la informació correcta i suficient perquè pugui valorar si vol o no participar en l'estudi. Per a això, llegiu aquest full informatiu amb atenció i nosaltres li aclarirem els dubtes que li puguin sorgir

Participació voluntària

Ha de saber que la seva participació en aquest estudi és voluntària i que pot decidir o no participar o canviar la seva decisió i retirar el consentiment en qualsevol moment, sense que per això s'alteri la relació amb el seu metge ni es produeixi cap perjudici en el seu tractament

Descripció i objectiu de l'estudi

Vostè ha estat diagnosticat de COVID19. L'objectiu d'aquest estudi és determinar el nombre de casos amb de lesions pulmonars de pacients que han patit pneumònia greu per COVID-19, el nombre de morts a mig termini i valorar la seva qualitat de vida.

Se li farà un seguiment d'un any i les visites es realitzaran cada 3 mesos. La primera visita es realitzarà via telefònica i la resta de visites de forma presencial. En aquestes visites es valorarà el seu estat general, i realitzaran analítiques de sang, qüestionaris de qualitat de vida, proves de capacitat pulmonar, un escàner i depenen dels casos, una ecografia de tòrax i una ecocardiografia.

Confidencialitat

Tota la informació recopilada sobre vostè, incloses les mostres, s'identificaran amb un número per garantir que es manté la confidencialitat de la seva identitat. La seva privacitat està regulada per la nova legislació a la UE sobre dades personals, en concret Llei Orgànica 3/2018, de 5 de desembre, de Protecció de Dades Personals i garantia dels drets digitals (LOPDGDD), publicada al BOE el 6 de desembre de 2018.
Només el seu metge té la informació que permet vincular el nombre al seu nom.
Totes les persones que intervinguin en el processament de les dades personals i que puguin identificar directament o indirectament al pacient tenen l'obligació de preservar la seva intimitat.
L'accés a la seva informació personal quedarà restringit el metge de l'estudi / col·laboradors, autoritats sanitàries, a el comitè ètic d'investigació clínica quan ho necessitin per comprovar les dades i els procediments de l'estudi, però sempre mantenint la confidencialitat dels mateixos d'acord amb la legislació vigent

Si vostè està d'acord a participar de forma voluntària en aquest estudi ha d'omplir el consentiment informat que s'adjunta a continuació.
Per qualsevol dubte o aclariment, no dubteu a plantejar-s'ho al seu metge

Investigador principal: Saioa Eizaguirre Anton
Telèfon de contacte: 972 941 343 ext.2491
Mail: pneumo.girona.ics@gencat.cat

ANNEX 5. Informed consent

CONSENTIMENT INFORMAT PACIENT

Títol de investigació: *Seguiment de pacients amb pneumònia greu per SARS-CoV2*

Jo,
(Nom i cognoms del pacient o representant legal)

- He llegit el full d'informació
- He pogut fer preguntes
- He rebut suficient informació sobre l'estudi
- La meva decisió de participar és completament voluntària. Puc canviar d'opinió i / o retirar de l'estudi en qualsevol moment, sense que es vegi perjudicada la meva assistència mèdica o els meus drets legals

He parlat amb
(Nom i cognoms de l'investigador)

Dono el meu consentiment per participar en l'estudi.

Signatura pacient	Signatura d'investigador
Nom:	Nom:
Data:	Data:

ANNEX 6. Ethics committee approval

Hospital Universitari de Girona
Doctor Josep Trueta

Avinguda de França s/n.
17007 Girona
Telèfon 972 940 200
www.gencat.net/ics/trueta

INFORME DEL COMITÈ D'ÈTICA D'INVESTIGACIÓ AMB MEDICAMENTS

El Comitè Ètic d'Investigació amb Medicaments CEIm GIRONA en la seva reunió del 27/05/2020 (Acta nº 12/2020) després de l'avaluació de l'estudi codi CEIM: **2020.099**

Seguiment de pacients amb pneumonia greu per SARS-CoV2. Codi. COVID-PNEUMO Protocol v1:19/05/2020, Full d'Informació i consentiment informat v2:02/06/2020, en català i castellà, amb la Dra. SAIOA EIZAGUIRRE ANTON com investigadora principal.

Considera que:

1. L'estudi avaluat compleix els requisits metodològics i tècnics.
2. La competència dels investigadors i els mitjans disponibles són apropiats per a dur a terme l'estudi.
3. Els riscos i molèsties previsibles de la investigació són acceptables en relació amb els beneficis esperat.
4. El procés de selecció dels subjectes participants es apropiat.
5. Es considera adequat el procediment previstos per la informació i obtenció del consentiment informat proposat per aquest estudi.
6. El CEIm GIRONA , tant en la seva composició com en els seus PNT's, compleix amb les normes de BPC (CPMP/ICH/135/95).

EMET INFORME FAVORABLE per la realització de l'estudi.

Sra. Marta Riera Juncà
Secretaria CEIM Girona
Girona, 30/06/2020

Hospital Universitari de Girona
Doctor Josep Trueta
Comitè Ètic
d'investigació Clínica
Institut Català de la Salut

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