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PULMONARY FIBROSIS AFTER SEVERE COVID-19 PNEUMONIA: PRELIMINARY RESULTS OF A 12-MONTH FOLLOW-UP STUDY

A PROSPECTIVE COHORT STUDY

RESEARCH PROJECT

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ABBREVIATIONS

6MWT: 6 minutes walking test

ACE2: angiotensin-converting enzyme 2

ARDS: Acute respiratory distress syndrome

ATS/ERS: American Thoracic Society/European Respiratory Society

BMI: Body mass index

CEIC: *Comitè d'ètica d'investigació clínica* [Clinical Research Ethics Committee]

CI: Confidence Interval

COVID-19: Coronavirus disease of 2019

CPAP: Continuous positive airway pressure

CRP: C reactive protein

CT: Computed tomography

CURB-65: Confusion, urea, respiratory rate, blood pressure – 65 years of age or older

DAD: Diffuse alveolar damage

DLCO: Diffusing capacity for carbon monoxide

DLP: Dyslipidemia

DM: Diabetes mellitus

ECM: Extracellular matrix

EGF: Epidermal growth factor

FEV_1: Forced expiratory volume during first second

FiO_2: Fraction of inspired oxygen

FVC: Forced vital capacity

GGO: Ground glass opacity

HRCT: High-resolution computed tomography

ICC-LUS: International Consensus Conference on Lung Ultrasound

ICU: Intensive care unit

ILD: Interstitial lung disease

IPF: Idiopathic pulmonary fibrosis

IQR: Interquartile range

KCO: Carbon monoxide transfer coefficient

LDH: Lactate dehydrogenase

LUS: Lung ultrasound

MERS: Middle East respiratory syndrome

MRC: Medical Research Council

PaO_2: partial pressure of arterial oxygen

PAP: Pulmonary artery pressure

PCR: Polymerase chain reaction

PE: Pulmonary embolism

PEEP: Positive end-expiratory pressure

PFT: Pulmonary function test

PH: Pulmonary hypertension

RR: Relative risk

RV: Residual volume

SARS: Severe acute respiratory syndrome

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2

SD: Standard deviation

SEPAR: *Sociedad Española de Neumología y Cirugía Torácica*

SGRQ or SG: Saint George's Respiratory Questionnaire

TAPSE: Tricuspid annular plane systolic excursion

TMPRSS2: Type 2 transmembrane serine protease

TRV: Tricuspid regurgitation velocity

TTE: Transthoracic echocardiogram

WHO: World Health Organization

ABSTRACT

BACKGROUND: After suffering from COVID-19, it is unclear whether recovered patients will have long-term health consequences. Early studies, with short follow-up time, suggest a reduction in pulmonary function, exercise capacity and quality of life in these patients. Additionally, some studies indicate that recovered patients, alike SARS and MERS, may develop pulmonary fibrosis. However, if these will be persistent over the years is uncertain.

PURPOSE: The aim of this study is to determine the long-term health consequences with a longer follow-up time and to determine the incidence, the impact, and the risk factors of pulmonary fibrosis in patients after severe COVID-19 pneumonia.

METHODS: This prospective cohort study includes 108 patients hospitalized in Girona with severe COVID-19 pneumonia diagnosis. Pulmonary function test, 6 minutes walking test, Saint George's Respiratory Questionnaire, laboratory tests, chest X-ray, HRCT, lung ultrasound and transthoracic echocardiogram were performed at 1, 3 and 6 months after hospital discharge. Medical visit and exams at 12 months after discharge are pending, therefore, we present preliminary results. HRCT findings were analysed for parenchymal abnormalities, and patients were divided into two groups, A and B (with and without pulmonary fibrosis respectively).

RESULTS: A total of 108 patients (74 men, 34 women; mean age $\pm$ SD 60,95 $\pm$ 13,70) were included. Dyspnea at 6 months after discharge was persistent in 53,9% of the patients. Impaired DLCO % predicted was found in 51,92% of the patients, being average diffusion capacity lower in patients with pulmonary fibrosis (71,25 $\pm$ 18,73) than in patients without pulmonary fibrosis (80,53 $\pm$ 15,65) (p=0,008). In 35,6% of the patients, pulmonary diffusion normalized at 6 months. Distance walked in 6 minutes improves 44,3m from 3 to 6 months (p=0,001). Saint George's total score improves from 3 to 6 months (median [IQR] 19,52% [7,50-34,51] vs 16,16% [5,50-30,31]) (p=0,022). Pulmonary fibrosis was observed in 43,4% of the patients. Patients over 60 years old have 2,04 higher risk (95%CI 1,37 – 3,04) of developing pulmonary fibrosis than patients under 60 years old. Patients with pulmonary fibrosis, had during hospital stay, a higher peak LDH (p=0,034) and a lower lymphocytes count (p=0,001) than patients without pulmonary fibrosis.

CONCLUSIONS: Hospitalized patients with severe COVID-19 pneumonia are at risk of developing long-term health consequences, including pulmonary fibrosis. Patients with evidence of fibrosis had worse pulmonary diffusion and worse exercise function, although this was not expressed in a reduction in quality of life. Patients aged 60 or more have a higher risk of pulmonary fibrosis.

KEY WORDS: COVID-19, follow-up study, pulmonary fibrosis, severe COVID-19 pneumonia

INTRODUCTION

Pandemic and COVID-19 survivors

Coronavirus disease 2019 (COVID-19) was declared on 11 March 2020 as a pandemic by the World Health Organization (WHO) (1). First cases of coronavirus occurred in December 2019 in Wuhan, as some hospitals of the area detected several cases of unexplained pneumonia related to a seafood market, and has since then spread worldwide (2). As of 22nd January 2021, there has been 96.012.792 confirmed cases and more than two million deaths around the world according to the WHO (3).

COVID-19 vaccination has already started in European Union and should be available soon for every European citizen (4). This fact would imply the beginning of the end of the pandemic. However, for patients recovered from COVID-19, this might not be the end yet, as residual abnormal lung function and fibrotic remodelling on CT have been suggested in early analysis, especially if they suffered from severe COVID-19 pneumonia (5).

Meanwhile we battle against this pandemic, how to manage COVID-19 sequalae is a challenge. COVID-19 sequelae may vary depending on the patient, from mild as fatigue and myalgia, to severe as decreased pulmonary function, significant cardiac abnormalities, etc. that leads to a worse quality of health. Some studies reported that around 3/4 patients still have persistent symptoms after COVID-19 recovery (6,7). These findings are consistent with available data from previous severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) survivors cohort studies (1).

As mentioned above, some studies already reported persistent symptoms, abnormal patterns on CT, impaired lung function and exercise capacity in COVID-19 survivors after hospital discharge. However, most of them had a small sample and a short duration of follow-up (around 3 months after discharge) (7).

To our knowledge, few studies like this provides such complete information about long-term follow-up of patients after severe COVID-19 pneumonia, up to 6 months, including data regarding respiratory symptoms, pulmonary function, exercise capacity, quality of life (SGRQ), transthoracic echocardiogram (TTE), analytical parameters, HRCT, chest X-ray and lung ultrasound (LUS). Furthermore, we assess evolution of this parameters during the follow-up and with a considerable study sample (n=108).

The present research project aims to assess long-term health consequences of severe COVID-19 pneumonia after hospital discharge. We focused primarily in respiratory consequences, as many studies revealed that the lung is the most affected organ (1). Furthermore, due to its similarity to SARS and MERS, and the likely development of pulmonary fibrosis after discharge, added to the clinical significance that this entails; patients were compared depending on the presence or not of pulmonary fibrosis on HRCT (2,8).

To sum up, the research project objectives are: to determine the incidence of pulmonary fibrosis in patients after severe COVID-19 pneumonia; to determine the predictive factors for fibrosis in these patients; to assess pulmonary function, exercise capacity and quality of life during the following 6 months after discharge; and to determine if the proposed follow-up plan for these patients is adequate.

Disease presentation

COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Clinical presentation is typically non-specific and may vary between patients, from asymptomatic forms to severe interstitial pneumonia, acute lung injury and acute respiratory distress syndrome (ARDS). Half of people who develop symptoms do so during the first 5 days after infection. Disease usually lasts for 2 weeks in mild forms, and 3 to 6 weeks in severe forms (9).

In a study of 44.672 COVID-19 patients in China, disease severity varied widely: 81% patients had mild disease, 14% had severe disease, and 5% were critical (defined by respiratory failure, septic shock, and/or multiple organ dysfunction). Although few infected patients had comorbidities, most of hospitalized patients had one or more, being hypertension (1/2 patients), diabetes (1/4) and cardiovascular disease (1/4) the most common (10,11).

According to a systematic review that included more than 24.000 patients with COVID-19, the most common symptoms were fever (78%), cough (57%) and fatigue (31%) (12). Although fever and cough does not correlate with disease severity, dyspnea has been shown to be a good predictor of disease severity. Dyspnea was observed in >15% of infected people, but in 53-80% of hospitalized patients (10,13). Headache was observed in 11-34% of hospitalized COVID-19 patients. Gastrointestinal symptoms were observed in 18% of the patients in a meta-analysis of 60 studies. A European study found that 87% of 2.000 patients had loss of smell. Association to cardiovascular, thromboembolic and neurological complication, among others was identified (12).

Around 25% of hospitalized patients required intensive care. Mortality rate is age-dependent, reaching 30% in patients over 85 years old. Respiratory failure is the main cause of mortality, in almost 70% of the COVID-19 patients. Other causes of mortality are sepsis or multi-organ failure (28%), cardiac (14,6%) and renal (3,7%) failures (10,13).

Pathogenesis

SARS-CoV-2 binding and infection

Firstly, coronavirus spike (S) protein binds to the angiotensin-converting enzyme 2 **(ACE2)** cell surface receptor, expressed in host target cells. ACE2 is expressed, among others, in kidney, heart, intestine, nasal and bronchial epithelial cells, and pneumocytes, but especially in **alveolar epithelial (pneumocyte) type II cells** (10,14). Binding and uptake process are facilitated by another host cell protein, the type 2 transmembrane serine protease (TMPRSS2), which cleaves ACE2 and activates coronavirus spike protein (Figure 1)(10). As SARS-CoV-2 binds to ACE2, this leads to a ACE2 receptors downregulation that increases angiotensin-2 production by ACE1. **Angiotensin-2** high-levels could increase pulmonary vascular permeability and cause lung injury by upregulating TGF-β and connective tissue growth factor (13,15)

During first stages of infection, coronavirus affects alveolar epithelial cells, but as viral replication accelerates, **pulmonary capillary endothelial cells** are infected as well, and epithelial-endothelial barrier integrity compromised. Consequently, inflammatory response is accentuated, and T lymphocytes, monocytes and neutrophils recruited. At the same time, these cells release pro-inflammatory cytokines (IFN-α, IL-6, TGF-β, etc.) and chemokines, called “cytokines storm”. The result of this disproportionate cytokine release is an activated neutrophils infiltration into the alveolar space that leads to a fibroproliferative phase. Lymphopenia, a common COVID-19 feature, may occur as a consequence of infiltration of lymphocytes after alveolar epithelial cells injury (16).

In the late stage, if inflammatory response continues, a diffuse thickening of the alveolar interstitial may produce, increasing pulmonary vascular permeability and causing pulmonary edema filling alveolar airspaces. If severe, this can be expressed clinically as **acute respiratory distress syndrome (ARDS).** Parallel to this process, in severe COVID-19, thrombotic complications may occurred due to microthrombi formation as a consequence of inflamed lung tissues and pulmonary endothelial cells (10,17).

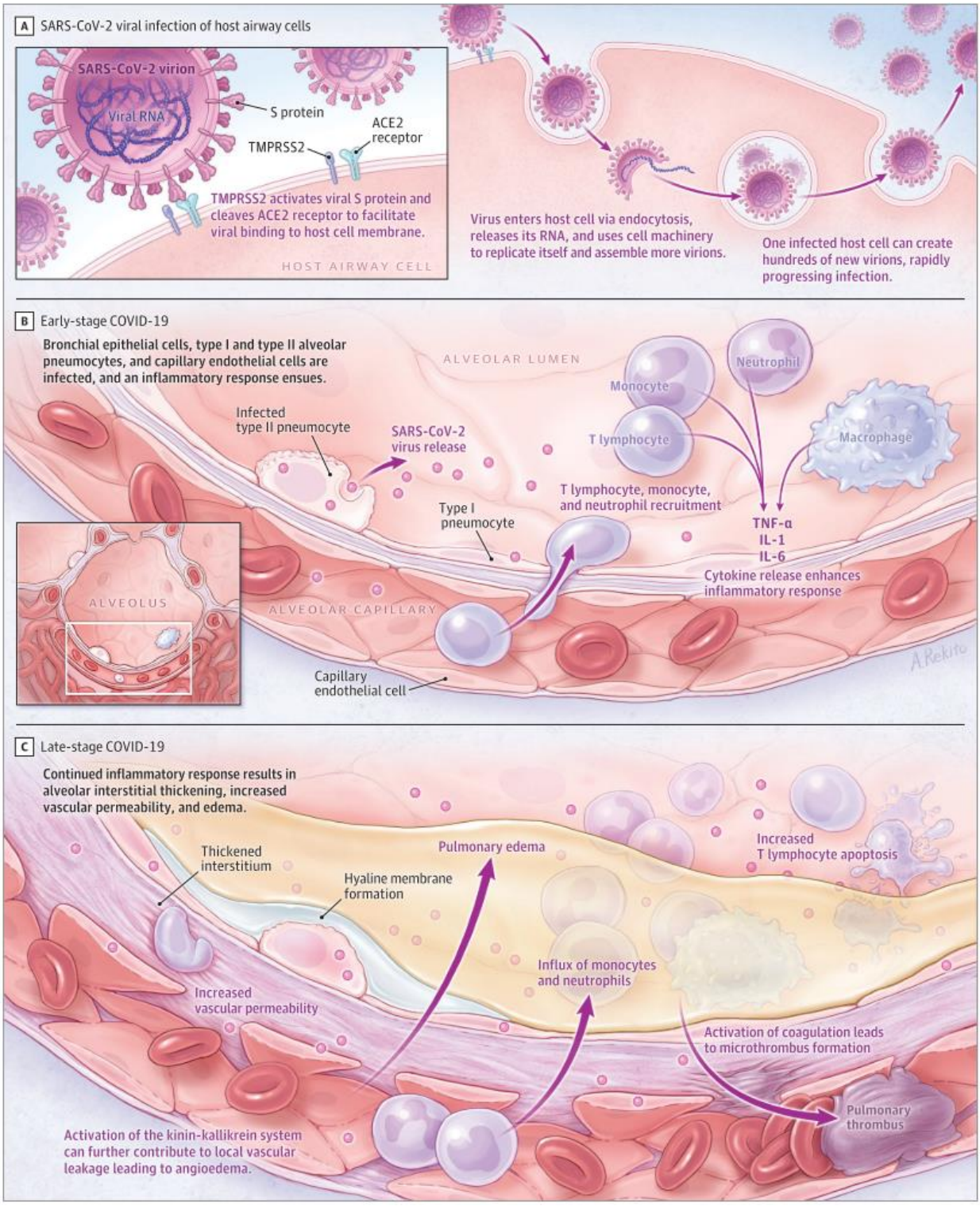

Figure 1 Immunopathogenesis of Coronavirus disease 2019 (COVID-19)(10)

Acute respiratory distress syndrome (ARDS)

It has been reported that 40% of patients with COVID-19 develop ARDS, and 20% of ARDS cases are severe (18). ARDS is a syndrome distinguished by non-cardiological pulmonary edema due to **pulmonary vascular permeability alteration** that produces severe respiratory distress, diffuse bilateral pulmonary infiltrates, and decreased of pulmonary distensibility. For its diagnosis, a PaO_2/FiO_2 <300mmHg with a minimum of 5 cmH_2O PEEP (or CPAP) is required. ARDS has a high mortality (Table 1) (19,20).

Table 1 Mortality rate depending on ARDS severity, according to (19).

ARDS Severity	*PaO_2/FiO_2 (mmHg)**	*Mortality (%)*
Mild	200-300	27%
Moderate	100-200	32%
Severe	<100	45%

*FiO_2= fraction of inspired oxygen; PaO_2= partial pressure of arterial oxygen; *= with a minimum of 5 cmH_2O PEEP (positive end expiratory pressure) or CPAP (continuous positive airway pressure)*

The main pathogenic event is an alteration of pulmonary microcirculation, producing a local vascular leakage, edema development and triggering complement and coagulation activation, as well as inflammatory cells recruitment. As vascular barrier is disrupted, this contributes to hemoconcentration, **pulmonary hypertension** and a ventilation/perfusion ratio alteration. These abnormalities lead to alveolar collapse, a reduction in lung volumes, a decreased of pulmonary distensibility, increased work of breathing and respiratory distress due to a shunt mechanism. At long-term, ARDS survivors present a TLC (1/3 patients) and DLCO reduction (1/2 patients) that may last for years (20).

The pathological feature of ARDS is **diffuse alveolar damage (DAD)** (6). DAD consists in edema, interstitial inflammation, hyaline membrane formation and interstitial fibrosis. The first phase (acute or exudative) takes place during the first week and its features are edema, exudation and hyaline membrane formation. The second phase (proliferative or organization) happens after one week, and it is characterized by hyperplasia of the alveolar epithelium and fibrosis. The last phase (residual) starts after two weeks, and it is distinguished for interstitial fibrosis and vascular abnormalities (20).

Treatment of ARDS consists in therapeutic measures of the primary disease. As COVID-19 has currently, no effective treatment, ARDS cannot be reversed. Treatment of respiratory distress with oxygen supplementation, CPAP or PEEP is done instead (10,13,20).

Pulmonary fibrosis

It is still unclear why some COVID-19 survivors recover from ARDS, whereas others develop progressive pulmonary fibrosis because of fibroblasts and myofibroblasts accumulation and extreme collagen production (6). ARDS appears to be the primary predictor factor for pulmonary fibrosis development in COVID-19. However, the ARDS associated to COVID-19 is different (high and low elastance type) compared to the traditional ARDS. Therefore, pathogenesis of pulmonary fibrosis in COVID-19 is different than pathogenesis of pulmonary fibrosis in IPF and other fibrotic lung diseases, mainly for being alveolar epithelial cells the basis for fibrotic remodelling, and not the endothelial cells (6).

After any lung injury, an inflammatory response occurs as an attempt to restore pulmonary architecture. Alveolar macrophages are key in the repair process by phagocytizing alveolar debris and producing cytokines and growth factors. After alveolar injury, **fibroblasts** migrate and invade alveoli, and transform into **myofibroblasts**. Fibroblasts migration and differentiation into myofibroblasts is influenced by **EGF, PDGF and TGF-β**. Fibroblasts synthesize **collagen** and **fibronectin**, creating an **organized fibroblastic extracellular matrix (ECM)** (21). Next, bronchiolar stem cells proliferate to remove damaged alveolar epithelium. This last step is stimulated by epidermal growth factor (EGF) and TGF-α. During these process, a deficit of surfactant (produced by alveolar epithelial cells) occurs, and therefore a reduction of lung distensibility (21).

Several studies have demonstrated **angiotensin-2** to be a potent inducer of DNA synthesis and fibroblast proliferation (it stimulates TGF-β). Furthermore, it has been proven that angiotensin-2 induces fibroblasts to produce collagen and ECM, and therefore, having pro-fibrotic effects. As SARS-CoV-2 binds ACE receptors, angiotensin-2 levels are increased. The imbalance of renin-angiotensin-system in older patients might contribute to SARS-CoV-2 infection, its lung injury and its pulmonary fibrosis development (22).

If the lung injury is associated to intact basement membranes, organized fibroblastic ECM is degraded or remodelled into normal interstitial. If lung injury is severe or persistent otherwise, with basement membranes damaged, fibroblasts continue producing collagen, resulting into a fixed or even progressive fibroblastic interstitial, and forming a scar tissue. This excessive production of ECM is manifested in CT scan as interlobular septal thickening and reticular pattern, associated to traction bronchiectasis (21).

Currently, there is not enough proof that any of the available options can be useful for the treatment of pulmonary fibrosis associated to COVID-19. Whether use of antiviral drugs decrease the risk of fibrosis evolution is still uncertain. In the case of antifibrotic drugs, pirfenidone and nintedanib, they reduce inflammation, so they could be administrated even during the acute phase of COVID-19 associated pneumonia (6). Lastly, although risk-benefit ratio needs to be evaluated, prolonged low-dose of corticoids may prevent fibrotic remodelling in COVID-19 survivors. Since angiotensin-2 might have an important role in fibrosis development, the use of angiotensin-converting-enzyme inhibitors or angiotensin-receptor blockers have been proposed as well (6,15).

As mechanism of pulmonary fibrosis in COVID-19 is different than usual and neither no current treatment options are available (6,23), the present research project emphasizes in pulmonary fibrosis development in COVID-19 survivors with the aim of determining its incidence, its long-term health consequences, and its predictive factors. Therefore, we can show pulmonary fibrosis clinical relevance, and in case risk factors are identified, the present research project may contribute in the future to an earlier diagnosis and prevention of pulmonary fibrosis after COVID-19.

Follow-up of patients after severe COVID-19 pneumonia

Follow-up strategy

By the time the study protocol was being developed, there was not enough evidence about the best follow-up plan for patients with severe COVID-19 pneumonia after discharge. The follow-up plan performed in the present study was based on the 23rd April 2020 recommendations of the main Spanish pneumologist organization, *Sociedad Española de Neumología y Cirugía Torácica (SEPAR)* [Spanish Society of Pneumology and Thoracic Surgery] (24,25). The follow-up algorithm of the present study may be seen in "DATA COLLECTION". By following-up these patients, we aim to identify short and long-term respiratory consequences of COVID-19 and therefore to reduce its effects in the affected patients; and we aim to identify the most life-limiting complications of severe COVID-19 pneumonia like pulmonary fibrosis, without performing an over-examination of the rest of the patients.

A study published on 24th August 2020 (26), suggested a follow-up strategy for severe COVID-19 patients after discharge (Figure 2). This follow-up strategy is very similar to ours and was lately adopted by the British Thoracic Society and the British Society of Thoracic Imaging.

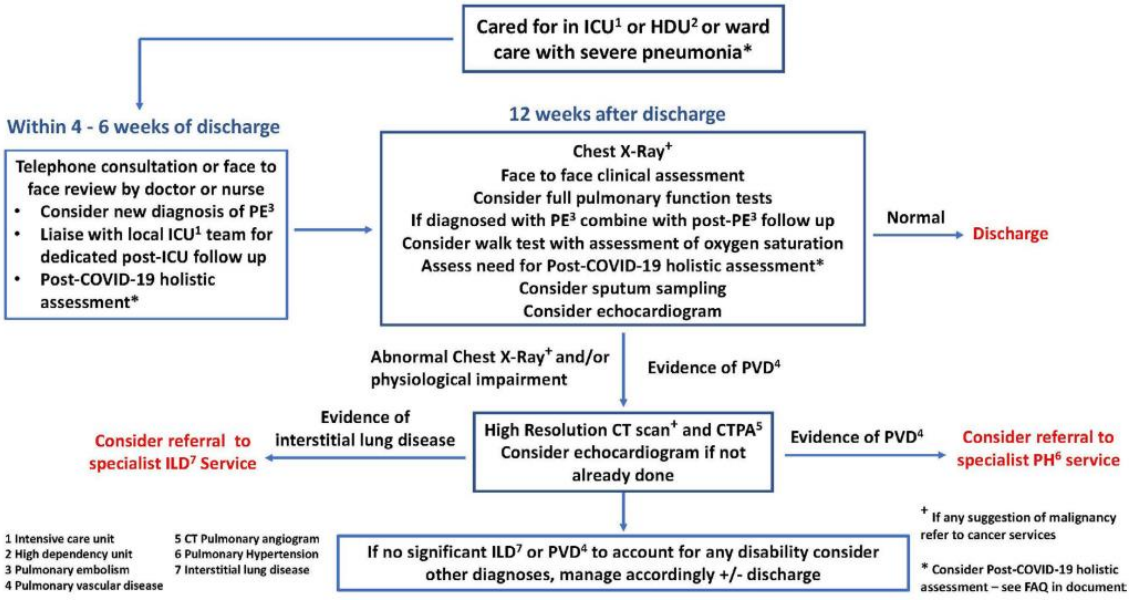

Figure 2 Respiratory follow-up algorithm of patients with severe COVID-19 pneumonia after discharge. This follow-up strategy, although being similar to ours, was performed instead by George et al. (26)

Chest CT findings

Typical CT feature during acute infection by SARS-CoV-2 is the presence of ground glass opacities (GGO), usually bilateral, predominantly in lower lobes, and with subpleural distribution (12). Ground glass opacities on chest CT represents interstitial inflammatory and edema in the lungs (10). In the dissipative phase, GGO usually absorbs, and in some cases, the lesions develop into fibrosis. As a review book, which is updated weekly (12), describes: "studies with longer follow-up are needed to evaluate long-term or permanent lung damage including fibrosis, as it seen with SARS and MERS. Pulmonary fibrosis is expected to be the main factor leading to pulmonary dysfunction and decline of quality of life in COVID-19 survivors after recovery".

Previous studies have observed CT features suggestive of fibrosis during the follow-up of SARS and MERS survivors. The incidence for such fibrotic remodelling was between 55-62% for SARS recovered patients (27), and 33% for MERS (21,28). SARS-CoV-2 belongs to Coronaviridae family, similar to SARS-CoV and MERS-CoV. SARS-CoV-2 and SARS-CoV share almost 80% of genetic code, whilst SARS-CoV-2 and MERS have 50% of identical sequence (21). Therefore, it is logical to expect related long-term consequences for COVID-19 survivors.

GGO was almost completely absorbed 5 months after discharge (7). A recent study observed that in patients after suffering from COVID-19 and who required hospitalization, the incidence of residual fibrosis in the HRCT one month after discharge was 39% (2). In another study that included 55 hospitalised patients, predominantly (51/55) with mild illness or non-severe pneumonia, interstitial thickening, considered as evidence of fibrosis, was observed in 27% of the patients (29). In a Chinese investigation including 81 patients after severe COVID-19 pneumonia, it was found that 52% of them developed fibrosis (5). However, an Italian study stated that hospitalized patients with mild forms (with normal ratio of the PaO2/FiO2 or mild hypoxemia) or moderate forms (with acute lung injury picture) were not at risk of developing pulmonary fibrosis. Nevertheless, they excluded patients with severe forms (with ARDS) (9).

Pulmonary function, exercise capacity and quality of life

After the SARS and MERS outbreak, there was a concern about whether recovered patients would have residual sequalae. Several studies found a persistent impairment of pulmonary function (PFT) and exercise capacity (6MWT) in SARS and MERS survivors, lasting months or even years after disease. DLCO impairment was observed one year later in 15,5-43,6% and 37% of recovered SARS and MERS patients, respectively (1,11). Pulmonary dysfunction improves gradually over months-years in recovered SARS patients (21).

By the time the present study was being developed, there were not much information about long-term consequences of COVID-19 in patients discharged from hospital, all studies published only collected data until 3 months or less. However, a recent study published on 8th January 2021 including data of 1733 patients 6 months after discharge showed that a considerable proportion of the patients had a DLCO lower than 80% predicted 6 months after discharge, varying from 22-56% depending on the severity of the disease. Average distanced walked in 6 minutes [IQR] was 495m [440-538] (7).

Chinese researchers found similar results in DLCO % predicted one month after discharge: 47,2% of patients had a pulmonary diffusion abnormality, with an average DLCO % predicted (SD) of 78,18 (14,29) (1). Another European study, that included 33 patients 6 weeks after suffering severe COVID-19, showed that median [IQR] of DLCO % predicted was 65% [53-73], and a distance walked in 6 minutes of 380m [180-470]. Saint George's Respiratory Questionnaire data was recorded as well: physical activity (activity score median= 54% [19-78]) was the main reduced score. Symptoms score was 34% [9-57], impacts score was 12% [2-33] and total score was 26% [7-42] (11).

A worsening in quality of life has been observed in 44,1% of recovered COVID-19 patients. Several studies indicated that 70-80% of patients that suffered from COVID-19, have at least one or more persistent symptoms after disease (6)

Pulmonary fibrosis risk factors

Currently, there is no approved treatment for COVID-19 and neither to reduce ARDS and pulmonary fibrosis development associated to COVID-19 (6). However, the newly literature suggests that in order to stop pulmonary fibrosis development, any potential antifibrotic therapy should be performed during the first week of ARDS (6). Therefore, the identification of predictive factors early in the disease becomes essential, as this would allow clinicians to identify those patients at risk.

Although there are not reliable biomarkers for ARDS development at this moment, some analytical parameters have been found to correlate with mortality and severity outcome (6). A retrospective study with 485 patients performed in Wuhan (16) found LDH, CRP and lymphocytes values to predict COVID-19 mortality. **LDH** high levels reflects tissue destruction and is regarded as a common sign of tissue damage. In patients with severe ILD, there is an important increase of LDH, being one of the most important biomarkers of lung injury. Therefore, LDH correlates with disease severity.

On the other hand, **CRP** increased levels reflets persistent inflammatory response, and is an important prognostic factor for ARDS. Finally, **lymphopenia** might be due to infiltration of lymphocytes after alveolar epithelial cells injury, and also could be associated to a higher disease severity and mortality (16).

In the present research project, the association of pulmonary fibrosis development and LDH, CRP, lymphopenia, as well as ferritin, has been analysed. Seric **ferritin** is a known acute inflammatory marker, especially in critical illness (like sepsis and systemic inflammatory response syndrome) in which correlates with disease severity. Furthermore, it has been proposed that ferritin has a key role in the development of chronic inflammation and fibrosis in some organs, such as lungs (6). Significantly higher ferritin is common in severe COVID-19 and suggests worse prognosis. It has been suggested COVID-19 to be part of the hyperferritinemic syndrome (17).

Some studies underline that **duration of disease** plays an important role for pulmonary fibrosis development after ARDS. A cohort study of 159 autopsies from patients that had ARDS, showed that 4% of patients with a disease duration <1 week, 24% of patients with a disease duration of 1-3 weeks, and 61% of patients with a disease duration of >3 weeks had fibrotic remodelling (6).

Another risk factor for this fibrotic evolution is **advanced age,** similarly to MERS and SARS-CoV, especially if age over 60 years old. The exact reason is unknown; however, older people are more susceptible to SARS-CoV-2 infection and are more prone to suffer severe forms of the disease. Apoptosis resistance of fibroblast and myofibroblast might be a reason (6,21).

The presence of **comorbidities** such as hypertension, diabetes and coronary artery disease, as well as clinical history of smoking increase disease severity (6,21).

JUSTIFICATION

As many people worldwide get infected by SARS-CoV-2, the current concern among clinicians is to determine whether recovered COVID-19 patients will have long-term health consequences. Early literature reported that a significant proportion of patients have persistent symptoms, and that some of them develop pulmonary fibrosis after COVID-19 recovery (2,6,7). Nevertheless, "studies with longer follow-up are needed to evaluate long-term or permanent lung damage including fibrosis, as it seen with SARS and MERS. Pulmonary fibrosis is expected to be the main factor leading to pulmonary dysfunction and decline of quality of life in COVID-19 survivors after recovery" (12). However, pulmonary fibrosis impact in patients recovered from COVID-19 has not been yet recorded. In this way, one of the study objectives is to observe if pulmonary fibrosis leads to a worse pulmonary function, a reduced exercise capacity and a declined quality of life.

Currently, there is no treatment that has proven to be effective for pulmonary fibrosis associated to COVID-19 (6). New literature suggests that, in case any potential antifibrotic therapy shows to be effective, this should be performed during the first week of ARDS, before pulmonary fibrosis development (6). ARDS seems to be the primary predictor factor for pulmonary fibrosis in patients recovered from COVID-19, nevertheless, it remains unclear why some of them recover from ARDS, whereas others develop pulmonary fibrosis (6). Therefore, we assume that the identification of the predictive factors for pulmonary fibrosis development is essential, as this would allow clinicians to recognize those patients at risk.

By following-up these patients, we aim to identify long-term health consequences of COVID-19. Further, we also aim to assess the development of pulmonary fibrosis and to determine its clinical impact and its predictive factors. Although several studies have suggested residual sequelae few months after discharge, it is uncertain whether this will persist over the years. Thus, we here present a more complete and longer follow-up of patients after severe COVID-19 pneumonia.

HYPOTHESIS

- Pulmonary function, exercise capacity and quality of life improves from 3 to 6 months in patients after severe COVID-19 pneumonia
- Patients with pulmonary fibrosis have worse pulmonary function, worse exercise capacity and poorer quality of life compared to those without pulmonary fibrosis
- Patients over 60 years old have a higher risk of developing pulmonary fibrosis after severe COVID-19 pneumonia than patients under 60 years old
- Patients with pulmonary fibrosis have higher body mass index as well as higher LDH, CRP and ferritin values, and lower lymphocytes values than patients without pulmonary fibrosis

OBJECTIVES

Main objective

1) To determine the incidence of pulmonary fibrosis in patients after severe COVID-19 pneumonia.

Secondary objectives

2) To assess the evolution of pulmonary function, exercise capacity and quality of life in patients after severe COVID-19 pneumonia and compare the results between patients with and without pulmonary fibrosis
3) To determine if patients over 60 years old have a higher risk of developing pulmonary fibrosis after severe COVID-19 pneumonia than patients under 60 years old
4) To assess if obesity as well as analytical parameters such as LDH, CRP, ferritin and lymphocytes values are predictive factors for pulmonary fibrosis in patients after severe COVID-19 pneumonia
5) To assess if the diagnostic tests performed in this study are clinically significant for the follow-up of patients after severe COVID-19 pneumonia

METHODOLOGY

Study design

This is originally a single-group, prospective, observational cohort study. The cohort is further divided into two groups: group A (with signs of pulmonary fibrosis) and group B (without signs of pulmonary fibrosis) based on their HRCT findings at 3 months.

As it will be explained in "DATA COLLECTION AND PROCEDURES" section, the original study includes four medical visits: at 1, 3, 6 and 12 months after hospital discharge. HOWEVER, THE PRESENT RESEARCH PROJECT ONLY INCLUDES DATA UNTIL 6 MONTHS. THEREFORE, RESULTS ARE PRELIMINARY, not completed, as the original study is still taking place and medical visit at 12 months is pending.

Setting

The present study is unicenter, being developed in Hospital Universitari de Girona Doctor Josep Trueta by Pneumology Services (more information about the research team in the section "WORKING PLAN AND RESEARCH TEAM").

Study population

Patients discharged from Pneumology Service of the Hospital Universitari de Girona Doctor Josep Trueta between March and June 2020 diagnosed of severe Covid-19 pneumonia. Severe pneumonia was defined as a CURB-65 score of 3 or more, according to the British Thoracic Society (30).

Subjects selection

Inclusion criteria

- Patients over 18 years old
- Patients discharged from Pneumology Service diagnosed of Covid-19 by positive PCR and with severe pneumonia
- Patients willing to sign the written informed consent and able to understand it

Exclusion criteria

- Patients that do not want to be included in the study
- In case of pregnant women, they could be included in the study, but no radiological image would be performed during pregnancy

Sample size

A minimum of 97 patients will be included to estimate incidence of pulmonary fibrosis due to severe COVID-19 pneumonia with a 95% confidence interval and a $\pm$10% precision. Finally, 108 patients were included in the study.

Sampling

No sampling was needed. All the patients who met inclusion criteria, but no exclusion criteria were included in the study.

Measure instruments

HRCT: scanning took place with patient in supine position. All CT images were reviewed by a radiologist with clinical experience in chest imaging. In addition, images were transmitted to the post-processing workstation and reconstructed using high-resolution and conventional algorithm. After the images were reviewed, the investigation team recorded radiologist report's most significant features into the database.

Pulmonary function tests: FVC and FEV_1 were measured by spirometry 15 minutes before and after of 400µg salbutamol inhalation. TLC and RV were measured by body plethysmography. Finally, DLCO and KCO were measured by pulmonary diffusion capacity tests. The haemoglobin value was also taken for correcting the DLCO. These tests were performed with patient seated and following the American Thoracic Society/European Respiratory Society guidelines for such tests (31–33). PFTs results are dependent upon age, sex, and weight; therefore, PFTs results are expressed as "% reference of predicted value", in which predicted value is calculated by mathematical equations following ATS/ERS mentioned guidelines.

Lung ultrasound: this test was performed by an expert pneumologist in lung ultrasound, blinded to patient's clinical history. It was performed with patient in supine position for anterior chest wall examination, and in lateral decubitus position for lateral and posterior chest wall examination. Chest is divided in twelve zones: 6 for each hemithorax. Furthermore, each hemithorax is usually divided into anterior, lateral and posterior areas (Image 1). In conclusion, LUS was performed following the International Consensus Conference on Lung Ultrasound (ICC-LUS) recommendations (34–36).

Variables related to lung ultrasound were assessed for both hemithorax (right and left): if any zone of a hemithorax was positive for the variable, that hemithorax was reported as positive for such variable.

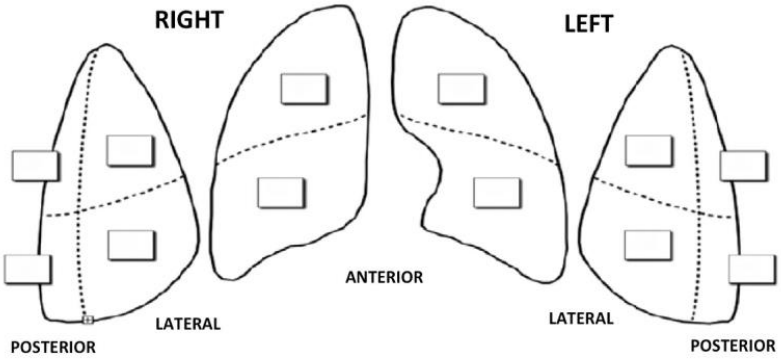

Image 1 Twelve zones' model for lung ultrasound (37)

STUDY VARIABLES

Dependent variables

Study dependent variables were divided in: one primary outcome, and several secondary outcomes.

Primary outcome

One-hundred and six patients with severe COVID-19 pneumonia performed a follow-up chest HRCT at three months after hospital discharge. First of all, the results of CT were analysed for parenchymal abnormality and evidence of fibrosis, being pulmonary fibrosis our primary outcome.

Pulmonary fibrosis: the primary outcome of the study is the presence or not of pulmonary fibrosis, defined as the presence in chest HRCT at 3 months of any of the following signs: reticulation, architectural distortion and/or traction bronchiectasis with or without honeycombing (2,5,8,38) This is a nominal dichotomous variable (there is pulmonary fibrosis/ there is not). Patients will be analysed based on the evidence of pulmonary fibrosis and divided into two groups: group A (with pulmonary fibrosis) and group B (without pulmonary fibrosis) (Table 2). Study variables will be compared between both groups in order to answer our objectives.

Previous studies have showed many interstitial HRCT abnormalities besides pulmonary fibrosis in COVID-19 patients (10,12). However, interstitial lung diseases (ILDs) have important prognosis and survival differences among them, as some forms of ILDS associated with GGO are potentially treatable; meanwhile, ILD associated with fibrosis is not reversible and persists during time (6,15).

Table 2 This table shows how HRCT findings were reported and its classification.

HRCT findings	**Classification group**
GGO + architectural distortion and/or traction bronchiectasis	Group A
Honeycombing	
Loss of volume + distortion and/or traction bronchiectasis	
Loss of volume + GGO + architectural distortion and/or traction bronchiectasis	
Reticulation	
GGO	Group B
Atelectasis	Group B
Bronchiectasis	
Loss of volume	
Other	
Normal (no significant findings)	Group B

GGO = ground glass opacity

It is important to note that pulmonary fibrosis variable was defined by HRCT at 3 months. The research team worked based on the premise that there would not be any changes in HRCT at 6 months. If any changes exist, this is considered in “RESULTS” section.

Secondary outcomes

In the present study we are managing different types of variables to answer the described objectives. With the aim of helping the reader, dependent variables have been divided into seven blocks:

BLOCK 1: Variables related to chest HRCT: some findings in HRCT, although were not defining for pulmonary fibrosis, were informed as pathological and have been also associated to COVID-19, including interstitial features (2,39). These findings may have clinical and functional repercussion as well. These are nominal qualitative variables:

- *HRCT pattern (architectural distortion/atelectasis/ bronchiectasis/ GGO/ honeycombing/ loss of volume/ normal/ other/ reticulation/ traction bronchiectasis)*. Definitions of chest HRCT patterns can be found in "ANNEXES" section (Annex 1)
- *Localization (unilateral; bilateral)*
- *Distribution (peripheric; central).*
- *Lobes affected (all; lower lobes; upper lobes; right upper lobe; middle lobe; right lower lobe; left upper lobe; left lower lobe; lingula; left hemithorax; right hemithorax)*

BLOCK 2: Variables related to quality of life: with the aim of assessing quality of life in patients after severe Covid-19 pneumonia every patient answered the Saint George's Respiratory Questionnaire (SGRQ) (Annex 2). Also, Barthel was evaluated. These are continuous quantitative variables, measured as a score from 0 to 100% (worse).

- *Saint George symptoms*
- *Saint George activity*
- *Saint George impact*
- *Saint George total*
- *Barthel*

It is important to note that SGRQ has been validated for chronic obstructive pulmonary disease and asthma, among others, but it is still unknown if it is a useful tool for patients recovered from COVID-19 as well (40). This will be mentioned in "DISCUSSION" section.

BLOCK 3: Variables related to pulmonary function. Pulmonary function has been assessed performing Pulmonary Function Test (PFT)**:** PFTs are a useful tool to assess pulmonary function in clinical practice. Survivors of SARS and MERS have pulmonary function impairments after discharge, even years later (1,11). Recent studies of COVID-19 show similar abnormalities (1,7). A decline of 2-6% of FVC over 6 months or a reduction greater than 15% in DLCO, are mortality predictors in IPF (41). The following parameters are being analysed (Table 3). These are continuous quantitative variables:

- *FVC (litres).*
- *FVC (% predicted)*
- FEV_1 *(litres)*
- FEV_1 *(% predicted)*
- *TLC (% predicted)*
- *RV (% predicted)*
- *DLCO (% predicted)*
- *KCO (% predicted)*

Table 3 Summary of Pulmonary Function Test acronyms

FVC = forced vital capacity
FEV_1= forced expiratory volume during first second
TLC = total lung capacity
RV = residual volume
DLCO = diffusing capacity for carbon monoxide
KCO = carbon monoxide transfer coefficient

BLOCK 4: Variables related to exercise function. Exercise function has been assessed performing the 6 minutes walking test (6MWT). The 6MWT is a practical and simple test that provides a global measure of functional capacity (42). Although it does not distinguish between cardiovascular, pulmonary, and neuromuscular factors it provides an assessment of overall functional ability and it is also a useful tool for prognosis and predictive of survival, especially for idiopathic pulmonary fibrosis (IPF).

Generally, healthy people walk 400m or more, depending on age, height, and gender. A distance lower than 350m predicts higher mortality in most of chronic respiratory diseases. An improvement of >24-45m in walking distanced is considered clinically significant for ILD (43). A decline of 50m or more walking distance over 2 years predicts mortality in IPF patients. A drop in oxygen saturation during test is a prognostic factor for interstitial lung disease (41,42,44). These are discrete quantitative variables:

- *Distanced walk (meters)* at the end of test performance
- *Mean oxygen saturation (%)* during test performance
- *Minimal oxygen saturation (%)* during test performance
- *Basal oxygen saturation (%)* before test performance

BLOCK 5: Variables related to pulmonary vascular disease. Most of the patients with ARDS develop pulmonary hypertension (PH), according to (20), and also secondary PH is an important comorbidity in IPF (41). Therefore, the investigation team considered appropriate to perform a transthoracic echocardiogram (TTE) in patients after severe COVID-19 pneumonia. Further, pulmonary embolism in patients suffering from COVID-19 was described (10,26). So those patients that already had a pulmonary embolism related to COVID-19 or who had high levels of D-dimer (>2.500) had a CT pulmonary angiography performed.

- ***Pulmonary hypertension*** *(PH) (yes/no).* It is a nominal dichotomous variable. PH gold standard diagnosis is made by right heart catherization; however, this test is highly invasive, so a TTE was performed instead. PH was diagnosed by a professional cardiology following the European Society of Cardiology guideline, that suggests PH diagnosis based on probability grades (45) (Tables 4 and 5).

Table 4 Echocardiographic probability of pulmonary hypertension (11).

Peak tricuspid regurgitation velocity (m/s)	Presence of other echo 'PH signs'[a]	Echocardiographic probability of pulmonary hypertension
≤2.8 or not measurable	No	Low
≤2.8 or not measurable	Yes	Intermediate
2.9–3.4	No	
2.9–3.4	Yes	High
>3.4	Not required	

PH = pulmonary hypertension

Table 5 Echocardiographic signs suggesting pulmonary hypertension used to assess the probability of pulmonary hypertension in addition to tricuspid regurgitation velocity measurement (49)

A: The ventricles[a]	B: Pulmonary artery[a]	C: Inferior vena cava and right atrium[a]
Right ventricle/ left ventricle basal diameter ratio >1.0	Right ventricular outflow Doppler acceleration time <105 msec and/or midsystolic notching	Inferior cava diameter >21 mm with decreased inspiratory collapse (<50 % with a sniff or <20 % with quiet inspiration)
Flattening of the interventricular septum (left ventricular eccentricity index >1.1 in systole and/or diastole)	Early diastolic pulmonary regurgitation velocity >2.2 m/sec	Right atrial area (end-systole) >18 cm^2
	PA diameter >25 mm.	

PA = pulmonary artery.
[a]Echocardiographic signs from at least two different categories (A/B/C) from the list should be present to alter the level of echocardiographic probability of pulmonary hypertension.

- ***Pulmonary embolism*** *(PE) (normal, partial PE resolution, total PE resolution, no changes compared to previous angio-CT).* Pulmonary embolism is evaluated with a pulmonary CT angiography. This is a nominal qualitative variable in which we compare the new angio-CT to the previous one if they had during hospital stay.

BLOCK 6: Variables related to lung ultrasound (LUS). LUS could be a useful tool during the follow-up of patients after severe Covid-19 pneumonia (Table 6). This exam emits no radiation and has already showed to be useful for the early detection of COVID-19, and also to assess the disease severity (37). These are nominal qualitative variables:

- *A lines (yes/no)*
- *B lines (no/B3/B3+B7/B7/B)*
- *Pleural disruption (yes/no)*
- *Pleural thickness (yes/no)*
- *Pleural effusion (yes/no)*
- *Parenchymal consolidation (yes/no)*

Table 6 Definitions of lung ultrasound variables. Adapted from (50,51)

VARIABLE	DEFINITIONS
A LINES	Horizontal lines that are hyperechogenic, parallel and equidistant from each other, located at a multiple distance below the pleural line between the transducer and the pleural line.
B LINES	Vertical lines that are hyperechogenic and originates from the pleural line and continues to the end of the ultrasound image. - *No*: absence of B lines. - *B3*: separation of 3mm between three or more B lines. - *B7*: separation of 7mm between three or more B lines - *B3 + B7*: presence of both B3 and B7 lines - *B*: fewer than 3 isolated B lines
PLEURAL DISRUPTION	Interruption of pleural line
PLEURAL THICKNESS	Thick hypoechoic band superficial to pleura-lung interphase.
PLEURAL EFFUSION	Disappearance of "lung sliding" sign, located in slopes zones and visualized as a chamber, usually anechoic, limited below by diaphragm, in surface by parietal pleura, and in deep by visceral pleura.
PARENCHYMAL CONSOLIDATION	Hypoechoic structure with irregular margins and air bronchogram

BLOCK 7: Variables related to chest X-ray. Like LUS, this test could be more appropriate than HRCT for long-term follow--up due to its low radiation (compared to CT). The following nominal qualitative variables are being analysed:

- *Pathological? (yes/no)*
- *Pulmonary abnormalities (infiltration; loss of volume; atelectasis; condensation; bronchiectasis; interstitial; ground glass; others).* Definitions of chest X-ray patterns may be found in "ANNEXES" section (Annex 1)
- *Localization (unilateral; bilateral)*
- *Distribution (peripheric; central).*
- *Lobes affected (same as HRCT)*

Covariates

The chosen covariates may be looked at the table below (Table 7). Study covariates are independent variables, but they may act also as cofounding variables (i.e., presence of chronic respiratory disease may be a cofounding variable for pulmonary function test; age and hypertension; etc.). Further information about variables like definitions and measure instruments may be read in the complementary text of this section.

Table 7 Covariates.

	COVARIATE	**TYPE**	**CATEGORIES OR VALUES**
A. CLINICAL INFORMATION	*Gender*	Dichotomous qualitative	Woman/man
	Age (years)	Continuous quantitative	(It will be presented as mean and SD)
	BMI (kg/m2)	Continuous quantitative/ ordinal qualitative	<18.5 Underweight 18.5-24.9 Normal 25-29,9 Overweight 30-34,5 Obesity I 35-39,9 Obesity II ≥40 Obesity III
B. COMORBIDITIES	*Smoker*	Nominal qualitative	Yes/no/ex-smoker
	Hypertension	Dichotomous qualitative	Yes/no
	DM		
	DLP		
	Chronic respiratory disease		
	Cardiovascular disease		
C. RESPIRATORY SYMPTOMS	*MRC dyspnoea*	Ordinal qualitative	0/1/2/3/4
	Cough	Dichotomous qualitative	Yes/no
	Pleuritic chest pain		
	Anosmia		
	Diarrhoea		

D. ANALYTICAL PARAMETERS	*Haemoglobin (g/dL)*	Continuous quantitative	(It will be presented as mean ± SD or median [IQR])
	Haematocrit (%)		
	Lymphocytes count (K/mcL)		
	LDH (U/L)		
	Ferritin (ng/mL)		
	C-reactive protein (mg/dL)		
	Troponins (ng/L)		
	D-dimer (ng/mL)		
	Fibrinogen (mg/dL)		
E. HOSPITAL STAY	*Length of hospital stay (days)*	Discrete quantitative	(It will be presented as median and IQR)
	Rate of ICU admission (%)	Continuous quantitative	
F. TREATMENT	*Corticoids, prednisone*	Dichotomous qualitative	Yes/no

Nominal qualitative variables will be presented as n (%). BMI = body mass index. DLP = dyslipidemia. DM = diabetes mellitus. ICU= intensive care unit. IQR= interquartile range. LDH = lactate dehydrogenase. MRC = Medical Research Council. SD= standard deviation

A. CLINICAL INFORMATION:

- *Gender*
- *Age*
- *Body mass index (BMI).* BMI is calculated through weight (kg) and height (m2). These data were collected during visit 2 by nursery. Mentioned categories were made according to the BMI classification of World Health Organization (WHO).

Body mass index might be correlated to age, this will be considered when analysing both parameters by stratifying results, so confounding is avoided.

B. COMORBIDITIES: presence or not of the following comorbidities has been determined by a search on clinical history of patients. Some comorbidities, such as obesity, hypertension and diabetes have shown to be risk factors for severe COVID-19 (26). These comorbidities had to be diagnosed before Covid-19 hospitalization.

- *Smoker*
- *Hypertension*
- *Diabetes mellitus (DM)*
- *Dyslipidemia (DLP)*
- *Chronic respiratory disease*: defined as presence of such chronic conditions that may compromise pulmonary function, like asthma or chronic obstructive pulmonary disease.
- *Cardiovascular disease*: defined as presence of such conditions that may alter cardiovascular function, like coronary artery disease or heart failure.

In one hand, personal history of smoking or chronic respiratory disease can by themselves produce lung abnormalities and consequently a modification of the results of some variables (act as a cofounding variables), such as: HRCT findings, PFTs, walking test, pulmonary hypertension… (21). In the other hand, cardiovascular disease can lead also to pulmonary hypertension. Therefore, some findings in these tests may not be clear whether they are caused because of COVID-19 or because of their personal history.

When analysing these patients, results must and will be checked carefully. In both cases, a meticulous search on patient's clinical history will be done to avoid confounding. This search has the aim to check for previous reports of the mentioned tests and hence clarify if the parameters were altered before or after COVID-19 episode.

C. RESPIRATORY SYMPTOMS:

- *Modified Medical Research Council (mMRC) dyspnoea*. Categorized following the MRC grade of dyspnoea (Table 8)

Table 8 Grade of dyspnea according to the Modified Medical Research Council Dyspnea scale

Grade of dyspnea	Description
0	I only get breathless with strenuous exercise
1	I get short of breath when hurrying on level ground or walking up a slight hill
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
3	I stop for breath after walking about 100 yards or after a few minutes on level ground
4	I am too breathless to leave the house or I am breathless when dressing

- *Cough*: defined as new presence of cough after COVID-19 hospitalization or worsening
- *Pleuritic chest pain:* defined as new presence of pleuritic chest pain after COVID-19 hospitalization or worsening
- *Anosmia*: defined as new presence of anosmia after COVID-19 hospitalization or worsening
- *Diarrhoea*: defined as new presence of diarrhoea after COVID-19 hospitalization or worsening

Defining as new presence or symptoms worsening, we avoid those conditions that may produce such symptoms *per se*.

D. ANALYTICAL PARAMETERS: the following parameters have been analysed by blood test by experts in Hospital Universitari de Girona Doctor Josep Trueta and surroundings health care centre's laboratories:

- *Hemoglobin (g/dL)*
- *Haematocrit (%)*
- *Lymphocytes count (k/mcL)*
- *Lactate dehydrogenase (LDH) (U/L)*
- *Ferritin (ng/mL)*
- *C-Reactive protein (CRP) (mg/dL)*
- *Troponins (ng/L)*
- *D-dimer (ng/mL)*
- *Fibrinogen (mg/dL)*

E. HOSPITAL STAY: the count for length of hospital stay includes the admission day (i.e., if a patient was hospitalized from 5/03/2020 to 8/03/2020, that makes a total count of 4):

- *Length of hospital stay (days)*
- *ICU admission rate (%)*

F. TREATMENT: a prolonged intake of low-dose corticoids may prevent fibrotic remodelling after ARDS in COVID-19 (15). Therefore, patients in this study that had significant GGO during follow-up HRCT and benefits/risk was favourable, were asked to take prednisone. This factor must be treated like independent variable as could change HRCT findings at 6 months.

- *Prednisone (yes/no).*

Prednisone dose was in most cases: 30mg/24h for 15 days + 20mg/24h for 15 days + 10mg/24h for 15 days + 5mg/24h until next HRCT was performed. However, if the patient had many comorbidities, especially diabetes, or had small GGO in the HRCT, a lower prednisone dose was considered, consisting of: 15mg/24h for 15 days + 10mg/24 for 15 days + 5mg/24h until next HRCT was performed. After HRCT, prednisone intake was revised.

DATA COLLECTION AND PROCEDURES

Although the study is being developed in Hospital Josep Trueta, not all the information regarding patients belongs to this hospital. To have a more reliable and complete data about patients, during the phase of data collection the Research Team has searched into *Historia Clínica Compartida de Catalunya (HC3)* for those patients in which health care service has been performed for different hospitals or health care units, for example to collect data about blood tests results.

Data has been collected with the aim of including all relevant aspects of clinical history, quality of life (Saint George respiratory questionnaire), respiratory functional study, gas exchange, pulmonary and cardiac echography, radiology, and laboratory parameters associated to COVID-19.

Follow-up strategy

A total of 4 visits will be done: one telematic and three presential. In each one of them data will be collected, and the following complementary exams will be performed.

IN THE PRESENT RESEARCH PROJECT, DATA HAS BEEN COLLECTED UNTIL VISIT Nº3 (AT 6 MONTHS). Visit nº 4 (at 12 months) is pending. Therefore, the present research project PRESENTS PRELIMARY RESULTS UNTIL 6 MONTHS. This period covers all data collected until finals December when last patients have had visit nº3.

During hospital stay

Results of the next variables have been gathered searching into patient's clinical history. This data was collected retrospectively. In case of blood parameters, these results correspond to extreme values after checking all blood test done during hospital stay, even if patient initially stayed in a different hospital than Girona. In case of length of hospital, days were counted alike if patient was at first externally hospitalised. However, the cause of hospitalization had to be COVID-19 pneumonia, no other was admitted.

- Blood test parameters:
    - Peak LDH (U/L)
    - Peak CRP (mg/dL)
    - Peak ferritin (ng/mL)
    - Lowest lymphocytes (count) value (K/mcL)
- Length of hospital stay (days)
- ICU rate admission

Visit nº 1 (via phone) → 1 – 1'5 months after hospital discharge

This visit took place via phone, clinical data was collected, and a chest X-ray was performed as well. However, this is not new as it is a common practice after suffering a severe pneumonia:

- Respiratory symptoms and clinical condition at 1 month
- Chest X-ray at 1 month

Visit nº 2 (presential) → 2'5 – 3'5 months after hospital discharge

The study was explained to the patient and an information sheet was delivered (Annex 3). Informed consent was asked (informed consent is picked retrospectively as visit nº 1 is part of common clinical practice) (Annex 4).

Collected data regarding visit at 1 month was checked. Exams findings were informed to the patient.

- Respiratory symptoms and clinical condition at 3 months
- Quality of life (SGRQ) and Barthel at 3 months
- PFT at 3 months
- 6-minutes walking test at 3 months
- Blood test at 3 months: haemoglobin (g/dL); haematocrit (%); lymphocytes count (K/mcL); LDH (U/L); ferritin (ng/mL); CRP (mg/dL); troponins (ng/L); D-dimer (ng/mL); fibrinogen (mg/dL).
- Sputum culture if expectorate
- HRCT at 3 months
- Pulmonary angiography CT (if previous PE or D-dimer >2.500 ng/mL)
- Lung ultrasound at 3 months
- Transthoracic echocardiogram at 3 months

Visit nº 3 (presential) → 5'5 – 6'5 months after hospital discharge

Collected data regarding visit at 3 months was checked. Exams findings were informed to the patient. The patient was asked whether they still wanted to participate in the study or not.

- Respiratory symptoms and clinical condition at 6 months
- Quality of life (SGRQ) at 6 months
- Chest X-ray (if CT or X-ray was normal at 3 months)

The following exams were performed only in case they were altered at 3 months:

- PFT at 6 months
- 6-minutes walking test at 6 months
- Blood test at 6 months: haemoglobin (g/dL); haematocrit (%); lymphocytes count (K/mcL); LDH (U/L); ferritin (ng/mL); CRP (mg/dL); troponins (ng/L); D-dimer (ng/mL); fibrinogen (mg/dL).
- Sputum culture if expectorate
- HRCT at 6 months

Visit nº 4 (presential) → 11,5 – 12,5 months after hospital discharge

Collected data regarding visit at 6 months will be checked. Exams findings will be informed to the patient.

- Respiratory symptoms and clinical condition at 12 months
- Quality of life (SGRQ) and Barthel at 12 months
- Chest X-ray (if CT or X-ray was normal at 6 months)

The next exams will be performed only in case they were altered at 6 months:

- PFT at 12 months
- 6-minutes walking test at 12 months
- Blood test at 12 months: haemoglobin (g/dL); haematocrit (%); lymphocytes count (K/mcL); LDH (U/L); ferritin (ng/mL); CRP (mg/dL); troponins (ng/L); D-dimer (ng/mL); fibrinogen (mg/dL).
- Sputum culture if expectorate
- HRCT at 12 months

If LUS and TTE performed at 3 months showed any relevant findings, these exams will be repeated again at 12 months.

STATISTICAL ANALYSIS

SPSS20.0 software (Chicago, IL) was used for statistical analysis. Qualitative variables were described as percentages. Quantitative variables were described using mean with standard deviation (SD) if normally distributed, or median with interquartile range (IQR) if non-normally distributed. For the most important study variables, data were reported also as mean and 95% Confidence Interval (95%CI). Shapiro-Wilk and Kolmogorov-Smirnov tests were used to test the null hypothesis that a sample came from a normally distributed population. Shapiro-Wilk was used for those variables with <50 individuals; if sample was >50 individuals, Kolmogorov-Smirnov test was used instead.

The following statistical hypothesis tests were used:

- Chi-squared test: to compare frequencies of two nominal qualitative variables. This test was used if all expected values were >5.
- Fisher's exact test: same as chi-squared but used when any expected values were 5 or less.
- McNemar test: in paired samples, to compare frequencies of two qualitative variables with 2 or more categories
- Likelihood ratio test: to compare a nominal dichotomous variable with a nominal non-dichotomous variable
- T-test: to compare the means of two independent samples if normally distributed. Before t-test application, variance was tested using Levene's test.
- Paired sample t-test: same use as t-test but for paired samples.
- Mann-Whitney U test: to compare the means of two independent samples when non-normally distributed
- Wilcoxon Signed-rank test: same use as Mann-Whitney U test but for paired samples.
- Spearman rank correlation test: to determine association between two quantitative variables when non-normally distributed

P<0,05 was considered statistically significant.

WORKING PLAN AND RESEARCH TEAM

Please, note the difference between “original study” and “research project” uses, as the first one describes the study being carried out by Pneumology Service and the last one describes my Final Degree Project. As described below, data collection and database are common for both, study and project; but protocol study, although having the same structure, was rewritten and adjusted to accomplish the research project objectives.

Research team

The research team will be formed by:

- The principal investigator, Saioa Eizaguirre, a pneumologist from Hospital de Girona, who has coordinated the original study, written the original protocol study, conducted the initial bibliographical research, helped with the data collection and has taken care of medical visits of the patients
- Laura Sebastian, pneumologist from Hospital de Girona, who helped with the data collection and has taken care of medical visits of the patients along with Saioa Eizaguirre
- Gladis Sabater, pneumologist from Hospital de Girona, who validated pulmonary function tests and revised radiological images along with Ramon Orriols and me
- Ramon Orriols, Head of Pneumology Service, who helped in the study coordination
- Eduard Barrio, pneumologist, who performed LUS in all the patients
- Other pneumologists and nurses who helped in data collection of pulmonary function tests, 6 minutes walking test and Saint George’s Respiratory Questionnaire
- Daniel Ramos, who assisted to some of the patients’ medical visits, did the main bibliographical research for the present research project, rewrote the original protocol study to adjust it to the present research project, developed the Excel database, analysed data through SPSS, and presented results and conclusions

Working plan

The study has been conducted for 9 months, (time when the present research project is presented), and it is still carrying out, for at least 6 months more until visit 4 is completed.

- Phase 0: Preparation (April – June 2020)
    - Conduction of bibliographic research and summarization of the current state of COVID-19
    - Design of the best follow-up plan for patients after severe COVID-19 pneumonia
    - Study and protocol design
    - Informed consent and information sheet elaboration
    - Ethical and legal approval by CEIC
- Phase 1: Data collection and database development (June – December 2020)
    - During this period, medical visits from number 1 to 3 (from 1 month to 6 months after hospital discharge) took place
    - Data regarding medical visits were collected and stored in a Microsoft Excel database
- Phase 2: Statistical analysis and results (December 2020 – January 2021)
    - Microsoft Excel database was adjusted and imported into SPSS
    - Data was analysed through SPSS and tables and figures were created
    - Analysis results were described
- Phase 3: Interpretation and discussion of the results. Conclusions (January 2021)
- Phase 4: Publication and dissemination of the results of THE RESEARCH PROJECT (January - February 2021)

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- Phase X: Visit at twelve months after hospital discharge completed and all data finally collected. New statistical analysis and presentation of the final results of THE ORIGINAL STUDY (Sometime by the end of the year 2021)

Table 9 Chronogram

	2020									**2021**								
Phases:	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP
PHASE 0																		
Bibliographic research																		
Design of follow-up strategy																		
Protocol design																		
CEIC approval																		
PHASE 1																		
Medical visits																		
Data collection																		
Database development																		
PHASE 2																		
Database importing to SPSS																		
Statistical analysis																		
Results description																		
PHASE 3																		
Results interpretation and discussion																		
PHASE 4																		
Publication and dissemination of the results																		
PHASE X																		
Original study development																		

ETHICAL AND LEGAL ASPECTS

It is important to note that this study eas validated by many organizations and structures in order to assess its ethically feasible. First of all, the study has been drafted according to the World Medical Association *Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects of June 1964*, more specifically its October 2013 revision, therefore respecting the following principles:

- The principle of **autonomy** would not be in conflict as every patient has been handed an information sheet and have signed an informed consent document in order to be drafted for this study. Patients can drop out of the study whenever they want without any prejudicial effect.

- The principle of **nonmaleficence** could be challenged considering that patients are having a chest X-ray and at least one CT scan performed; therefore, they are being irradiated. However, this is justified because benefits overweigh risks, as the implication of pulmonary fibrosis CT signs may change medical behaviour and consequently patient prognosis. Also, in order to avoid unnecessary radiation, CT scans in visits 3 and 4 have been limited for only those patients that already had a previous pathological CT; using lung ultrasound or chest X-ray in the rest of the patients.

- The principle of **beneficence** would also not be in conflict as this study has the wellbeing of the patient and the bettering of society in mind, as its main goal is to determine the long-term health consequences and pulmonary fibrosis development in patients after severe COVID-19 pneumonia. Thus, this may help to reduce its effects, the propose a follow-up plan, and in the future, probably to avoid pulmonary fibrosis in these patients

- Lastly, the principle of **justice** would not be in conflict, as every patient over 18 years old can be included in this study. One may think this study is limited for those only who had severe pneumonia, however this is due to a demonstrated higher incidence of long-term health consequences in these patients

To further ensure the ethical feasibility, this study was approved by ***Comitè d'ètica d'investigació clínica*** **(CEIC) [Clinical Research Ethics Committee]** of the Hospital Universitari de Girona Doctor Josep Trueta. The document that demonstrates CEIC approval is attached in "ANNEXES" section (Annex 5). Any input and contributions from said committee was introduced in the study. Once the CEIC approved the study, permission has been asked to the direction of the centre to carry out the study.

As this study needs personal and sensitive data from the patients, the investigation team compromised to accomplish ***Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de derechos digitales (BOE núm. 294, de 6 de diciembre de 2018)*** which ensures the confidentiality and proper treatment of the patient data. In order to further ensure this mandate, the personal information of the patient was identified with a numeric code and only the investigators had access to it in case of needing it. Moreover, all the information was stored in an anonymous database, responsibility of the institution, and was treated accordingly to its participation to the present study.

Treatment, communication, and personal data transfer of patients must adjust to this law. Data collected in the present study can be used for further related investigations. ´

The author of this study declares no conflict of interest.

RESULTS

Descriptive analysis

Clinical information

Originally, there were 111 patients rolled for this study, but three of them dropped out the study and another one died during the follow-up. However, in the last case, primary outcome and some secondary outcomes were already collected, so its data was considered. Therefore, data showed in this study includes 108 patients.

Their mean (SD) age was 60,95 (13,70), among which 74 (68,5%) where male and 34 (31,5%) were female. Their mean Body Mass Index (SD) was 29,47 (5,89). Normal distribution was found for both variables, age, and BMI (Figure 3).

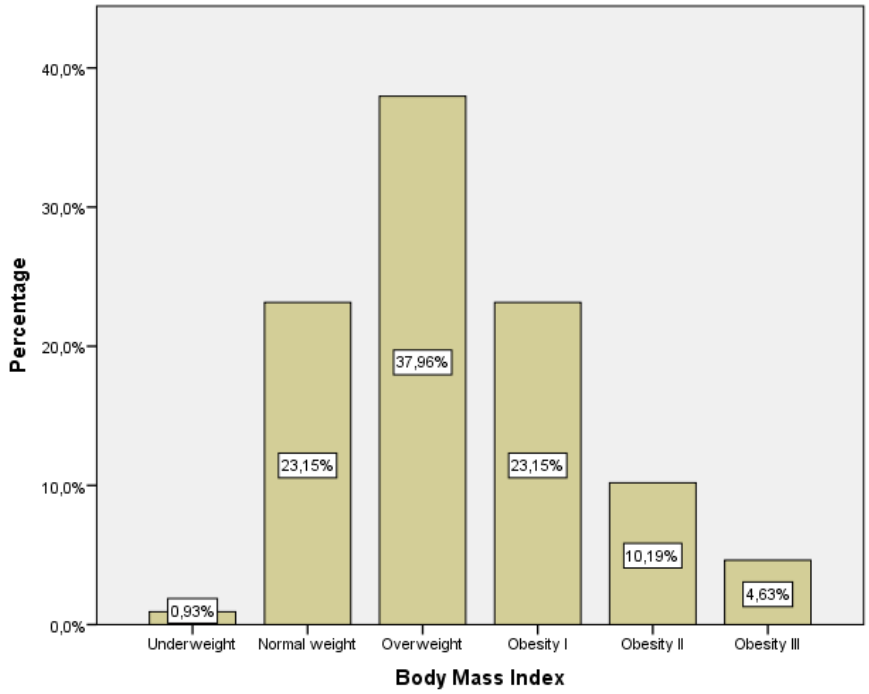

Figure 3 Classification of Weight Status by Body Mass Index.

Common comorbidities included hypertension (50 cases, 46,3%), diabetes mellitus (25 cases, 23,1%), dyslipidemia (36 cases, 33,3%), respiratory disease (25 cases, 23,1%) and cardiovascular disease (21 cases, 19,4%). Only 5 patients were smokers (4,6%) and 39 of them ex-smokers (36,1%).

The median [IQR] length of hospital stay was 21 days [14-34] and ICU admission rate was 47,7%. Among the patients that needed intensive care: 47,2% of them spent less than two weeks in ICU; 35,2% between 2 weeks and 1 month; and 15,6% a month or more.

On the day of visit 1 (telematic), one month after hospital discharge: 64,7% of patients had dispnea, 7,8% cough, 4,9% pleuritic chest pain, 1% anosmia and 1% had diarrhoea. Data about anosmia and diarrhoea was not collected on the following visits. Cough and pleuritic chest pain among patients had similar percentages during follow-up. However, the percentage of dispnea changed between visits. Dispnea diminished to half (50,0%) of the patients on visit two, showing statistical significance (p=000) but with no differences on visit number three (53,9%) (p=0'59).

Pulmonary function

AT 3 MONTHS

Pulmonary function test was performed successfully on 97 patients. However, four spirometry, eleven body plethysmography (lung volume) and five diffusion capacity tests failed in the spare 11 patients.

Anomalies were noted in DLCO % predicted in 54 cases (51,92%), RV % pred in 17 (16,3%), FVC % pred in 15 (14,4%), KCO % pred in 15 (14,4%), FEV_1 % pred in 13 (12,5) and TLC % pred in 11 (11,3%).

DLCO % predicted mean is 76,59% [95%CI 73,20 - 79,97] and therefore, under normal range (80-120% predicted) (Table 10) (Figure 4).

Table 10 Pulmonary function test at three months after hospital discharge

PARAMETERS		AT THREE MONTHS
SPIROMETRY	FVC (% predicted)	95,09 ± 16,34
	FVC <80% pred	n= 15 (14,4%)
	FEV_1 (% predicted)	96,27 ± 17,85
	FEV_1 <80% pred	n= 13 (12,5%)
lung volume	TLC (% predicted)	96,60 ± 14,70
	TLC <80% pred	n= 11 (11,3%)
	RV (% predicted)	101,57 ± 23,08
	RV 120>% pred	n= 17 (16,3%)
diffusion	DLCO (% predicted)	**76,59 ± 17,41**
capacity	DLCO <80% pred	**n= 54 (51,92%)**
	KCO (% predicted)	98,59 ± 16,29
	KCO <80% pred	n= 15 (14,4%)

Data are presented as mean ± SD or n (%). All pulmonary function parameters showed a normal distribution. DLCO: diffusing capacity for carbon monoxide; FEV_1: forced expiratory volume during first second; FVC: forced vital capacity; KCO: carbon monoxide transfer coefficient; RV: residual volume; TLC: total lung capacity

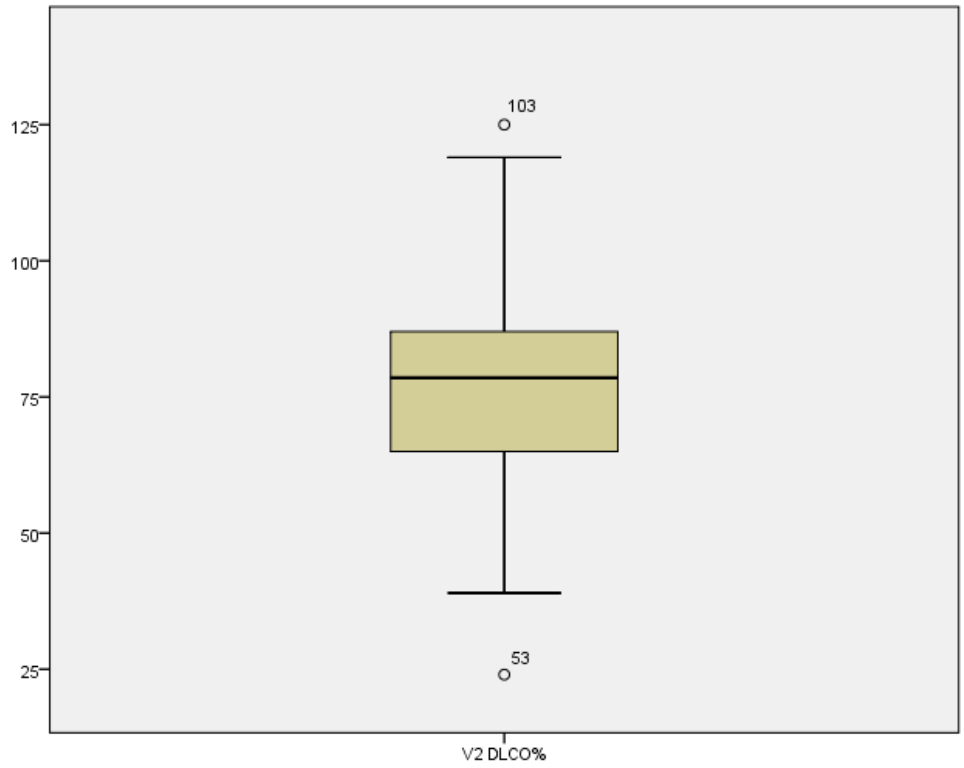

Figure 4 Box plot of DLCO (% predicted) after 3 months distribution

AT 3 MONTS VS AT 6 MONTHS

Pulmonary function parameters cannot be compared directly between visit 2 (at three months) and visit 3 (at six months), as only those patients with low performance had a PFT in visit 3. Therefore, we have only selected data of those patients that had both PFTs and assessed pulmonary function evolution (Table 11).

A total of 35 patient had both PFTs performed, at 3 and 6 months. Among these 35 patients, 31 (88,6%) had a DLCO <80% predicted after 3 months. However, after 6 months this number decreased to 20 (57,1%) patients, showing statistical significance (p=0,001) using McNemar test for paired sample. Therefore, in this study, 35,6% of those patients that had both PFTs performed and a DLCO <80% predicted after 3 months, had a normalization of DLCO % pred after 6 months.

Also, 9 patients (25,7%) showed a KCO <80% pred after 3 months. After 6 months only 2 (5,7%) of them still had an abnormal KCO % pred, showing statistical significance (p=0,016).

Table 11 Comparison between pulmonary function at three and six months after hospital discharge

PARAMETERS		AT 3 MONTHS	AT 6 MONTHS	P VALUE
SPIROMETRY	FVC (% predicted)	85,91 ± 14,66	90,11 ± 16,28	0,057
	FEV_1 (% predicted)	89,66 ± 15,67	93,31 ± 18,09	0,134
LUNG	TLC (% predicted)	85,28 ± 12,69	90,72 ± 11,78	**0,004**
VOLUME	RV (% predicted)	89,16 ± 24,81	95,26 ± 20,11	0,175
DIFFUSION	DLCO (% predicted)	62,69 ± 15,21	73,34 ± 18,75	**0,000**
CAPACITY	KCO (% predicted)	91,20 ± 15,15	102,29 ± 17,70	**0,003**

Data are presented as mean ±SD. Comparisons between quantitative data was performed using Paired Sample T-test. This table shows data about only those patients that had both pulmonary function tests performed, at 3 and 6 months after hospital discharge; this includes a total of 35 patients. DLCO: diffusing capacity for carbon monoxide; FEV_1: forced expiratory volume during first second; FVC: forced vital capacity; KCO: carbon monoxide transfer coefficient; PFT: Pulmonary Function Test; RV: residual volume; TLC: total lung capacity

Exercise function

AT 3 MONTHS

After 3 months, the 6 minutes walking test was performed in all but 4 patients (n=104). Median [IQR] distanced walk was 399 [324-434] meters, basal oxygen saturation 98% [98-98], mean oxygen saturation during test 97% [96-98] and minimal oxygen saturation during test 96% [94-97].

Among all, 57 (54,8%) patients walked less than 400m, and 34 (32,7%) patients walked less than 350m. Only 13 (12,5%) patients had a mean oxygen saturation during test lower than 95%, being the lowest mean value 91%. For minimal oxygen saturation, 27 (26%) patients had a <95% value during test, but only one of them had a <90% value.

Spearman rank correlation test (correlation coefficient) was used to assess if DLCO % pred levels is associated to distance walked (0,245), mean oxygen saturation (0,297) or minimal oxygen saturation (0,217) during test. Results were found statistically significant in the three cases, however, for all of them a weak association was found.

AT 3 MONTHS VS AT 6 MONTHS

Initially, those patients that had walked less than 400 meters (57 patients, 54,8%) at three months would perform another 6MWT at six months. However, due to agenda and programming problem, added to COVID-19 second wave, only 13 patients had both 6MWT performed. Therefore, comparison to assess exercise function evolution will be limited to those individuals (n=13).

There were no statistically significant differences between oxygen saturation at 3 months and at 6 months. However, mean distanced walk (SD) increased from 350,1m (81,2) at 3 months to 394,4m (94,4) at 6 months, showing statistical significance (p=0,001), which means a total increase of 44,3m.

Quality of life

All patients answered SGRQ at visit two. Only 3 (2,8%) patients had a total value in SGQR of 0 after three months. Saint George's Respiratory Questionnaire abnormalities did not follow a normal distribution. Therefore, results are expressed as median [IQR]. After 3 months, SGQR score for symptoms were 20,94% [9,63-37,49], for activity 30,49% [12,22-59,46] and for impact 8,79% [3,06-25,93]. Total score was 19,52% [7,50-34,51].

On the day of visit 3, 10 patients missed SGQR. After 6 months, 6 (6,1%) patients had a total score of 0. Median and interquartile range for SGQR scores after 6 months are shown in table below. Comparative among results has been made to determine if exists improvement or worsening of quality of life (Table 12).

Table 12 Comparison of Saint George's Respiratory Questionnaire scores for the different areas after 3 and 6 months.

Parameters	*After 3 months*	*After 6 months*	*p-value*
SG symptoms	20,94% [9,63-37,49]	25,27% [11,95-38,73]	**0,031**
SG activity	30,49% [12,22-59,46]	21,04% [0-49,93]	**0,000**
SG impact	8,79% [3,06-25,93]	7,82% [1,22-19,35]	0,123
SG total	19,52% [7,50-34,51]	16,16% [5,50-30,31]	**0,022**

Data are presented as median [IQR]. P-value was calculated by Wilcoxon Signed-rank test. SG= Saint George

BARTHEL

A total of 83 (76,9%) patients had a Barthel score of 100. 21 (19,4%) patients had a Barthel score between 75 to 95; and the rest, 4 (3,7%) patients had a score lower than 75 points.

Pulmonary hypertension

Transthoracic echocardiogram was performed successfully in 104 patients after 3 months. Three patients did not perform TTE and another one had poor acoustic windows, so TTE assessment was difficulted. In the rest 104 patients TTE was performed, but PAP, TAPSE and TRV could not be measured in 39, 4 and 31 cases respectively. Cardiology service reported 11 (10,2%) cases of pulmonary hypertension: 8 of them were informed as mild; 1 as mild-moderate; and 2 as severe (Table 13).

Table 13 Transthoracic echocardiogram results.

PARAMETERS		**RESULTS**
Pulmonary hypertension	expressed as n (%)	11 (10,2%)
PAP mmHg	expressed as median [IQR]	33 [26,50-37,00]
Right ventricular dilatation	expressed as n (%)	11 (10,2%)
TAPSE mm	expressed as mean (SD)	22,61 (3,31)
TRV m/s	expressed as median [IQR]	2,35 [2,20-2,62]

PAP= pulmonary artery pressure; TAPSE= tricuspid annular plane systolic excursion; TRV= tricuspid regurgitation velocity

Lung ultrasound

Lung ultrasound was performed successfully in 94 patients after 3 months (Table 14).

Table 14 Lung ultrasound findings for each hemithorax.

		Right hemithorax	**Left hemithorax**
A lines		93 (98,9%)	92 (97,9%)
B lines	B3	52 (55,3%)	46 (48,9%)
	B3 + B7	1 (1,1%)	0 (0%)
	B7	8 (8,5%)	6 (6,4%)
	B	1 (1,1%)	0 (0%)
Pleural disruption		55 (58%,5)	57 (60,6%)
Pleural thickness		60 (63,8%)	60 (63,8%)
Pleural effusion		2 (2,1%)	3 (3,2%)
Parenchymal consolidation		0 (0%)	0 (0%)

Data are presented as n (%)

Analytical parameters

Blood test was performed in all but 18 and 27 patients after 3 and 6 months respectively, due to agenda and programming problem. During hospital stay, patients had increased LDH levels (median= 388 U/l [IQR: 318-501]), an increased ferritin (median= 1193 ng/ml [IQR: 679-1906]), an increased CRP (median= 21 mg/dl [IQR: 10,6-34,4]) and a low lymphocytes value (median= 0,5 K/mcl [IQR: 0,4-0,8]). At the time of follow-up after 3 and 6 months, previously mentioned analytical parameters were in the normal range for most patients (Table 15).

Table 15 Analytical parameters during hospital stay and at follow-up.

	REFERENCE VALUES	DURING HOSPITAL STAY	AFTER 3 MONTHS	AFTER 6 MONTHS
HEMOBLOBIN, G/DL	m: 13,5-18 w: 11,5-16	not collected	14,3 [13,3-15,3]	14,4 [13,4-15,5]
HAEMATOCRIT, %	m: 43-49 w: 35-45	not collected	44 [41-46]	44 [41-47]
LYMPHOCYTES, K/MCL		**0,5 [0,4-0,8]**	2,1 [1,6-2,6]	2,1 [1,8-2,6]
LDH, U/L	135-225	**388 [318-501]**	185 [163-208]	188 [165-231]
FERRITIN, NG/ML	30-400	**1193 [679-1906]**	95 [57-160]	102 [50 – 185]
CRP, MG/DL	0-0,5	**21,0 [10,6-34,4]**	0,18 [0,09-0,33]	0,24 [0,09-0,37]
TROPONINS, NG/L	<14	not collected	8,1 [5,3-15,2]	7 [3,8-12,8]
D-DIMER, NG/ML	0	not collected	0 [0-0]	0 [0-0]
D-DIMER >0 NG/ML		not collected	16 (18,4%)	13 (17,1%)
FIBRINOGEN, MG/DL	150-450	not collected	401 [353-447]	437 [377-487]

Data are presented as median [IQR] or n (%) as well in case of D-Dimer. Values during hospital stay correspond to extreme values (lowest value for lymphocytes; and highest values for LDH, ferritin and CRP). LDH= lactate dehydrogenase; CRP= C reactive protein

D-DIMER AND PULMONARY CT ANGIOGRAPHY

Although D-dimer median was not elevated, 18,4% and 17,1% of patients had high values after 3 and 6 months, respectively. Patients who have had a pulmonary embolism associated to COVID-19 or D-dimer values >2.500 ng/ml during hospital stay underwent angioCT of pulmonary vessels. A total of 19 angioCT were performed: 9 (47,4%) of them were informed as “normal”; 9 (47,4%) as “full resolution of previous PE”; and 1 (5,2%) as “no changes to previous PE”.

Chest X-ray

Ninety-four chest X-ray were performed 1 month after hospital discharge. Among all, 55 (58,5%) were informed as normal while 39 (41,5%) as pathological. Among pathological chest X-ray, most predominant findings were infiltration (23 patients, 58,97%) and interstitial (9 patients, 23,08%) (Figure 5).

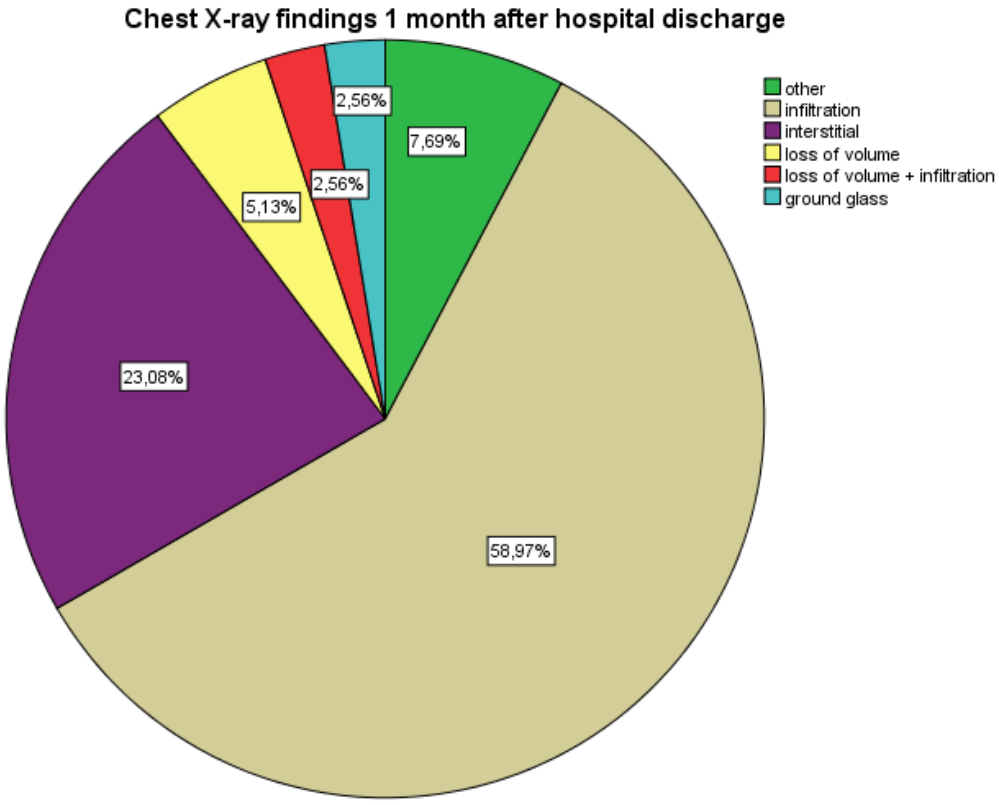

Figure 5 Chest X-ray findings 1 month after hospital discharge among those informed as pathological

Abnormalities were usually bilateral (71,1%) and involving one or both lower lobes (81,6%). Unilateral and peripheric distribution was found in 21,1% and 7,8% patients, respectively.

Five patients repeated chest X-ray on day of the follow-up visit 3. None of them presented changes to previous radiography.

HRCT and corticoids

HRCT AT 3 MONTHS

Chest HRCT was performed in 106 patients after 3 months. In 20 (18,9%) patients no significant abnormalities were found. The rest 86 (80,1%) patients had some abnormality. Fibrosis signs (reticulation, architecture distortion, traction bronchiectasis, honeycomb) were found in 43,4% of the patients. Ground glass opacity as single abnormality or associated to other findings was present in 46,2% of the patients. Loss of volume were found in 5,7% (Table 16).

Table 16 HRCT findings after 3 months.

HRCT findings	*n (%)*
Atelectasis	5 (4,7%)
Bronchiectasis	1 (0,9%)
GGO	24 (22,6%)
GGO + distortion and/or traction bronchiectasis	**20 (18,8%)**
Honeycomb	**1 (0,9%)**
Loss of volume + reticulation	**1 (0,9%)**
Loss of volume + GGO + reticulation	**5 (4,7%)**
Reticulation	**19 (17,9%)**
Other	10 (9,4%)
Normal	20 (18,9%)

Data are presented as n (%). GGO= ground glass opacity; HRCT= high resolution computed tomography

Among pathological chest CT, findings were usually bilateral (81,3%) and peripheric (96,3%). In 78,8% of the cases, at least one of the lower lobes were involved.

HRCT AT 6 MONTHS. USE OF CORTICOIDS FOR GGO

Those patients that had HRCT abnormalities probably associated to COVID-19 were summoned to repeat another HRCT at 6 months. Also, if ground glass opacity was found in HRCT at three months and risks/benefits was favourable, patient was asked to take corticoids, prednisone (prednisone dose is described in "STUDY VARIABLES"). Afterwards, dose was decreased progressively. To determine if corticoids are a potential treatment for residual GGO is not an objective of the present study. However, as administration of corticoids were part of clinical practice and its utility is not clear yet, data was collected, expecting that our findings could be used in further studies.

Although being candidates to corticoids treatment, five patients were rejected because risks/benefits was not favourable: two had minimal ground glass in CT scan with minimal clinical repercussion; and three had many comorbidities. Therefore, 44 patients were asked by phone to take corticoids after CT results: 31 patients started corticoids treatment; 7 patients could not be contacted by phone; 5 patients refused treatment; and 1 patient dropped off treatment because of secondary effects.

A total of 58 HRCT after 6 months were performed; 9 more HRCT are awaiting. A comparison between HRCT at 3 and 6 months was made for each patient. Fibrotic signs did not change from 3 to 6 months. However, ground glass improved in most of the patients (81,4%). Degree of GGO improvement was classified in 5 grades based on radiologist report (Table 17).

Table 17 Degree of improvement of GGO comparing at 3- and 6-months HRCT.

DEGREE OF GGO IMPROVEMENT		**N (%)**
0	No improvement / no changes	8 (18,6)
1	Slight improvement	8 (18,6)
2	Significant improvement	15 (34,9%)
3	Nearly resolution	8 (18,6%)
4	Complete resolution	4 (9,3%)

Data are presented as n(%). A total of 43 patients were analysed. GGO= ground glass opacity. HRCT= high resolution computed tomography

A total of 43 patients were analysed to determine if there is any association between corticoids intake and improvement of GGO in 6 months HRCT. Five patients started corticoids treatment after the HRCT at 6 months, so they were put into "No corticoids" group as intervention must be before CT scan (Table 18).

Table 18 Contingency table showing relation between corticoids treatment and GGO improvement in HRCT at 6 months (compared to previous one, at 3 months).

		GGO improvement in HRCT at 6 months		**Total**
		Yes	**No**	
Corticoids treatment	**Yes**	22	2	24
	No	13	6	19
Total		35	8	**43**

GGO= ground glass opacity.

As seen in table above, 22/24 (91,7%) patients treated with corticoids had improvement of GGO in the HRCT performed at 6 months; compared to 13/19 (68,4%) of spontaneous improvement (without corticoids). This difference among groups, however, is not statistically significant (p= 0,111), calculated with Fisher's exact test.

Pulmonary fibrosis: comparison of different groups

As mentioned above, 46 (43,4%) of the study subjects showed pulmonary fibrosis signs in HRCT at 3 months. These patients were included in Group A (with pulmonary fibrosis). The others 60 (56,6%) without pulmonary fibrosis findings were included in Group B (without pulmonary fibrosis). A comparison of the two groups for the study variables has been made to answer our objectives.

Characteristics and predictive factors

Patients in group A were older than those in group B (mean age ± SD 66,28 ± 13,19 vs 57,22 ± 12,90) (p= 0,001). Patients over 60 years have 2,04 higher risk (RR= 2,04 [95%CI 1,37 – 3,04]) of developing pulmonary fibrosis compared to patients under 60 years old. Age >60 years and fibrosis have been stratified for hypertension variable to calculate relative risk: hypertension does not act as a confounding factor. It has been hypothesized BMI to be a risk factor for fibrosis development; however, no differences were found between groups A and B comparing median nor status weight categories.

The peak LDH during hospital stay was over normal range (normal range= 135-225 U/l) for both groups, but higher in group A (median [IQR] 422 [189] vs 376 [155]) (p= 0,034). Lowest lymphocytes count during hospital stay was lower in group A than in group B (0,40 [0,3] vs 0,65 [0,5]) (p= 0,001). At 3 months, fibrinogen was slightly higher in patients in group A than in group B (415 [114] vs 385 [74]) (p=0,040). Troponins at three months were also higher in group A than in group B (11,7 [11,5] vs 7,1 [7,5]) (p=0,007). No statistical differences were found among analytical parameters at 6 months between groups, except for higher total lymphocytes count in group A than in group B (mean ± SD 2,42 ± 0,79 vs 2,04 ± 0,60) (p=0,018).

Length of hospital stay was distinctly higher in patients in group A compared to patients in group B (median days [IQR] 27 [25] vs 17 [12]) (p= 0,000). However, no statistical differences were found for ICU rate of admission (Table 19).

Table 19 Analysis of characteristics and predictive factors for pulmonary fibrosis.

PARAMETERS	B - NO PULMONARY FIBROSIS GROUP	A - PULMONARY FIBROSIS GROUP	P VALUE
Age	57,22 ± 12,90	66,28 ± 13,19	**0,001**
BMI	29,85 ± 5,86	29,35 ± 5,81	0,664
Male, expressed as n (%)	40 (66%)	34 (73,9%)	0,421
Comorbidities, expressed as n (%)			
- **Smoker**	3 (5%)	2 (4,3%)	0,701
- **Hypertension**	24 (40%)	26 (56,5%)	0,091
- **Diabetes**	15 (25%)	10 (21,7%)	0,695
- **Dyslipidemia**	19 (31,7%)	17 (40,0%)	0,569
- **Respiratory disease**	13 (21,7%)	12 (26,1%)	0,595
- **Cardiovascular disease**	9 (15%)	12 (26,1%)	0,156
Analytical parameters during hospital stay			
- **Peak LDH, U/l**	376 [155]	422 [189]	**0,034**
- **Peak CRP, mg/dl**	18,83 [22,84]	23,85 [23,73]	0,090
- **Lowest lymphocytes count, K/mcl**	0,65 [0,5]	0,40 [0,3]	**0,001**
- **Peak ferritin, ng/ml**	1183 [1227]	1370 [1268]	0,510
Analytical parameters at 3 months			
- **Hemoglobin, g/dl**	14,35 [1,9]	14,25 [2,6]	0,386
- **Hematocrit, %**	44 [5]	44 [6]	0,721
- **Lymphocytes count, K/mcl**	2,1 [0,9]	2,2 [1,1]	0,731
- **LDH, U/l**	184,5 [34]	187,5 [67]	0,356
- **Ferritin, ng/ml**	88,5 [102]	99,5 [160]	0,073
- **CRP, mg/dl**	0,19 [0,27]	0,16 [0,24]	0,934
- **Troponins, ng/l**	7,1 [7,5]	11,7 [11,5]	**0,007**
- **D-dimer, ng/ml**	0 [0]	0 [0]	0,270
- **D-dimer >0 ng/ml, n (%)**	11 (22%)	5 (13,8%)	0,409
- **Fibrinogen, mg/dl**	385 [74]	415 [114]	**0,040**
Length of hospital stay, days	17 [12]	27 [25]	**0,000**
ICU rate of admission, n (%)	26 (44,1%)	25 (54,3%)	0,296

Data are presented as mean ± SD or median [IQR], unless otherwise stated. P value was calculated by chi-square, Fisher's exact test, t-test or Mann-Whitney U test as appropriate. BMI= body mass index; CRP= C reactive protein, ICU= intensive care unit; LDH= lactate dehydrogenase

Impact on pulmonary function, exercise function and quality of life

Dispnea at 1 month was more common in group A than in group B (81% vs 53,4%) (p= 0,004). Many pulmonary function parameters had statistical differences between groups, although only DLCO mean for group A was under reference values (Table 20). TLC % predicted was lower in group A than in group B (mean ± SD 92,79 ± 15,52 vs 99,22 ± 13,41) (p= 0,032). RV % predicted was lower in group A than in group B (95,02 ± 15,07 vs 105,71 ± 19,68) (p=0,021). KCO % predicted was lower in group A than in group B (95,18 ± 17,90 vs 101,78 ± 14,41) (p= 0,042).

The most altered pulmonary function parameter was DLCO % predicted in group A, with statistical differences between groups, being lower in patients with pulmonary fibrosis (71,25 ± 18,73 vs 80,53 ± 15,65; p= 0,008) (Figure 6). Consequently, DLCO predicted <80% was more common in patients of group A (68,2%) than in group B (39,7%) (p=0,004).

Patients of group A had a worse performance in 6 minutes walking test than patients in group B, having walked on average 25,5 meters less (p=0,031). SGRQ total score at 3 nor 6 months did not show any statistical differences between groups. No other significant differences were found between groups.

Table 20 Impact of pulmonary fibrosis on pulmonary function, exercise function, quality of life and symptoms.

PARAMETERS	B - NO PULMONARY FIBROSIS GROUP	A - PULMONARY FIBROSIS GROUP	P VALUE
Symptoms, expressed as n (%)			
- **Dispnea at 1 month**	31 (53,4%)	34 (81,0%)	**0,004**
- **Dispnea at 3 months**	26 (43,3%)	27 (58,7%)	0,117
- **Dispnea at 6 months**	28 (50%)	26 (59,1%)	0,365
Pulmonary function test at 3 months			
- **FVC % pred**	95,07 ± 16,51	94,44 ± 16,34	0,849
- **FEV_1% pred**	95,54 ± 18,85	96,47 ± 16,72	0,797
- **TLC % pred**	99,22 ± 13,41	92,79 ± 15,52	**0,032**

- **RV % pred**	105,71 ± 19,68	95,02 ± 25,07	**0,021**
- **DLCO % pred**	80,53 ± 15,65	71,25 ± 18,73	**0,008**
- **DLCO <80% pred, expressed as n (%)**	23 (39,7%)	30 (68,2%)	**0,004**
- **KCO % pred**	101,78 ± 14,41	95,18 ± 17,90	**0,042**
6 minutes walking test at 3 months			
- **6MWT meters**	406,5 [89]	381 [123]	**0,031**
- **6MWT mean oxygen saturation, %**	97 [2]	96 [2]	**0,011**
- **6MWT minimal oxygen saturation, %**	96 [2]	96 [3]	**0,035**
- **6MWT basal oxygen saturation, %**	98 [0]	98 [0]	**0,026**
Saint George's Respiratory Questionnaire at 3 months			
- **SG symptoms %**	25,15 [30,44]	16,98 [20,04]	**0,049**
- **SG activity %**	35,46 [45,63]	29,41 [47,76]	0,959
- **SG impact %**	9,06 [24,36]	7,33 [20,96]	0,351
- **SG total %**	20,11 [29,02]	17,85 [28,51]	0,448
Saint George's Respiratory Questionnaire at 6 months			
- **SG symptoms %**	28,56 [26,74]	19,58 [24,84]	0,102
- **SG activity %**	18,77 [48,27]	23,30 [53,16]	0,911
- **SG impact %**	6,18 [17,27]	7,92 [18,92]	0,702
- **SG total %**	15,61 [24,58]	17,30 [24,27]	0,874
Barthel	100 [0]	100 [5]	0,333
Echocardiography			
- **PH, expressed as n (%)**	3 (5,2%)	8 (18,2%)	0,052
- **PAP, mmHg**	31,50 [9]	34,00 [14]	0,104
- **TAPSE, mm**	22 [5]	23 [6]	0,329
- **TRV, m/S**	2,30 [0,3]	2,42 [0,52]	0,054

Data are presented as mean ± SD or median [IQR], unless otherwise stated. P value was calculated by chi-square, Fisher's exact test, t-test or Mann-Whitney U test as appropriate. 6MWT: 6 minutes walking test; DLCO: diffusing capacity for carbon monoxide; FEV1: forced expiratory volume during first second; FVC: forced vital capacity; KCO: carbon monoxide transfer coefficient; PAP: pulmonary artery pressure; PH: pulmonary hypertension; RV: residual volume; SG: Saint George; TAPSE: tricuspid annular plane systolic excursion; TLC: total lung capacity; TRV: tricuspid regurgitation velocity

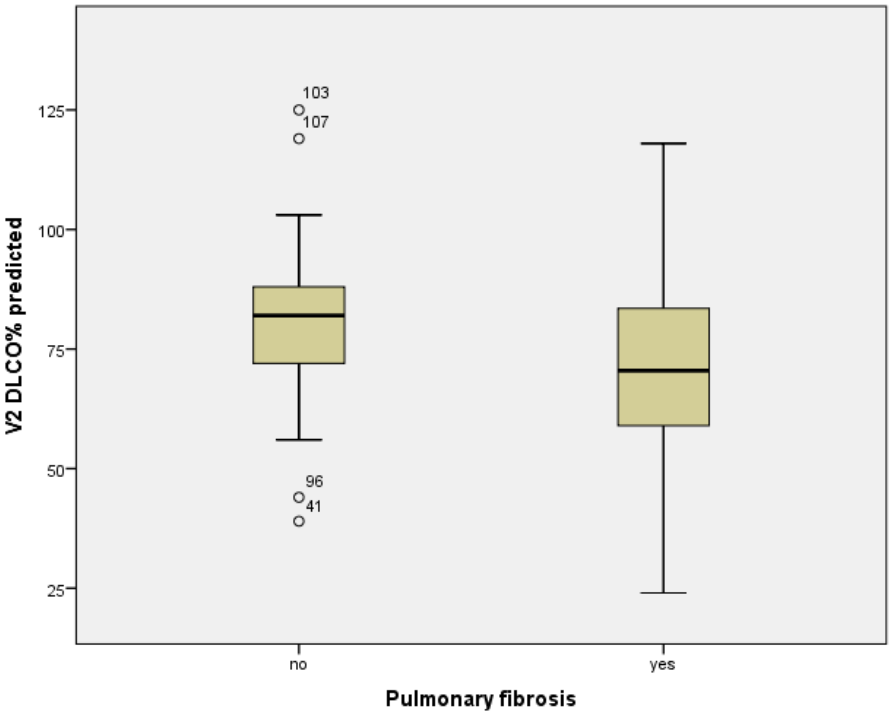

Figure 6 Box plot of DLCO% predicted distribution comparing patients with and without pulmonary fibrosis. V2 DLCO= diffusing capacity for carbon monoxide at the time of visit two

Association with chest X-ray and lung ultrasound findings

CHEST X-RAY (AT 1 MONTH)

Chest X-ray pattern clearly differs depending on the presence of pulmonary fibrosis (p=000; likelihood ratio test) (Figure 7). Most patients with pulmonary fibrosis in HRCT at 3 months already had a pathological chest X-ray at 1 month (68,3%); being the most common findings: infiltrate (46,3%) and interstitial (17,1%).

Among patients that showed an infiltrate pattern in chest X-ray, 82,6% had pulmonary fibrosis, compared to 17,4% that did not have pulmonary fibrosis. By cons, among patients with a normal chest X-ray, only 24,1% of them showed later fibrosis in HRCT, compared to 75,9% that did not show fibrosis.

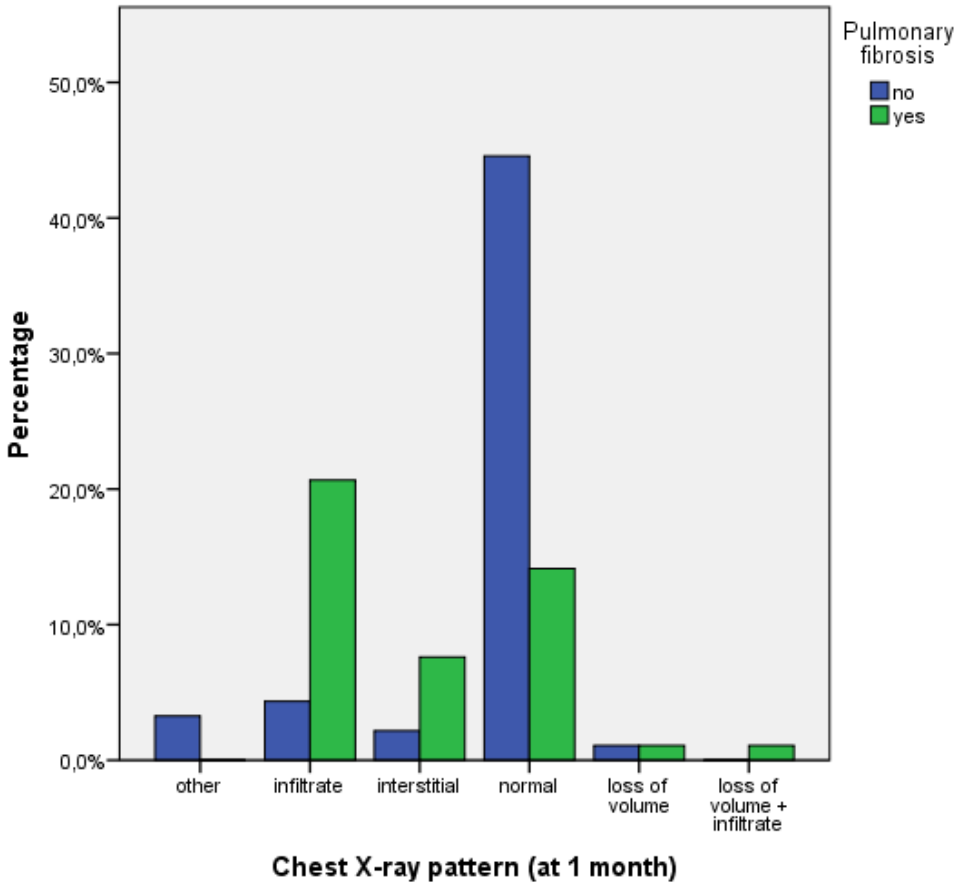

Figure 7 Comparative of radiological pattern in chest X-ray 1 month after hospital discharge depending on presence or not of pulmonary fibrosis in HRCT. HRCT= high resolution computed tomography

LUNG ULTRASOUND

No statistically significant differences were found for lung ultrasound (LUS) variables but for B lines. LUS B-lines findings clearly differs depending on the presence or not of pulmonary fibrosis (p= 0,001 for right hemithorax and p=0,003 for left hemithorax; likelihood ratio test) (Figures 8 and 9). Likelihood ratio of pulmonary fibrosis was calculated for each lung ultrasound finding and for both hemithorax. Mean of both hemithorax is presented next.

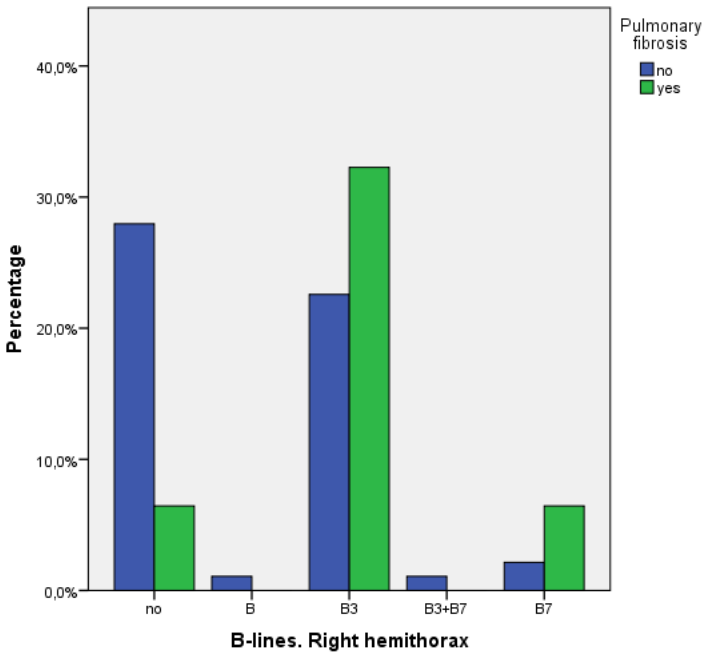

Figure 8 Lung ultrasound findings for right hemithorax depending on presence or not of pulmonary fibrosis signs in HRCT

Only 22,97% of the patients that showed no B lines in lung ultrasound, had fibrosis signs in HRCT. By cons, if B3 lines were present, 60,42% of patients had pulmonary fibrosis.

79,7% of patients who had fibrosis had B3 and/or B7 lines in LUS. Also, 65,9% of patients without fibrosis had no B-lines.

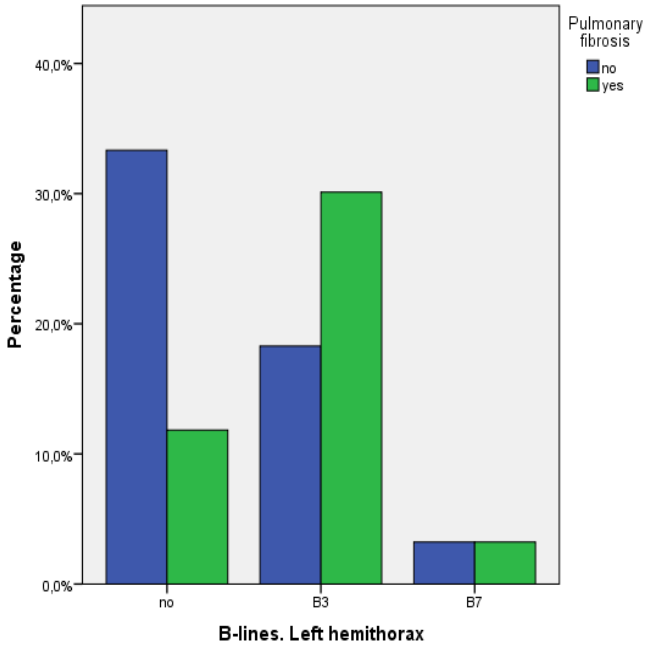

Figure 9 Lung ultrasound findings for left hemithorax depending on presence or not of pulmonary fibrosis signs in HRCT

DISCUSSION

After the SARS and MERS outbreak, there was a general concern among clinicians about whether recovered patients would have long-term health consequences (12,29). During the following years, several cohort studies observed an increased incidence of pulmonary fibrosis in these patients (21,27,28). Likewise, a significant proportion of patients showed an impaired pulmonary diffusion and exercise capacity (1,11).

In this study, we found that around half of the patients still had dyspnea 6 months after discharge. Impaired DLCO % predicted was found in 51,92% of the patients, being average DLCO % predicted lower in patients with pulmonary fibrosis (mean ± SD 71,25 ± 18,73) than in patients without pulmonary fibrosis (80,53 ± 15,65) (p=0,008). In approximately a third of the patients with an altered DLCO % pred, this normalized at 6 months. Distance walked in 6 minutes improves 44,3m from 3 to 6 months (p=0,001). Saint George's total score improves from 3 to 6 months (median [IQR] 19,52% [7,50-34,51] vs 16,16% [5,50-30,31]) (p=0,022). Pulmonary fibrosis was observed in 43,4% of the patients. Patients over 60 years old have 2,04 higher risk (95%CI 1,37 – 3,04) of developing pulmonary fibrosis than patients under 60 years old. Patients with pulmonary fibrosis, had during hospital stay, a higher peak LDH (p=0,034) and a lower lymphocytes count (p=0,001) than patients without pulmonary fibrosis.

Clinical information

We observed that the patients included in our study were older and with more underlying comorbidities, such as respiratory and cardiovascular disease, than the patients participating in similar studies (1,2,7,29) Thus, they have a worse health condition and could be more susceptible to suffer severe COVID-19 and its consequences. We found that, although most of the respiratory symptoms were ceased six months after discharge, dyspnea persisted in around half of the patients. We reported a higher proportion of patients with dyspnea than a similar 6-month follow-up study (53,9% vs 26%). This might be due to a misinterpretation of what is dyspnea and what is fatigue, as the same study reported fatigue in 63% of the patients (7).

Short and long-term health consequences

The results of pulmonary function in the present study showed that DLCO % at three months after hospital discharge was under normal range, having 51,92% of the patients an impaired pulmonary diffusion. These results are consistent with a similar study, which found that 22-56% of the patients had a DLCO <80% predicted, varying on disease severity (7). This is higher than observed in SARS and MERS recovered patients one year after discharge (1,11), though longer follow-up studies are required to determine if these results will persist. We believe many of them will recover, as we reported that in approximately one third of the patients that had a decreased DLCO % predicted value at 3 months, this normalized after 6 months.

Although the trend is to slightly improve exercise capacity, we reported that at 3 months after hospital discharge 32,7% of the patients had walked less than 350m. A distance <350m predicts higher mortality in most of chronic respiratory diseases (43). A close surveillance of these patients could be justified.

We observed that the study participants had a decreased quality of life 3 months after discharge, being physical activity and symptoms the most affected categories. Nevertheless, this improves slightly 6 months after discharge.

Pulmonary hypertension was suggested via transthoracic echocardiogram in 10,2% of the study subjects. We do not have previous echocardiogram of these patients, however, it is known that COVID-19 may lead to ARDS, and that ARDS contributes to pulmonary hypertension development (18,20). No further pulmonary embolisms were noticed in the angioCT performed three months after discharge.

Pulmonary fibrosis

Chest HRCT at 3 months after discharge showed that 43,4% of the patients had residual fibrosis, similar to reported in SARS and MERS (21,27,28). These results are consistent with the reported findings of similar studies, pointing that 27-52% of COVID-19 patients who required hospitalization had fibrosis signs in the HRCT after three months (2,5,29). The previous studies had differences on disease severity (length of hospital stay, requirement of supplemental oxygen or mechanical ventilation, etc.), suggesting that severity itself may influence fibrosis development.

In most of the patients, GGO absorbed partial or completely 6 month after discharge, similar to another research (7). GGO absorption was greater among those patients who were treated with corticoids (prednisone); however, these findings were not statistically significant and additional studies are required.

Previous literature suggested “pulmonary fibrosis to be the main factor leading to pulmonary dysfunction and decline of quality of life in COVID-19 survivors after recovery” (12), although this was not yet demonstrated. In the present study we showed that those patients with pulmonary fibrosis after severe COVID-19 pneumonia had a marked worse pulmonary function, especially pulmonary diffusion, as well as a slight worse exercise capacity. However, this was not expressed in a declined quality of life, measured by SGRQ. Actually, we found a lower score of SGRQ symptoms at 3 months in pulmonary fibrosis group (p=0,049). We considered this as borderline as it is not biologically plausible. It is important to mention that SGRQ has not been validated for community acquired pneumonia but for asthma and chronic obstructive pulmonary disease, therefore, these results might not adequate to reality (40).

There is currently no treatment options for pulmonary fibrosis (6), therefore, early diagnosis and prevention is essential. Although obesity was not identified as a predictive factor, we observed that patients over 60 years have 2,04 higher risk (RR= 2,04 [95%CI 1,37 – 3,04]) of developing pulmonary fibrosis after severe COVID-19 pneumonia,

compared to patients under 60 years old. Therefore, we demonstrated that advanced age might be a potential risk factor for the development of pulmonary fibrosis in COVID-19 patients, similarly to SARS and MERS. It is unclear the exact reason, although it has been pointed out that apoptosis resistance of fibroblast and myofibroblast could be an explanation (6,21). Alike, angiotensin-2 stimulates the proliferation of fibroblast and induces collagen and ECM synthesis. The imbalance of renin-angiotensin-system in older patients could contribute to SARS-CoV-2 infection, its lung injury and its development to lung fibrosis (22).

Those patients with pulmonary fibrosis had a higher peak LDH and lower lymphocytes count during hospital stay than those patients without pulmonary fibrosis, suggesting that these parameters might be predictive factors for the fibrotic remodelling. On one hand, LDH high levels reflects tissue destruction and correlates well with disease severity. In ILDs it has been found LDH to be one of the most important biomarkers of lung injury (16). On the other hand, lymphopenia in COVID-19 could be due to a lymphocytes infiltration after alveolar epithelial cells injury, and could be associated to a higher disease severity and mortality (16). Likewise, length of hospital stays, which is related to disease severity, might be useful for its prediction.

Chest X-ray and lung ultrasound were performed to avoid HRCT and unnecessary radiation. Both exams showed different patterns depending on the presence or not of pulmonary fibrosis. Consequently, although further studies are needed to determine the real utility of these tests, chest- X-ray and LUS could be useful tools during the follow-up of patients after COVID-19 pneumonia to detect and identify those patients that are likely to have pulmonary fibrosis. Nonetheless, it must be considered that the presence of B3 lines in LUS is not an indicator of pulmonary fibrosis by itself but ground glass opacities. By cons, B7 lines do suggest interlobular septum thickening (46). As some patients with fibrotic remodelling had GGO in the HRCT too, and additionally GGO can precede fibrosis, this may act as a cofounding factor.

Strengths and limitations of the study

Nevertheless, there were some limitations in this study. Firstly, this is a single-group observational study, with no control group, so study results might be influenced by some patients' conditions. Besides, baseline data of pulmonary function and exercise capacity are unavailable, additionally, an elevated number of study participants had respiratory (25 cases) and cardiovascular (21 cases) disease, so results might be over-estimated. The observed impaired pulmonary function and exercise capacity cannot be directly attributed to COVID-19.

Secondly, this study only included patients after severe COVID-19 pneumonia, with a higher probability of lung injury and long-term sequalae (26). This means that our findings cannot be extrapolated to every COVID-19 recovered patient, as we did not analyse mild and moderate forms of disease. Finally, some data of a few patients are missing, especially chest X-ray at 1 month, blood tests at 3 and 6 months, and LUS. The reasons are: lack of programming due to error; or because the patient did not attend to medical centre the day he/she was cited. This could be considerate a **lost to follow-up**.

Among the strengths of this study, we find that no restrictions in the inclusion of patients were applied, as all the patients after being discharged could participate in the study and only three patients declined to follow-up. This is important as this minimizes **selection bias**. Also, chest X-ray and HRCT were revised by three different people: Ramon Orriols, Gladis Sabater and me, so **misclassification bias** is unlikely.

To our knowledge, few studies like this provides such complete information, with a considerable study sample, about long-term follow-up of patients after severe COVID-19 pneumonia, up to 6 months after discharge. We analysed data regarding respiratory symptoms, pulmonary function, exercise capacity, quality of life (SGRQ), TTE, analytical parameters, HRCT, chest X-ray and LUS. Furthermore, as some tests and medical visits were performed more than once, we were able to assess the clinical course of recovery of severe COVID-19 pneumonia.

CONCLUSIONS

In conclusion, pulmonary fibrosis develops in 43,4% of patients after severe COVID-19 pneumonia. Pulmonary function is usually normal at 3 months after discharge, except for DLCO % predicted, which is decreased in 51,92% of the patients. However, pulmonary diffusion recovers in a third of the patients at 6 months after discharge. Exercise capacity and quality of life slightly improves from 3 to 6 months after discharge, although half of the patients still presented dyspnea after 6 months. Patients with pulmonary fibrosis had a marked lower pulmonary diffusion and a slightly reduction in exercise capacity, compared to patients without pulmonary fibrosis. However, this did not correspond to a poorer quality of life.

It was observed that patients over 60 years old have 2,04 higher risk (95%CI 1,37 – 3,04) of developing pulmonary fibrosis than patients under 60 years old, after suffering from severe COVID-19 pneumonia. Body mass index was not shown to be a predictive factor for fibrotic remodelling, and neither do so CRP and ferritin levels. Nevertheless, high peak LDH and low lymphocytes count during hospital stay could be a useful tool for the prediction of pulmonary fibrosis development.

Although further studies are needed to assess the adequacy of the tests, the exams performed in this study were clinically significant as they helped to the management and follow-up of the patients, and in the case of chest X-ray and lung ultrasound, statistical differences were found between patients with and without pulmonary fibrosis.

We believe that further studies are needed to determine if the residual sequelae of COVID-19 persist over the years, as well as to help clinicians to establish the best follow-up strategy for these patients. Although vaccination has already started, many recovered patients are still facing the COVID-19 consequences.

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ANNEXES

Annex 1: Chest X-ray and HRCT findings definitions (38)

Definitions based on Fleischner Society Glossary of Terms for Thoracic Imaging (38)

Findings	Chest X-ray	HRCT of the chest
Architecture distortion		Distorted appearance of lung anatomy, usually associated with pulmonary fibrosis and loss of volume
Atelectasis	Reduced volume accompanied by increased opacity in the affected part of the lung	Reduced volume accompanied by increased attenuation in the affected part of the lung
Bronchiectasis		Bronchial dilatation with no alterations on the accompanying pulmonary artery (signet ring sign), lack of tapering of bronchi, and identification of bronchi within 1 cm of the pleural surface.
Condensation/ consolidation	Homogeneous increase in pulmonary parenchymal attenuation that obscures the margins of vessels and airways walls	
Ground glass opacity	Area of hazy increased lung opacity, usually extensive, within which margins of pulmonary vessels may be indistinct.	Hazy increased opacity of the lung, with preservation of bronchial and vascular margins. GGO is less opaque than consolidation, in which bronchovascular margins are obscured.
Honeycombing	Closely approximated ring shadows, typically 3-10 mm in diameter with walls 1-3 mm in thickness, that resemble a honeycomb.	Clustered cystic air spaces, typically of comparable diameters on the order of 3-10 mm but occasionally as large as 2.5 cm. Usually sublpleural and characterized by well-defined walls.

Infiltration/ infiltrate	Region of pulmonary opacification caused by airspace or interstitial disease	
Interstitial	Pattern that, in the acute phase includes ground glass opacities, often with some sparing of individual lobes, producing a geographic appearance; dense opacification is seen. In the chronic phase, includes reticular opacities.	
Loss of volume	Loss of total lung volume	
Reticulation	Collection of small linear opacities that produce an appearance resembling a net	Interlobular septal thickening, intralobular lines or cyst walls of honeycombing.
Traction bronchiectasis		Irregular bronchial dilatation caused by surrounding retractile pulmonary fibrosis.

Annex 2 Saint George's Respiratory Questionnaire (47)

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: 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.

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

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 4: Informed consent

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

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 5 Ethics committee approval

Hospital Universitari de Girona
Doctor Josep Trueta

Avinguda de França s/n.
17007 Girona
Telèfon 972 940 200
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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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