BACHELOR'S DEGREE IN MEDICINE

FINAL UNDERGRADUATE DISSERTATION

"Respiratory sequelae aftermath of SARS-COV2 pneumonia: a retrospective cohort study."

Academic year 2021-2022.

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At Castellón, 18th March 2022

TRABAJO DE FIN DE GRADO (TFG) - MEDICINA

EL/LA PROFESOR/A TUTOR/A hace constar su **VISTO BUENO** para la Defensa Pública del Trabajo de Fin de Grado y **CERTIFICA** que el/la estudiante lo ha desarrollado a lo largo de 6 créditos ECTS (150 horas)

TÍTULO del TFG:

"Respiratory sequelae aftermath of SARS-COV2 pneumonia: a retrospective cohort study"

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This dissertation is dedicated to all the people
we lost due to the COVID-19 infection.

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ABBREVIATIONS

SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus.

SARS: Severe Acute Respiratory Syndrome.

COVID-19: Coronavirus Disease 2019

WHO: World Health Organization.

HGUCS: Hospital General Universitario de Castellón.

CEIm: Committee for the Ethics of Research with Medicines.

ATS: American Thoracic Society

ERS: European Respiratory Society

STROBE: Strengthening the Reporting of Observational Studies in Epidemiology.

ICU: Intensive Care Unit.

BMI: Body Mass Index

COPD: Chronic Obstructive Pulmonary Disease

CT: Computed Tomography

GGO: Ground-Glass Opacity

IMV: Invasive Mechanical Ventilation.

NIV: Non-Invasive Ventilation.

HFNC: High Flow Nasal Cannula Oxygen.

ACE-2: Angiotensin-Converting Enzyme 2.

RNA: Ribonucleic Acid.

6MWT: 6 Minute Walk Test.

PFT: Pulmonary Function Tests.

FVC: Forced Vital Capacity.

FEV1: Forced Expiratory Volume in 1 second.

DLCO: Diffusing Capacity for Carbon Monoxide.

DM: Diabetes Mellitus.

HBP: High Blood Pressure.

VIF: variance inflation factors.

ABSTRACT

Introduction: Respiratory sequalae are a major concern after COVID-19 infection. The need for follow-up and study of COVID-19 patients is imperative to provide the best quality of care, and to design tailored programs for patients' cardiopulmonary and psychological rehabilitation. We aim to assess and describe functional respiratory parameters, changes in chest CT at the 6-month follow-up and their correlation with sociodemographic variables and respiratory comorbidities.

Study design and methods: This analytical retrospective cohort study evaluated discharged patients from Hospital General Universitario de Castellón (HGUCS) with COVID-19 infection or pneumonia diagnostic during the months from March to December 2020. We assessed respiratory sequalae with pulmonary function tests and chest CT at the 6-month follow-up.

Results: Altogether, 35, aged 63.7±9.9 years, out of the 346 patients admitted to the Pneumology Service of the HGUCS were included in the study. Predominantly, they were male, overweight, and middle aged. At the 6-month follow-up 45.7% of patients had a DLCO< 80% and 51.4% presented with abnormal findings in CT scan.

Discussion: The main variable that suggested an association with a worse course of the infection was BMI (p-value 0.07). Variables linked to higher incidence of respiratory sequalae were active/former smoking habit (log odds=2.46, p-value 0.06) and the severity of the infection (log odds=4.13, p-value 0.02). In conclusion, six months after hospital discharge, pulmonary abnormalities and functional impairment are highly prevalent in patients who survived COVID-19 infection. The implementation of a post-hospitalization follow-up program should be considered in patients who suffered a severe COVID-19 infection.

Keywords: COVID-19, SARS-COV2, sequelae, pulmonary function, interstitial fibrosis, pneumonia.

RESUMEN

Introducción: Las secuelas respiratorias son una importante preocupación tras la infección por COVID-19. El seguimiento y estudio de pacientes que han superado la enfermedad es imperativo para ofrecer la mejor calidad asistencial y programas de rehabilitación personalizados. En este estudio, evaluamos y describimos parámetros respiratorios funcionales, cambios en la TAC a los 6 meses y su posible correlación con variables sociodemográficas y comorbilidades respiratorias previas.

Métodos y diseño: Este estudio de cohortes retrospectivo analítico evaluó pacientes del HGUCS diagnosticados de infección o neumonía por COVID-19 durante los meses de marzo a diciembre de 2020. Para valorar las secuelas respiratorias se realizaron pruebas de función pulmonar y TAC torácica 6 meses después del alta.

Resultados: Se incluyeron en el estudio 35 pacientes, con media de edad de 63.7±9.9 años, de los 346 ingresados en el servicio de Neumología del HGUCS. Mayoritariamente eran hombres, con sobrepeso y de mediana edad. A los 6 meses, el 45.7% tenían una DLCO<80 % y el 51.4 % presentaba irregularidades en la TAC.

Discusión: La principal variable que sugiere una peor evolución de la infección fue el IMC (p-valor 0.07). Variables relacionadas con una mayor incidencia de secuelas respiratorias fueron: tabaquismo (log odds=2,46, p-valor 0.06) y gravedad de la infección (log odds=4,13, p-valor 0.02). En conclusión, seis meses tras el alta, las anomalías pulmonares y el deterioro funcional pulmonar son muy prevalentes en los pacientes que sobrevivieron a la infección por COVID-19. Debemos considerar el potencial beneficio de la implementación de un programa de seguimiento en estos pacientes.

Palabras clave: COVID-19, SARS-COV2, secuelas, función pulmonar, fibrosis intersticial, neumonía.

1. Introduction

On March 11, 2020, the World Health Organization (WHO) declared the novel coronavirus (COVID-19) outbreak a global pandemic (1). Since then, COVID-19 cases have risen to over 400 million worldwide, and more than 6 million deaths have been recorded, according to current data from the Johns Hopkins Coronavirus Resource Center (2). The need for follow-up and study of patients who suffered from COVID-19 infection is imperative to provide the best quality of care, and to design tailored programs for patients' cardiopulmonary and psychological rehabilitation. To design these tailored programs, it is crucial to identify the poor prognosis variables related to the infection. These variables will allow us to distinguish those patients with the greatest need for follow-up consultation.

COVID-19 disease is caused by an RNA virus from the Coronaviridae family called Coronavirus type 2, which causes severe acute respiratory syndrome (3), abbreviated SARS-COV2. The first evidence of this virus was discovered in December 2019 in Wuhan, China. The human-to-human transmission of the virus (4) enabled its fast worldwide expansion, causing a health emergency of international magnitude (5).The infection has a very wide spectrum of clinical manifestations, from asymptomatic with a favorable prognosis to patients who require hospitalization and undergo rapid progression to an acute respiratory distress syndrome (ARDS) and may require admission to an intensive care unit (3,6). The WHO Working Group on the Clinical Characterisation and Management of COVID-19 infection recently defined a Clinical Progression Scale (7):

1. Mild disease: patients with SARS-COV2 RNA detected and who did not require hospitalization.
2. Moderate disease: patients that were symptomatic and required assistance and hospitalization but did not require ICU stay during their hospitalization. This category includes patients who needed oxygen supplementation by mask or nasal prongs during their stay and those who did not require any oxygen therapy.
3. Severe disease: patients that were symptomatic and required hospitalization plus oxygen support therapy that included: oxygen by non-invasive ventilation (NIV), high flow nasal cannula oxygen (HFNC), or intubation and mechanical ventilation.

It is still unclear what the long-term effects of COVID-19 will be, but, as COVID-19 causes SARS, data from previous SARS virus pandemics can be used to predict its evolution. In 2003, SARS-COV1 infected more than 8,000 people (8) and long-term

respiratory sequelae were observed in survivors, highlighting the presence of residual pulmonary fibrosis. In the study led by Tansey et al. (2007) (9) they evaluated 117 SARS-COV1 patients at 3, 6 and 12 months after hospital discharge, observing a decrease in the 6-minute walk test (6MWT) in 18% of the participants, which was associated with dyspnea and fatigue. They also identified the psychological impact of the disease, since 51 patients required up to 668 consultations in psychiatry or psychology, mainly for anxiety reasons. Furthermore, in 2005 Hui et al (10) followed 110 survivors and concluded that the exercise capacity and health status of SARS survivors was considerably lower (mean distance of 502 m) than that of a normal population at 6 months assessed with the 6MWT. Age (β coefficient −3.31 (SE 0.88), $p<0.001$) and female sex (β coefficient −67.62 (17.41), $p<0.001$) were significantly negative predictors of the walking test. They also performed respiratory function tests where 15.5% of patients had impaired DLCO. Moreover, researchers found a significant negative correlation between the extent (%) of radiographic abnormalities, measured by CT scan, and FVC ($r=-0.23$, $p=0.02$) and DLCO ($r=-0.29$, $p<0.01$).

In addition, Zhang et al. (2020) (11) published a prospective cohort study initiated in 2003, in which they followed up 78 health professionals diagnosed with SARS-COV1 infection for 15 years. They evaluated both the pulmonary and bone components using pulmonary CT imaging, pulmonary function tests, and MRI of the hip joint. In 2006, they assessed lung function by spirometry, dividing the cohort into those with CT abnormalities and those without. They observed that in the group with pulmonary injuries determined by CT scan both forced expiratory volume in 1 second/forced vital capacity (FEV1/FVC ratio) and FEF25%–75% were significantly reduced in the group with pulmonary injuries determined by CT scan. They also observed that damages in the lung tissue decreased radically between 2003 and 2004 ($t=-2.56$, $p=0.01$), however, from 2004 they remained stable until the end of the study in 2018, evidencing the importance of early pulmonary rehabilitation.

There are still not many published works about the sequelae of the new SARS-COV2 infection, and, given its recent spread, they are limited to describe its short-term effects.

The method used to search the relevant literature involved using PubMed database and different search strings were pulled in November 2021. The criteria to be included are peer-reviewed journal articles written in English:

1. PubMed search for MeSH terms “COVID-19” and “pneumonia”: 144,977 papers have been reduced to 15 after refining the search with “Lung function” and

"Pulmonary Fibrosis", reading the abstracts to focus on sequalae aftermath methodologies. Snowball effect with documents cited by the previous 15 selected.

2. PubMed search for MeSH terms "COVID-19", "asthma" and "phenotypes": 6 results. Snowball effect with documents cited by the previously 6 selected documents.
3. PubMed search for MeSH terms "COVID-19" and "COPD": 286 papers reduced to 2 after refining the search with "Risk assessment" and reading the abstracts to focus on sequalae aftermath of the infection methodologies.

Using these search criteria, and after eliminating duplicities, 26 papers were categorized as studies focused on respiratory sequelae aftermath of SARS-COV2 pneumonia.

The commonalities reported are significant pulmonary and psychological involvement(12–14). In the 3-month cohort study conducted by Gónzalez et al. (2021) (12), they followed 62 patients who had been admitted to the ICU between March and June 2020 with a diagnosis of SARS due to COVID-19. The most frequent symptom was dyspnea, experienced by 46.7% of the patients. Additionally, they observed abnormalities in the diffusing capacity of less than 80% in 82% of patients; a decrease in the 6MWT, where the mean distance was 400 meters and, regarding CT results, a fibrotic pattern in 21.1% and a reticular pattern in 49.1%. They found that some factors associated with the severity of lung damage were age and the mean time of invasive mechanical ventilation (p= 0.40). Moreover, in the study published by Safont et al. (2021) (13), pulmonary function tests, detection of biomarkers in circulating plasma, and radiography and chest CT were performed during outpatient visits to 313 patients who had previously suffered from SARS-COV2 pneumonia in the previous 6 months. They concluded that the proportion of patients with DLCO < 80% was 54.6 and 47% at 6 months after discharge, while 68.35% of severely ill patients showed ground glass opacities and 38.46%, parenchymal bands observed by CT scan. Some factors associated with diffusion alteration at 6 months were female sex (OR: 2,97; CI of 95%: 1,74-5,06; p = 0,001), and age (OR: 1,03; CI of 95%: 1,01-1,05; p = 0,005).

Clinical exploration and imaging techniques evidence the impact of the infection. Comparing studies about these two coronaviruses, we see a similar pattern of similarity in the lung tissue damage supported by CT scans (ground glass opacities and signs of fibrosis). The impact the infection has is evidenced both in clinical exploration and imaging techniques. We can observe that the outcomes in the 1-year follow-up of the SARS-COV1 and the studies we currently have of the short impact of SARS-COV2 pneumonia have similar outcomes in the respiratory function tests and imaging results,

as well as clinical tests such as the 6MWT, and the dyspneic sensation described by patients. Moreover, psychological impact of both infections has shown to be significant, demanding programs of rehabilitation for these patients that include not only medicine specialists but teaming closely with psychology professionals.

Therefore, considering the resemblances between the 2003 SARS-COV1 pandemic and the 2019 SARS-COV2 pandemic, it is reasonable to think that the complications and long-term impact will be similar, producing morbidity in part of the affected population and requiring close follow-up in many areas of health care.

Additionally, knowing the devastating impact COVID-19 infection has on the lung tissue, it is reasonable to fear the impact this virus may have in patients with previous respiratory pathologies such as asthma o COPD. A study carried out by Guan et al. (2020) (15) in 2020 with a sample of 1590 patients showed that COPD had a higher risk for ICU admission, death and need of invasive ventilation. They also observed that 62.5% of the severe cases of SARS-COV2 infection were patients with underlying COPD. Furthermore, in a recent Spanish study led by Barrasa et al. (2020) (16) from the 48 ICU patients in the sample the prevalence of those with COPD was 38%. The systematic review carried out by Leung et al. (17) stated that COPD patients have not only a higher risk of presenting with severe COVID-19 pneumonia but also a poorer clinical outcome. They theorized that this finding may be related to limited underlying lung reserves or increased expression of angiotensin-converting enzyme 2 (ACE-2) receptor in small airways, which the SARS-COV2 virus uses as a cell entry (18), binding itself. It has been determined that there is an anti-inflammatory potential of ACE2/Angiotensin-(1-7)/MAS receptor axis. ACE-2 inhibits the activity of angiotensin II by converting angiotensin I to angiotensin 1-9 and angiotensin II to angiotensin 1-7, which binds to the MAS1 proto-oncogene (MAS) receptor giving this process anti-inflammatory effects. Subsequently, there is a shift within the ACE/ACE-2 balance, as the particles of the SARS-COV2 are blocking ACE-2 receptors, towards a predominance of ACE leading to increased pro-inflammatory effects and tissue damage (19) observed in COVID-19 infection. Current smokers also have increased expression of ACE-2 receptors (20), making us question if this might be the explanation of their poorer clinical prognosis when diagnosed with SARS-COV2 pneumonia (21).

Concerning asthma, Muñoz et al. (2021) (22) raised the question whether asthma also could be a risk factor for suffering from severe COVID-19 pneumonia. They performed a cross sectional analysis and estimated that the prevalence of COVID-19 hospitalized

asthmatic patients form March 2020 to June 2020 was of 3.2%, compared to the general prevalence in the area (6%) showing that not only it didn't appear to be a risk factor but a protective one.

Chronic asthma treatment is composed by a combination of inhaled or systemic corticosteroids and β2-agonists. When studying the current COVID-19 pneumonia treatment we find that the basic scheme also consists of corticosteroid boluses combined with antiretrovirals such as Remdesvir or in some cases Anti-IL-6 receptor Monoclonal Antibodies (Tocilizumab) (23). Studies have shown that inhaled corticosteroids alone or in combination with bronchodilators can suppress the replication of the coronavirus and decrease the production of cytokines (24). We postulate that if these patients contract the virus they would be on the current treatment for the infection since day 0, making their clinical prognosis during hospitalization milder.

Although short-term radiologic and pulmonary function tests outcomes have been reported in patients with noncritical disease, little is known about the outcomes of patients with underlying pulmonary pathologies such as asthma or COPD and those who developed a severe COVID-19 infection during hospitalization.

The question remains as to whether asthma patients may have a better prognosis if diagnosed with COVID-19 pneumonia and the underlying reason. It could be related to their chronic treatment with corticosteroids and bronchodilators. On the other hand, COPD patients with treatment schemes similar to asthmatic patients, supposedly have poorer outcomes. Perhaps this is due to previous smoking habit and chronic injuries in the lung tissue. As our sample comes from the admission records of the Pneumology Service of the Hospital General Universitario de Castellón it has a large quantity of patients with history of pulmonary pathologies (asthma and COPD) since they were prioritized in this Service at admission. We aspire to identify if these factors are associated with a higher incidence of respiratory sequelae or poorer clinical prognosis during their hospitalization and follow-up.

We aim to obtain a global view of the patients who were admitted between March and December 2020 for COVID-19 pneumonia or infection and who were or are being followed up by the post-COVID-19 Pneumology consultation with the goal of improving care practice after the acute process and identifying those population groups with higher risk of severe COVID-19 infection hospitalization and need of closer follow-up. We hope our study findings will add knowledge of the respiratory consequences of this novel coronavirus and its clinical features.

2. Main, secondary objectives and hypotheses.

2.1. Objectives

Main objective

1. To describe the respiratory sequelae, evaluated with respiratory function tests and CT-scan, after 6 months in patients admitted to the Pneumology Service of the Hospital General Universitario de Castellón due to pneumonia or SARS-COV2 infection from March 2020 to December 2020.

Secondary objectives

2. To determine risk and prognostic factors of severe disease during hospitalization in the same population group.
3. To assess the impact of pneumonia or COVID19 infection on respiratory function using spirometry and the pulmonary carbon monoxide diffusion test and restrictive pulmonary alterations using imaging tests (high-resolution chest CT) in the same population group.
4. To sequentially relate the different treatment schemes that were used in the period defined by the study and the possible impact they had in our sample of patients.

2.2. Hypotheses

1. Given the previous studies conducted on patients with SARS-COV1 and SARS-COV2 that showed decreased pulmonary function (9–13), we expect to find decreased values of DLCO, FVC and FEV1 in respiratory function tests and fibrosis signs in CT-imaging in our sample of patients.
2. As mean time of invasive ventilation and ICU stay have been associated with the severity of lung damage after hospitalization (12), we presume patients who had a poor course of the infection during hospitalization will present higher incidence rate of respiratory sequelae at follow-up compared to those whose infection severity was moderate.
3. As smoking has been identified as a risk factor for pulmonary problems (21), we expect patients that are active or former smokers will show higher incidence rate of respiratory sequelae after their admission for pneumonia or SARS-COV2 infection compared to patients that were never smokers.
4. Patients with previous respiratory pathologies, such as COPD, have shown a higher risk of needing invasive ventilation and poor course of the infection (15–17), we presume our sample of severe hospitalized patients will show higher incidence rate of

underlying COPD and respiratory sequelae after their admission for pneumonia or SARS-COV2 infection compared to those without this pathology.

5. Given the studies conducted with asthmatic patients that evidenced a possible protective effect of the pathology with the severity of the COVID-19 infection (22), and the studies that associate it with their chronic corticosteroid and beta-blocker treatment(22,24), we expect our sample of asthmatic patients will present a better SARS-COV2 clinical progression during their hospitalization compared to the general population.

3. Material and methods

3.1 Design and setting

This study was set as an analytical, observational, retrospective cohort study with the aim of assessing respiratory sequelae on patients who had undergone hospital stay due to COVID-19 pneumonia in the Pneumology Service of the Hospital General Universitario de Castellón. Additionally, we seek to describe their hospitalization during the acute process and the factors associated with the severity of the disease.

3.2 Participants

The sample was selected from the patients residing in the province of Castellón, who were admitted to the Pneumology Service of the Hospital General Universitario de Castellón with diagnosis of SARS-COV2 pneumonia or infection between the months of March and December 2020. The inclusion criteria for this study were age >18 years, positive nasopharyngeal swab to SARS-COV2 at admission and follow-up at the outpatient COVID-19 clinic at Hospital General Universitario de Castellón. We excluded patients with a life expectancy of less than a year, passed away during hospitalization, and patients who were unable to perform the pulmonary function tests after discharge.

Patients included did not provide their informed consent as the study was carried out using an anonymized database without any personal identifying data. Moreover, as this was a retrospective study that covered a timespan of 6 months from the year 2020, contacting each patient and collecting their informed consent was practically impossible. As a result, this study possesses an exemption of having the patient's informed consent issued by the Committee for the Ethics of Research with Medicines (CEIm) of the Hospital General Universitario de Castellón.

3.3 Sample size

The sample size was not calculated prior to the study initiation due to a number limited database. We included all the patients admitted to the Pneumology Service of the Hospital General Universitario de Castellón that fulfilled the inclusion criteria. The period selected for this retrospective analysis was from March to December 2020 since the post COVID follow-up had been implemented for these admissions.

3.4 Variables and instrumentation

The acute episode of hospitalization was reviewed, and different variables were collected:

- Severity of the disease during hospitalization: we divided the cohort of patients by their disease severity according to the WHO Clinical Progression Scale (7) in moderate disease or severe disease, as all of our patients required hospitalization.
- Additional variables collected: use of corticosteroid boluses; use of antiretrovirals and, if so, which ones; use of Tocilizumab; use of hydroxychloroquine; respiratory therapy required during hospitalization; and need and days of ICU stay.

After the acute process of COVID-19 pneumonia or infection, patients were discharged from the Pneumology Service and given an appointment at six months to the outpatient post-COVID-19 consults at Hospital General Universitario de Castellón. During the time between discharge and the outpatient consult, patients were required to perform a pulmonary function test (collecting data of DLCO, FVC and FEV1) and undergo a CT-scan reviewed and informed by the department of Radiology of the Hospital General Universitario de Castellón.

- Respiratory sequalae measured by pulmonary function tests and CT-scan.
    - Pulmonary function tests. All patients included in the study underwent standard pulmonary function tests with an ergospirometry system (MasterScreen PFT-Pro Jaeger). We measured forced expiratory volume in 1 second (FEV1), vital capacity, forced vital capacity (FVC) and Carbon Monoxide Diffusing Capacity (DLCO). The hemoglobin value was evaluated before each test to apply the appropriate correction to DLCO values. The spirometer was calibrated the day of the test by a trained technician who also coached the patient during said test. A pneumologist was responsible for validation and interpretation of the results following the American Thoracic Society (ATS) and European Respiratory Society (ERS) guidelines(25).
    - Imaging. All patients included in the study underwent a chest X-ray at admission and a CT scan 6 months after discharge. Patients were scanned

using a 16 multidetector CT scanner (Aquilion; Canon Medical Systems). During the acquisition of these scans, patients were in the supine position in the craniocaudal direction at end inspiration. All images were reviewed by experienced radiologists from the Hospital General de Castellón and described for the presence of ground glass opacities and fibrotic or reticular lesions. The Fleischner Society glossary of terms for thoracic imaging (26) was used to define the presence of fibrotic pattern (architectural distortion, honeycombing, reticular opacities). The resulting images were visualized with a picture archiving and communication system (PACS).

- Sociodemographic and comorbidity data was obtained retrospectively and included: age, sex, BMI, smoking habit and history of respiratory pathologies (asthma and COPD) and chronic treatment with corticosteroids and/or bronchodilators. Additional variables obtained were history of other known diseases (DM, HBP), COVID-19 vaccination status and whether they had been discharged from the COVID19 outpatient consult.

3.5 Ethics

The study was carried out complying the international ethical principles (Declaration of Helsinki, Brazil, 2013) and applicable national legislation (Law 14/2007 on biomedical research). The data was treated in a coded form and only used for the purposes of the study. The confidentiality of the patients included in the study will be guaranteed in accordance with the provisions of the "Ley Orgánica de Protección de Datos Personales" (15/1999 December 13th).

The study possessed a favorable report for its realization by the Committee for the Ethics of Research with Medicines (CEIm) of the Hospital General Universitario de Castellón (**Annex 1**).

3.6 Statistical analysis

We followed the "Strengthening the Reporting of Observational Studies in Epidemiology" (STROBE) guidelines for reporting observational studies (27). The database was composed using an Excel sheet and statistical analyses were performed using Jamovi version 2.0 (28).

A descriptive analysis of all study variables was performed, calculating mean and standard deviations (SD) for the quantitative variables and frequencies, and percentages for categorical variables. Normality was checked with the Shapiro–Wilks's test. For quantitative variables, group median comparison was carried out using the non-

parametric U-Mann Whitney test as the data didn't follow a normal distribution. For qualitative variables, comparison of frequencies between moderate and severe disease was carried out with the non-parametric Fisher's exact test for dichotomous variables due to the small sample size and as the data didn't follow a normal distribution.

A logistic regression model was carried out to study prognostic factors for lower DLCO values at 6 months. Full model included: age, severity of COVID19 infection during hospitalization, respiratory comorbidities (COPD or asthma) and smoking habit (smoker or former smoker versus never-smoker) as independent variables.

A binomial logistic regression was performed to identify factors associated with presence of fibrotic pattern determined at CT-scan 6 months after discharge. The model included as independent variables: age, sex, BMI, severity of COVID19 infection, respiratory comorbidities (COPD or asthma) and smoking habit (smoker or former smoker versus never-smoker).

A second binomial logistic regression was carried out to study the factors associated with a greater severity of the COVID19 infection. This model included as independent variables: age, BMI, respiratory comorbidities (COPD or asthma) and smoking habit (smoker or former smoker versus never-smoker).

The potential problem of multicollinearity has been explored by means of the variance inflation factors (VIF). The VIF values are below 3, therefore, multicollinearity is not a concern. The statistical cut-off for significance was set at $\alpha \leq 0.05$ although values that reach a $\alpha \leq 0.1$ of significance will also be discussed.

4. Results

Between Jan 1 and Jan 31, 2022, this analytical, observational, retrospective cohort study evaluated 346 patients who were admitted for SARS-COV2 infection or pneumonia from March 2020 to December 2020 to the Pneumology Service of the Hospital General Universitario de Castellón. 223 patients' data was not collected due to the numerous waves of the pandemic and the overload of the healthcare. After applying the exclusion criteria above mentioned, 55 of them were considered eligible for this study.

The final sample consisted of 35 patients who completed follow-up at 6 months and could be included in the study. (**Fig 1.**)

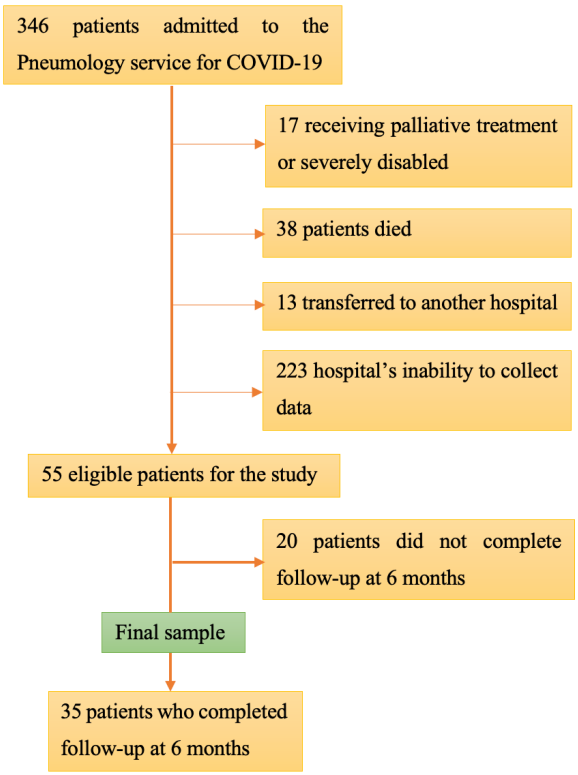

Fig.1. Flowchart showing patients with COVID-19 included in the study.

The sample of patients consisted of 24 men and 11 women aged 63.7±9.9 with a BMI of 30.8±5.9. The characteristics of our study population are displayed in **Table 1** and splatted by the severity of the COVID-19 infection during hospitalization. 51.4% of the sample were former smokers. The moderate COVID-19 infection group was composed by 25 patients and the severe COVID-19 infection group of 10 patients. Regarding their respiratory comorbidities, the prevalence of asthma and COPD was 20% and 31.4% respectively. Five (50%) of the severe COVID-19 group had a history of COPD and two (20%) of them, of asthma. The median hospitalization days was 14.4 days in the total group, whereas in the severe COVID-19 group the hospitalization was longer, with a mean of 24.4 days. Three (8.6%) patients required admission to the ICU with a mean stay of 5.3 days. Patients were mostly treated with Metilprednisolone (82.9%). Additionally, four (11.4%) patients were treated with Tocilizumab. Six (17.1%) participants were treated with antiretrovirals (one (16.7%) with Remdesvir and five (83.3%) with Lopinavir/Ritonavir) and seven (20%) were administered Hydroxychloroquine in early

stages of the pandemic. The great majority of our sample (94.3%) has received at least 1 dose of the COVID-19 vaccine as they became available.

Table 1. Characteristics of the enrolled patients.

Characteristic **Data**	Total *n*=35	Moderate COVID-19 *n*= 25	Severe COVID-19 *n*= 10
Age, years	63.7 (9.9)	62.9 (14.8)	65.6(15.7)
Sex			
Male	24 (68.6%)	17 (68%)	7 (70%)
Female	11 (31.4%)	8 (32%)	3 (30%)
Duration of hospitalization, days	14.4 (9.9)	10.4 (5.4)	24.4 (11.6)
Requirement of ICU	3 (8.6%)	-	3 (30%)
Mean of ICU stay, days	5.33 (2.1)	-	5.33 (2.1)
Body mass index, kg/m²	30.8 (5.9)	29.7 (5.5)	33.7 (6.2)
Treatment during hospital stay			
Hydroxychloroquine	7 (20%)	5 (20%)	2 (20%)
Antiretrovirals	6 (17.1%)	4 (15%)	2 (20%)
Metilprednisolone	29 (82.9%)	20 (80%)	9 (90%)
Tocilizumab	4 (11.4%)	1 (4%)	3 (30%)
Smoking habit			
Never smoker	14(40%)	11 (44%)	3 (30%)
Former smoker	18 (51.4%)	12 (48%)	6 (60%)
Active smoker	3 (8.6%)	2 (8%)	1 (10%)
Respiratory comorbidities			
Asthma	7 (20%)	5 (20%)	2 (20%)
COPD	11 (31.4%)	6 (24%)	5 (50%)
Vaccination status			
Vaccinated with at least 1 dose	33 (94.3%)	24 (96%)	9 (90%)
Not vaccinated	2 (5.7%)	1 (4%)	1 (10%)

Data are in n (%) *or mean* (SD).

The pulmonary function tests results and CT scans findings at the 6-month follow-up are shown in **Table 2**.

Regarding our first hypothesis expecting to find decreased values of DLCO, FVC and FEV1 in respiratory function tests and fibrosis signs in CT-imaging in our sample of patients, we found that at the 6-month follow-up 45.7% of patients had an impairment of lung diffusion (DLCO< 80% of predicted). Patients from the severe disease group showed statistically worse levels of DLCO. According to our study protocol the 35 participants had undergone a CT scan at 6 months. Almost half of our patients had no radiological sequelae, whereas 51.4% of the participants presented with abnormal findings in CT scan. Moreover, 90% of those who required respiratory support therapy with high flow oxygen or mechanical ventilation during hospitalization, presented with respiratory sequalae determined by CT imaging, showing predominantly fibrotic pattern or ground glass opacities.

Table 2. Pulmonary function tests and CT findings of patients at 6 months follow-up.

Test / Data	Total *n*=35	Moderate COVID-19 *n*= 25	Severe COVID-19 *n*= 10
Pulmonary function tests results			
FVC *(% of predicted)*	86.2 (16.1)	86.3 (14.4)	86.1 (20.6)
FEV1 *(% of predicted)*	82 (20.9)	82.3 (20)	81.2 (24)
DLCO *(% of predicted)*	81.5 (26.8)	89.5 (25.4)	60 (17.5)
DLCO *<80% of predicted*	16 (45.7%)	7 (28%)	9 (90%)
CT findings results			
Normal CT pattern	17 (48.6%)	15 (60%)	1 (10%)
Abnormal CT findings			
Ground glass opacities	12 (34.3%)	7 (28%)	5 (50%)
Fibrotic pattern	14 (40%)	5 (20%)	9 (90%)

Data are in n (%) *or mean* (SD).

To assess our initial hypotheses regarding factors possibly associated with worse COVID-19 infection severity, we carried out hypotheses contrast tests detailed in **Table 3**.
Levels of DLCO at the 6-month follow-up of severe COVID-19 patients (Mdn= 68) were lower than those whose infection severity was moderate (Mdn= 89.7). A Mann-Whitney U test indicated that this difference was statistically significant, U ($N_{moderate}$=25, N_{severe}=10)=30, p value <0.05. As we previously hypothesized, patients who had a poor course of the infection during hospitalization and those with moderate infection show a different median distribution of respiratory sequelae, in this case DLCO, at follow-up.
Levels of BMI of severe COVID-19 patients (Mdn=33.7) were higher than those with moderate infection (Mdn=29.9). A Mann-Whitney U test indicated that this difference was nearly statistically significant, U ($N_{moderate}$=25, N_{severe}=10)=60, p value 0.07.

Regarding the qualitative association analyses test (Fisher's exact test), no statistical significance was found between the two groups of infection severity. However, although not statistically significant, history of COPD suggested a possible association with worse clinical course during COVID-19 infection (relative risk of 1.57, CI 0.8-2.9, p-value 0.2).

Table 3. Hypotheses contrast test.

COVID19 infection severity	**Statistical test**	Fisher's exact test	Mann Whitney U test
Variables			
Age, years		-	113 (0.674)
Sex (M=1, W=2)		RR 0.98 (0.91)	-
Body mass index, kg/m²		-	60 (0.04) *
Smoking habit		RR 1.47 (0.7)	-
Respiratory comorbidities			
Asthma		RR 1 (1)	-
COPD		RR 1.57 (0.2)	-
Pulmonary function tests results			
FVC *(% of predicted)*		-	110.5 (0.61)
FEV1 *(% of predicted)*		-	110 (0.59)
DLCO *(% of predicted)*		-	30 (0.02) **

***p<0.05, *p<0,1,*

In Fisher's exact test: RR= relative risk (p-value), and:

H_0: there is no relationship or association between COVID 19 infection severity and the independent variables

H_1: the variables are dependent, there is a relationship between the two variables.

In Mann Whitney U test: statistic (p-value), and:

H_0: there is no difference between the median of the two groups of COVID-19 infection severity regarding the target variables ($Md_1=Md_2$)

H_1: there is a difference between the median of the two groups of COVID-19 infection severity regarding the target variables. ($Md_1 \neq Md_2$)

Factors associated with altered values of DLCO are detailed in the first column of **Table 4** with a logistic regression analysis. A severe infection during hospitalization (patients who required respiratory support therapy with high flow oxygen or mechanical ventilation) was a statistically significant predictor of diffusion impairment at 6-month follow-up.

A binomial regression analysis (second column of **Table 4**) showed that factors associated with the presence of a fibrotic pattern at 6-month follow-up were a severe infection during hospitalization and an active or former smoking habit.

Consequently, statical analyses support our second hypothesis (p value of 0.02) of higher incidence rate of respiratory sequelae (decrease of DLCO values and fibrotic pattern) at follow-up in patients with severe infection course during hospitalization compared to those whose infection severity was moderate.

Moreover, the binomial regression (second column of **Table 4**) estimate (log odds=2.46) indicated that an active or formerly active smoking habit corresponded, on average, to odds increase of 2.46 of presenting fibrotic signs in CT-scan, these findings were nearly statistically significant with a p value of 0.06. Therefore, regarding our initial hypothesis of a possible association between smoking habit and respiratory sequelae, we find that

patients who were active or former smokers showed a positive relation with respiratory sequelae, in this case fibrotic pattern at 6-month follow-up.

A third binomial regression model (third column of **Table 4**) was carried out with the aim of identifying associated factors with a critical clinical course of COVID-19 during hospitalization. Although the model fit was not statically significant ($R^2_{adjusted}$ of 0.17, p-value 0.2) higher BMI values suggested a possible association with a severe infection during hospitalization. Regarding our fourth and fifth hypothesis, with this binomial regression model we can't determine a statistically significant association between respiratory comorbidities, such as asthma or COPD, and a severe or moderate COVID-19 infection during hospitalization.

Table 4. Regression models.

DEPENDENT VARIABLES	DLCO values at 6 months [(a)]	Fibrotic pattern at 6 months (0-1) [(b)]	COVID-19 severity (0-1) [(b)]
INDEPENDENT VARIABLES			
Age	-0.38 (0.30)	-0.01 (0.06)	-0.02 (0.04)
Sex *(M=1, W=2)*	-	-1.24 (1.72)	-
Body mass index, *kg/m²*	-	0.19 (0.12)	0.15 (0.09) *
Smoking habit (*0= never smoker, 1=smoker/former smoker)*	13.33 (9.75)	2.46 (1.43) *	-0.24 (1.13)
Respiratory comorbidities (0= none, 1=present)			
Asthma	8.92 (10.37)	-1.02 (1.61)	0.11 (1.13)
COPD	-9.96 (10.11)	-0.86 (1.35)	1.74 (1.17)
COVID 19 infection severity *(Moderate = 1, Severe =2)*	-27.43 (9.44) **	4.13 (1.91) **	-
Intercept	110.63 (27.86) **	-7.491 (3.79) **	-6.15 (3.99)
Model fit measures	Adjusted R^2 0.2, F value 2.32 **	Adjusted R^2 0.46 X^2value 19.8 **	Adjusted R^2 0.17 X^2value 6.39

***p<0.05, *p<0,1; (a) Logistic regression, (b) binomial regression.*

Data are estimate (SE).

In binomial regression estimates represent the log odds of fibrosis/severe infection vs. fibrosis/moderate infection.

5. Discussion

5.1. Key results

As of March 2022, two years after the pandemic officially started, 464.528.525 people worldwide have been infected by SARS-COV2 (2). After the SARS-COV1 outbreak in 2003, there was an important question for hospitals and doctors: will recovered SARS patients face any long-term clinical sequelae? According to the study carried out from 2003 to 2018 by Zhang et al. (11) they followed SARS-COV1 patients for 15 years, they observed that damages in the lung tissue decreased radically between 2003 and 2004 ($t = -2.56$, $p = 0.01$), however, from 2004 they remained stable until the end of the study in 2018, evidencing the importance of early pulmonary rehabilitation. Moreover, in 2006, they observed that FEV1/FVC ratio and FEF25%–75% were significantly reduced in the group with pulmonary injuries determined by CT scan.

Considering the similarities between the SARS-COV1 and the SARS-COV2 we ask ourselves the same question today with the COVID-19 pandemic, as its long-term respiratory sequelae remain unknown. This retrospective cohort study of patients with severe and moderate COVID-19 infection found CT abnormalities such as fibrotic pattern signs and DLCO impairment at the 6-month follow-up after hospital discharge. Regarding pulmonary function tests, 45.7% of patients presented an impairment of lung diffusion (DLCO <80%). From this group, 90% were patients who had undergone a severe infection during hospitalization, requiring respiratory support therapy with high flow oxygen or mechanical ventilation.

Chest CT abnormalities were found in 51.4% of our patients, predominantly, fibrotic pattern and ground glass opacities. The proportion of these abnormalities was higher in the severe infection group, where 90% of patients showed fibrotic pattern at the 6-month follow-up. Another study that also performed a 6-month follow-up (13) showed that the main striking effect in COVID-19 survivors is diffusion abnormality and their sample showed CT abnormalities in 66% of the patients, mainly in those with a severe infection. This result is in line with our findings, although the rate of reticular and fibrotic lesions was higher in our sample (40% vs. 22.12%).

Our findings have suggested BMI as a factor associated with a worse course of the infection during hospitalization (p-value 0.07) if the statistical cut-off for significance was set at an α-value of 0.10. Variables linked to higher incidence of respiratory sequalae were active or former smoking habit and the severity of the infection. These findings

encourage the importance of quality clinical interviews and proper triage. Patients who would be more likely to develop severe adverse outcomes of COVID-19 and respiratory sequalae would benefit from early detection upon hospitalization.

Regarding the implication of previous respiratory comorbidities, such as asthma or COPD, in the severity of the infection or the long-term respiratory sequalae, our findings were not statistically significant. Nonetheless, history of COPD suggested a possible association with worse clinical course during COVID-19 infection (relative risk of 1.57, CI 0.8-2.9, p-value 0.2). On the other hand, although not reaching statistical significance, our data suggested that history of asthma corresponded, on average, to an odds decrease of 1.02 of presenting fibrotic signs in CT-scan (CI -4.21-2.11, p-value 0.4). These findings align with previous studies that suggest a potential protective effect of asthma and hypothesize that COPD may be a risk factor of worse infection course. The underlying reason remains unknown, but other studies (22–24) suggest that it could it be related to their chronic treatment with corticosteroids and bronchodilators. Perhaps COPD patients have higher risk of severe COVID-19 infection due to their previous smoking habit, as we have seen that smoking habit is linked to a higher incidence of respiratory sequalae (odds increase of 2.46 of presenting fibrotic signs in CT-scan, p-value 0.06).

Concerning the treatment scheme followed during hospitalization, we observed that the proportion of patients who were treated during hospitalization with glucocorticosteroids was 82.9%. Our study participants were those who survived the acute process and that were able to undergo respiratory function tests, we theorize that empirical treatment with glucocorticosteroids may have a potential beneficial effect during acute infection and could be helpful in selected patients. Further studies with a larger sample and exact dosage of treatment are required to validate this hypothesis, as well as studying the treatment scheme of patients who did not recover from the acute process.

In summary, our results go in line with the existing literature, supporting previous claims of Safont et al. (2021) (13) and González et al. (2021) (12). They also have several clinical implications, the most important one being that as more respiratory sequalae have been observed in severe infection patients, close follow-up after their hospital discharge is highly encouraged. This highlights the need to maintain the specialized post-COVID-19 outpatient consults in selected patients, as well as respiratory and physical rehabilitation programs. Although the long-term pulmonary sequelae are still unknown, data suggests critically ill patients with COVID-19 should be close monitored after discharge.

5.2. Study limitations

Our study has various limitations. First, the cohort of the present study consisted of a small sample from a single city. A larger and more heterogenous sample of multiple locations would be more favorable for future studies to achieve an external validation of the results.

Another key limitation was patient selection bias, as we only included patients who had completed their 6-month follow-up. Many discharged patients did not fulfill this inclusion criteria. These missing patients may have perceived they made a full recovery or felt unable or unwilling to attend extra visits. Consequently, the real number of patients experiencing respiratory sequelae might have been lower if all had participated in the study. Furthermore, patients in our study were mainly those who had a history of respiratory comorbidities prior to the infection or the more severe cases, as they were the ones prioritized to be admitted in the Pneumology Service of the Hospital General Universitario de Castellón. As a result, the scenario we portray in this study gives an insight into the cases that will have the highest risk of developing complications.

As the data was limited from the start because of the constraints we just mentioned, we worked with the available data and did not calculate the ideal sample size for the study. Moreover, the analyses of data collected retrospectively over a very long period, the different waves of COVID19 infection, and its toll on the health professionals, caused an inevitable loss of data, both in terms of quantity and quality, which potentially distorted the results.

Finally, it is impossible to know with the available data whether the lung lesions detected at the 6-month follow-up were present before our study and the potential bias this may have in our results.

5.3. Interpretation

In conclusion, patients who survived severe COVID-19 infection show a higher proportion of respiratory sequalae, mainly DLCO impairment and fibrotic signs in CT-scan, compared to those whose infection course was moderate at the 6-month follow-up. A thorough assessment of potential comorbidities, such as high BMI or former/active smoking habit, may help establish risk stratification of patients with COVID-19 at hospital admission.

Although the long-term pulmonary sequelae are still unknown, these data support the need of close follow-up for these patients. Consequently, the implementation of a post-

hospitalization follow-up program including CT-scans and pulmonary function tests should be considered in patients who suffered a severe COVID-19 infection.

5.4. Future lines of research

Given our results suggesting a possible association of asthma or COPD with COVID-19 infection, an interesting approach for future studies might be analyzing a larger sample of patients, some of them with respiratory comorbidities and some of them without any history of previous respiratory diseases. This larger sample would increase the statistical power and facilitate subgroup analyses stratified by the respiratory comorbidities (asthma and COPD). This way we might be able to fully comprehend the impact these pathologies have in a worse or better outcome after the infection and hospitalization, both the severity of said infection and the long-term sequalae.

Regarding the potentially beneficial effect of using glucocorticosteroids as treatment in the acute process, future studies with exact dosage values, moment of treatment and studying the treatment scheme of patients who did not recover from the acute process would be desirable to encourage this hypothesis.

Finally, the reversibility of the respiratory sequalae described in this study is uncertain at this point because not enough time has elapsed since the pandemic outbreak. Therefore, studies should continue data collection in order to perform long-term analyses that would allow to clarify this issue and explore the possible risk and prognostic associations in a sufficiently long timeframe.

6. Acknowledgements

I would like to start thanking all the patients who participated in this study, without them none of this would have been possible. I would also like to acknowledge the Hospital General Universitario de Castellón and all the healthcare professionals who collected the data, even during the worse moments of the pandemic.

To my supervisor, Dr. Margarita Marín, for her guidance, all her dedication, effort, and support throughout this project

To my family who re-read this dissertation as many times as I changed a coma. Thank you for giving me your advice and helping me along the way. To my dad or, as he calls himself, my "personal coach", for always having the right encouraging words to pick myself up after a bad exam or a hard day. This degree is a long-distance run, as my mother puts it, and I have had the best running partners I could have asked for. I know I wouldn't be writing these words if it weren't for you.

Special mention to my big sister, who always puts all my worries into perspective and always believes in me. Even though we are miles apart, you make it feel like we are side by side.

To my friends, inside and outside university. For all those coffee dates after hours of studying, weekend trips and movie sessions at home after exams season. Your support and understanding gave me the strength and motivation to get where I am today.

Finally, to every professor who gave me the knowledge and the tools to become the doctor I will soon be.

To everyone who accompanied me along the way, thank you.

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8. Annexes

ANNEX 1. Favorable report for the study realization by the Committee for the Ethics of Research with Medicines (CEIm) of the Hospital General Universitario de Castellón.

CEIm

GENERALITAT VALENCIANA

CASTELLÓ DEPARTAMENT DE SALUT

INFORME COMITÉ DE ÉTICA DE LA INVESTIGACIÓN CON MEDICAMENTOS (CEIm)
HOSPITAL GENERAL UNIVERSITARIO DE CASTELLÓ

Doña Berta Claramonte Clausell, Secretaria del Comité de Ética de la Investigación con Medicamentos del Hospital General Universitario de Castelló,

CERTIFICA

Que el Comité de Ética de la Investigación con medicamentos (CEIm) del HOSPITAL GENERAL UNIVERSITARIO DE CASTELLÓ, tras la evaluación de las aclaraciones solicitadas a Dª Margarita Marín, en su reunión del día 20 de diciembre, del Proyecto de Investigación (TFG): Estudio Observacional retrospectivo de las secuelas respiratorias tras neumonía por SARS-COV2.

Servicio: Neumología Hospital General Universitario de Castellón
Investigador principal: Dra. Margarita Marín Royo
TFG: Dª Elena Gisbert Muñoz

Y teniendo en consideración las siguientes cuestiones:

1. Cuestiones relacionadas con la idoneidad del investigador y sus colaboradores.
2. Cuestiones relacionadas con la idoneidad de las instalaciones.
3. Cuestiones relacionadas con la idoneidad del protocolo en relación con los objetivos del estudio y se consideran justificados los riesgos y las molestias previsibles para el sujeto.
4. Consideraciones generales del estudio.

EMITE UN INFORME FAVORABLE

A tener en cuenta:

El Comité tanto en su composición como en los PNT cumple con las normas de BPC (CPMP/ICH/135/95) y con el Real Decreto 223/2004, y su composición actual es la siguiente:

Presidente	**D. Mario Ferrer Vázquez** Facultativo Especialista Pediatría
Vicepresidente	**D. Raimundo García Boyero** Jefe Sección Servicio de Hematología
Secretaria	**Dª Berta Claramonte Clausell** Facultativo Especialista Neurología
	D. José Vicente Castelló Carrascosa Facultativo Especialista Alergología
	D. Juan Vicente Esplugues Mota Farmacólogo Clínico
	D. Raúl Ferrando Piqueres Jefe Servicio de Farmacia
	D. Jesús Lucas Garcia Facultativo Especialista Pediatría
	Dª Eufemia Marcos González Diplomada en Trabajo Social
	Dª Maria Teresa Pitarch Saborit Miembro lego
	Dª Rocío Ramos Aparici Facultativo Especialista Anestesiología y Reanimación
	Dª María Ramos Trujillo Médico Documentalista. Experta en Protección de Datos

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CSV:NVRBMAQ3:GPP38PFE:MAJKATA1 **URL de validació:**https://www.tramita.gva.es/csv-front/index.faces?cadena=NVRBMAQ3:GPP38PFE:MAJKATA1

Dª Maria Esther Roselló Sastre
Facultativo Especialista Anatomía Patológica
Dª Ana Sánchez Llopis
Facultativo Especialista en Urología
D. Carlos J. Soriano Navarro
Facultativo Especialista Cardiología
D. Juan Francisco Tosca Flores
Licenciado en Medicina y Cirugía. Experto en BPC

Que en dicha reunión del Comité de Ética de la Investigación con medicamentos se cumplió el quórum preceptivo legalmente

Que en el caso de que se evalúe algún proyecto del que un miembro sea investigador/colaborador, éste se ausentará de la reunión durante la discusión del proyecto.

Lo que firmo en Castellón a,

Firmat per Berta Claramonte Clausell el 24/02/2022 11:22:35

Secretaria Técnica CEIm