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Pulmonary sequelae in recovered critical COVID-19 patients: clinical, radiological, and pulmonary functional assessment.

Sequelas pulmonares da COVID-19 após recuperação em pacientes críticos: avaliação clínica, radiológica e funcional pulmonar

FMUP

março, 2022

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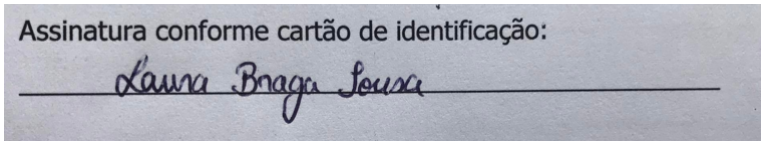

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DESIGNAÇÃO DA ÁREA DO PROJECTO

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Pulmonary sequelae in recovered critical COVID-19 patients: clinical, radiological, and pulmonary functional assessment.

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ASSINALE APENAS UMA DAS OPÇÕES:

É AUTORIZADA A REPRODUÇÃO INTEGRAL DESTE TRABALHO APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☐
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Faculdade de Medicina da Universidade do Porto, 04/03/2022

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1. **Title:** Pulmonary sequelae in recovered critical COVID-19 patients: clinical, radiological, and pulmonary functional assessment.

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Abstract in English – 245 words
Main text – 2687 words

2. Abstract in Spanish

Objetivo: Describir las secuelas pulmonares de la COVID-2019 grave tres meses después de la curación.

Diseño: En un estudio de cohorte prospectivo, se evaluó en consulta a sobrevivientes de COVID-19 que habían ingresado en cuidados intensivos, 3 meses después de la curación, clinically, radiologically and functionally.

Ámbito: Los pacientes ingresados en la Unidad de Cuidados Intensivos de Enfermedades Infecciosas de Hospital São João, Oporto, a tertiary hospital in Portugal.

Pacientes o participantes: Sobrevivientes de COVID-19 grave de marzo a diciembre de 2020.

Intervenciones: no hay intervenciones

Variables de interés principales: puntuación de cuestionario Severe Respiratory Insufficiency-Portuguese, secuelas de tumografía computorizada (TC) de tórax y pruebas de función pulmonar.

Resultados: 58% de los pacientes tenían al menos una anomalía en la TC. La presencia de un cáncer activo y mayor tiempo de hospitalización se asociaron positivamente con el desarrollo de secuelas en la TC. Las pruebas de función respiratoria mostraron principalmente un déficit en la capacidad de difusión del monóxido de carbono. Clínicamente, el dominio más afectado fue el de los síntomas acompañantes y el sueño.

Conclusiones: La mayoría de los pacientes presentaron secuelas en la TC de tórax a los 3 meses del alta, pero una minoría presentó alteraciones en las pruebas de función respiratoria. Un cáncer activo y una larga hospitalización son factores de riesgo de secuelas pulmonares en la TC de tórax. La edad, el sexo femenino y las comorbilidades son factores de riesgo para la permanencia de sintomas. Los pacientes COVID-19 grave necesitan seguimiento.

Palabras clave: COVID-19"; "pulmonar"; “secuelas”

Abstract in English

Objective: Describe the pulmonary sequelae of severe COVID-2019 three months after cure.

Design: In a prospective cohort study, survivors of COVID-19 who had been admitted to intensive care were assessed in consultation, 3 months after cure, through a validated questionnaire – Severe Respiratory Insufficiency, through a thorax CT scan, and through pulmonary function tests.

Setting: Patients admitted to Infectious Diseases Intensive Care Unit of a tertiary Hospital (São João Hospital, Porto, Portugal) discharged alive were invited to be assessed, three months after cure.

Patients or participants: Survivors of severe COVID-19 from March to December 2020.

Interventions: There are no interventions

Main variables of interest: Severe Respiratory Insufficiency-Portuguese score, chest CT scan sequelae, and pulmonary function tests.

Results: 58% of the patients had at least one abnormality on the CT-scan. The presence of an active cancer and a lengthier hospitalization were positively associated with the development of chest CT-scan sequelae. Respiratory function tests showed mainly a deficit in the diffusing capacity for carbon monoxide. Clinically, the domain most affected was attendant symptoms and sleep. Females, older patients, and those with comorbidities had lower SRI-PT scores.

Conclusions: Most of the patients had chest CT-scan sequelae 3 months after discharge, but a minority had abnormalities in respiratory function tests. The presence of active cancer and a lengthier hospitalization are risk factors to lung sequelae in chest CT-scan. Age, female sex, and comorbidities are risk factors for the permanence of symptomatic sequelae. Patients with severe COVID-19 disease need post-discharge care.

Keywords: “COVID-19”; “pulmonary”; “sequelae”

247 words in the abstract

3. Text:

a) Introduction

In December 2019, a new coronavirus (SARS-CoV-2) emerged in Wuhan City and it quickly spread around the world.[1] The manifestations of COVID-19 present at illness onset vary from asymptomatic to severe respiratory symptoms[2, 3]. This all depends on the severity of the infection, the host response, the physiological reserve, the comorbidities of the patient, the time elapsed between onset of the disease and observation in the hospital, and responsiveness of the patient to hypoxemia.[2]

Given the large number of people being infected with SARS-CoV-2 during this pandemic and that most people recover from severe, mild, or asymptomatic conditions, it is imperative to generate scientific information on how the health of recovered individuals may be affected in a post-acute phase.[4-7]

Post-acute COVID syndrome (<12 weeks) and long COVID (≥12 weeks) are terms created to describe the sequelae at different stages. The prevalence of various symptoms in each of these phases has been examined in some systematic reviews already published. In the chronic post-COVID phase, fatigue (0.48; 95% CI, 0.23–0.73), sleep disturbance (0.44, 95% CI, 0.08–0.85), and dyspnoea (0.39; 95% CI 0.16–0.64) were the most prevalent symptoms.[7-9]

It is known that there may be permanent lung damage in people who have survived previous coronavirus infections[10, 11] and recent studies showed that it is possible to see permanent fibrosis after COVID-19 pneumonia.[6, 7, 11, 12] Post-infection COVID-19 patients showed altered respiratory function. The most important factor affected was the carbon monoxide diffusion capacity, in close to 40% of patients.[13] Well-designed studies taking into consideration the infection severity and based on the pulmonary function guidelines are required.

With our study, we pretend to systematically assess the lung sequelae of COVID-19 in different groups of patients admitted to intensive care, in a multidimensional way. Patients were evaluated clinically, radiologically, and functionally.

b) Patients and Methods

In a tertiary university hospital in Portugal (Centro Hospitalar Universitário de São João, Porto), we decided to carry out a prospective cohort study to evaluate lung sequelae of adult survivors who were critically ill with COVID-19. Patients who had been hospitalized in the Infectious Diseases Intensive Care Unit (ID-ICU) between March and December 2020 were selected. Those who accepted to participate were invited to be assessed three months after being cured of COVID-19. All patients provided written informed consent. This study was approved by the local Ethics Committee.

Patients included in the study had been hospitalized for more than 24 hours, primarily due to COVID-19, and had to be alive 3 months after being cured of COVID-19. Diagnosis of COVID-19 infection was established by the positivity of the laboratory test based on viral RNA detection by real-time polymerase chain reaction (RT-PCR) from the nasopharyngeal swab. The COVID-19 cure criteria were changed in September 2020 according to the Portuguese Directorate-General Health: initially, the patient was considered cured after two negative PCR nasopharyngeal swabs; after September 2020 cure was defined as a clinical improvement after 20 days of symptoms (critical illness). Exclusion criteria included persistent hospitalization, death within 3 months after discharge, and being under 18 years old.

Data extracted from the electronic patients' clinical records. That data included medical history, COVID-19 evolution, medical procedures, and treatments needed during hospitalization. Lung protected invasive mechanical ventilation (IMV) was defined as plateau pressure inferior to 30 cmH_2O and driving pressure inferior to 20 cmH_2O[(14)]. The pulmonary sequelae of each patient were assessed clinically (in an outpatient appointment through a validated questionnaire – Severe Respiratory Insufficiency), radiologically (through a thorax CT scan), and functionally (through pulmonary function tests).

Clinical assessment was performed by a medical doctor investigator in the study. Apart from the clinical evaluation, a validated questionnaire – Portuguese Severe Respiratory Insufficiency (SRI-PT) was applied. We applied the SRI-PT because it is validated to the Portuguese population[9] and evaluates the following seven dimensions: Respiratory Complaints, Physical Functioning, Attendant Symptoms and Sleep, Social Relationships, Anxiety, Psychologic Well-Being, and Social Functioning. The questionnaire had in total sixty different questions and the answers of the patients could range from -2 (lowest level of concordance with each affirmation) to +2 (highest level of concordance with each affirmation). The data of the questionnaires were then analysed for each dimension and those results were converted to percentages, according to published scoring guidance. Higher values (in percentage) would indicate a better health-related quality of life. The Portuguese version of the SRI questionnaire and guidance for scoring can be downloaded, free of charge for research purposes, from the website of the German Respiratory Society [(15)]. To consider the answers given valid, we accepted only the questionnaires with

at least 50% of the answers filled in each domain.

Concerning the radiological assessment, a chest CT scan was performed and further evaluated by a radiologist. In some patients, it was possible to compare 3 month-CT scan with another performed in the acute phase of the disease.

The functional respiratory assessment was performed with a corporeal plestimography and CO diffusion capacity test and evaluated by a pneumologist.

All participants for whom the variables of interest were available were included in the final analysis. For missing data, no assumptions were made. Continuous variables were presented with the most suitable central tendency and dispersion measurements according to their distribution (mean and standard deviation for normally distributed variables and median and interquartile range (IQR) for not-normal distributed variables). Categorical variables were expressed as frequencies and percentages. Statistical tests were also selected according to the variables' distribution. A two-sided significance level of less than 0.05 was considered. Analysis was performed with the IBM SPSS statistics 27.

c) Results

Seventy-two patients were included (Table 1): 47 (65.3%) were male and 25 (34.7%) were female. The median age was 67 years old (IQR 16 years). The most common comorbidities were hypertension (42 patients, 58.3%), dyslipidaemia (36 patients, 50.0%), and diabetes (27 patients, 37.5%). The median duration of hospital stay was 19 days (IQR=25 days) and the median time of being exclusively in the ICU was nine days (IQR=16 days). Thirty (41.7%) of the patients required intubation with IMV, 29 (40.3%) of the patients were on high flux nasal oxygen and 13 (18,1%) of the patients were submitted to non-invasive ventilation.

Sixty-seven patients were submitted to a chest CT scan three months after discharge. Twenty-eight (41.8%) of patients had a normal chest CT-scan and 39 (58.2%) had at least one abnormality on CT-scan: 23 (31.9%) had ground-glass opacities. Some patients had evidence of fibrosis: eight (11.1%) patients had fibrotic atelectasis, seven (9.7%) had bronchiolectasis, six (8.3%) had bronchiectasis and five (6.9%) had usual interstitial pneumonia fibrosing disease. Two (2.8%) patients had emphysema and one (1.4%) showed a crazy-paving pattern.

Patients who had chest CT-scan sequelae at 3 months had a significantly lengthier hospitalization (p=0.026). The median number of days spent in the hospital of patients who had thorax CT-scan sequelae (21 days, IQR=25) was superior in comparison to the number of days spent in the hospital by patients who had normal thorax CT-scan (13 days, IQR=22).

The presence of an active cancer was associated with the development of chest CT-scan sequelae and this association was statistically significant (p=0.046). No significant association was found between chest CT-scan sequelae and length of stay in ID-ICU (p=0.099), body mass index (p=0.059), type of ventilatory support (p=0.638), length of IMV (p=0.854), length of non-invasive ventilation (p=0.448), use of lung-protective ventilation (p=0.907) and lowest value of the PaO2/FiO2 ratio (p=0.994).

Results of the respiratory function tests three months after discharge were available for 46 patients. Respiratory function tests were normal in 30 (65.2%) of the patients and 16 (34.8%) of the patients had at least one abnormality. Nine (12.5%) patients had a deficit in the diffusing capacity for carbon monoxide (DLCO), four (5.6%) patients had restrictive abnormalities, and one (1.4%) had both restrictive and obstructive abnormalities. Patients submitted to lung-protective ventilation during hospitalization had significantly fewer abnormalities in respiratory function tests (p=0.021). Most patients with lung-protective ventilation (81.8%) had normal respiratory function tests. All the patients who ventilated without a lung-protective ventilation had some alteration in respiratory function tests. No significant association was found between abnormalities in respiratory function tests and length of stay in ID-ICU (p=0.136), length of hospitalization (p=0.188), body mass index (p=0.514), type of ventilatory support (p=0.166), length of intubation with mechanical ventilation (p=0.150), length of non-invasive ventilation (p=0.052) and lowest value of the PaO2/FiO2 ratio (p=0.157).

Seventy-one (98.6%) patients answered to the SRI-PT questionnaire. The median score of the SRI-PT total scale was 72.0% (IQR=27.3). The results of the questionnaires showed that the domains most affected were, in descending order of frequency, attendant symptoms and sleep (in median 67.9%; IQR=32.1), social relationships (68.8%; IQR=37.5), psychologic well-being (69.4%; IQR=33.3), anxiety (70.0%; IQR=40.0), physical functioning (75.0%; IQR=33.3), social functioning (79.2%; IQR=33.3) and respiratory complaints (84.4%; IQR=34.4). The total scale SRI-PT was superior in men (median 76.3%, IQR=22.6) when compared with women (median 59.9%, IQR=25.83) and there was a statistically significant difference (p<0.001). Older patients had lower SRI-PT scores, and this difference was statistically significant (*p*=0.031). Patients with comorbidities had significantly lower scores of SRI-PT in relation to patients without comorbidities (*p*=0.046). SRI-PT total scale of the patients who had comorbidities was in median 71% (IQR=24.7), compared with a median of 86.35% (IQR=8.58) in the patients who had no comorbidities. SRI-PT total scale of the patients who had dyslipidaemia was inferior (median of 66.45%, IQR=17.95) compared to patients who had no dyslipidaemia (median of 80.9%, IQR=35.3) and this difference was significant (*p*=0.047). The higher the patients 'body mass index, the lower the value of the SRI-PT total scale (*p*=0.038). No significant association was found between SRI-PT total scale and length of stay in ID-ICU (*p*=0.318), length of hospitalization (*p*=0.181), type of ventilatory support (*p*=0.313), length of intubation with mechanical ventilation (*p*=0.606), non-invasive ventilation (*p*=0.781), use of lung-protective ventilation (*p*=0.855) and lowest value of the PaO2/FiO2 ratio PaO2/FiO2 (*p*=0.348).

d) Discussion

There have been many concerns about the sequelae of COVID-19 [3]. In our study, we focused on monitoring the lung complications, the most common in COVID-19 recovered patients. However, we also applied a validated questionnaire to monitored other dimensions that could be affected by COVID-19. We should recognize that non-respiratory sequelae also require some type of ongoing care.[12]

Most of the patients still have abnormalities in the convalescent thoracic CT-scan. Ground glass opacities and some manifestations of fibrosis (fibrotic atelectasis and bronchiolectasis) were the most common findings. This is consistent with data from previous long term follow-up studies that include patients with severe COVID-19.[3, 6, 7, 9, 12, 16] We do not know if these sequelae will improve with time, since this evaluation is a relatively early (3 months after cure of COVID-19). We continue to follow our cohort to document if there is any improvement.

A curious find in our study was that the presence of an active cancer was also related to lung sequelae in CT scans, which suggests that the disease is more severe in these group of patients. It is known that cancer patients are at a higher risk of acquiring COVID-19 [17], so this is of special concern. This may have a mechanism related to a cytokine storm characterized by high concentrations of proinflammatory cytokines and chemokines present in severe presentations of COVID-19 and in some types of neoplasms. [18] There are also several cohort studies that prove that the in-hospital mortality of cancer patients is significantly higher than that of the general population.[17, 19, 20]

Contrary to the results of the CT scan, respiratory function tests were completely normal in most of patients. When there were abnormalities, the more frequent finding was a deficit in the DLCO. This indicates a disorder in structure and microvasculature of lungs and may represent microthrombus formation in the lungs as previously reported in autopsy cases of COVID-19 diseases.[21-23] Hypercoagulable state has been frequently reported in COVID-19 and elevation in D-dimer is frequently seen.[24] A follow-up study of the pulmonary function and related physiological characteristics of COVID-19 survivors three months after recovery found an association between elevated serum D-Dimer and decreased diffusion capacity in follow-up respiratory function tests *[25]*, which can explain our results.

A significant association between alteration in convalescent lung function tests and protective ventilation was found: patients submitted to lung-protective ventilation had fewer abnormalities in the respiratory tests. This finding is corroborated by several other studies related or not to COVID-19 [26] and can be explained by the fact that patients with severely affected lungs, forced us to ventilate outside the limits of protective ventilation, and will have consecutively more abnormalities in respiratory tests. In contrast, no association was found between the use of protective ventilation and chest CT-scan sequelae, which leads us to hypothesize that chest CT-scan sequelae will be less important than sequelae in respiratory function tests in predicting COVID-19 sequelae.

The results of the questionnaires showed that the domains most affected were attendant symptoms and sleep, social relationships, psychosocial well-being, anxiety, and physical function, which is concordant with previous studies. [7-9, 27-32] The total scale SRI-PT was superior in men, which is also consistent with data from other studies. [7, 27, 33] Older patients, the patients who had comorbidities in general, the patients who had dyslipidaemia, and those with higher body mass index had also lower SRI-PT scores indicating an inferior quality of life. These findings matched our expectations and the results of other studies [27, 31, 32] . They are not specific to COVID-19 patients because they would also be expected in non-infected patients.

The COVID-19 mostly affects the respiratory system, but is increasingly recognized as a systemic disease, with neurologic sequelae, most frequently in those with severe illness. Therefore, a pulmonary[34-36] and cognitive rehabilitation[37-39] program is very important in these patients. It is necessary to rule out long-term pulmonary and cognitive sequelae and provide rehabilitation to minimize the potential negative effects on physical and psychosocial functioning and, finally, quality of life of survivors. Vaccination is also extremely important to prevent secondary respiratory infections[40]. Currently, there is no conclusive scientific evidence available to guide the treatment of post covid pulmonary sequelae. Observational studies show that these radiological abnormalities resolve in most patients without any specific treatment. The management of suspected lung fibrosis should be managed by experts with experience in the follow-up of fibrotic interstitial lung disease.

This study has some limitations. Firstly, as previously stated, it was an observational single centre study, so results should be interpreted with caution. Secondly, the study was performed during the first wave of COVID-19, when the ventilatory strategies and supportive care were not so refined. Thirdly, the absence of pre-COVID-19 or acute phase assessments (chest CT-scan, pulmonary function tests, and previous SRI-PT total scores) and the absence of a non–COVID-19 control group, limited the ability to conclude that our findings after three months were directly related to COVID-19. However, even with this lack of data, we believe that the CT-scan abnormalities observed were due to COVID-19. Finally, we cannot conclude with our data if the abnormalities observed were persistent following COVID-19 or worsened after COVID-19 recovery or occurred at a late post-discharge period.

The results of our study support that the patients with severe disease need post-discharge care. Longer follow-up studies in a larger population are necessary to understand and manage long-term sequelae in patients who suffered from COVID-19. British Thoracic Society guidance on Respiratory follow-up of patients with COVID-19 pneumonia has defined follow-up algorithms for COVID-19 pneumonia patients, which suggests a chest radiography follow-up at three months after discharge and consider full respiratory function evaluation based on the severity of the disease[16], but there is still a lack of standardized guidelines regarding the management of post-COVID-19 patients implying that each hospital adapts its resources according to its needs. We believe that the recommendations and

suggestions of this work can help to further develop and implement radiological, functional, and clinical protocols for follow-up on post-COVID-19 patients with respiratory impairment.

5. Funding

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6. Conflict of Interest

The authors declare that they have no conflicts of interest.

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8. References

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9. Tables

Table 1: Characteristics of enrolled patients.

Age, median (IQR) y	67,0 (16)
Women	25 (34,7%)
Men	47 (65,3%)
BMI, median (IQR) kg/m2	28,1 (6,7)
Comorbidities	68 (94,4%)
Hypertension	42 (58,3%)
Dyslipidemia	36 (50%)
Diabetes	27 (37,5%)
Overweight	22 (30,6%)
Obesity	16 (22,2%)
Cardiac disease	15 (20,8%)
Active cancer	7 (9,7%)
SOA	6 (8,3%)
Hepatic disease	6 (8,3%)
COPD	4 (5,6%)
Kidney disease	4 (5,6%)
Autoimmune disease	3 (4,2%)
Alcohol misuse	2 (2,8%)
Asthma	2 (2,8%)
Hematologic disease	2 (2,8%)
Neurologic disease	1 (1,4%)
HIV infection	1 (1,4%)
Transplanted	1 (1,4%)
Smoking	13 (18,1%)
Chronic medication	38 (52,8%)
SAPS II, median (IQR)	31 (24)
SAPSIII, median (IQR)	31 (24)
APACHE, median (IQR)	17 (6)
IMV	30 (41,7%)
NVI	29 (40,3%)
HFNO	13 (18,1%)
IMV, median no. of days (IQR)	13 (14)
NIV, median no. of days (IQR)	3 (8)
Length of hospital stay, median no. of days	19 (25)
Length of ID-ICU stay, median no. of days	9 (16)
Lowest PaO_2/FiO_2 median (IQR)	86 (44)

Data are n (%), n/N (%), or median (IQR- interquartile range).

Abbreviations: BMI-body mass index; SOA- sleep obstructive apnea; COPD- Chronic obstructive pulmonary disease; IMV- invasive mechanical ventilation; NVI- non-invasive ventilation; HFNO- high-flow nasal cannula for oxygen therapy; ID-ICU- Infectious diseases- intensive care unit.

Anexo 1- *Reporting guidelines*

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	***(a)*** **Indicate the study's design with a commonly used term in the title or the abstract. "**Design: In a prospective cohort study (…) it was an observational single centre study, "	4,11
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found "survivors of COVID-19 who had been admitted to intensive care were assessed in consultation, 3 months after cure, through a validated questionnaire – Severe Respiratory Insufficiency, through a thorax CT scan, and through pulmonary function tests."	4
Introduction			
Background/rationale	2	**Explain the scientific background and rationale for the investigation being reported "**Given the large number of people being infected with SARS-CoV-2 during this pandemic and that most people recover from severe, mild, or asymptomatic conditions, it is imperative to generate scientific information on how the health of recovered individuals may be affected in a post-acute phase"	5
Objectives	3	**State specific objectives, including any prespecified hypotheses** "to systematically assess the lung sequelae of COVID-19 in different groups of patients admitted to intensive care, in a multidimensional way. Patients were evaluated clinically, radiologically, and functionally."	5
Methods			
Study design	4	**Present key elements of study design early in the paper** "we decided to carry out a prospective cohort study to evaluate lung sequelae of adult survivors who were critically ill with COVID-19."	6
Setting	5	**Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection** "In a tertiary university hospital in Portugal (Centro Hospitalar Universitário de São João, Porto) (…) Patients who had been hospitalized in the Infectious Diseases Intensive Care Unit (ID-ICU) between March and December 2020 were selected. Those who accepted to participate were invited to be assessed three months after being cured of COVID-19"	6-7
Participants	6	***(a)*** **Give the eligibility criteria, and the sources and methods of selection of participants.** "Patients included in the study had been hospitalized for more than 24 hours, primarily due to COVID-19, and had to be alive 3 months after being cured of COVID-19. Diagnosis of COVID-19 infection was established by the positivity of the laboratory test based on viral RNA detection by real-time polymerase chain reaction (RT-PCR) from the nasopharyngeal swab. (…) Exclusion criteria included persistent hospitalization, death within 3 months after discharge, and being under 18 years old."	6-7
		Describe methods of follow-up "Data extracted from the electronic patients' clinical records. That data included medical history, COVID-19 evolution, medical procedures, and treatments needed during hospitalization.(…) The pulmonary sequelae of each patient were	

		assessed clinically (in an outpatient appointment through a validated questionnaire – Severe Respiratory Insufficiency), radiologically (through a thorax CT scan), and functionally (through pulmonary function tests)." **(*b*) For matched studies, give matching criteria and number of exposed and unexposed -** not applicable, this was not a matched study	
Variables	7	**Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable** "Lung protected invasive mechanical ventilation (IMV) was defined as (…) Clinical assessment was performed by a medical doctor investigator in the study. Apart from the clinical evaluation, a validated questionnaire (:..) SRI-PT because it is validated to the Portuguese population and evaluates the following seven dimensions: (…) the answers of the patients could range from -2 (lowest level of concordance with each affirmation) to +2 (highest level of concordance with each affirmation). The data of the questionnaires were then analysed for each dimension and those results were converted to percentages, according to published scoring guidance. (…) Concerning the radiological assessment, a chest CT scan was performed and further evaluated by a radiologist. (…) The functional respiratory assessment was performed with a corporeal plestimography and CO diffusion capacity test and evaluated by a pneumologist."	6-7
Data sources/ measurement	8*	**For each variable of interest, give sources of data and details of methods of assessment (measurement).** "Data extracted from the electronic patients' clinical records. That data included (…) Clinical assessment was performed by a medical doctor investigator in the study. Apart from the clinical evaluation, a validated questionnaire – Portuguese Severe Respiratory Insufficiency (SRI-PT) was applied. (…) Concerning the radiological assessment, a chest CT scan was performed and further evaluated by a radiologist. (…) The functional respiratory assessment was performed with a corporeal plestimography and CO diffusion capacity test and evaluated by a pneumologist. **Describe comparability of assessment methods if there is more than one group** not applicable, there was only one group	7
Bias	9	**Describe any efforts to address potential sources of bias** not applicable	
Study size	10	**Explain how the study size was arrived at** "Those who accepted to participate were invited to be assessed three months after being cured of COVID-19. (…) All participants for whom the variables of interest were available were included in the final analysis. (…) Seventy-two patients were included (Table 1) (…)"	6-8
Quantitative variables	11	**Explain how quantitative variables were handled in the analyses. "**Continuous variables were presented with the most suitable central tendency and dispersion measurements according to their distribution (mean and standard deviation for normally distributed variables and median and interquartile range (IQR) for not-normal distributed variables). Categorical variables were expressed as frequencies and percentages." **If applicable, describe which groupings were chosen and why.** "not applicable, there was only group."	7
Statistical methods	12	**(*a*) Describe all statistical methods, including those used to control for confounding** Statistical tests were also selected according to the variables' distribution. A two-sided significance level of less than 0.05 was considered. Analysis was performed with the IBM SPSS statistics 27.	7

		(*b*) Describe any methods used to examine subgroups and interactions not applicable, there were no subgroups and there weren´t used methods for examine for interactions **(*c*) Explain how missing data were addressed** Missing data was not included in the analysis **(*d*) If applicable, explain how loss to follow-up was addressed** Not applicable **(*e*) Describe any sensitivity analyses** Sensitivity analysis was not performed.	
Results			
Participants	13*	(a) **Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed** "Seventy-two patients were included (…) Sixty-seven patients were submitted to a chest CT scan three months after discharge. (…) Results of the respiratory function tests three months after discharge were available for 46 patients. (…) Seventy-one (…) patients answered to the SRI-PT questionnaire." **(b) Give reasons for non-participation at each stage N**on applicable, none of the study participants refused to participate during the study, after they gave their initial consent to be included. **(c) Consider use of a flow diagram** Not applicable.	8-9
Descriptive data	14*	(a) **Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders** "Patients included in the study had been hospitalized for more than 24 hours, primarily due to COVID-19, and had to be alive 3 months after being cured of COVID-19." **(b) Indicate number of participants with missing data for each variable of interest** Non applicable **(c) Summarise follow-up time (eg, average and total amount)** "Those who accepted to participate were invited to be assessed three months after being cured of COVID-19."	6 6
Outcome data	15*	**Report numbers of outcome events or summary measures over time** "Twenty-eight (41.8%) (…) and lowest value of the PaO2/FiO2 ratio PaO2/FiO2 (p=0.348)."	8-9

Main results	16	***(a)*** **Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included** There weren´t obtained confounder-adjusted estimates. **(*b*) Report category boundaries when continuous variables were categorized** There were no categorized continuous variables. **(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period** Not relevant.	
Other analyses	17	**Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses** These analyses were not performed.	
Discussion			
Key results	18	**Summarise key results with reference to study objectives** "Most of the patients still have abnormalities in the convalescent thoracic CT-scan. Ground glass opacities and some manifestations of fibrosis (fibrotic atelectasis and bronchiolectasis) were the most common findings. (…)A curious find in our study was that the presence of an active cancer was also related to lung sequelae in CT scans, which suggests that the disease is more severe in these group of patients. (…)Contrary to the results of the CT scan, respiratory function tests were completely normal in most of patients. When there were abnormalities, the more frequent finding was a deficit in the DLCO. (…) patients submitted to lung-protective ventilation had fewer abnormalities in the respiratory tests. (…)The results of the questionnaires showed that the domains most affected were attendant symptoms and sleep, social relationships, psychosocial well-being, anxiety, and physical function, which is concordant with previous studies (…)The total scale SRI-PT was superior in men, which is also consistent with data from other studies. Older patients, the patients who had comorbidities in general, the patients who had dyslipidaemia, and those with higher body mass index had also lower SRI-PT."	10-11
Limitations	19	**Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias** "We do not know if these sequelae will improve with time, since this evaluation is a relatively early (3 months after cure of COVID-19). We continue to follow our cohort to document if there is any improvement. (…) This study has some limitations. Firstly, as previously stated, it was an observational single centre study, so results should be interpreted with caution. Secondly, the study was performed during the first wave of COVID-19, when the ventilatory strategies and supportive care were not so refined. Thirdly, the absence of pre-COVID-19 or acute phase assessments (chest CT-scan, pulmonary function tests, and previous SRI-PT total scores) and the absence of a non–COVID-19 control group, limited the ability to conclude that our findings after three months were directly related to COVID-19. However, even with this lack of data, we believe that the CT-scan abnormalities observed were due to COVID-19. Finally, we cannot conclude with our data if the abnormalities observed were persistent following COVID-19 or worsened after COVID-19 recovery or occurred at a late post-discharge period."	10-12
Interpretation	20	**Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence** "This is consistent with data from previous long term follow-up studies that include patients with severe COVID-19 (…) which suggests that the disease is more severe in these group of patients. It is known that cancer patients are at a higher risk of acquiring COVID-19. A follow-up study of the pulmonary function and related physiological characteristics of COVID-19 survivors three months after recovery found an association between elevated serum D-Dimer and decreased diffusion	10-11

		capacity in follow-up respiratory function tests, which can explain our results.(…) is corroborated by several other studies related or not to COVID-19 and can be explained by the fact that patients with severely affected lungs, forced us to ventilate outside the limits of protective ventilation, and will have consecutively more abnormalities in respiratory tests. In contrast, no association was found between the use of protective ventilation and chest CT-scan sequelae, which leads us to hypothesize that chest CT-scan sequelae will be less important than sequelae in respiratory function tests in predicting COVID-19 sequelae. (…) attendant symptoms and sleep, social relationships, psychosocial well-being, anxiety, and physical function, which is concordant with previous studies. The total scale SRI-PT was superior in men, which is also consistent with data from other studies.(…) matched our expectations and the results of other studies. They are not specific to COVID-19 patients because they would also be expected in non-infected patients."	
Generalisability	21	**Discuss the generalisability (external validity) of the study results** "it was an observational single centre study, so results should be interpreted with caution."	11
Other information			
Funding	22	**Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based** This study has no funding.	13

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

Anexo 2- *Normas da revista – Medicina Intensiva*

MEDICINA INTENSIVA will consider for publication those works based on topics related to the practice of intensive medicine, medical emergencies, and critical care medicine in coronary units. Manuscripts will be evaluated for publication if they meet the following requirements: the material is original, presentation is clear, the methodology of the study is appropriate, the results are valid, the conclusions are reasonable, and the information is relevant. MEDICINA INTENSIVA complies with the guidelines of the International Committee of Medical Journal Editors: Uniform requirements for manuscripts submitted to biomedical journals. If the authors have further questions that are not answered within these instructions, they should refer to http://www.icmje.org.

Types of articles, sections
The MEDICINA INTENSIVA journal is comprised of the following sections:
Original Articles.
This category includes randomised clinical trials, cohort studies, studies on screening or diagnostic tests, cost-effective analyses, meta-analyses, systematic reviews, decisionmaking evaluation studies, other interventionist studies, and case-control studies. Meta-analyses and systematic reviews must be registered in PROSPERO. This section will include clinical articles as well as animal research or experimental studies. The maximum length of the text must not exceed 3,000 words (excluding the Resumen/Abstract, Tables and References). The information that cannot be included in the manuscript due to this word count limit can be published as electronic supplementary material (ESM), which has no length limitations, with addition of the tables and figures considered opportune. The maximum allowed literature references is 40. Up to 6 Tables and Figures will be admitted (e.g. 4 Tables and 2 Figures). In multicentre studies, the number of authors will be limited to 12; the rest will appear at the end of the article. The total number of Tables and Figures will not exceed 6. The length of the structured Resumen/ Abstract will be 250 words.
Retirado de: https://www.editorialmanager.com/medintensiva/default1.asp