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Update in SARS-CoV-2 pneumonia

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Respiratory consequences after COVID-19: outcome and treatment

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ABSTRACT

The SARS-CoV-2 (COVID-19) pandemic represents the infection with the highest lethality, but also the one that has caused the most sequelae and multi-organ consequences, especially respiratory, in the last century. Several actions have been required in the field of respiratory and intensive care medicine to reduce mortality and chronicity. The consequences of COVID-19 are multiple and encompass different physical, emotional, organizing, and economic aspects, which will require a multidisciplinary, transversal, and collaborative approach. This review includes the observations and results of published retrospective and prospective studies on post-COVID19 respiratory sequelae, especially after severe pneumonia with associated adult respiratory distress syndrome (ARDS).

Keywords: post-COVID respiratory dysfunction, post-COVID sequalae

INTRODUCTION

The SARS-CoV2 viral infection (COVID-19) is a global threat with hundreds of millions of affected patients worldwide [1]. As global rates for COVID-19 survival have increased, many are wrestling with the long-term sequelae and more interest has grown concerning the prevalence and appropriate management of residual lung disease in survivors of COVID-19. Post-covid19 lung syndrome would be considered if persistent radiological infiltrates and the consequent physiological respiratory deterioration are present for more than 12 weeks after the acute phase, envisioning post-covid lung sequelae if not resolved after 12 months [2,3].

The major cause of death in COVID-19 is the respiratory failure due to adult respiratory distress syndrome (ARDS) after the cytokine storm, with frequent microvascular thrombotic events and multi-organ system failure [1,2]. Around 60% of patients with ARDS induced by the SARS-CoV-2 viral infection improve clinically and radiologically after 2-3 weeks of treatment [4-6]. However, lung recovery is often slow, sometimes with supplemental oxygen required upon returning home [4-6]. In a minority of cases, clinical-radiological signs of pulmonary fibrosis have been observed in the first chest computed tomography (CT) performed after surviving the acute phase [6,7]. The induced lung fibrotic changes usually improve but in a minority of cases progress, which may associate worsening quality of life and increasing mortality risk [7-11]. Persistent inflammatory abnormalities on chest images beyond the acute illness period have been reported in several cohorts, and observational studies have suggested development of pulmonary fibrosis in a subset of patients [2,5,12-16].

Increasing evidence based on prospective post-covid19 follow-up protocols or retrospective cohorts has suggested different forms of post-COVID-19 lung sequelae that require a multidisciplinary approach [9,13]. Dyspnea, anxiety-depression, fatigue, or muscle weakness are frequent post-covid clinical problems that require an individual approach, including rehabilitation, psychological support, neurological and/or respiratory management, depending on patient features [9] (Table 1). The type of predominant post-covid dysfunction the patient may have depends on different factors, such as disease severity and in-hospital complications, age, gender, and patient comorbidities [12]. While most mild to moderate COVID-19 cases improve and present lung recovery over time, those survivors from severe covid19 that required high-flux nasal cannula (HFNC), non-invasive ventilation (NIV) or intubation and mechanical ventilation (IMV) frequently show interstitial lung abnormalities and pulmonary functional impairment over 6 and 12 months [12-15] (Figure 1). In fact, persistent interstitial changes with respiratory physiological impairment have been described as the most frequent sequela in severe COVID-19 pneumonia survivors [12] (Figure 1). Like other types of lung response after ARDS, different factors and mechanisms could be involved in the devel-

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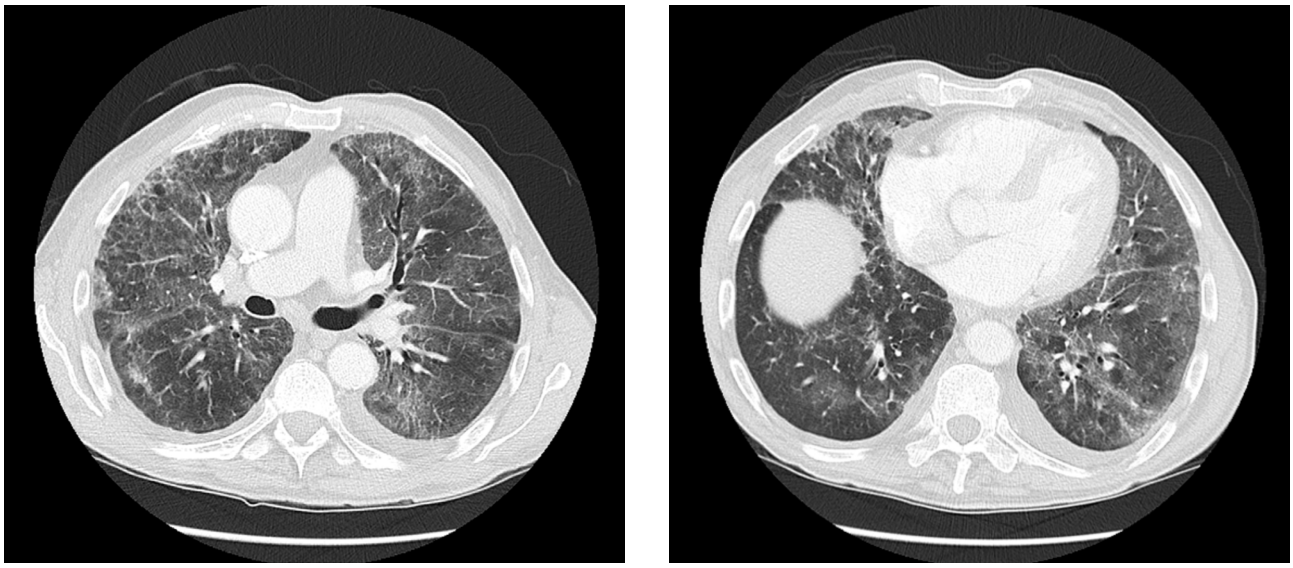
1.A) Thorax high resolution computed tomography (HRCT) shows predominant ground glass opacities, with some reticulation and isolated traction bronchiectasis.



1.B) Thorax HRCT shows predominant fibrotic-like changes; bilateral reticulation and traction bronchiectasis, with lung volume loss, and very limited ground glass opacities.

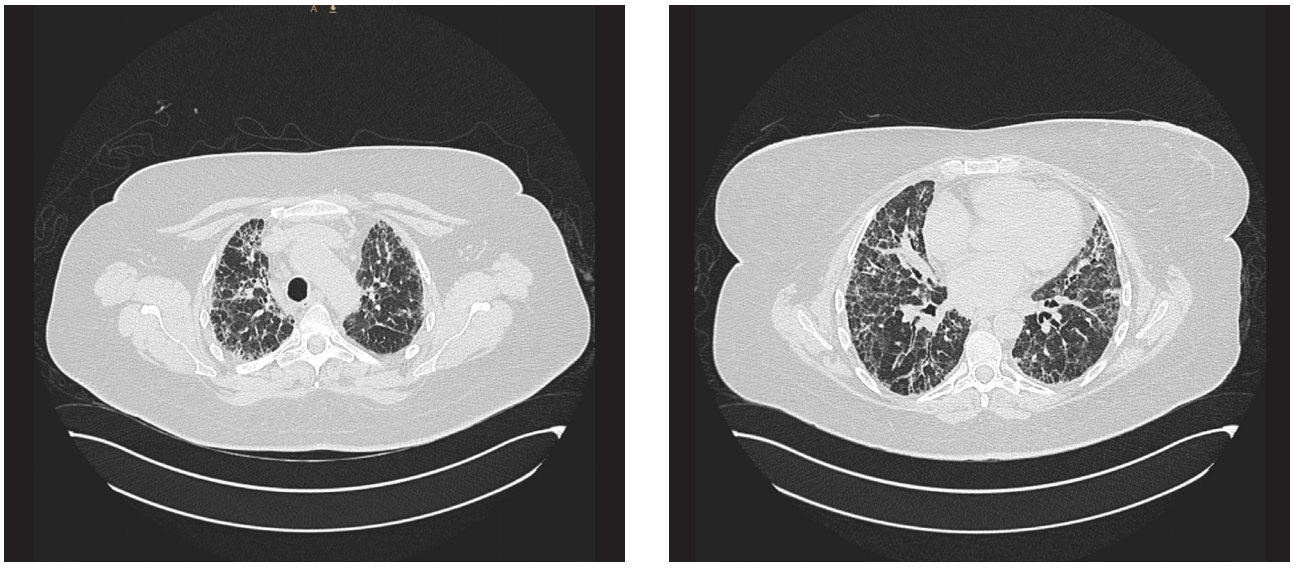


Figure 1 | **Different radiological features of post-covid short-term post-covid lung patients. Here we present two real post-covid cases after 2 months from hospital discharge to differentiate what would be considered "predominant ground glass opacities" versus "predominant fibrotic-like changes".**

opment of post-acute interstitial lung changes and the capacity of repairing *ad integrum* [17,18]. On the other hand, increased risk of pulmonary vascular disease during or after COVID-19 has been also described [19].

Therefore, post- COVID-19 respiratory dysfunction frequently involves muscle, vascular and parenchymal components. Long-term outcomes in different populations are likely to vary.

POST-COVID-19 LUNG SYNDROME: PATIENT FEATURES AND PREDICTIVE FACTORS

Several studies are currently ongoing worldwide to better define what the post-COVID-19 lung syndrome represent. However, to identify those patients with respiratory dysfunction due to persistent lung abnormalities after suffering cov-

id19 pneumonia, optimization of patient follow-up and treatment is necessary [9].

Evidence from previous coronavirus outbreaks - severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) - suggested that persistent respiratory abnormalities were present after severe acute infection [20]. Although long-term studies for SARS and MERS lung sequela were scarce and included a limited number of cases, persistent interstitial changes and pulmonary function deterioration correlated with disease severity, illness duration and age of the patient [20]. Interstitial lung disease (ILD) was reported in 28% at one-year post-SARS and 1.8% at 15-years post-SARS [2,20].

Although several reports analyzing hospitalized COVID-19 cohorts have demonstrated a high incidence of short-term lung interstitial changes with respiratory functional impairment after recovery from the acute phase [2,5,10,11,12-15,21-29], longer follow-up studies on these patients are limited and provide analyzes of no more than one-year [5,21-29]. The proportion of patients with some residual CT abnormality at 2-4 months after hospital discharge ranges from 52% to 85% [5,21-29]. This variability depends in part on the number of patients with severe or critical COVID-19 included in each cohort [2,5,21-29]. Sonnweber, et al showed that post-covid19 survivors improved the mean CT severity score at 3 months follow-up in all cases, but higher score of residual CT changes was present in those severe and critical COVID-19 cases [5]. Furthermore, prospective long-term studies have shown radiological normalization at 1-year CT in most cases that didn't require ventilatory support (IMV, NIV or HFNC) during hospitalization [5,21-29]. Despite the low proportion of cases with interstitial CT abnormalities at 12 months (5-24%), most of them had presented severe or critical COVID-19 that required ventilatory support [21,27-29]. Therefore, the incidence and type of residual interstitial CT abnormalities seems to depend on the severity of the COVID-19 acute phase.

Understanding the post-COVID-19 lung syndrome is complicated due to the varying interpretation of radiological CT findings among the studies, the limited number of longitudinal cohorts analyzing data over time, and the scant information concerning histologic correlation in the different time-points of post-acute COVID-19 lung remodeling. Furthermore, the methodology for analyzing the type and extension of interstitial CT abnormalities is extremely variable depending on the study, especially for identifying interstitial fibrosis [30]. A recent classification of radiological CT post-covid19 interstitial persistent changes has been proposed: 1) predominantly ground glass; 2) mixed ground glass and fibrotic; 3) predominantly fibrotic [30] (Figure 1). This differentiation could help in the clinical practice to better analyze the long-term predictive factors and setting the potential differences in the initial treatment strategies of post-acute persistent interstitial changes [15]. Predominant ground glass opacities are more frequent than fibrotic signs during the initial months after discharge [2,5,10-14,21-30]. Other frequent post-covid CT abnormalities are decreased attenuation areas attributed to small airways disease or hypoperfusion [31]. Identified predictive factors of persistent fibrotic changes at six and twelve months include age and severity of acute phase [13,22,25,27,29].

Table 1 Most frequent persistent symptoms after COVID-19 infection

Organ or system	Persistent post-COVID-19 symptoms
Respiratory system	Dyspnea Anosmia and/or ageusia Cough Difficulties for deep breathing Chest pain
Muscle deconditioning	Muscle weakness Muscle pain
Neurocognitive	Difficulties to pay attention Loss of short-term memory Poor quality of sleep Insomnia Nightmares
Psychological	Anxiety Depression
Digestive	Chocking Feeling of stomach bloating Diarrhea
Cardiovascular	High arterial pressure Tachycardia
Others	Weight lost Autoimmune disorders/signs

Through the inflammatory response, SARS-CoV-2 could activate different mediators of the coagulation cascade as well as cause an endothelial dysfunction after targeting the ACE-2 positive endothelial cells [19,32]. On the chest-CT pulmonary vascular alterations can be seen such as vascular thickening, which is not seen in pneumonia of other etiologies different than covid19 [19]. As we have previously mentioned, decreased DLCO can be observed in many patients which suffered from covid19 pneumonia. However, it is possible that this impairment is not only explained by a restriction mechanism but because of vascular changes [32]. Mejia-Renteria et al performed an observational prospective study in which they showed that patients after the acute phase (>100 days) presented a reduced vascular function compared to control patients as well as compared to patients with acute covid19 pneumonia [33]. Therefore, they suggest that changes in the endothelial cells could lead to vascular dysfunction, contributing to chronic complications of the infection and potential long term-vascular post-covid effects [33].

Although several uncertainties remain to be clarified, prospective ongoing longitudinal studies and multidisciplinary expert consensus will be crucial to better define the post-covid lung patterns and outcomes [17].

POST-COVID LUNG DYSFUNCTION: CLINICAL FOLLOW-UP AND TREATMENT APPROACH

Persistent respiratory symptoms after COVID-19 are investigated by pulmonary follow-up after hospital discharge including forced spirometry, plethysmography, diffusion lung capacity of carbon monoxide (DLCO), and the 6-minutes walking test (6MWT) for measuring exercise capacity and oxygen saturation [9,34-36]. The current statements on post-covid19 recommend a pulmonary follow-up in all hospitalized COVID-19 cases, especially those that required some non-invasive or invasive respiratory supportive therapy during admission [9,34-36]. Most data indicate that the extent of residual abnormal pulmonary parenchymal involvement significantly correlates with DLCO [5,10,12-15,21-29]. Decrease in forced vital capacity (FVC) at 3-months after discharge has been primarily described in those cases that suffered more severe COVID-19 but didn't significantly correlate with the residual CT abnormalities [27]. FVC and DLCO impairment may be due to different post-covid abnormalities, including not only the interstitial changes but also the muscle weakness or endothelial-vascular dysfunction [9]. However, FVC, DLCO and the 6MWT have been useful for monitoring patients with post-covid interstitial syndrome [27]. Radiologically, low-dose CT performed supinely should be sufficient in the majority of post-COVID patients on follow-up [30]. Expiratory CT would be used for those cases with suspicion of distal airflow obstruction [31]. Single or dual energy contrast enhanced (DECT) studies should be performed on those patients with suspicion of vascular involvement, depending on clinical and functional evaluation, for instance those cases with persisting abnormal gas exchange despite normalization of lung parenchyma on CT [30].

Breathlessness and cough are the most common respiratory symptoms in patients with post-covid interstitial or/and vascular persistent abnormalities after severe-critical COVID-19 [5,26-29]. Other frequently associated symptoms are fatigue, neurocognitive dysfunction, psychological and sleep disorders, join pain and muscle weakness [5,13,27-29] (Table 1). Therefore, the initial required therapeutic approach should be multidisciplinary and individualized depending on the patient's needs, but always including functional rehabilitation, symptoms relief and psychological support in a holistic way [9,34-37]. Muscle deconditioning is usually present in COVID-19 survivors, with limited capacity for exercise [37]. Respiratory physiotherapy has demonstrated to be a crucial factor for improving pulmonary function [3,37].

Due to scarcity of published evidence, no agreement exists about the pharmacological treatment of patients after COVID-19 who present with persistent interstitial abnormalities [9,34,35]. However, those symptomatic patients that present respiratory dysfunction and CT predominant ground glass opacities are frequently treated with an empiric systemic steroid treatment [15,34]. Strategies to reduce the severity and progression of post-COVID-19 are unclear. An observational prospective study with no placebo-control arm suggested that low-dose corticosteroid treatment in post-covid patients that presented persistent interstitial changes and symptoms at 6 weeks after discharge was well tolerated and associated a rapid significant improvement [15]. No agreement exists for the treatment approach of post-covid patients that present predominant fibrotic persistent CT abnormalities [34]. Initially, considering the potential pro-fibrotic pathways that COVID-19 could trigger by acting on ACE-2 enzyme and inducing alveolar epithelial cell damage (among other pathways), the potential benefit of anti-fibrotic medications was suggested [8,15]. Currently, clinical trials with antifibrotic drugs, nintedanib (NCT04619680,NCT04541680) and pirfenidone (NCT04607928), including patients with predominant pulmonary fibrotic changes after covid are ongoing. The results of these studies will clarify it the anti-fibrotic approach in these specific cases could be beneficial. Finally, lung transplantation has been a treatment option for patients with progressive pulmonary fibrosis and severe respiratory failure after weeks or months from the onset of infection [38].

CONCLUSIONS

Respiratory consequences after COVID-19 infection are common, especially in those cases that required hospitalization and respiratory support during the acute phase and involves muscle and parenchymal dysfunction. The systematic follow-up of severe COVID-19 patients has enabled to identify different types of post-covid respiratory cases that require a patient-centered integral approach, including rehabilitation, respiratory physiotherapy, emotional and nutritional support, as well as an individual evaluation of parenchymal distortion regarding interstitial changes for the potential need of medication (usually low-dose corticosteroids) and thrombotic vascular events (anticoagulant approach). The frequency of post-covid lung sequela will depend on the severity of the acute infection. Therefore, since the severity of the acute infection is decreasing with the advent of covid-vaccination and the last less-severe covid strains, probably the proportion of patients with post-covid lung consequences will decline in the future. However, patients with post-COVID-19 respiratory dysfunction exist and the optimization of their treatment for reducing the potential chronicity remains a challenge. Increasing research evidence is giving us more and better information about how to better manage these patients. But first, the recognition of this healthcare problem by the healthcare authorities is crucial for working together to mitigate the future consequences and also to support the current post-covid patients.

CONFLICTS OF INTEREST

Authors declare no conflicts of interest

REFERENCES

1. WHO.COVID-19 situation report. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports

2. Pan F, Ye T, Sun P, Gui S, Liang B, Li L, Zheng D, Wang J, Hesketh RL, Yang L, Zheng C. Time course of lung changes at chest CT during recovery from coronavirus disease 2019 (COVID-19). Radiology.2020:200370.
3. Soriano J, Murthy S, Marshall J, Relan P, Diaz J, WHO Clinical Case Definition Working Group on Post-COVID-19 condition. Lancet Infect Dis. 2021;S1473-3099(21)00703-9.
4. McDonald LT. Healing after Covid-19: are survivors at risk for development of pulmonary fibrosis? Am J Physiol Lung Cell Mol Physiol. 2021;320(2):L257-L265
5. Sonnweber T, Sahanic S, Pizzini A, Luger A, Schwabl C, Sonnweber B, Kurz K, Koppelstätter S, Haschka D, Petzer V, Boehm A, Aichner M, et al. Cardiopulmonary recovery after COVID-19: an observational prospective multicentre trial. Eur Respir J. 2021;57(4):2003481.
6. Rubin GD, Ryerson CJ, Haramati LB, Sverzellati N, Kanne JP, Raoof S, et al. The role of chest imaging in patient management during the COVID-19 pandemic: A Multinational Consensus Statement from the Fleischner Society. Chest. 2020;158(1):106-116
7. George PM, Barratt SL, Condliffe R, Desai SR, Devaraj A, Forrest I, Gibbons MA, Hart N, Jenkins RG, McAuley DF, Patel BV, Thwaite E, Spencer LG. Respiratory follow-up of patients with COVID-19 pneumonia. Thorax.2020;75(11):1009-1016
8. George PM, Wells AU, Jenkins G. Pulmonary fibrosis and COVID-19: the potential role for antifibrotic therapy. Lancet Respir Med.2020;8:807-815
9. Sibila O, Molina-Molina M, Valenzuela C, Ríos-Cortés A, Arbillaga-Etxarri A, Torralba Y, Diaz-Perez D, Landete P, Mediano O, Tomás L, Rodriguez Pascual L, Jara-Palomares L, López-Reyes R, de la Rosa D. Spanish Society of Pulmonology and Thoracic Surgery (SEPAR) consensus for post-COVID-19 clinical follow-up. Open Respiratory Archives.2020;2:278-283.
10. Kamal M, Abo Omirah M, Hussein A, Saeed H. Assessment and characterization of post-COVID-19 manifestations. Int J Clin Pract. 2021:75(3):e13746.
11. Zhang C, Wu Z, Li JW, Tan K, Yang W, Zhao H, Wang GQ. Discharge may not be the end of treatment: Pay attention to pulmonary fibrosis caused by severe COVID-19. J Med Virol. 2021;93(3):1378-1386.
12. Diaz A, Bujnowski D, McMullen P, Lysandrou M, Ananthanarayanan V, Husain AN, Freeman R, Vigneswaran WT, Ferguson MK, Donington JS, Madariaga MLL, Abdelsattar ZM. Pulmonary parenchymal changes in COVID-19 survivors. Ann Thorac Surg. 2021:S0003-4975(21)01307-2
13. Huang L, Yao Q, Gu X, Wang Q, Ren L, Wang Y, Hu P, Guo L, Liu M, Xu J, Zhang X, Qu Y, Fan Y, Li X, Li C, Yu T, Xia J, Wei M, Chen L, Li Y, Xiao F, Liu D, Wang J, Wang X, Cao B. 1-year outcomes in hospital survivors with COVID-19: a longitudinal cohort study. Lancet 2021;398:747–758
14. Bellan M, Baricich A, Patrucco F, Zeppegno P, Gramaglia C, Balbo PE, Carriero A, Santa Amico Ch, Avanzi GC, Barini M, Battaglia M, Bor S, Cantaluppi V, Cappelano G, Ceruti F, Chiocchetti A, Clivati E, Giordano M, Cuneo D, Gambaro E, Gattoni E, Loro A, Manfredi M, Morosini U, Murano F, Paracchini E, Patti G, Pinato DJ, Raineri D, Rolla R, Sainaghi PP, Tricca S, Pirisi M. Long-term sequelae are highly prevalent one year after hospitalization for severe COVID-19. Sci Rep. 2021;11:22666.
15. Myall K , Mukherjee B, Castanheira AM, Lam JL, Benedetti G, Mak SM, Preston R, Thillai M, Dewar A, Molyneaux Ph, West A. Persistent post-COVID-19 inflammatory interstitial lung disease: an observational study of corticosteroid treatment. Ann Am Thorac Soc.2021;18(5):799-806.
16. Hui DS, Wong KT, Ko FW, Tam L, Chan D, Woo J, Shung J. The 1-year impact of severe acute respiratory syndrome on pulmonary function, exercise capacity, and quality of life in a cohort of survivors. *Chest*. 2005. 128(4):2247-61.
17. Wells AU, Devaraj A, Desai SR. Interstitial Lung Disease after COVID-19 Infection: a catalog of uncertainties. Radiology. 2021;299(1):E216-E218.
18. Kligerman S, Franks T, Galvin J. Organization and fibrosis as a response to lung injury in diffuse alveolar damage, organizing pneumonia, and acute fibrinous and organizing pneumonia. RadioGraphics. 2013;33:1951-1975.
19. Potus F, Mai V, Lebret M, Malenfant S, Breton-Gagnon E, Lajoie AC, Boucherat O, Bonnet S, Provencher S. Novel insights on the pulmonary vascular consequences of COVID-19. Am J Physiol Lung Cell Mol Physiol. 2020 Aug 1;319(2):L277-L288
20. Zhang P, Li J, Liu H, Han N, Ju J, Kou Y, Chen L, Jiang M, Pan F, Zheng Y, Gao Z, Jiang B. Long-term bone and lung consequences associated with hospital-acquired severe acute respiratory syndrome: a 15-year follow-up from a prospective cohort study. Bone Res.2020;8:8.
21. Balbi M, Conti C, Imeri G, Caroli A, Surace A, Corsi A, Mercanzin E, Arrigoni A, Villa G, Di Marco F, Bonaffini PA, Sironi S. Post-discharge chest CT findings and pulmonary function tests in severe COVID-19 patients. Eur J Radiol. 2021;138:109676
22. Caruso D, Guido G, Zerunian M, Pilidori T, Lucertini E, Pucciarelli F, Polici M, Rucci C, Bracci B, Nicolai M, Cremona A, Dominicis Ch, Laghi A. Postacute sequelae of COVID-19 pneumonia: 6-month chest CT follow-up. Radiology. 2021
23. Ayoubkhani D, Khunti K, Nafilyan V, Maddox T, Humberstone B, Diamond I, Banerjee A. Post-covid syndrome in individuals admitted to hospital with covid-19: retrospective cohort study. BMJ. 2021;372:n693
24. Morin L, Savale L, Pham T, Colle R, Figueiredo S, Harrois A, et al. Four-Month clinical status of a cohort of patients after hospitalization for COVID-19. JAMA. 2021;325(15):1525
25. Han X, Fan Y, Alwalid O, Li N, Jia X, Yuan M, et al. Six-Month Follow-up Chest CT findings after Severe COVID-19 Pneumonia. Radiology. 2021:203153
26. Guler S, Ebner L, Aubry-Beigelman C, Bridevaux P, Brutsche M, Clarenbach Ch, Garzoni Ch, Geiser T, Lenoir A, Mancinetti M, Naccini B, Ott S, Piquilloud L, Prella M, Que Y, Soccal PM, von Garnier Ch, Funke-Chambour M. Pulmonary function and radiological features 4 months after COVID-19: first results from the national prospective observational Swiss COVID-19 lung study. Eur Respir J. 2021;57:2003690.
27. Wu X, Liu X, Zhou Y, Yu H, Li R, Zhan Q, Ni F, Fang S, Lu Y, Ding X, Liu

H, Ewing RM, Jones MG, Hu Y, Nie H, Wang Y. 3-month, 6-month, 9-month, and 12-month respiratory outcomes in patients following COVID-19-related hospitalization: a prospective study. Lancet Respir Med. 2021;9:747-754.

28. Vijayakumar B, Tonkin J, Devaraj A, Philip K, Orton Ch, Desai S, Shah P. CT lung abnormalities after COVID-19 at 3 months and 1 year after hospital discharge. Radiology. 2021.211746.
29. Steinbeis F, Thibeault Ch, Doellinger F, Ring RM, Mittermaier M, Ruwwe-Glösenkamp Ch, Alius F, Knape P, Meyer HJ, Lippert LJ, Helbig ET, Grund D, Temmesfeld-Wollbrück B, Suttorp N, Sander LE, Kurth F, Penzkofer T, Witzenrath M, Zoller T. Severity of respiratory failure and computed chest tomography in acute COVID-19 correlates with pulmonary function and respiratory symptoms after infection with SARS-CoV-2: an observational longitudinal study over 12 months. Resp Medicine. 2022;191:106709.
30. Solomon J, Heyman B, Ko JP, Condos R, Lynch D. CT of postacute lung complications of COVID-19. Radiology. 2021.301;E383-E395.
31. Franquet T, Giménez A, Ketai L, Mazzini S, Rial A, Pomar V, Domingo P. Air trapping in COVID-19 patients following hospital discharge: retrospective evaluation with paired inspiratory/expiratory thin-section CT. Eur Radiol. 2022;28:1-10.
32. Huertas A, Montani D, Savale L, et al. Endothelial cell dysfunction: a major player in SARS-CoV-2 infection (COVID-19)?. Eur Respir J. 2020;56(1):2001634.
33. Mejia-Renteria H, Travieso A, Sagir A, et al. In-vivo evidence of systemic endothelial vascular dysfunction in COVID-19. Int J Cardiol. 2021;345:153-155.
34. Funke-Chambour M, Bridevaux PO, Clarenbach CF, Soccal PM, Nicod LP, von Garnier C. Swiss COVID Lung Study Group and the Swiss Society of Pulmonology. Swiss recommendations for the follow-up and treatment of pulmonary Long COVID. Respiration.2021;100(8):826-841.
35. Andrejak C, Cottin V, Crestani B, Debieuvre D, Gonzalez-Bermejo J, Morelot-Panzini C, Stach B, Uzunhan Y, Maitre B, Raherison C. Guide for management of patients with possible respiratory sequelae after a SARS-CoV-2 pneumonia. Support proposals developed by the French-speaking Respiratory Medicine Society. Rev Mal Respir. 2021;38:114-121
36. National Institute for Health and Care Excellence COVID-19 rapid guideline: managing the long-term effects of COVID-19. Dec 18, 2020. https://www.nice.org.uk/guidance/ng188
37. Rinaldo RF, Mondoni M, Parazzini EM, Pitari F, Brambilla E, Luraschi S, Balbi M, Sferrazza Papa GF, Sotgiu G, Guazzi M, Di Marco F, Centanni S. Deconditioning as main mechanism of impaired exercise response in COVID-19 survivors. Eur Respir J. 2021;58:2100870
38. Bharat A, Machuca TN, Querrey M, Kurihara C, Garza-Castillon R Jr, Kim S, Manerikar A, Pelaez A, Pipkin M, Shahmohammadi A, Rackauskas M, Kg SR, Balakrishnan KR, Jindal A, Schaheen L, Hashimi S, Buddhdev B, Arjuna A, Rosso L, Palleschi A, Lang C, Jaksch P, Budinger GRS, Nosotti M, Hoetzenecker K. Early outcomes after lung transplantation for severe COVID-19: a series of the first consecutive cases from four countries. Lancet Respir Med. 2021;9(5):487-497.