Respiratory complications of COVID-19

Issa Al-Jahdhami[1], Khalid Al-naamani[1], Adhra Al-Mawali[2,3] and Sami M Bennji[4*]

[1]Department of Medicine, Armed Forced Hospital, Muscat, Oman
[2]Centre of Studies & Research, Ministry of Health, Oman
[3]Strategic Research Program for Non-Communicable Diseases, The Research Council (TRC), Oman.
[4]Thoracic Oncology Unit, Sultan Qaboos Comprehensive Cancer Care and Research Center, Muscat, Oman.

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***Corresponding author:** *saminj12@gmail.com*

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Abstract

COVID-19 pandemic has been associated with a high short-term morbidity and mortality, on the long-term, COVID-19 complications may lead to a major impact on the community and the health care the pulmonary sequelae are expected to rise significantly in the future. The lungs are the main organs affected by COVID-19. A wide variety of long-term respiratory complications secondary to COVID-19 have been described ranging from persistent symptoms and radiological changes to an impaired respiratory physiology, vascular complications and pulmonary fibrosis. Despite all of that, the respiratory sequalae post-acute SARS-CoV-2 infection has not been fully explored until now. Furthermore, the main treatment for most of the COVID-19 respiratory complications is still symptomatic and supportive care. In this review article we shed the light on the post COVID-19 complications based on the latest available evidence, focusing on pulmonary fibrosis, treatment directions, and recommendations to the physicians.

Keywords: COVID-19, post COVID-19 complications, Pulmonary fibrosis

Introduction

In December 2019 a novel coronavirus was identified as a cause of pneumonia in large number of cases in the city of Wuhan in China[1]. The virus spread rapidly leading to a pandemic.[1] The world health organization (WHO) designated the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection as corona virus disease (COVID-19).[1] COVID-19 pandemic has been associated with a high short-term morbidity and mortality. On the long-term COVID-19 complications may lead to a major impact on the community and the health care system. This is simply because pulmonary sequelae are expected to rise significantly in the near future.[2] The clinical and radiological features of acute SARS-CoV-2 infection have been well described in multiple studies. However, the long-term consequences on the lungs are not well described and most of what have been published is limited to case reports, case series or observational studies. Due to the large number of SARS-CoV-2 infection patients worldwide, the load of post COVID-19 pulmonary complications are expected to be high.[3] The aim of this review article is to summarize the known long-term respiratory complications of COVID-19 based on the current available evidence.

Symptomatology

Persistent symptoms appear to be common post COVID-19. It has been noticed that up to 75% of patients failed to return to their normal health post COVID-19 with fatigue being the main complaint along with muscle weakness, anxiety, depression, and sleep disturbance.[2,3] These symptoms have been observed irrespective of the radiological or physiological abnormality.[4] In a cross-sectional study by Galal I et al. looking at the post COVID-19 symptoms, 86% had persistent post COVID-19 symptoms. Myalgia and arthralgia were present in 60% of the patients while chest pain and dyspnea were observed in about 30% of them. The post COVID-19 persistent symptoms were mainly described among patients with

comorbidities and those who had severe disease during the acute phase[5]. Dyspnea is one of the commonest symptoms that persist post COVID-19, with 23% to 66% of patients reporting significant residual shortness of breath in various studies (8 – 12) weeks post discharge with few requiring supplemental oxygen.[6,7] There were patients who experienced ongoing symptoms the so-called Long COVID, which was observed more in females under the age of 50 with no clear reason, this could be due to the fact that females are more likely to survive severe acute disease compared to men.[8,9,10] (Table 1) Ani Nalbandian et al. in a recent review suggested the term chronic post COVID syndrome to be used for symptoms, clinical or physiological features persisting beyond 12 weeks from the onset of acute COVID-19 without other clear cause.[6]

Table 1: Summary of post COVID-19 symptomatological, radiological and physiological features.

Symptomatology	Radiology	Physiology
Fatigue Myalgia Dyspnea Chest pain Cough Arthralgia Anxiety Depression Sleep Disturbances	**Common:** GGO Consolidation Interstitial thickening parenchymal bands Crazy paving Traction bronchiectasis Mosaic attenuation **less common:** Bronchiectasis Cavitations lymphadenopathy and pleural effusion	**PFT**: Low FVC Low FEV1 Low TLC Low DLCO Low FEV1: FVC ratio **Exercise:** Decreased 6MWT Reduced Vo2 max

Radiology

High resolution computed tomography (HRCT) plays an important role in the diagnosis of some acute COVID-19 cases and monitoring the progress of the disease process during hospitalization[11]. Radiological changes post viral pneumonia has been described.[12] In a recent systematic review and meta-analysis, ground glass opacity (GGO), consolidation, and fibrosis were observed post (non-COVID-19) viral pneumonitis.[12] Although GGO and consolidation improved over time, the fibrosis persists for years. In a prospective study from Beijing that investigated the long-term effect of SARS infection among health care workers identified that after 12 months from infection; the CT scan changes were confined to less than 10% of the lung.[13] In the same study, 15 years follow up of the SARS infection survivors, showed that the majority of the parenchymal changes on CT improved by the end of the first year but remained stable thereafter.[13] In a single-center prospective study investigating the radiological changes of SARS infection 6 weeks post discharge from hospital, the major interstitial changes were organizing pneumonia in 59% and GGO in 38% .[14] GGO and irregular lines post COVID-19 pneumonia are similar to the long-term changes seen post SARS and influenza infections.[2] The radiological features post COVID-19 pneumonia are variable, ranges from GGO with or without consolidation, interstitial thickening, parenchymal bands, crazy paving to traction bronchiectasis.[15] These changes which are mainly peripherally distributed. Less common features include: bronchiectasis, lymphadenopathy and pleural effusion.[15] Mosaic attenuation is another common finding post COVID-19 which may indicate either small airway disease or pulmonary vascular disease.[16] (Fig 1) (Table 1). Although some of the HRCT features such as GGO and consolidation resolve with time, however, others like reticulation and parenchymal bands persist.[15] In addition, a study shows that among patients who had severe COVID-19 pneumonia, 44% had abnormal chest X-ray (CXR) at 6 months.[17] In one cohort of patients followed up for 4- 6 weeks post COVID-19, 32% had interstitial changes on the CT chest.[4]

Another study showed that at 6 months follow up post severe COVID- 19 pneumonia, 35% had fibrotic like changes, 27% had residual GGO and 38% had complete radiological resolution.[18] In this study, age above 50 and severe disease during the acute phase were predictors of the fibrotic changes which significantly decreased on follow up CT at 6 months. Systematic review and meta-analysis of 15 studies investigating (in over three thousand patients) follow up CT scans and PFT post COVID-19 at 1- 6 months after discharge (average 3 months) showed residual CT changes in 55.7%.[19] It is not clear yet if the post COVID-19 fibrotic changes are going to persist or regress with time. We recommend CT studies over one year and also future CT chest studies that examine the relationship between patterns longitudinally.[20]

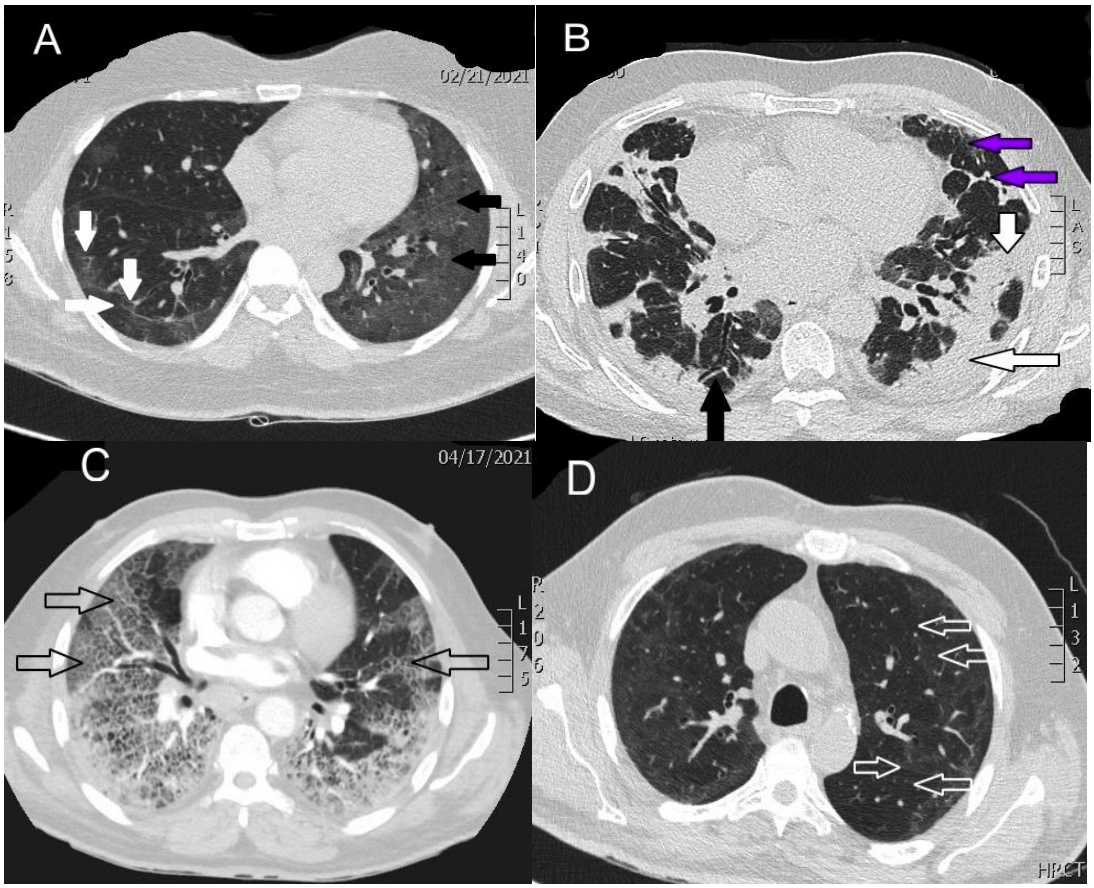

Figure 1: HRCT showing different patterns: A) diffuse GGO (black arrows) and parenchymal bands (white arrows). B) COP (white arrows), reticulations (blue arrows),

traction bronchiectasis (black arrow). C) crazy paving. D) mosaic attenuation.

Physiology

Impaired respiratory function is one of the sequelae of COVID-19 pneumonia. Pulmonary function test (PFT) showed that total lung capacity (TLC), forced vital capacity (FVC), and forced expiratory volume (FEV1) were lower than the normal reference values after severe COVID-19.[16] Diffusing capacity for carbon monoxide (DLCO) seems to be the most common physiological abnormality with very high sensitivity in monitoring post COVID-19 pulmonary complications.[17] It has the advantage of assessing both the interstitial as well as the vascular component.[17,21] It also correlates with disease severity[16]. The prevalence of impaired DLCO is variable among different studies due to variation in the time point of testing and heterogeneity of the patients tested. In severe cases of COVID-19 pneumonia impairment was observed in more than 60% [22] while in another study, 26% of the patients who had severe COVID 19 pneumonia had a DLCO less than 80% of predicted at 6 months.[18] Patients who required only oxygen or invasive mechanical ventilation (IMV) are more likely to have severe DLCO impairment compared to those who required non-invasive ventilation (NIV) without major differences in the other physiological parameters.[17] This is because patients who required oxygen only, were less likely to receive steroids and heparin compared to the sicker group as the study was conducted before the results of the RECOVERY trail came out. Xiaoneng Mo et al. performed Spirometry and DLCO in 110 patients with COVID-19 on the day of discharge from hospital and were able to show that 47.2% had impaired DLCO and 25% had reduced TLC , this was related to the severity of the disease.[23] In a recent systematic review, about 40% of patients who recovered from acute viral pneumonitis had abnormal DLCO at 12 months and about 25% had reduced TLC[22]. In cohorts of patients who survived COVID-19 severe pneumonia, DLCO impairment was reported in 58% at 6 months.[12,17, ,24] Furthermore, the

maximum aerobic capacity (Vo2 max) has also been reported to be decreased post COVID-19.[25] The respiratory obstructive pattern has also been reported post COVID-19 pneumonia.[22] In the post-acute COVID-19 Chinese study, the median 6-min walking distance was reported to be lower than normal reference values for healthy population in about 25% of patients at 6 months. This was similar to what was reported in SARS and MERS-CoV survivors[2,26] (Table 1). A recent study showed that early physiological assessment before discharge could overestimate the long-term impact of COVID-19 as many factors contribute to that impairment in the acute phase [27], and the current British Thoracic Society (BTS) guidelines recommend performing PFT for COVID-19 patients at 3 months post discharge.[28]

Pulmonary fibrosis

Viral pneumonia is a potential cause of pulmonary fibrosis. Two retrospective observational longitudinal studies that reported the incidence of pulmonary fibrosis post viral pneumonia, demonstrated that viral pneumonia was a risk factor of pulmonary fibrosis with a relative risk of 20% compared to those without it.[29] In addition, patients who had viral pneumonia and pulmonary fibrosis were relatively younger. In systematic review and study by Fabbri L, et al. the fibrotic changes post viral infection (SARS-CoV-2 and influenza) persist for years post infection.[12] Post COVID-19 pulmonary fibrosis has been observed as one of the major complications of COVID-19, with an estimated prevalence of more than one third of severe pneumonia survivors[24].

Post COVID-19 fibrosis at 4 months was higher in mechanically ventilated COVID-19 survivors than those who did not require mechanical ventilation with an incidence of 72%, and 20% respectively.[30] Moreover, patients who had fibrosis are mainly males, elderly with severe disease during admission and high inflammatory markers like LDH, CRP.[15,16,30]

Furthermore, other risk factors for pulmonary fibrosis post COVID-19 that have been identified include long ICU stay and IMV, smoking, obesity, chronic alcoholism as well as shorter telomere that has been shown to play a role in the development of fibrotic ILD[32] (Table 2). It has been shown by many studies that the use of high flow oxygen could also contribute to the development of pulmonary fibrosis.[31]

Table 2: risk factors for post COVID-19 pulmonary fibrosis

Risk Factors for Post COVID-19 Fibrosis
Age >55
High inflammatory markers including CRP, IL-6 ,serum LDH and D-dimer levels
Length of hospitalization > 20 days
Length of ICU stay and mechanical ventilation
Initial CT findings (coarse reticular pattern, parenchymal bands, Irregular interface, interstitial thickening)
Smoking
Chronic Alcoholism

Patients with mild to moderate COVID-19 pneumonia may not be at risk for post COVID-19 pulmonary fibrosis.[32] The pathogenesis is a complex interplay between the virus and the immune system response with downstream immune signaling activation.[33] Pulmonary fibrosis results from abnormal repair of lung injury that could be caused by various mechanisms including viral infections, inflammation or idiopathic.[21] In severe forms of lung injury due to COVID-19 the basement membrane is damaged, and the repair process of the tissue damage ends up with the formation of fibroblastic tissue and scaring leading to architectural distortion and fibrosis.[33] Although, in ARDS, the fibrotic phase is one of the pathological features,[21] however, the exact reason why not all patients develop fibrosis remains unknown. Fibrosis post ARDS - unlike idiopathic pulmonary fibrosis (IPF) - does not have a prominent honeycombing

pattern and does not progress over time. Thus for that reason the pathological findings in post COVID-19 fibrosis seems to be different from that of IPF with alveolar epithelial cell injury being the predominant finding rather than the endothelial cells.[34,21]

Thrombosis

COVID-19 may predispose patients to arterial and venous thrombosis (VTE) which is associated with high morbidity and mortality.[35] The pathogenesis of thrombosis has been attributed to a complex interplay between excessive inflammation, platelet activation, endothelial dysfunction, and stasis.[36,37] However, more studies are required to understand the exact mechanism. The pathophysiology is related to intravascular hyper inflammation leading to microangiopathic endothelial damage.[34] The risk of pulmonary embolism (PE) appears to be high; and in some reports was up to one - third of COVID-19 patients who underwent CT pulmonary angiogram (CTPA).[38]Intrestingly, an epidemiological study that investigated the incidence of venous and arterial thrombotic complications at 30 days in COVID-19 hospitalized patients compared to influenza patients, reported that the thrombotic complications were diagnosed in 23% of patients with COVID-19 while only 3.6% of all hospitalized influenza patients.[39] These complications were observed more in ICU patients. A study from china compared the incidence of VTE in hospitalized patients with COVID-19 to those hospitalized with community - acquired pneumonia (CAP) and it reported no difference in VTE rate, However, one of the limitations of this study that there was a selection bias in the study where the COVID-19 patients were younger with less comorbidities.[40] Moreover, a case series of a population cohort from Scotland demonstrated significantly increased risk of myocardial infarction (MI) and ischemic stroke along with VTE.[41] It should be noted that the VTE risk persisted longer than the arterial thrombotic complications.

In one cohort of patients followed up at 6 weeks post COVID-19 pneumonia, 2% had previously undiagnosed PE that could have either been missed or developed post discharge[42] (Figure 2). A retrospective study by Cheng Fang et al. investigated all CTPA done for COVID-19 patients in a tertiary care center in China, showed that 40% had evidence of PE, mostly at segmental and subsegmental level.[34] D dimer and Wells criteria were found to be not useful to decide which patients are at higher risk of PE . Mainly PEs mostly happened in the second or third week of disease onset.[34]The European Respiratory Society (ERS) guidelines strongly recommend that patients hospitalized with COVID-19 should be offered a form of anticoagulation despite the low-quality evidence.[43] Although the evidence for extended anticoagulation post discharge is lacking, it still can reduce the VTE risk at the cost of an increase in bleeding. Importantly, when used it should be considered on a case-by-case basis in those patients who have high VTE risk and low bleeding risk.[42] Additionally, patients who develop PE during the acute phase should be followed up at 3 months post discharge with Echocardiography and CTPA[44]and if there is no evidence for residual thromboembolic disease and/or pulmonary hypertension then anticoagulation can be discontinued.

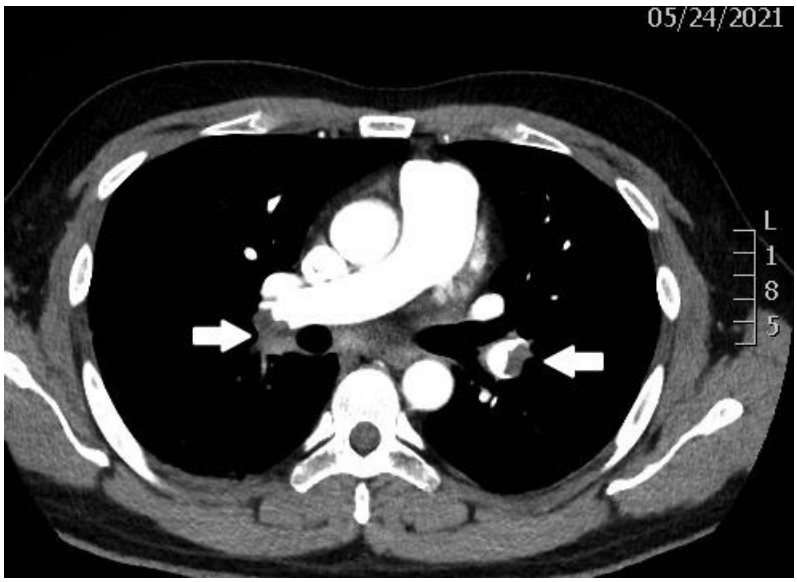

Figure 2: Bilateral filling defects in the main pulmonary arteries (arrows) representing

bilateral pulmonary embolism

Other respiratory complications

There is a wide variety of other respiratory complications secondary to COVID-19. **Bronchiectasis** ,which in general carries a poor prognosis, and has been reported after severe COVID-19, could be either due to the disease itself or secondary to superimposed bacterial infection.[45] There is limited data about bronchiectasis in patients who survived COVID-19. However, knowing that infection is the most common cause of bronchiectasis, it is expected that we will find many cases of post COVID-19 bronchiectasis in the future. Studies on survivors of SARS showed that a small number of patients developed bronchiectasis and it evolved over long periods of follow-up.[46,47] In a study from China on 81 patients post COVID-19, 11% had evidence of bronchiectasis[48]. Furthermore, **Cavitary lung disease** is another complication of COVID-19. Vijairam Selvaraj et al reported a case of post COVID-19 bilateral lung cavities where other etiologies of were negative.[49] A study from UAE showed that 7% of patients who were admitted with COVID-19 pneumonia developed cavitation, the majority of them were ICU patients.[50] The cavities were either single or multiple and the size ranging from 3 to 10 cm with thick smooth walls and fluid level.

The incidence of **Pneumothorax** in hospitalized patients with COVID-19 is around 1%. It has been reported in patients with and without ventilatory support.[51] The overall survival of those who developed pneumothorax was about 63%. Age above 70 carried a poor prognosis.[51]Furqan et al. reported a case of spontaneous pneumothorax in a patient post COVID-19 disease three months after discharge from hospital.[52] Another case of delayed recurrent pneumothorax was reported 4 weeks after discharge from hospital.[53] The exact mechanism for the development of delayed pneumothorax is not fully understood but it could be related to damage of the alveolar

walls due to the ongoing inflammatory process or the formation of small alveolar blebs. Additionally, vigorous cough could be a contributing factor for the occurrence of pneumothorax.[54] Therefore, physicians should consider the possibility of the development of spontaneous pneumothorax in patients who recovered from COVID-19 pneumonia if their respiratory status deteriorates suddenly. It should be managed according to established guidelines for secondary spontaneous pneumothorax.

Treatment and prevention of post COVID-19 pulmonary fibrosis

Currently, there is no proven treatment for post COVID-19 pulmonary fibrosis with many ongoing studies investigating different treatment options. In a small single-center prospective observational study, 30 patients who had severe COVID-19 pneumonia and remained symptomatic at 6 weeks post discharge with impaired PFT and features of organizing pneumonia on CT chest were offered prednisone 0.5mg/kg for 3 weeks. There was a clear improvement in the dyspnea score with increase FVC by 9.6% and in TLCO by 31.5%. In addition, a significant improvement in the six-minute walk test (6MWT) was observed.[14] The repeat chest CT scan also demonstrated remarkable improvement without any major complications of steroid us.[14] The question remains whether this improvement is due to the steroid treatment or the normal recovery trajectory of the lung.

Saha et al. reported three cases of post H1N1 ARDS related fibrosis who were treated, after discharge, with the combination of prednisolone, azithromycin and pirfenidone for up to one year, there was improvement in oxygenation, 6 MWT and HRCT changes.[55]Further research is required to understand the exact mechanisms as well as the measures of early interventions that may improve the outcome. The current thinking is that early intervention during severe pneumonia may decrease the post COVID-19 complications. However, it is still not clear what is the best intervention until now.[24] Furthermore, the two approved antifibrotic medications

(Pirfenidone and Nintedanib) to treat IPF has been proven to decrease lung function decline[56, 57]. For post COVID-19 fibrosis, the current postulation is to start antifibrotic medications early, however, the use of Pirfenidone at the acute phase may lead to hepatic toxicity. Additionally, Nintedanib is associated with high risk of bleeding[21]. Currently, there are ongoing trials investigating the role of anti-fibrotic medications in post COVID-19 pulmonary fibrosis. Phase III NINTECOR (NCT04541680) and phase IV ENDCOV-I trials (NCT04619680), are investigating the benefits of Nintedanib 150 mg twice daily on the changes in post- COVID-19 pulmonary fibrosis patient's FVC. Another phase II (NCT04607928) and a phase III trials (NCT04282902) are exploring the role of pirfenidone.[58]

Since there is currently no effective treatment for post COVID-19 pulmonary fibrosis, the risk of fibrosis can be reduced by protective measures to minimize ventilator associated lung injury (VALI), such as lung protective ventilation and smoking cessation.[16] Furthermore, rehabilitation may be considered early before discharge as it improves respiratory function despite the lack of strong evidence.[21]

Lung transplant has become a treatment option for a wide variety of end-stage lung diseases. Bharat et al. reported the success of the first two United States (US) lung transplantations which were performed in patients with severe fibrosis related to COVID-19.[56] It was reported that both patients had excellent results and were able to be free of any oxygen support after 4-8 weeks post transplantation.[59] In addition, a recent case series of 12 patients who had bilateral lung transplantations, in USA, Italy, Austria and India, for post severe COVID-19 ARDS that did not improve despite prolonged ventilation and extracorporeal membrane oxygenation (ECMO), showed that transplantation in COVID-19 related ARDS had similar survival as non-COVID-19 patients.[57] The authors recommended that patients can be listed for transplant if they spent more than 4 weeks in ICU and showed no signs of lung recovery despite full medical care. Additionally, patients also have to fulfill the usual criteria for lung transplantation.[60] The

challenges in transplant surgeries include: the risk of getting an infection with COVID-19 again in the transplanted lungs, ventilator related infections, technical difficulties during surgery especially in patients who required pleural procedures, severe deconditioning due to prolonged ICU stay. Moreover, and the fact that we don't know, with certainty, if the native lung may recover after severe COVID-19 related injury with a better survival than transplanted lungs.[59]

Recommendations

The BTS guidelines recommend a follow-up CXR at 4-6 weeks post discharge for patients who are admitted with severe COVID-19 pneumonia and managed in ICU, high dependency unit, or ward, and at 12 weeks for those who had non-severe COVID-19 pneumonia.[29] It also recommends that if there is no improvement in CXR changes and/or the patient has persistent respiratory symptoms, then a full PFT, 6MWT, echocardiography, sputum for microbiology and referral for rehabilitation to be considered. If the CXR changes persist and there is physiological impairment, HRCT and CTPA should be considered.[28] Patients with post COVID-19 complications require to follow up with a chest physician.[61] It should be noted that the role of bronchoscopy, with or without lung biopsy, for patients who have persistent or new radiological changes post COVID-19 pneumonia remains unclear.[62]

Conclusion

COVID-19 disease survivors especially those who had severe acute phase may develop a wide range of post COVID-19 complications which are associated with high morbidity and mortality. Currently, there is a lack of specific treatment for most of the post COVID-19 lung complications. Long-term follow up and future strong evidence is mandated to determine the exact mechanisms and the potential treatment interventions at all stages of the disease. Clinical,

physiological and radiological monitoring and early referral to chest physicians must be considered post discharge in all COVID-19 survivors. Furthermore, long-term follow-up may determine the exact prevalence and whether some of the complications such as fibrosis will be permanent and irreversible.

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