

The Effects of COVID-19 on Patients with Pulmonary Hypertension

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INTRODUCTION

As we all know, the world has been dealing with the global COVID-19 pandemic for more than a year, since the first reports from China in Dec 2019. More than 250 million people worldwide have been infected with this new strain of coronavirus, SARS-CoV-2, and more than 5 million have died.

COVID-19 illness is typically a respiratory infection, most commonly a typical “cold”, but it can also be more severe, like a “flu” (influenza-like). Pneumonia is the most serious infection associated with COVID-19. Patients with COVID-19 pneumonia may need hospitalization, and possibly even admission to the intensive care unit (ICU). COVID-19 patients with pneumonia are at the highest risk of dying from COVID-19, typically from the complications, including respiratory failure and ARDS (Acute Respiratory Distress Syndrome).

It is clear that some people are at higher risk of more serious illness and dying from COVID-19. This includes patients who are older, or who suffer with other illnesses, including diabetes, high blood pressure, heart disease, and chronic lung disease.

Pulmonary hypertension (PH) is a form of chronic lung disease, which can result in heart failure specifically of the right ventricle (RV). Patients with PH have been concerned about their risk for being infected with SARS-CoV-2 and suffering severe COVID-19. We will address 4 specific questions of relevance to PH patients concerned about COVID-19.

1. Are PH patients at higher risk of being infected with SARS-CoV-2 virus?
2. Are PH patients at risk of more severe COVID-19 disease and/or death?
3. How has the COVID-19 pandemic affected the care of PH patients?
4. What are other effects of the COVID-19 pandemic on PH patients?

1. ARE PH PATIENTS AT HIGHER RISK OF BEING INFECTED WITH SARS-COV-2 VIRUS?

Background. COVID-19 is a respiratory infection, characterized by severe pneumonia in the most ill patients. As such, patients with PH could be at higher risk, as has been observed in patients with other chronic lung diseases, eg COPD. Some PH patients

may be at higher for SARS-CoV-2 infection because of other factors, including being older (>50), being non-White ethnic background, and having cardiovascular conditions, such as hypertension, diabetes, and left-sided heart failure. Although PH patients can have right-sided (right ventricle) heart failure, this has not been found to be a risk for SARS-CoV-2 infection.

In contrast to concerns about higher risk of infection, PH patients could actually be at lower risk of COVID-19. Many PH patients can be somewhat isolated, because of the effects of PH, including physical limitations, as well as psychosocial issues, which may reduce exposure to other people infected with SARS-CoV-2. Moreover, many PH patients are better medically educated, and already rigorously adhere to care procedures, including daily use of medications, regular physical activity, and thus, they may also be more likely to follow public health recommendations, eg. social distancing, mask-wearing, etc. Indeed, in a national survey from China, including 120 patients and 23 family members of patients, 98.6% of participants reported they were in home quarantine during the COVID-19 outbreak.{Zhou 2020}

Studies. Thus far, the evidence shows that PH patients have not suffered SARS-CoV-2 infection more often than other people. Indeed, in the largest survey of 58 US Centres in 30 different states, data was obtained from a total of 16,979 PH patients, and only 50 PH patients (including PAH and CTEPH) had been diagnosed with COVID-19.{Lee 2020} The overall risk of new SARS-CoV-2 infection was 2.9 per 1000, which was very similar to the overall risk of 2.4 cases per 1,000 in the US estimated by the Centres for Disease Control (CDC). It is noteworthy that this incidence of new SARS-CoV-2 infection in PH patients varied from 1.4/1000 in states with lower SARS-CoV-2 infection rate vs 4.6/1000 in high-risk states. Similarly, in another international survey of 47 PH centres from 28 mainly European countries, only 70 PH patients (PAH and CTEPH) had suffered COVID-19, lower than expected.{Belge 2020}

Question 1: Are PH patients at higher risk of being infected with SARS-COV-2 virus?

Message. PH patients do not appear to be at any higher risk of SARS-CoV-2 infection. Indeed, PH patients may be at lower risk due to the generally higher health literacy of PH patients and their regular attention to their own care, following public health guidelines and remaining at home during the pandemic.

2. ARE PH PATIENTS AT RISK OF MORE SEVERE COVID-19?

Most patients who get infected with SARS-CoV-2 have a short-lived, minor “cold”-like illness with few or no symptoms. A minority of SARS-CoV-2 infections lead to more severe COVID-19 illness characterized by pneumonia that may require hospitalization, with a risk of respiratory failure and other organ failure, and possibly need for intensive care unit (ICU) care such as intubation (insertion of breathing tube) for artificial respiration. Indeed, more severe COVID-19 is associated with greater blood and lung inflammation which results in more damage to the blood vessels of the lungs. More severe COVID-19 is also associated with a higher risk of death.

PH Patients Could be at Higher Risk of Severe COVID-19

Background. If PH patients were to get infected with SARS-CoV-2, it is a concern that they might suffer more severe COVID-19. In part, this concern is based on many parallels between PH and COVID-19. For example, COVID-19 causes inflammation and damage to the lungs, and especially the blood vessels of the lungs. These are the very same blood vessels already injured and not working properly in PH patients. Moreover, the innermost lining cells in pulmonary blood vessels, known as endothelial cells (EC), are activated, damaged, and these EC can die in COVID-19 patients.{Ackermann 2020} In PH patients, these same pulmonary blood vessel EC are already activated and damaged.{Huertas 2020} Thus, SARS-CoV-2 infection in a PH patient could cause more pulmonary blood vessel and EC damage, leading to more severe COVID-19.

In addition, damage to blood vessels and EC in patients with COVID-19 increases the development of abnormal blood clots (thrombosis). Blood clots have been found in up to 10% of patients hospitalized with COVID-19 and up to 35% in COVID-19 patients who became seriously ill and needed admission to ICU.{Piazza 2020, Klok 2020} This includes blood clots anywhere in the body, most commonly new clots forming directly in the pulmonary blood vessels, or deep vein thrombosis in the leg veins from which blood clot can break off and travel to the lungs (pulmonary emboli). Thrombosis in the pulmonary vessels could worsen PH and worsen right-sided heart failure in any PH patient, but especially in patients with previous pulmonary emboli who already have chronic thromboembolic PH (CTEPH). Moreover, even in patients without PH, pulmonary vascular thrombosis increases the risk of developing PH, specifically CTEPH.

Studies. There are a few reports of serious COVID-19 in PH patients. In a survey of 32 PH centres from PHA US, 13 PAH patients with COVID-19 were identified. 7 of these patients required hospitalization for supplemental oxygen, of which 3 became seriously ill with respiratory failure and required intubation and artificial respiration, including 1 who died.{Horn 2020} Similarly, in the above-survey of 47 PH centres, PH patients had a higher risk of dying from COVID-19 than the general population.{Belge 2020} Specifically, the rate of death was 19% for PH patients (20% for PAH and 14% for CTEPH), compared to the risk of death from COVID-19 in the general population of 5.9-16.3% in these countries.

In another small retrospective study of 11 PAH patients who had been diagnosed with SARS-CoV-2 infection in New York City, 9 were hospitalized and 7 required care in the ICU. COVID-related mortality rate was 36.4%, suggesting potentially more severe COVID-19 in PH patients.{Sulica 2021} Of note, all deaths occurred in COVID-19 PH patients hospitalized at non-PH expert centres, suggesting that PAH expertise may improve outcomes in PH patients who suffer COVID-19.

PH Patients May be at Less Risk of Severe COVID-19

Background. Interestingly, PH patients could potentially be at less risk of severe COVID-19, for several reasons. For example, angiotensin converting enzyme-2 (ACE-2) is a protein found on the surface of multiple cells, including endothelial cells (EC) which line the inside of blood vessels. ACE-2 is the essential cell surface protein which binds to the spike 'S' protein of SARS-CoV-2 in order to facilitate cell entry of the virus. Some PH patients, especially idiopathic PAH, are known to have lower levels of ACE-2, which could prevent SARS-CoV-2 entry into EC and thus protect from COVID-19.

Moreover, commonly PH-targeted medications may protect PH patients from more severe COVID-19. Endothelin receptor antagonists (ERAs; eg. ambrisentan, bosentan, macitentan) and phosphodiesterase type 5 inhibitors (PDE-5i; eg. sildenafil, tadalafil) could block the ACE-2 protein, preventing SARS-CoV-2 virus entry into cells. Indeed, PH medications may also lessen blood and lung inflammation, which could make COVID-19 less severe. {Nuche 2020} ERA medications can also block damage and death of cells in the lungs, which could prevent more severe COVID-19 lung damage and reduce death of patients. {Badagliacca 2020}

Studies. There are several reports of PH patient with COVID-19 who had very mild cases, with symptoms similar to a common cold and no need for any supplemental oxygen or artificial respiration. {Mandler 2020} For example, in 10 female PAH patients from 1 Spanish PH centre with COVID-19, 5 had only mild symptoms, 5 developed pneumonia and were hospitalized but none required ICU and none died. {Nuche 2020} Similarly, CTEPH patients may also suffer less severe COVID-19. {Segura de la Cal 2020} This may be due to routine, chronic anticoagulant medications in CTEPH patients which may prevent blood clot formation in COVID-19. Another small study of COVID-19 in 4 patients (PAH, CTEPH) on various PH medications observed no worsening of right-sided heart failure and no deaths. {Scuri 2020}

Question 2. Are PH patients at risk of more severe COVID-19?

Message. Based on overlap in the biology between COVID-19 and PH, some PH patients infected with SARS-CoV-2 have suffered more severe COVID-19, leading to higher risk of hospitalization, ICU admission, and death. However, some PH patients with COVID-19 also seem to have done better than expected, which may be due to the beneficial effects of PH medications and anticoagulants on pulmonary arteries and lungs, as well as the benefits of PH expert care. Overall, PH patients are at some risk of more severe COVID-19, but this does not seem to be higher than people without PH.

3. HOW HAS THE COVID-19 PANDEMIC AFFECTED THE CARE OF PH PATIENTS?

Background. It has been recommended that the care of PH patients be centralized through PH expert centres. Initial PH patient evaluation includes clinical assessment as well as key testing, such as echocardiogram, V/Q lung scan, CT pulmonary angiogram,

and right heart catheterization (RHC). Moreover, regular follow-up is essential to reassess clinical patient status, as well as repeat specific testing, eg. 6-minute walk test (6MWT) and echocardiogram. This permits consideration of optimal medical therapy, eg. initiation of additional or novel PH-targeted medications. Most typically, such care would be through in-person visits with PH care teams and consist of comprehensive care, including patient-relevant education around PH, medications, and self-monitoring.{McGoon 2019} Indeed, patients who are lost to follow-up from PH centres are at higher risk for worsening PH, often related to low levels of health literacy and incomplete understanding of their PH.{Ryan 2021}

Early in the COVID-19 pandemic, it became clear that the care of PH patients was disrupted, including appointment cancellations, changes in access to or timing of necessary testing, and interruption of treatment plans. COVID-19 public health restrictions necessitated the transition of much of face-to-face outpatient healthcare to virtual care, in order to reduce the congestion in hospitals and clinics. Further, this transition to virtual care could exacerbate disparities in access to healthcare, and could potentially worsen clinical outcomes in some patients.

Effects of COVID-19 Pandemic on Access to Care

Studies. The above survey of 58 US PH Centres found a 60% decrease in the weekly number of in-person visits.{Lee 2020} Similarly, there was nearly 50% decrease in the number of new referrals to 7 German PH Centres, resulting in fewer admissions to hospital for PH care.{Yogeswaran 2020}.

COVID-19 restrictions necessitated a change in the form of communication between patients and their care teams, as well as marked changes in diagnostic testing. For example, the above US survey found that around 90% of 58 US PH centres were doing less echocardiograms, nuclear V/Q lung scans, and RHCs in PH patients.{Lee 2020} Most concerning, there was a marked overall decrease in the number of tests, as 46-69% of centres had reduced the number of tests by more than 60%. This reduced or delayed testing increases the risk that PH patients are misdiagnosed, not diagnosed as early as possible, or not diagnosed at all. For example, the reduction in V/Q scans, and the fact that 12% of centres had completely stopped performing them, would make it much harder to accurately diagnose CTEPH.{Lee 2020}

Other barriers may have additionally hindered patients from receiving appropriate care. For example, patients in Poland with cardiopulmonary diseases were initially advised against seeking non-urgent medical care to minimize the risk of SARS-CoV-2 transmission.{Kopec 2020} As a result, among 105 PH patients, while 22 of them had symptoms suggestive of clinical deterioration, only 7 of these patients (32%) contacted their PH care team. Indeed, about 50% of these patients indicated that they were fearful of contacting healthcare providers and ultimately decided to delay or entirely avoid healthcare contact due to the pandemic.{Kopec 2020}

Care of PH Patients During the COVID-19 Pandemic

Transition to virtual care. While traditional in-person care has been cancelled, delayed or rescheduled during the COVID-19 outbreak, some of the limitation in patient care has been addressed by virtual care, including telephone and video assessments. Indeed, the number of telehealth visits has dramatically increased, which could mitigate the disruptive effects of reduced in-person care. For example, an online study of 1073 PH patients and relatives of patients across 52 countries found that only 12% of patients accessed care in traditional in-person settings during the COVID-19 pandemic.{Godinas 2021} Thanks to the transition to virtual care, only 11% reported difficulties in accessing PH care, and 81% of PH patients were satisfied there was no disruption of their regular care. Similarly, in the above study of US PH centres, the number of weekly telephone and video-enabled visits increased more than 10-fold.{Lee 2020}

Virtual assessment of patients. The transition to virtual care during the COVID-19 pandemic offers opportunities for more comprehensive PH care, including potentially increased access to healthcare teams, especially for those with access to telehealth technologies (phone, computer, etc.). Virtual care will also require new approaches to the assessment of PH patients, including a greater importance on patient reported outcomes (PROs). For example, evaluation of patients' health-related quality of life (HRQoL) is already standard in PH expert centres, using tools such as EmPHasis-10 and SYMPACT. These measures capture the patients' perspectives on their symptoms, their function, and the burden of living with PH, and as such, are essential to healthcare providers fully understanding a patient's feelings and concerns. These tools can easily be shared with patients, and the scores shared verbally during virtual assessment, or captured electronically into an online database.

Virtual care will also require new approaches to assessment of patients' functional capacity. The 6-minute walk test (6MWT) is used routinely to assess patients' functional capacity, in order to assess PH severity, monitor patient progress, and evaluate benefits of treatment. The 6MWT requires standard conditions to produce reliable, accurate results, which may not be possible through tele-health. However, there are new options, including other types of exercise testing, eg. the incremental shuttle walk test (ISWT), which is more adaptable to virtual use and is already validated.{Wesley Milks 2021} Video assessment could permit direct observation of a patient's functional capacity in their home, including on exertion (eg. climbing a flight of stairs) and during their Activities of Daily Living (ADLs). Moreover, novel technologies including "wearables", eg. Fitbit, can be used to measure patients' exercise capacity, as well as more routine, daily physical activities. Novel, technology-driven devices (eg. Accelerometry) that can be worn ("wearable") can continuously measure patients' biologic data, eg. daily steps, heart rate, oxygen levels, sleep stages and quality. The future integration of this "biometric" data into healthcare systems may be helpful, as abnormal changes may alert care teams that a patient is starting to get more ill and may need medical attention.{Wesley Milks 2021}

Physical examination of patients is essential in the assessment of PH severity, and especially presence of right-sided (right ventricular) heart failure, which is a direct complication of PH and contributes importantly to patients' symptoms, disability and risk of death. Indeed, the presence of swelling of feet and ankles (edema) and increased pressure in the jugular vein (JVP) in the neck are key indicators of right-sided heart (RV) failure. Patients and their caregivers can be taught to assess edema and to measure JVP, with reliable information comparable to in-person measurement by a physician.{Wesley Milks 2021}

Other Effects of the COVID-19 Pandemic on PH Care

In PH patients being treated with PH medications, interruptions in treatment plans may threaten patient health status. In the above study of PH care in China during COVID-19, 70% of PH patients experienced a medication shortage, while 24.2% discontinued medication and 7.0% changed their medications without consulting their doctor.{Zhou 2020} This was due to the cost of medications as well as medication accessibility during lockdowns. There may be marked differences in access to PH medications between countries. For example, only 3% of PH patients experienced shortage-related interruptions in PH medication use in the online multinational study of 52 countries. Concerningly, in the few patients affected, medication shortages lasted for more than 1 month for 41% of patients.{Godinas 2021}

Moreover, the COVID-19 pandemic has presented a challenge in the initiation of new medications, and in particular the initiation of parenteral infusion prostanoids, including intravenous epoprostenol (Caripul), and subcutaneous or intravenous treprostinil (Remodulin). For example, in the above study of 58 US PH Centres, 30% of Centres limited new prescriptions for these prostanoid infusions.{Lee 2020} Similarly, in the study of 7 German PH Centres, there was a reduction of new PH medication prescriptions by 26-45%.{Yogeswaran 2020} Moreover, although lung transplantation remains the final treatment option for severely ill PH patients, during the COVID-19 pandemic, 27% of 58 US centres referred fewer patients for lung transplant.{Lee 2020}

PH patients may be concerned about their PH getting worse because of reduced in-person assessments, less testing, and potential medication shortages. These concerns could actually motivate some PH patients to focus on being more aggressive in their treatment, as was reported by 62.5% of patients in the Chinese survey above.{Zhou 2020} Fortunately, most PH patients have remained generally well during the pandemic. In the above online study in 52 countries, 76% of PH patients remained stable, while only 14% felt worse.{Godinas 2021} The sense of worsening was attributed to worsening of PH as well as a lack of exercise given public health restrictions, including quarantines, lockdowns and social isolation.

Question 3. How has the COVID-19 pandemic affected the care of PH patients?

Message. The pandemic has disrupted the care of PH patients in many ways, including less in-person visits, less PH-relevant testing, less aggressive PH treatment, and

shortages of some PH medication. However, care has largely remained accessible throughout COVID-19, due in part to enhanced virtual care practices, which provide new and future opportunities for better, regular assessment of PH patients.

4. WHAT ARE OTHER EFFECTS OF THE COVID-19 PANDEMIC ON PH PATIENTS?

Effects of the Pandemic on Health Inequities

Marked inequities in general healthcare have been recognized, even before the COVID-19 pandemic. Disparities in healthcare relate to social determinants of health, including race, ethnicity, gender, sexual orientation age, and socio-economic status (SES).{Ryan 2021, Talwar 2016} It has been recognized that marginalized groups, such as racial minorities, members of LGBTQ+ community, people with disabilities, etc., experience cardiovascular and physiologic stress responses to prejudice.{Sawyer 2012} Moreover, the above social factors and associated marginalization directly influence individual choices regarding where one lives, resulting environmental effects on health and health behaviors, all of which have important implications for outcomes of illness, including PH.{Talwar 2017, Sofianopoulou 2019}

COVID-19 has disproportionately affected specific people, including the elderly, visible minorities and low SES groups, and has exacerbated known inequities in healthcare.{Hou 2020} Specifically with regards to PH, reduced in-person visits and testing have resulted in further delays in diagnosis, as well as barriers to continuing and especially new therapies. All of these issues more greatly affect patients already at risk based on the above social factors. The above-mentioned increase in virtual care could improve access to healthcare and patient assessment during the COVID-19 pandemic, but ideally requires access to the internet and mobile technologies. Sadly, patients without such access are typically those who are already underserved and have poor health outcomes due to social factors.

Effects of the Pandemic on Mental Health of PH Patients

The COVID-19 pandemic has resulted in mental health struggles in many people. This includes fear of getting infected with SARS-CoV-2, getting seriously ill with COVID-19 and perhaps not surviving. There may also be concerns about reduced occupational activity and loss of income, social isolation and less time spent with friends and family, as well as reduced recreational and entertainment activities.

PH also has known, important effects on the mental health of patients, including higher rates of anxiety, depression, and existential distress.{Lo 2019} The mental health challenges in PH are a result of patients facing a serious illness, associated with symptoms of shortness of breath and fatigue, resulting in disability, loss of individual and social roles, and potential worsening leading to hospitalization and risk of death. Appropriate management of PH can also be overwhelming for patients and their caregivers, requiring intensive education about PH and complex medications, dealing

with side-effects of medications, and need for self-monitoring and healthy behaviours, eg. good nutrition, low sodium intake, regular exercise.

PH patients have been very concerned about getting ill with COVID-19, and the effects on their PH and their overall health. For example, 47% of PH patients in the above survey of 52 countries reported anxiety about their health status during the COVID-19 pandemic.{Godinas 2021} Similarly, in the above Chinese survey, 24.2% described panic, and almost half (48.3%) recognized that they felt “even worse because I am already sick.”{Zhou 2020} On a positive note, a majority (63.3%) of these patients expressed a feeling that they should “cherish life”.

CONCLUSIONS

PH patients do not appear to be at a higher risk of COVID-19. Indeed, PH patients may be at lower risk of being infected with SARS-CoV-2 infection, due to the increased health-related conscientiousness among PH patients. PH patients who do get infected with SARS-CoV-2 can suffer very severe COVID-19, with a risk of hospitalization, ICU admission, and death, but there might be some protection from PH medications. During the global pandemic, public health restrictions and PH patient anxiety around COVID-19 illness led to some patient hesitancy in seeking out appropriate healthcare.

Lack of appropriate and timely healthcare threatens the stability of PH patients and increases their risk of harm during the COVID-19 pandemic and potential future public health crises. PH patients need to remain in close contact with their expert PH care teams. The care of PH patients was challenged by the COVID-19 pandemic, with impacts ranging from cancelled testing and delayed appointments to medication shortages. The rapid transition to new models of care, including expanded virtual healthcare, provided important access to care for PH patients. Optimal virtual care of PH patients today and into the future will require new technologies to remotely assess and monitor patients’ biometrics, function, and wellbeing. Moreover, PH patients will require access to technology as well as specific training to fully engage in their own virtual care.

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