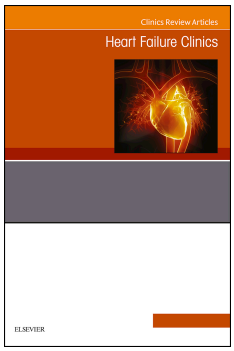
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.



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Management of COVID-19 in patients with pulmonary arterial hypertension

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Synopsis

In this review, we discuss the evidence regarding the course and management of COVID-19 in patients with pulmonary arterial hypertension (PAH), the challenges in PAH management during the pandemic and, lastly, the long-term complications of COVID-19 in relation to pulmonary vascular disease. The inherent PAH disease characteristics, as well as age, comorbidities and the patient's functional status act synergistically to define prognosis of COVID-19 in patients with PAH. Management of COVID-19 should follow the general guidelines, while PAH-targeted therapies should be continued. The pandemic has caused a shift towards telemedicine in the chronic care of PAH patients. Whether COVID-19 could predispose to the development of chronic pulmonary hypertension is a subject of future investigation.

Keywords: COVID-19; pulmonary arterial hypertension

Key points:

- PAH is a significant comorbidity that can lead to unfavorable outcomes during COVID-19.
- PAH-targeted therapies should be continued during the course of COVID-19.
- The development of chronic pulmonary hypertension after COVID-19 remains to be investigated.

Introduction

The COVID-19 pandemic has caused over 6 million deaths worldwide as per April 2022, while model data suggest that the toll of the pandemic on mortality could be at least three times greater (1). Early in the course of the pandemic, observational studies from China indicated that patients with comorbidities were particularly vulnerable to complications from the SARS-CoV-2 infection and at high risk for severe disease and mortality (2). Patients with history of cardiovascular disease, diabetes and cancer remain at increased risk for complications from COVID-19. In fact, nationwide inpatient data from Germany show that deceased hospitalized patients were more commonly elderly (≥70 years), with a higher Charlson comorbidity index compared to survivors and were more likely to suffer from cardiovascular comorbidities (hypertension 52%, coronary artery disease 23%, and heart failure 31%) (3).

On the other hand, pulmonary arterial hypertension (PAH) is associated with significant morbidity and mortality. In PAH, elevated pulmonary vascular resistance and the development of decompensated right heart response are eventually the key mechanisms leading to death for the majority of patients. PAH-related hospitalizations amount to ~30 per million population annually and are associated with 6% inpatient mortality (4). A primary cardiac discharge diagnosis is recorded in almost half of the PAH-related hospitalizations, but primary cardiac hospitalizations show a decreasing trend from 2001 through to 2014 falling from 52.9% to 41.4% of all hospitalizations (5). Extra-cardiac reasons for hospitalization in PAH patients are overall associated with greater inpatient mortality than a primary cardiac diagnosis (6.9% vs 5.3%). Remarkably, a sepsis diagnosis is associated with a 25% risk for inpatient mortality, while pneumonia with 9.4% and respiratory insufficiency or arrest with 21.4%.

The aforementioned evidence and rationale suggest that PAH patients could be at increased risk for complications and, subsequently, worse outcome following COVID-19. In this review, we discuss the evidence regarding the course and the management of COVID-

19 in patients with PAH, the challenges in PAH management during the pandemic and, lastly, the long-term complications of COVID-19 in relation to pulmonary vascular disease (Figure 1).

Early evidence: Could PAH patients have favorable outcomes during COVID-19 infection?

Early studies in the course of the pandemic showed controversial results regarding the outcome of patients with PAH and suggested that the SARS-CoV-2 infection could have a favorable outcome in this population (Table 1). A case series of 13 patients from over 32 US expert PH center in late March 2020 showed that intubation was required only in 3 patients, while only one patient died (6). Similarly, in a case series of 4 patients in the Lombardy region of Italy, none of the patients developed acute right heart failure and all survived the disease (7). Lastly, a case series from Spain comprising 10 patients with PAH and COVID-19 (7 of them in a low risk status) showed that 70% of patients required hospitalization, while none of them died, an unexpectedly favorable outcome (8). These results led the investigators to form hypotheses that certain pathophysiological features of PAH, as well as benefits attributed to the targeted medical PAH therapies could lead to a protective effect in COVID-19. The suggested mechanisms included reduced viral entrance through decreased angiotensin converting enzyme (ACE)-2 expression in PAH, an attenuated response to lung perfusion changes due to basal abnormal lung perfusion in PAH and chronic vasodilator treatment, especially the protective effect of endothelin receptor antagonists against acute respiratory distress syndrome (ARDS).

Further evidence

The largest study conducted comes from the French PH registry and included 211 patients with pre-capillary PH (among them 58.3% with a diagnosis of PAH) and a diagnosis of COVID-19 from February 2020 to April 2021 (9). In this prospective cohort, 32.2% of

patients were hospitalized in a common ward, while an additional 27.5% of patients were hospitalized in intensive care unit (ICU); the median length of stay was 9 (5-15) days. High-flow nasal cannula and corticosteroids were increasingly used after September 2020, while the proportion of patients receiving mechanical ventilation (11.1%) was similar between the two first waves of the pandemic. One fourth of patients (24.6%) died (23% among group 1 PH), the proportion was 41.3% of hospitalized patients. Half of patients who died and nearly a quarter of the hospitalized ones had documented limitations to care escalation (incl. do-not-resuscitate orders). The study was powered for limited inferential analysis regarding mortality; however, significant predictors of mortality were male sex, older age and comorbidities (including chronic renal failure and chronic lung disease), which were more significant than the PH group per se.

Two large surveys conducted early in the pandemic, one led by European investigators and one from the US, provide more evidence and confirm such findings regarding the outcomes of COVID-19 in patients with PAH. In the survey of 47 PH centers from 28 countries worldwide (including 18 European countries), 70 COVID-19 cases were reported among PAH or chronic thromboembolic pulmonary hypertension (CTEPH) patients from 17 April 2020 up to 10 May 2020 (10). The median age of the cohort was 50-59 years and most patients (59%) were under a combination of targeted PAH therapies. The outcomes were not favorable for this PH cohort, since 46% were hospitalized in general wards, and 17% required ICU admission, while mortality was high (20%) for patients with PAH.

The US survey was conducted from 17 April 2020 to 1 May 2020 among 58 center directors of expert PH clinics. A total of 50 patients with PAH or CTEPH with recognized COVID-19 were reported; the cumulative incidence of COVID-19 among this population was similar to the concurrent at the time CDC population estimate of COVID-19 cumulative incidence in the general US population. The results were similar to the European cohort, since 30% of patients were hospitalized (22% in an ICU) and 12% of patients died (11).

We have recently conducted a study among 9 expert PH centers in Greece, cumulatively for 499 PAH or CTEPH patients, covering a larger period of the pandemic, from

late February 2020 (beginning of the pandemic in Greece) to late August 2021 (12). We reported 18 cases with PAH or CTEPH and COVID-19, and among them 12 cases with PAH. The incidence risk of COVID-19 among the PH population was 3.6%, lower than the concurrent incidence risk of 4.8% among the Greek general population. In the PAH subgroup, the hospitalization rate was 33.3% and the mortality rate was 16.7% (2/12 patients). Of the two patients who died, one was >75 years old with a history of cancer, while the other one had significant comorbidities. Both required long-term oxygen therapy at home, indicating the severity of the underlying disease.

Lastly, in an Italian nationwide multicenter survey, the incidence of COVID-19 during the first peak of the pandemic (March-May 2020) was comparable to the general population, however, mortality was 45% (9 patients out of 20 patients with confirmed SARS-CoV-2 infection in total) (13).

Collectively, the aforementioned results indicate that the earlier data and the more recent observations do not match, and that PAH is a significant comorbidity that can lead to unfavorable outcomes during COVID-19 (Table 1). In our opinion, additional comorbidities among PAH patients (such as diabetes mellitus, obesity, and cardiopulmonary comorbidities), as well as advanced age, play as an important role as the severity of the underlying pulmonary vascular pathology, perhaps even a larger one. Frailty has been shown to be a better predictor of disease outcomes in COVID-19 than age and comorbidities alone (14) and we suggest that this also applies to the PAH population, where age, comorbidities, functional status, as well as the inherent PAH disease characteristics act synergistically to define prognosis. However, we must bear in mind that all of these studies were conducted during the pre-vaccination era, and also do not concern the Omicron variants. Thus, the characteristics of the pandemic are now changed and, therefore, different case fatality and hospitalization rates may apply for the PAH population as well.

Management of SARS-CoV-2 infection in PAH

In general, SARS-CoV-2 infection in the context of PAH should be managed according to the current SARS-CoV-2 treatment guidelines, however several considerations must be accounted for, especially when it comes to drug-drug interactions (15). All experts and societies agree that PAH-targeted medication should be continued in patients with PAH during the course of infection with SARS-CoV-2. Drug treatment should be continued irrespective of the severity of COVID-19 in patients with PAH in order to maintain clinical stability and avoid right heart decompensation.

Although patients with PAH are particularly vulnerable and comorbid, post-exposure prophylaxis to SARS-CoV-2 with monoclonal antibodies is no longer recommended because the Omicron variant, which is now predominant in most countries, is not susceptible to them. The introduction of new antiviral therapies changed the landscape of the non-severe (no need for oxygen or hospitalization) COVID-19 management for the general population, since drugs such as molnupiravir, nirmatrelvir-ritonavir, but also remdesivir, have received conditional recommendation for patients who are at risk for progressing to severe COVID-19. However, nirmatrelvir-ritonavir is a strong CYP3A inhibitor and, therefore, co-administration with PDE5 inhibitors is prohibited and must be avoided because it increases the concentration of these PAH drugs. In addition, bosentan, riociguat and calcium channel blockers may also have potential interactions and the co-administration is not recommended. On the other hand, no significant interactions are expected with the use of molnupiravir and PAH-targeted therapy.

The management of hospitalized and unstable patients with PAH and concomitant COVID-19 is particularly challenging since hypoxia and the systemic inflammatory response are difficult to treat (16). PAH-targeted drug treatment should be continued, although its composition or route of administration (for example i.v. for patients who cannot tolerate oral treatment or intubated patients) must be discussed with the PH expert team. The management of ventilation is difficult. In general, efforts must be concentrated to maintain an oxygen saturation >90% and high-flow nasal cannula is an important ally towards that goal. However, in case of persistent hypercapnia, non-invasive ventilation may benefit patients,

but it must be used with caution because it can further impair right ventricular function. Intubation should be discouraged in patients with PAH because of the high risk of death during the induction of general anesthesia. Maintaining a stable blood pressure (with systemic vasopressors), optimizing the fluid status (removal of excess fluids with diuretics or hemofiltration), and supporting the cardiac output (with careful use of inotropes) is of particular importance (16). Concerning COVID-19 specific treatment its use in patients with PAH and severe or critical COVID-19 is recommended. From September 2020 using data from the SOLIDARITY and RECOVERY trials systemic corticosteroids are strongly recommended for patients with severe or critical COVID-19 (15). In addition, there is strong recommendation for the use of interleukin-6 inhibitors (tocilizumab or sarilumab) in this group of patients (15).

The use of PAH-targeted medication in the treatment of COVID-19 in patients without baseline PAH has theoretical basis due to the proven anti-inflammatory effects and reduction effects on pulmonary artery blood pressure, lung edema and remodeling of drugs such as endothelin receptor antagonists, phosphodiesterase 5 inhibitors, riociguat and prostacyclin (17). However, their use could also be dangerous since a drop in pulmonary blood pressure in patients with lung lesions might result in an increase in ventilation/perfusion mismatch and a decrease in blood oxygenation. Some clinical studies showed positive results for the use of inhaled vasolidators (inhaled epoprostenol, iloprost or nitric oxide) or iloprost in PaO2/FiO2, however their use is not yet studied in randomized studies (18–20). In addition, studies for the use of endothelin antagonists or PDE5 inhibitors in severe COVID-19 without baseline PAH are lacking (21). Only recently, a non-controlled study of 25 patients with COVID-19 pneumonitis showed suggested good toleration of sildenafil, without hemodynamic, oxygenation, or dead space deterioration and amelioration in echocardiography and biomarkers (22).

Lastly, we should bear in mind that the vaccination is the most effective way to prevent infection with SARS-CoV-2 and the potentially fatal and disabling complications of COVID-19. All patients with PAH should receive a primary and booster vaccination and

follow the general vaccination planning recommendations as these will form in the future. Significant efforts should be made by the treating physicians to reassure patients and reduce their anxiety regarding the potential adverse events of vaccines. No safety concerns in this particular subgroup of patients have been reported (23).

Pulmonary arterial hypertension ambulatory treatment during the pandemic

Similar to other chronic diseases, the management of patients with PH in general, and PAH in particular, has been considerably challenging during the pandemic. The “exposure risk” of these vulnerable patients for routine follow-up, diagnostic or laboratory testing was high especially in the earlier phases of the pandemic. In addition, the diagnostic pathway of incident PAH cases, as well as the initiation and up-titration of new PAH-targeted therapies during the pandemic was particularly challenging.

In a large survey among Italian centers, Badagliacca et al. observed a 71.4% reduction of in-person visits during the first two months of the pandemic (March-April 2020) compared to the same period in 2019 with a similar reduction to conducted paraclinical tests (13). A similar decline in patients visits, diagnostic testing and overall clinic staffing was observed in a multicenter survey from the US (11). The most common reason for declining visits was a hospital/health system mandate, as well as the fear of patients and physicians for the contraction of COVID-19. In another worldwide survey conducted from 17 April 2020 to 10 May 2020, 8 out of 10 patients with either PAH or CTEPH were provided with a remote consultation (either by video- or tele-conferencing), whereas only 3% of them did not receive any consultation at all during this pandemic period (10).

The COVID-19 has imposed a significant burden on the healthcare system and has subsequently caused a disruption of clinical care pathways of chronic diseases such as PAH. In PAH, it is important to maintain a close relationship between the patient and the caring PAH expert center, since a tight monitoring and treatment titration is mandated to achieve stratification in the low risk category and avoid hazardous clinical outcomes (24). Especially in the earlier phases of the pandemic, it was important to streamline chronic

outpatient care to achieve two goals: (i) offload physicians who dealt with increasing workload in the inpatient service and (ii) protect patients from an environment of increased infection risk such as the outpatient health services. Telehealth programs exploit the advantage of video conference and have been introduced during the pandemic in order to remotely evaluate and monitor the symptoms and functional status of patients (25). Although telemonitoring does not permit a comprehensive physical examination or extensive diagnostic tests, it has been increasingly used, and according to our experience they help expert centers reach medical decisions regarding interventions and therapy titration (26). In a study from a Japanese referral PH center, telemedicine was effective in reducing travel distances and suggested that social networking-video calls may be useful especially for patients who need advanced care, such as patients receiving parenteral prostanoids (27). However, older patients may experience difficulties adjusting to the new technologies and therefore more frequent, telephone visits, rather than video-call visits, would be desirable to reduce anxiety. The overall impact of the first waves of the pandemic on depression and anxiety in patients with PAH has been substantial, with problems stemming mostly from the fear of contracting COVID-19 and the difficulties in specialized care access (28,29).

Lately, in the new phases of the pandemic, which are characterized by vaccination coverage, including boosters, and also the dominance of the Omicron variant with subsequent milder forms of COVID-19, chronic care is gradually returning to pre-pandemic levels. It is to acknowledge though that the merits of telehealth may and should remain for particularly stable, low-risk patients and also when local outbreaks appear.

Long-term complications of COVID-19 in relation to pulmonary vascular disease in patients without baseline pulmonary hypertension

The SARS-CoV-2 is a virus that shows great affinity to the endothelium and significant vascular changes have been described in patients with COVID-19. These vascular changes can affect both the macro- as well as the microvasculature, and are evident in the whole

vascular wall, from the lumen to the perivascular regions, as a result of thrombotic *in situ* microangiopathy and a complex immune-inflammatory cascade (30). Some patients continue to experience symptoms following the acute phase of COVID-19, the so-called "long COVID" syndrome, pertaining to persistent damage in several organs, including the pulmonary vasculature (31). The changes observed in the lung vessels of patients with COVID-19 share many common features with the ones observed in patients with PH; namely, medial hypertrophy and smooth muscle cell proliferation (32). The prevalence of PH during the acute phase of COVID-19 is also high (33,34). In a study of 21 mechanically ventilated patients with COVID-19 who underwent right heart catheterization, low pulmonary vascular resistance, coherent with a blunted hypoxic vasoconstriction, high cardiac output and post-capillary pulmonary hypertension characterized the hemodynamic profile (35). In addition, there is a known increased incidence of pulmonary embolism, as well as *in situ* pulmonary thrombosis, in patients with COVID-19, as well as in those recovering from COVID-19, which could theoretically predispose to an increased incidence of chronic thromboembolic disease in the future (36–38). Taken together, these data have sparkled the hypothesis that COVID-19 could predispose to the development of chronic PH. However, this is a subject of future investigation since long-term cohort studies are still lacking.

Conclusion

PAH is a serious comorbidity that can have a negative impact on the clinical outcomes related to COVID-19. Prognosis is determined by a combination of the underlying PAH disease features and risk stratification, along with other factors such as age, functional status and comorbidities. The treatment of mild and severe COVID-19 in patients with PAH should follow the general recommendations, and PAH-targeted treatments should not be interrupted during the course of the disease. The epidemic has placed a significant stress on PAH chronic care, prompting a move toward telemedicine. Finally, COVID-19 may increase the risk of developing chronic PH in patients without baseline PH; however, long-term evidence is currently scarce.

Clinical Care Points

- Nirmatrelvir-ritonavir is a strong CYP3A inhibitor and, therefore, co-administration with PAH drugs is prohibited and must be avoided.
- PAH-targeted drug treatment should be continued, although its composition or route of administration must be discussed with the PH expert team.
- High-flow nasal cannula is an important ally towards maintaining oxygen saturation in severe COVID-19. In case of persistent hypercapnia, non-invasive ventilation may benefit patients, but it must be used with caution. Intubation should be discouraged in patients with PAH because of the high risk of death.
- Limitation of care is a case-by-case decision and not categorical.

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Conflicts of interest

Authors' contribution

IF and GG contributed to the conception or design of the work. IF and GG contributed to the acquisition, analysis, or interpretation of data for the work. IF drafted the manuscript. GG critically revised the manuscript. Both gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

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Table

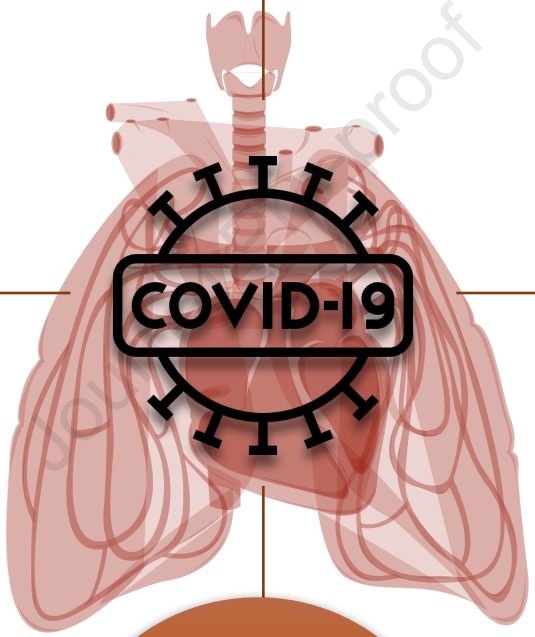
Table 1. Studies reporting COVID-19 infection among patients with pulmonary arterial hypertension.

Study	Centers	Countries	Study period	Population	N of patients	COVID-19 incidence	Hospitalization rate	Case fatality rate
Sulica et al.(39)	1	US	March-May 2020	PAH + CTEPH	11	3.1%	81.8%	45.4%
Horn et al.(6)	32	US	Late March 2020	PAH	13	NR	53.8%	7.7%
Scuri et al.(7)	1	Italy	NR	PAH	4	NR	100%	0%
Nuche et al.(8)	1	Spain	Until 10 April 2020	PAH	10	2.9%	70%	0%
Belge et al.(10)	47	28 countries worldwide	17 April 2020 to 10 May 2020	PAH + CTEPH	70	NR	70%	19%
Lee et al.(11)	58	US	17-24 April 2020	PAH + CTEPH	50	0.29%	30%	12%
Farmakis et al.(12)	9	Greece	February 2020-August 2021	PAH + CTEPH	18	3.6%	44.4%	22.2%
Badagliacca et al.(13)	25	Italy	1 March 2020-1 May 2020	PAH	20	0.46%	45%	45%
Godinas et al.(29)	Patient survey	52 countries worldwide	May-June 2020	PAH + CTEPH	9	1%	NR	NR
Montani et al. (9)	26	France	February 2020-April 2021	Pre-capillary PH	211	2.7%	59.7%	24.6%

PAH: pulmonary arterial hypertension, CTEPH: chronic thromboembolic pulmonary hypertension

PAH is a significant comorbidity that can lead to unfavorable outcomes during COVID-19

PAH-targeted therapies should be continued during the course of COVID-19



The merits of telehealth may and should remain for low-risk patients and also when local outbreaks appear

Development of chronic pulmonary hypertension after COVID-19 remains a question