

An Update on Pulmonary Hypertension in Coronavirus Disease-19 (COVID-19)

Ajay Kumar Mishra¹ MD, Amos La² MD, Kamal Kant Sabu¹ MD, Anu Anna George¹ MD, Dr. Kevin Martin³ MD, Dr. Jennifer Sargent⁴ DO

¹Resident, Department of Internal Medicine, St Vincent Hospital, Worcester, MA

²Fellow in Department of Pulmonology and Critical Care Medicine, Mayo Clinic, Rochester

³Division of Pulmonary and Critical Care, Department of Internal Medicine, Worcester, MA, United States

⁴Associate Program Director, Department of Internal Medicine, St Vincent Hospital, Worcester, MA

Summary. Coronavirus 19 disease (COVID-19) continues to be a pandemic with global implications. Respiratory system involvement is the most common manifestation in symptomatic patients. In this literature review, we describe the diagnosis, management, and implications of pulmonary hypertension (PH) among patients with COVID-19. We defined pulmonary hypertension as increasing mean pulmonary artery pressure (mPAP) of ≥ 25 mm Hg at rest. In our literature search, we identified 4 articles with details on pulmonary hypertension. Among these, two reported various echocardiographic details for diagnosing pulmonary hypertension. In 1 study evidence of pulmonary hypertension was noted in 13.4% of patients. Patients with severe COVID-19 were reported to have a higher proportion of pulmonary hypertension as compared to mild COVID-19 disease [22% vs 2%]. Elevated pulmonary artery systolic pressure was significant in predicting mortality. COVID-19 patients with chronic obstructive pulmonary disease, congestive heart failure, myocardial injury, pulmonary embolism, and prior pulmonary hypertension were at a higher risk of worsening pulmonary hypertension. Multiple mechanisms for developing pulmonary hypertension that have been postulated are i) concomitant worsening myocardial injury, ii) cytokine storm, endothelial injury, hypercoagulability attributing to development of venous thromboembolism, iii) and the presence of thrombotic microangiopathy. Among patients with severe COVID-19 disease and pulmonary hypertension, complications including acute respiratory distress syndrome, acute myocardial injury, the requirement of intensive care unit admission, the requirement of mechanical ventilation, and mortality are higher. (www.actabiomedica.it)

Key words: Pulmonary Hypertension; COVID-19; Risk factors; Mechanism; Outcome

Introduction

Coronavirus disease 2019 (COVID-19) continues to be a pandemic which has resulted in a significant global health crisis. As of May 30th, it has involved 188 countries, and affected more than 1.7 million patients in the United States.¹ Symptomatic patients predominantly seem to have respiratory manifestations. Patients with advanced chronic obstructive lung disease, comorbid cardiovascular illnesses are

reported to be at a higher risk of poorer outcome.² Pulmonary hypertension (PH) continues to be a disease with significant implications on short-term, and long-term survival. There is a paucity in clinical literature reporting pulmonary hypertension among patients with COVID-19. We did a systemic review to obtain the available data on clinical manifestation, diagnosis, management of pulmonary hypertension in patients of COVID-19.

Methods

In this review we searched major electronic databases including Pub Med, Embase, Medline, and Google scholar for articles on COVID-19 and pulmonary hypertension. Key words that were used for search were “COVID-19”, “Coronavirus disease 2019” “pulmonary hypertension”, “pulmonary artery hypertension”, “pulmonary venous hypertension”, and “idiopathic pulmonary hypertension”. Studies reporting clinical details of COVID-19 patients with pulmonary hypertension were included. We also included studies which had reported the presence of pulmonary hypertension among their patients irrespective of patient outcome. Publications including clinical trials, retrospective cohort studies, cross-sectional studies, case controlled studies, case series, case reports were included in this review. We excluded all articles which did not provide any patient related information. Opinions, letters, recommendations, guidelines without clinical details were excluded. All articles published between 1 December 2019 to 30 May 2020 were included in this review. We included English peer reviewed articles which were published in scientific journals.

Definitions

We included studies that defined pulmonary hypertension as increasing mean pulmonary artery pressure (mPAP) of ≥ 25 mm Hg at rest. Precapillary pulmonary hypertension if reported had to be defined

as (mPAP) of ≥ 25 mm Hg, with Pulmonary capillary wedge pressure (PCWP) < 15 mm Hg, and Pulmonary vascular resistance (PVR) ≥ 3 Wood. Post capillary pulmonary hypertension was defined as (mPAP) of ≥ 25 mm Hg, with Pulmonary capillary wedge pressure (PCWP) > 15 mm Hg.³ We also tried to incorporate the 2015 ESC/ERS clinical classification of pulmonary hypertension of reported patients.

ECHO: Echocardiography reporting estimated pulmonary artery systolic pressure (PASP) from tricuspid (TR) jet velocity, right atrium size, right ventricular size, right atrium to left atrium ratio, interatrial septal bows, right ventricular outflow tract notching, E/A ratio of < 1 , lateral e', lateral E/e', pulmonary capillary wedge pressure, pulmonary artery diastolic pressure in patients with PH were also included in this review.⁴

Results

Clinical evidence

We identified two observational studies (1 retrospective, and 1 prospective) describing details of pulmonary hypertension among patients with COVID- 19. We also identified two case reports of

COVID 19 patients with pulmonary hypertension.⁵⁻⁸ Table 1 summarizes the details of the following studies in brief.

Deng et al. enrolled 112 patients with COVID -19 and looked for evidence of myocardial injury through echocardiography. They defined pulmonary hypertension as presence of 2 of the following parameters

Table 1. Studies reporting pulmonary hypertension in patients with COVID-19.

Number	Authors	Study type	Number of PH patent's	Diagnostic Method	mPAP	Type of PH	Predictors of outcome
1	Deng et al ⁵	Retrospective	(13.4%)	ECHO	- (Peak TR velocity > 2.8 m/s)	Group 2	+
2	Li et al ⁷	Prospective	(15%)	ECHO	48	Group 2	+
3	Zamanian et al ⁸	Case report	1	Invasive Monitoring	40	Group 1	-
4	Buja et al ⁶	Case series	1	CT chest	- (PA-3.4cm)	Group 2,4	+

PH: Pulmonary hypertension, ECHO: Echocardiography, mPAP: mean pulmonary artery pressure, CT: COmputed tomography, TR: Tricuspid regurgitation, PA: Pulmonary artery diameter

i) peak tricuspid regurgitation velocity of more than 2.8 m/s ii) right ventricle/left ventricle basal diameter ratio more than 1.0 iii) pulmonary acceleration time of less than 105 msec and/or mid- systolic notching; iv) signs of the increase of right atrial pressure in the form of inferior cava diameter more than 21 mm with decreased inspiratory collapse

They reported 13.4% patients with signs of pulmonary hypertension. While 21% of patients with severe COVID-19 had evidence of pulmonary hypertension only 2% of patients with mild to moderate disease had pulmonary hypertension. Presence of PH in their study was statistically significant in predicting the composite outcome including admission to intensive care unit, requirement of mechanical ventilation, and requirement of extracorporeal membrane oxygenation, mortality⁵

Li et al enrolled 120 patients with COVID-19, and obtained 2-dimensional speckle tracking echocardiography to look for evidence of right ventricular strain. In the study patients who succumbed to the disease had a mean pulmonary artery systolic pressure of 48 mm Hg, as compared to 28 mm Hg in the survivors. Additionally, in this study enlarged right heart chamber, diminished right ventricular function, and elevated pulmonary artery systolic pressures were statistically significant in predicting mortality at a median follow-up of 51 days.⁷

Zamarian et al. reported a 34-year-old female with vasoreactive idiopathic pulmonary hypertension, presenting with worsening symptoms following COVID-19. Patient was continued on her medications of nifedipine, tadalafil and macitentan. She was treated with inhaled nitric oxide, and was monitored with home-based daily healthcare. Patient continued to have significant clinical improvement, and did not require any hospital visit.⁸

Buja et al. reported a 34-year-old, morbidly obese (BMI of 51.6) young man, with concomitant heart failure with reduced ejection fraction (EF <20%) presenting with clinical features of severe COVID-19. CT thorax showed a dilated pulmonary artery with a diameter of 3.4 cm. Patient succumbed to his illness despite supportive medical treatment and was noted to have multiple, bilateral pulmonary embolism.⁶

Mechanisms

Interaction of COVID-19 and pulmonary hypertension is multifaceted. Two principal diseases that predispose to pulmonary hypertension, are also instrumental in worsening clinical outcome in COVID-19. Across multiple studies patients with chronic obstructive pulmonary disease, and heart failure have been shown to have poor clinical outcome.^{9,10} Studies on myocardial injury in patients with COVID-19, have consistently shown that patients with severe myocardial injury, have higher pulmonary hypertension and poor clinical outcome.^{5,7,11} In a few studies an association has been found between the presence of myocardial injury, and pulmonary hypertension, however causality has not yet been established.¹²

COVID-19 patients are predisposed to venous thromboembolism due to excessive inflammation in the background of cytokine storm, hypoxia related free radical injury, prolonged immobilization, endothelial inflammation, thrombotic microangiopathy, and diffuse intravascular coagulation.^{13,14} Klok et al. noticed the presence of pulmonary embolism (PE) in 25 (13.6%) of the 184 patients with severe COVID-19 requiring intensive care unit admission. These patients had developed pulmonary embolism despite systemic thromboprophylaxis. Similarly, venous thromboembolism was reported in 7(58%) out of the 12 patients with severe COVID-19 who underwent postmortem autopsy. Among these patients, PE was attributed to be the principal cause of death in 33% (N=4). In a particular patient, autopsy showed acute, multiple, bilateral, segmental pulmonary thromboembolism even though CT was negative for any evidence of pulmonary embolism.^{6,14} In COVID-19 patients, the presence of pulmonary embolism is crucial in the development of chronic thromboembolic pulmonary hypertension.¹⁵

Finally, multiple studies have shown that thrombotic micro-angiopathy primarily involving the lungs is an important pathophysiological mechanism in severe COVID-19 disease. Patients with severe COVID-19 related fatality have been reported to have pulmonary microvascular thrombi, perivascular CD4 + T-cell infiltrates, platelet aggregations, platelet rich clots, intracapillary neutrophil entrapment, increased megakaryocytes in pulmonary capillaries, and intra-and

extra capillary fibrin deposits on autopsy studies. Presence of endothelial injury, thrombosis, imbalance in vasoconstriction and vasodilation, inflammatory cells, platelets, cytokines can also contribute to pulmonary vascular remodeling.^{6,13,16}

Outcome

Studies on the effect of COVID-19 in patients with pulmonary hypertension is still lacking.

Studies on pulmonary hypertension among patients with COVID-19 have reported that presence of newly diagnosed pulmonary hypertension is higher among patients with severe COVID-19.^{5,7}

Pulmonary hypertension in these patients is associated with acute respiratory distress syndrome, acute heart injury, multi-organ dysfunction, increased inflammatory markers, requirement of intensive care unit admission, requirement of invasive mechanical ventilation, and requirement of extracorporeal membrane oxygenation, morbidity and mortality.^{2,5,7}

Figure 1. Mechanism, risk factors and outcome of pulmonary hypertension

Pulmonary Hypertension in COVID -19 patients



Disparities

Most imaging studies are focused towards reporting the obvious. Computed tomographic studies, echocardiographic studies, magnetic resonance imaging studies on COVID-19 patients consistently lack details on assessment of pulmonary artery anatomy and pressure. In a recent study by Bangalore et al, 14 patients with focal ST elevation were included. Nine of these patients underwent coronary angiogram. Five of these 14 patients had normal LV function, and 3 had normal angiogram. In this study, the authors did not mention the mPAP, or PCWP.¹⁷ A systemic review by Bao et al included 13 studies describing chest CT findings of COVID-19 patients, and 2738 participants lacked details on pulmonary trunk diameter, main pulmonary artery to ascending aortic diameter ratio, and other details of right ventricular function.¹⁸ In studies reporting presence of pulmonary embolism in patients with COVID-19 recording of pulmonary pressures have been inconsistent.¹⁹

Limitations

Invasive hemodynamic monitoring is the gold standard for assessing mean pulmonary artery pressures. Most patients presented in this literature review did not have invasive hemodynamic monitoring. In view of the technical difficulties associated with the COVID-19 pandemic, studies reporting echocardiographic evidence of pulmonary hypertension have been crucial in understanding the relationship between COVID-19 and pulmonary hypertension. There is limited literature on the impact of COVID-19 in patients with prior idiopathic pulmonary hypertension. This review is skewed towards post-capillary pulmonary hypertension, in patients with cardiac dysfunction as noted by echocardiography. Details of interactions between multiple cardiovascular agents, pulmonary hypertension medications on patients of COVID-19 are still limited.^{20,21} However, the strength of this review is that it includes the presently available literature on COVID-19 patients with pulmonary hypertension.

Conclusion and future perspectives

Pulmonary hypertension is being increasingly reported among patients with COVID-19. Chronic obstructive pulmonary disease, and heart failure are commonly seen in patients with pulmonary hypertension and severe COVID-19. Presence of pulmonary embolism, and thrombotic microangiopathy can also contribute to the development of pulmonary hypertension. Patients of severe COVID-19 with pulmonary hypertension are shown to have poorer clinical outcome.

Mention of the pulmonary artery systolic pressure in future studies reporting pulmonary embolism with CT chest, and cardiac dysfunction with echocardiography among COVID -19 patients would help in better understanding of the disease.

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Correspondence:

Dr. Ajay Kumar Mishra, MD

Department of Internal Medicine

St Vincent Hospital

123 summer street, Worcester, MA

Ajay.Mishra@stvincenthospital.com

Phone: 5083635000