Survival and Factors Impacting Survival in Patients with Pulmonary Arterial Hypertension and Chronic Thromboembolic Pulmonary Hypertension Who Underwent COVID-19 Infection

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Abstract

Introduction: The pathological processes of pulmonary hypertension and COVID-19 disease are similar. Both are characterized by vascular damage, severe micro thrombosis, and microvascular obliterative disease due to extensive endothelial dysfunction.

Objective:It was planned to present the clinical, radiological, and biochemical data of patients with pulmonary arterial hypertension(PAH) and Chronic Thromboembolic Pulmonary Hypertension (CTEPH) diagnosed with COVID-19, who were followed up in our pulmonary arterial hypertension (PAH) center, as well as to assess the survival rates and to investigate the factors impacting survival.

Methods: Patients who were diagnosed with COVID-19 between March 2020 and July 2021 and were followed up in the PAH center of our hospital, were included in the study. All information were obtained from the records in the hospital automation system.

Results:It was found that 24(7.2%) of the 331 patients who had been followed in the PAH center were diagnosed with coronavirus. The mean age of the patients was determined to be 53.54. It was found that 62.5% of the patients were female,54.2% had the etiology of CTEPH and 41.7% of the patients were in functional class II(WHO-FC II) before being infected with COVID-19.The survival rate was 79.2%. It was found out that the risk of mortality decreased by 0.007 times as the cardiac index increased, and the risk of mortality increased 10,233 times as the functional class increased.

Conclusion: Mortality rates due to COVID-19 infection were determined to be higher in PAH/CTEPH patients. The cardiac index values and current functional classes of the patients were associated with survival.

Keywords: Pulmonary arterial hypertension, chronic thromboembolic pulmonary hypertension, Mortality, Outcomes, COVID-19

Introduction

Pulmonary hypertension (PH) is a pulmonary vascular disease characterized by pulmonary arterial remodeling and vasoconstriction, resulting in elevated pulmonary artery pressure and ultimately right heart failure, with a clinical course and severity depending on the etiology. The coronavirus disease (COVID-19), which first broke out in Wuhan, China, has been termed as a severe acute respiratory syndrome caused by a novel coronavirus. According to the US Centers for Disease Control and Prevention (CDC), patients with underlying health conditions, including all types of lungs and cardiovascular disease, have an increased risk of developing serious illness when infected with SARS-CoV-2 (1).Hitherto, the number of pulmonary hypertension (PH) patients with COVID-19 has been reported to be relatively lower (2,3). It may be too early to come to this conclusion. Because the rate of PD patients in society is quite low. The fact that they mostly live in isolation from the community, close medical follow-up, and regular use of preventive medical treatments can explain the low incidence of infection. Besides, there are views that the medications used by these patients for pulmonary vasculopathy are therapeutic or protective in COVID-19 infection (4). The pathological characteristics of the endothelial cell structures of patients with PD infected with COVID-19 as well as the downregulation of angiotensin-converting enzyme 2 (ACE-2) receptors, which play the primary role in both intracellular entry and replication of coronaviruses, might also contribute to this (5,6). Myocarditis, myocardial infarction, cardiomyopathy, cardiogenic shock, acute cor pulmonale, and arrhythmias may occur in patients with COVID-19. Moreover, localized thrombosis in the pulmonary vessels is

common as well. There are limited publications regarding the consequences of COVID-19 in adults with PH, though the incidence of SARS-CoV-2 infection in patients with PH is comparable to the general population.

From March 17, 2019, when the first case emerged in our country, until July 2021, all pulmonary hypertension patients were followed closely both in PAH outpatient clinics and electronic communication channels. Throughout this period, patients who were diagnosed with COVID-19 and needed hospitalization were closely followed in the relevant services, and their data were recorded.

Method

This cross-sectional, clinical study was performed in the chest diseases department of a university hospital after the approval of the local Institutional Review Board (Ethics committee no: 2021/11-06). All participants gave written and informed consent.Patients with pulmonary arterial hypertension and CTEPH who were diagnosed with COVID-19 between March 2020 and July 2021 and were followed up in the adult PAH center of our hospital were included in the study. All clinical, radiological, demographic, and survival data were obtained from the records in the hospital automation system.

Statistical Method

Data were analyzed via the software of IBM SPSS V23. Whether the variables conformed to the normal distribution was analyzed using the Shapiro-Wilk test. Binary logistic regression analysis was employed to analyze the risk factors impacting mortality. Chi-square and Fisher's Exact tests were used to compare categorical variables based on the diagnosis groups. The Independent two-sample t-test was used to compare normally distributed data according to diagnosis groups, and the Mann-Whitney U test was used to compare data that were not

normally distributed. Results of the analysis were presented as mean ± standard deviation and median (minimum-maximum) for quantitative data, while categorical data were presented as frequency (percentage). The significance level was considered as $p<0.050$.

Results

It was found that 24 (7.2%) of the 331 patients who had been followed in the PAH center were diagnosed with coronavirus. The frequency distribution of the categorical variables and the descriptive statistics of the quantitative data are tabulated in detail in tables 1 and 2, and when the prominent results are considered, the mean age of the patients was 53.54 (min 18-max 86). It was determined that 62.5% of the patients were female, 45.8% had mild radiological involvement, 54.2% had the etiology of Chronic thromboembolic pulmonary hypertension (CTEPH), followed by IPAH, Eisenmenger's syndrome, scleroderma, in order of frequency. Moreover, it was found that 41.7% of the patients were in functional class II before COVID-19 (WHO-FC). It was found that 54.2% of the patients received riociguat treatment and 47.8% had comorbidity of Diabetes mellitus. Based on the RALE classification, the radiological staging was graded as mild for involvement below 25%, moderate for involvement between 25-50%, and severe for involvement above 50% (7).

When the diagnostic groups were divided into CTEPH and PAH, no significant difference was determined between the distributions of sex, survival, radiological involvement, and the last functional class before covid ($p>0.050$) A significant difference was found between the diagnosis groups (CTEPH/PAH) in terms of d-dimer median values ($p=0.004$). The median CTEPH value was found to be 2 and the PAH median value was 0.8. No significant difference was detected between the groups in terms of the other variables ($p>0.050$). The mean disease year was 4, and the mean hospitalization duration was 6.96 days, while the survival rate was 79.2%, and the mortality rate was 20.8%. Risk factors affecting mortality were analyzed as a binary logistic regression and Univariate model. Cardiac index and last functional class before

covid (according to the class assessments of WHO NYHA) risk factors were found to be statistically significant (p:0.047 and p:0.033, respectively). As the Cardiac index increases, the risk of mortality decreases by 0.007 times. On the other hand, as the number of functional classes increases, the risk of mortality increases 10,233 times (Table 3). Of the patients who were exitus, 2 had Eisenmenger syndrome, 2 had CTEPH and 1 had IPAH. ARDS did not develop in any patients who were exitus. The causes of death of the patients were recorded as worsening of pulmonary arterial hypertension due to infection. No correlation was found between the diagnosis of the disease and survival.

Discussion

According to the US Centers for Disease Control and Prevention (CDC), patients with underlying health conditions, including all types of lungs and cardiovascular disease, have an increased risk of developing serious illness when infected with SARS-CoV-2 (1).

Patients with PH are at potential risk for serious complications and high mortality due to related comorbidities, and unfortunately, they have worse outcomes compared to other patients. In pulmonary hypertension patients with COVID-19, the right ventricle might deteriorate rapidly due to hypoxemia and inflammatory cytokine release; hence, close clinical follow-up is required. Given the published articles on acute right heart failure developing after systemic infection, Ryan et al. (9) suggested that right heart failure and concomitant COVID-19 infection may lead to an increase in mortality in patients with pulmonary arterial hypertension (PAH) (10,11).

In the clinical evaluation of a PH patient with COVID-19, it was determined that the risk of developing decompensated right heart failure in patients with mild symptoms was considerably low (8). These patients can be followed up and treated at home. Yet, patients

with worsening respiratory symptoms need to be hospitalized. On the other hand, patients with severe respiratory symptoms should be monitored in intensive care units of centers that can provide advanced medical services, including extracorporeal life support and lung transplantation.

We consider that the high number of data we present as a single center would contribute to the data of other centers, albeit the data of pulmonary hypertension patients suffering from COVID-19 disease are limited across the world. Although specific diseases have been investigated in COVID-19 patients in various studies, the incidence of PAH/CTEPH has been scrutinized in considerably few studies (2,3).

Given the world data on COVID-19 disease, it has been revealed that while the comorbidities vary between countries, they include hypertension, diabetes mellitus, COPD, cardiovascular diseases, liver diseases, obesity, kidney diseases, and malignancy and that comorbidities contribute to mortality at varying percentages (12).

PAH/ CTEPH patients were not assessed as a separate group in these studies. In our study, when PAH/CTEPH patients were evaluated within themselves, we found that comorbidities were not associated with mortality; however, we are of the opinion that right heart failure accompanying pulmonary vascular pathology in these patients contributed to mortality. Because the community mortality rate was 2.8% in COVID-19, while the mortality rate was determined to be 20.8% in this group of patients in our study. In our study, the high functional classes, and low cardiac indexes of the patients with increased mortality in the last outpatient evaluation made us consider that it may be associated with developing heart failure. World Health Organization functional classes (WHO-FC) (Table 1) are a strong predictor of survival in patients with pulmonary hypertension (13). Previous data for patients with untreated IPAH or hereditary PAH indicates that median survival is 6 months in WHO-FC IV,

2.5 years in WHO-FC III, and 6 years in WHO-FC I and II. Likewise, a low cardiac index has been shown to be associated with survival (13). It can be considered that the intervening viral infection in these patients paves the way for a situation that accelerates this process.

In the study of Lee, data of PAH/CTEPH patients from 77 PAH centers were analyzed and 58 centers provided data for the study (14). In this study, it was noted that among 16,979 covid patients, 50 of them were PAH/CTEPH patients. In this study, it was hypothesized that the low number of cases was due to the fact that these patients isolated themselves well and that the medications they received improved vasculopathy. In this study, the cumulative incidence of pulmonary hypertension was recorded as 2.9/1000. This rate was determined to be similar to the population rates. However, the mortality rate was found to be 12% (14). It was slightly higher than the population rate. On the other hand, our mortality rate was 20.8%, which was a little higher than in this study. Those who died in our study were the patients with high-risk pulmonary hypertension. Regarding the Lee study, it was a survey study, the number of patients was smaller, and patient data were not recorded in detail. Functional class, BNP (B-type brain natriuretic peptide) values, cardiac index values, right heart catheterization measurements, walking tests, and inflammatory marker measurements (CRP, D dimer, lymphocyte, white blood cell, ferritin) of the patients of these centers were not evaluated.

The lower mortality rate compared to our center may be due to the fact that pulmonary hypertension patients consist of patients with a low functional class. No record related to this situation was found. Another reason may be that a large proportion of high-risk PAH patients maintain social distancing, and CTEPH patients are more educated and comply with the social distancing rule. Hence, the survival of high-risk patient groups may not be reflected in studies. We had COVID-19 patients in our center with low cardiac index and high functional class, though not very high in number, and we observed that these conditions were effective in mortality. Plus, our advantage as a center in these patients was that phone interviews and face-

to-face visits were never interrupted throughout the pandemic, which allowed for proper data generation.

In the study of Belge et al., another PAH center data collection study, patients with a diagnosis of COVID-19 were reported through a questionnaire in 19 PAH centers (15). Merely 6 centers reported patients. In this study, the total number of patients in all centers was 70, and the majority of the patients were with PAH and connective tissue diseases (15). In this study, the mean age of the patients was found to be 50-59 years. While the mean age in our study was similar, those with CTEPH constituted most of the patients in our center, followed by IPAH patients. The mortality rate of these centers was calculated as 19%. It was a rate similar to our mortality rate.

In their study, Horn et al. tried to collect the data of COVID-19 patient data from 32 pulmonary hypertension centers in the USA by questionnaire, but only 13 cases of COVID-19 were reported (5). Moreover, in this study, although the number of cases was lower, the case fatality rate was 19%, which was higher than the normal population (16,17). The reason for this may be that the patients have isolated themselves well since the beginning of the pandemic, or that the medications used by the patients for their diseases (endothelin receptor antagonist, prostacyclin analogs, phosphodiesterase 5 enzyme inhibitors, guanylate cyclase stimulators) may have minimized the COVID-19 infection damage thanks to their anticoagulant activities when treating vasculopathy. When our patient data were analyzed, the absence of cytokine storms and pulmonary embolism in any of the patients may be due to the protective effect of the medications received by these patients. The low cardiac index of the patients who were exitus may indicate that right heart failure, which increases during infection, is more effective in mortality than COVID-19 infection inflammation; thus, any infection is inevitable at this end. The fact that microvascular capillaritis has been demonstrated in autopsy studies in COVID-19 patients without PAH may question the early

use of PAH medications in this group of patients. Even, according to the consideration of an author, coronavirus itself can directly lead to pulmonary vascular pathology like HIV (17). This is a secondary cause of vasculopathy in patients with PAH/CTEPH, and it may worsen the patients, or it may lead to the occurrence of new PAH/ CTEPH in the future in patients without PAH/CTEPH (17). Because pulmonary vasculopathy, which was not detected in autopsy studies in SARS corono1 and H1N1 patients, was detected in corona patients. (18) Thus, it can be considered that PAH-specific medications could be effective in corona patients.

At the beginning of the pandemic, when the frequency of severe COVID-19 cases was lower among patients with PAH, it was interpreted that specific medications could be therapeutic or protective. There are many subgroups within the PAH group, and it is well-known that additional immunosuppressant drugs were used particularly in connective tissue diseases. In addition to the antifibrotic, anti-inflammatory, antiproliferative vasodilator, and antifibrotic effects of the medications used by patients receiving PAH specific treatment, the anticoagulant effects of prostanoids and the anticoagulant treatment of the majority of these patients would prevent microthrombus and vascular pathology (19). Yet, the number of cases all over the world is still not at an adequate level to be able to make this interpretation and constitute evidence.

The novel coronavirus SARS-CoV-2 exerts its effects in patients with COVID-19 through the interaction of its spike protein with ACE-2 receptors, which are highly expressed in lung alveolar cells and vascular endothelium (20). Lack or downregulation of ACE-2 impairs angiotensin II and reduces its effects on endothelial injury, vasoconstriction, and fibrosis (21). This results in increased pulmonary vasoconstriction and dysregulation of hypoxic vasoconstrictive mechanisms. On the other hand, there is a linear correlation between the

severity of lung injury in COVID-19 patients and plasma angiotensinogen II levels as well as viral load (22). Endothelial dysfunction is the starting point to initiate the cascade of events leading to ventilation/perfusion mismatch, hypoxia, vasoconstriction, and PH.

In the Sulica study, when evaluated retrospectively in a PAH center in New York, COVID-19 was detected in 11 of 350 patients, and the mortality rate was determined to be 36.6% (23). The causes of death in these patients were ARDS and kidney failure. The rate of admission to the intensive care unit was 63.3%. This figure was considered a high figure compared to our data. It was observed that 3 of the patients who were exitus had HIV-related PAH, and 1 of them had collagen tissue disease and kidney failure. Although there were many patients with collagen tissue, the mortality rate was not high among these patients. This might be associated with the improvement of pulmonary vasculopathy of the immunosuppressive agents they use. One collagen tissue patient died. The cause of death was kidney failure. The cause of death of other HIV patients was ARDS. None of our patients had HIV. In this study, patients with a high REVEAL risk score died. Considering the ESC risk assessment, which we use in daily practice, the patients who were exitus in our study were in the high-risk group as in this study (patients with a high functional class and a low cardiac index).

In the study of Jurge nuche, COVID-19 was detected in 10 of 350 patients. The mortality rate of the patients was found to be 9.4% (24). A significant correlation was found between mortality and blood CRP, lymphopenia, d dimer, oxygen saturation, and comorbidities (heart failure, kidney failure, diabetes). In our study, no correlation was found between these values and comorbidities and mortality. The fact that our patient data is more than this study indicates that our results are more acceptable. The reason why the mortality rate was lower in this study compared to other studies suggested that the patients were mild to moderate patients, and the medications used may have been effective.

Limitation

Although the number of cases was limited, mortality rates were determined to be higher compared to the general population. The underreporting of benign cases and the fact that these patients are patients who comply with the social distancing can be stated as the limitations of the study. Albeit the protective effect of the physiopathological changes in these patients and the medications they use is thought to be able to prevent and treat COVID-19 infection, further comprehensive studies are needed to demonstrate this finding.

In conclusion

COVID-19 infection may pose a serious threat in PAH/CTEPH patient groups. There is no successful treatment for COVID-19 yet. Although it is considered that the medications used by our patients in this group can prevent serious complications that may occur in COVID-19 patients, there is no compelling evidence. Mortality rates were found to be high in all studies, particularly in high-risk patients, though the incidence of the disease is similar to the whole population. In any case, these patients should be isolated in good conditions, social distancing should be maintained, attention should be paid to hygiene, and the follow-up should be performed carefully online, by phone, or face-to-face interview.

Author contributions

All authors contributed to the conception and design of the study, analysis and interpretation of the data, and critical revision of the manuscript

Conflict of interest

The author(s) declare that there is no conflict of interest.

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Table 1. Frequency distribution of categorical variables

	Frequency (n)	Percent (%)
Sex		
Male	9	37,5
Female	15	62,5
Etiology of pulmonary hypertension		
Eisenmenger's syndrome	3	12,5
IPAH (idiopathic pulmonary arterial hypertension)	6	25,0
CTEPH (Chronic thromboembolic pulmonary hypertension)	13	54,2
Scleroderma	2	8,3
Survival		
Exitus	5	20,8
Alive	19	79,2
Radiological involvement		
Severe	5	20,8
Mild	11	45,8
Moderate	7	29,2
Absent	1	4,2
Last functional class before Covid (WHO-FS)		
1	2	8,3
2	10	41,7
3	9	37,5
4	3	12,5
Treatment received for pulmonary hypertension		
Ambrisentan (Endothelin receptor antagonist)	1,0	4,2
Bosentan (Endothelin receptor antagonist)	7,0	29,2
Iloprost (prostacyclin analog)	4,0	16,7

Macitentan (Endothelin receptor antagonist)	3,0	12,5
Riociguat (guanylate cyclase stimulator)	13,0	54,2
Selexipag (prostacyclin analog)	2,0	8,3
Tadalafil (phosphodiesterase enzyme 5 inhibitors)	2,0	8,3
Treprostinil (prostacyclin analog)	1,0	4,2
Comorbidity		
Bronchiectasis	1,0	4,3
Diabetes Mellitus	11,0	47,8
Hypothyroidism	1,0	4,3
Hypersensitivity pneumonia	2,0	8,7
COPD	8,0	34,8
Absent	6,0	26,1

Table 2. Descriptive statistics of quantitative data

	N	Mean	S. deviation	Median	Minimum	Maximum
Age (years)	24	53,54	17,66	58,00	18,00	86,00
Disease duration (years)	24	4,00	3,65	3,00	1,00	12,00
Duration of hospital stay (days)	24	6,96	5,03	5,00	0,00	20,00
Hb (gr/dl)	24	13,67	2,55	14,00	8,00	18,00
White blood cell (µl)	24	7500,00	3665,59	6600,00	2000,00	16000,00
Lymphocyte (%)	24	14,33	9,41	12,50	1,60	35,00
Neutrophil (%)	24	79,92	11,22	78,50	55,00	97,00
CRP (mg/lt)	24	55,06	52,68	40,00	2,00	249,00
Ferritin (ng/ml)	24	149,50	270,14	60,50	11,00	1280,00
D dimer (µg/L)	24	2,71	3,92	1,05	0,30	18,00
BNP (pg/mL)	24	581,71	826,80	325,00	10,00	3884,00
AST (U/lt)	24	47,33	117,82	15,50	9,00	585,00
ALT (U/lt)	24	42,25	98,52	13,00	4,00	482,00
Uric acid (mg/dl)	24	6,89	2,52	7,20	1,30	12,00
Creatinine (mg/dl)	24	0,97	0,42	0,80	0,50	2,20
6-minute walk test before Covid (m)	24	286,33	99,43	280,00	92,00	450,00
BNP before covid	24	253,83	277,96	114,50	10,00	880,00
Pulmonary arterial pressure (mmHg)	24	78,38	29,47	71,00	12,00	135,00
Pulmonary vascular resistance (Wood units)	24	10,50	6,20	8,00	5,00	35,00
Cardiac index (lt/min/m2)	24	2,37	0,46	2,30	1,60	3,40
Right atrium area (cm^2)	24	22,46	7,75	20,00	14,00	40,00

Table 3. Examination of risk factors affecting mortality through binary logistic regression analysis

	Univariate	
	OR (95% CI)	p
Age (years)	0,979 (0,927 - 1,035)	0,460
Disease year (years)	1,193 (0,922 - 1,543)	0,180
Duration of hospitalization (days)	0,925 (0,739 - 1,157)	0,494
Hb(gr/dl)	1,117 (0,744 - 1,678)	0,593
White blood cell (µl)	1 (1 - 1)	0,432
Lymphocyte (%)	0,995 (0,893 - 1,108)	0,924
Neutrophil (%)	0,993 (0,908 - 1,085)	0,870
CRP (mg/lt)	1,012 (0,994 - 1,031)	0,188
Ferritin (ng/ml)	0,999 (0,994 - 1,004)	0,720
D dimer(µg/L)	0,907 (0,625 - 1,317)	0,608
BNP (pg/mL)	1,001 (1 - 1,003)	0,147
AST(U/lt)	1,006 (0,996 - 1,017)	0,237
ALT(U/lt)	1,007 (0,996 - 1,019)	0,220
Uric acid (mg/dl)	1,359 (0,838 - 2,204)	0,213
Creatinine (mg/dl) (mg/dl)	3,995 (0,44 - 36,287)	0,219
Last 6-minute walk test before Covid (m)	0,992 (0,98 - 1,004)	0,199
Pre-Covid BNP (pg/mL)	1,002 (0,999 - 1,005)	0,272
Pulmonary arterial pressure (mmHg)	0,994 (0,96 - 1,029)	0,743
Pulmonary vascular resistance (Wood units)	1,079 (0,932 - 1,249)	0,309
Cardiac index (lt/min/m2)	0,007 (0 - 0,929)	**0,047**
Right atrium area (cm^2)	1,016 (0,896 - 1,151)	0,806
Sex (male/female)	0,308 (0,04 - 2,352)	0,256
Radiological involvement (mild/moderate/severe)	2,463 (0,634 - 9,572)	0,193
Etiology of pulmonary hypertension	0,323 (0,087 - 1,203)	0,092

Last functional class before Covid (WHO-FS)	10,233 (1,213 - 86,29)	**0,033**

Quick Look

Current knowledge

The pathological processes of pulmonary hypertension and COVID-19 disease are similar.There is no cure for covid 19 yet. Mortality rates were found to be high in all studies, particularly in high-risk patients, though the incidence of the disease is similar to the whole population. The drugs used in pulmonary hypertension patients can also be used in the treatment of covid 19.

What this paper contributes to our knowledge

Patients with PH are at potential risk for serious complications and high mortality .We wanted to see the clinical course of covid 19 in this disease group. Protective effect of the physiopathological changes in these patients and the medications they use is thought to be able to prevent and treat COVID-19 infection.