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Pulmonary hypertension outcomes during the COVID-19 pandemic in Brazil

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TO THE EDITOR:

In March of 2020, COVID-19 was characterized by the WHO as a pandemic infection, and it has been considered an international public health emergency ever since. A few months after the start of the pandemic, Brazil was the country with the second highest number of confirmed COVID-19 cases worldwide. Risk factors for developing severe COVID-19, especially before vaccine availability, were advanced age and presence of comorbidities, such as cardiovascular and chronic pulmonary diseases.[1]

Pulmonary hypertension (PH) is a severe pathophysiological disorder, with pulmonary vascular involvement that can lead to right ventricular failure and death. Hospitalizations from any cause (i.e., PH-related or non-PH-related) are known to impact the outcomes of PH patients negatively.[2,3] However, conflicting data were made available on PH outcomes during the first year of the COVID-19 outbreak.[4,5] Subsequently, more robust studies showed a high COVID-19 mortality rate in PH patients.[6-9] Furthermore, in South America, there have been no reports on the impact of COVID-19 in PH patients so far. The purpose of the present study was to describe the estimated incidence rate and case-fatality rate of COVID-19 in PH patients followed at a PH referral center in Brazil.

All patients evaluated at the Pulmonary Hypertension Outpatient Clinic of the Federal University of São Paulo after the beginning of the pandemic (March of 2020), remotely or in person, were contacted between June and August of 2021 to identify those who had had COVID-19 confirmed by RT-PCR since the pandemic outbreak. Telephone contact was made at least three times on different days. All patients with a confirmed PH diagnosis were included in the present study and had their electronic medical records reviewed and their survival status assessed. The medical records of patients hospitalized at the *Hospital São Paulo* (the university hospital) were assessed, whereas self-reported information and hospital discharge summaries of patients hospitalized at affiliated hospitals were considered. Patients who had COVID-19 ($PH_{COVID\text{-}19(+)}$) were compared with patients who did not have COVID-19 ($PH_{COVID\text{-}19(-)}$). Comparisons between survivors and nonsurvivors were made using the chi-square test. Significance was set at $p < 0.05$. The research was approved by the university's ethics research committee (Protocol n. 38361220.3.0000.5505) and was conducted in accordance with the Declaration of Helsinki.

During the study period, 426 patients were evaluated, 272 of whom had a PH diagnosis (Panel 1A). PH patients had a mean age of 54 ± 17 years, and 71% were female. The most common PH etiologies were pulmonary arterial hypertension (PAH; 51.1%) and chronic thromboembolic PH (25.0%), 59.4% of whom were under double or triple combination therapy. Among the PH patients, 39 had had confirmed COVID-19; therefore, the estimated COVID-19 incidence rate was 14.3%. The overall COVID-19 incidence rate in the general Brazilian population during the same period was 9.7% (Panel 1B).[10]

The proportion of females in the $PH_{COVID\text{-}19(+)}$ group was higher when compared with the $PH_{COVID\text{-}19(-)}$ group (84.6% vs. 68.8%). No differences were found regarding age, PH etiology, and PH treatment between the groups (Panel 1C). Among $PH_{COVID\text{-}19(+)}$ patients, 41.0% had a New York Heart Association (NYHA) functional class III/IV and a cardiac index of 2.7 ± 0.7 L/min/m^2 in their most recent stratification assessment (Panel 1C).

In the $PH_{COVID\text{-}19(+)}$ group, hospitalization was required in 15 (38.5%) of the cases, and 44.4% were hospitalized at the university hospital. Approximately 50% (n = 8) of these hospital admissions were in the ICU, and 26% (n = 4) required mechanical ventilation. Complications during hospitalization were respiratory failure due viral pneumonia, in 6; right heart failure, in 4; and Guillain-Barré syndrome, thrombocytopenia with major bleeding, and anaphylaxis, in 1 each. Overall, there were 9 deaths: PAH, in 4; chronic thromboembolic PH, in 3; and multifactorial PH, in 2. No differences were found between survivors and nonsurvivors regarding age, sex, PH etiology, PH therapy, hemodynamics, comorbidities, and vaccination status. However, there was a high proportion of immunosuppressive therapy use and a tendency toward severe disease (NYHA III/IV), connective tissue disease, and obesity in nonsurvivors when compared with survivors (Panel 1C). All deaths were related either to acute COVID-19 or to PH decompensation after COVID-19. The case-fatality rate of COVID-19 in PH patients was 23.1% and that of PH alone (i.e., $PH_{COVID\text{-}19(-)}$) was 3.4% ($p < 0.0001$; Panel 1D). The overall case-fatality rate in the general Brazilian population during the same period was 2.7% (Panel 1D).[10]

To our knowledge, our study is the first describing the incidence rate and the case-fatality rate of COVID-19 among PH patients in South America. Our findings show that while the incidence rate of COVID-19 was similar between PH patients and the overall Brazilian population, the case-fatality rate was significantly higher among PH patients, indicating that PH patients infected with COVID-19 are significantly prone to worse outcomes in relation to patients without PH. With regard to account cardiovascular disease, the overall lethality rate was 2.3% in Wuhan, China, but there was an increase in mortality due to cardiovascular disease (10.5%), showing a high mortality risk in this population.[1] These findings are

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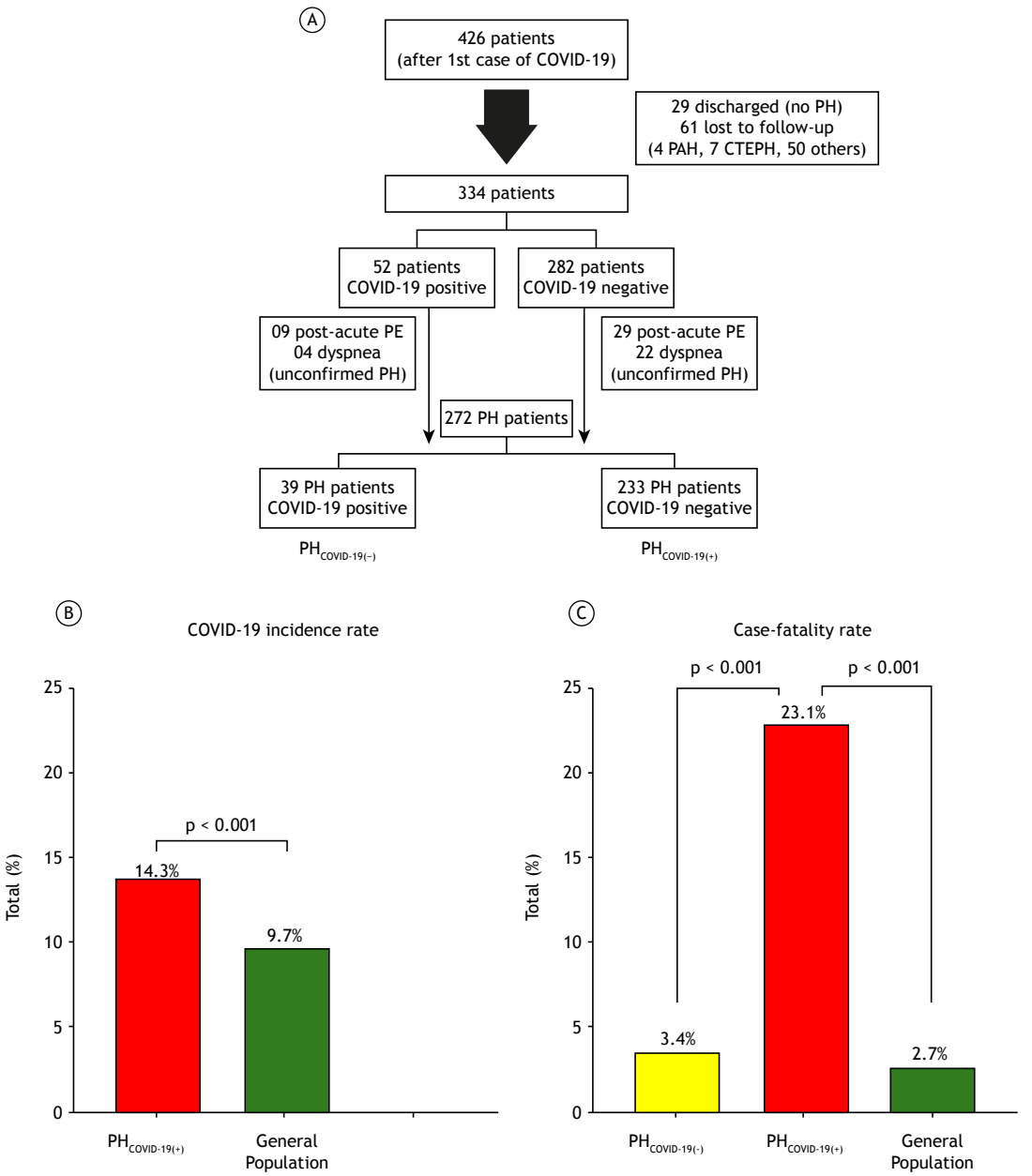
relevant especially for low- and middle-income countries and might help the care of PH patients, as new variants of COVID-19 still emerge in such geographical locations.

Our results indicate a high case-fatality rate of COVID-19 in PH patients, which is in line with previously published data from an international multicenter PH survey,[6] a U.S. single-center report,[7] the French PH registry,[8] and an Italian cohort.[9] In a recent cohort study in Italy, there were low incidence but high mortality rates due to COVID-19 in PAH patients.[9] In 2011, a study involving 205 patients with PAH showed that 16% of hospitalizations were due to infection and overall in-hospital mortality was 14%,[2] suggesting the increased mortality rate was due to COVID-19. It is of note that 67% of deaths among our patients with $PH_{COVID19(+)}$ were directly related to the acute phase of the infection. In the French cohort, the overall mortality was 24.6% and was associated with being male, being older, having comorbidities, and having more severe PH; nonetheless, no difference was found in relation to PH therapy.[8] Interestingly, this similar case-fatality rate was observed despite the fact that the availability of PH-specific drugs is lower in Brazil than in Europe and the USA. Besides that, $PH_{COVID-19(+)}$ patients presenting with connective tissue disease and receiving immunosuppressant therapy had lower survival rates, suggesting an additive effect in reducing cardiorespiratory function and in the number of COVID-19 complications, probably related to the lack of vaccination. At this writing, we have a decrease in the incidence of COVID-19 infection around the world; however, we still do not know the infection seasonality,



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Baseline characteristic	PH (n = 272)		p	PH + COVID-19 (n = 39)		p
	COVID-19 negative (n = 233)	COVID-19 positive (n = 39)		Survivors (n = 30)	Nonsurvivors (n = 9)	
Age, years	53 ± 16	53 ± 17	NS	51 ± 16	60 ± 20	NS
Female	159 (68.2)	33 (84.6)	0.039	25 (83.3)	8 (88.9)	NS
PH etiology						
PAH	119 (51.1)	20 (51.3)		16 (53.3)	4 (44.4)	
CTEPH	53 (22.7)	15 (38.5)	NS	12 (40.0)	3 (33.3)	NS
Inoperable/persistent	-	10 (66.7)		9 (75)	1 (33.3)	
Operable	-	5 (33.3		3 (25)	2 (66.7)	
Other PH	61 (26.2)	04 (10.3)		2 (6.7)	2 (22.2)	
PH therapy						
Monotherapy	51 (21.9)	07 (17.9)		05 (16.7)	2 (22.2)	
Double therapy	84 (36.1)	15 (38.5)	NS	11 (36.7)	4 (44.4)	NS
Triple therapy	20 (08.6)	04 (10.3)		03 (10.0)	1 (11.1)	
None	78 (33.5)	13 (33.3)		11 (36.7)	2 (22.2)	
Other treatment						
Immunosuppressant	-	10 (25.6)	-	4 (13.3)	6 (66.7)	0.001
Anticoagulant	-	18 (46.2)	-	13 (86.7)	5 (71.4)	NS
NYHA functional class	-					
I/II	-	23 (59.0)	-	20 (66.7)	3 (33.3)	0.075
III/IV	-	16 (41.0)	-	10 (33.3)	6 (66.7)	
Hemodynamic						
RAP, mmHg	-	10 ± 5	-	10 ± 5	9 ± 3	NS
mPAP, mmHg	-	49 ± 14	-	49 ± 15	45 ± 8	NS
PAOP, mmHg	-	11 ± 2	-	11 ± 2	10 ± 2	NS
IC, L/min/m^2	-	2.7 ± 0.7	-	2.7 ± 0.6	2.8 ± 0.8	NS
PVR, dyn.s.cm^{-5}	-	737 ± 417	-	722 ± 398	794 ± 525	NS
Comorbidities						
High blood pressure	-	13 (33.3)	-	11 (36.7)	2 (22.2)	NS
Connective tissue disease	-	12 (30.8)	-	7 (23.3)	5 (55.6)	0.066
Obesity	-	9 (23.1)	-	9 (31.0)	0 (0.0)	0.061
Liver disease	-	6 (15.4)	-	6 (20.0)	0 (0.0)	NS
Diabetes mellitus	-	6 (15.4)	-	5 (16.7)	1 (11.1)	NS
Coronary artery disease	-	4 (10.3)	-	4 (13.8)	0 (0.0)	NS
Chronic kidney disease	-	2 (5.1)	-	1 (3.3)	1 (11.1)	NS
≥ 2 comorbidities	-	12 (30.8)	-	10 (33.3)	2 (22.2)	NS
Vaccine before COVID-19 infection	-	9 (23.1)	-	8 (26.7)	1 (11.1)	NS

Values expressed as n (%) or mean ± SD.

Panel 1. In A, flow chart of patient selection process. COVID-19 incidence (In B) and case-fatality (in D) rates among the patients with pulmonary hypertension studied in comparison with the Brazilian general population. In C, table showing the characteristics of the patients with pulmonary hypertension studied with and without COVID-19. FUP: follow-up; PE: pulmonary embolism; PH: pulmonary hypertension; $PH_{COVID19(+)}$: patients with PH who had previous COVID-19; $PH_{COVID19(-)}$: patients with PH who did not have previous COVID-19; NS: not significant; PAH: pulmonary arterial hypertension; CTEPH: chronic thromboembolic pulmonary hypertension; NYHA: New York Heart Association; RAP: right atrial pressure; mPAP: mean pulmonary arterial pressure; PAOP: pulmonary artery occlusion pressure; CI: cardiac index; PVR: pulmonary vascular resistance;

the real long-term effectiveness of current vaccines, and the possibility of new more virulent emergent variants.

This study has some limitations. This was a single-center, observational retrospective study based on electronic medical records and patient-reported outcomes; therefore, our results may not apply to all PH patients. The study relied on the confirmation of COVID-19 by RT-PCR, which was available only for severe and hospitalized cases in Brazil during most of the study period; for that reason, the incidence rate of COVID-19 among PH patients might have been underestimated. For inpatients from affiliated hospitals, some details about hospitalization were missed because of self-reported information. Finally, this survey was conducted prior to the full vaccination of most of the patients studied. Hence, we were unable to evaluate the protective effect of full vaccination on the outcomes.

In summary, our report highlights the negative impact of COVID-19 on the outcomes of PH patients. Although the COVID-19 incidence rate was similar to that in the Brazilian general population, the case-fatality rate was higher in our patients. These findings are particularly relevant for low- and middle-income countries and could help with the care of PH patients,

as new COVID-19 variants continue to appear in these geographical locations.

AUTHOR CONTRIBUTIONS

All authors contributed to study conceptualization, as well as to the writing, reviewing, and editing of the manuscript. All authors approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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