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Chronic Dyspnea and Residual Pulmonary Vascular Sequelae After COVID-19 Pulmonary Embolism: A Retrospective Analysis

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ABSTRACT

During the COVID-19 pandemic, Brazil was one of the most affected countries. Patients presented higher risk of acute venous thromboembolism (VTE), in particular, pulmonary embolism (PE). However, long-term implications of these events remain unknown. A retrospective analysis from the FENIX study was conducted, and patients with COVID-19-related VTE during hospitalization were included. Further analysis, up to 6 months after the acute event, was performed exclusively in patients with PE. Persistence of dyspnea and exercise intolerance was evaluated through imaging, rest, and exercise functional tests. Cumulative incidence of VTE during hospitalization among COVID-19 survivors followed at the outpatient clinic was 17.7% ($n = 75/423$) and of acute PE was 9.9% ($n = 42/423$). Patients with PE were mostly male (66%), 56 ± 16 years old, and mainly classified as intermediate-low risk (74%). Dyspnea (mMRC≥ 1) up to 6 months of PE was present in 56% ($n = 19/34$), with a borderline association with parenchymal lung sequelae on chest CT scan ($p = 0.069$). Symptomatic patients upon follow-up presented lower FEV1 and FVC, as well as increased peak VD/VT ratio and ventilatory inefficiency. No signs of pulmonary hypertension (PH) were identified on echocardiogram (ECHO) and cardiopulmonary exercise testing (CPET). Persistence of dyspnea among post-PE related to COVID-19 was high. However, no cases of PH were found; follow-up findings may be related to pulmonary parenchymal and microvascular injury. Also, we cannot exclude association with long-COVID, in which pathophysiological mechanisms are multifactorial, involving chronic inflammatory changes and multiorgan dysfunction, highlighting the need for comprehensive evaluation of exercise intolerance through invasive CPET.

1 | Introduction

Coronavirus disease 2019 (COVID-19) was declared a pandemic in early 2020, with a median worldwide mortality rate estimated between 1.5% and 2.0%, and Brazil was one of the most affected countries [1]. Caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), it affected primarily the respiratory system, and pneumonia was the most common presentation, with frequent progression to acute respiratory distress syndrome (ARDS) [2] and association with multiple organ failure, especially during the first 2 years of the pandemic [3].

In addition, due to exacerbated inflammatory and immune-related responses during the acute phase, vascular damage and vasculopathy, through endothelial activation and fibrin deposition [4], were present early on and represented an increased incidence of venous thromboembolism (VTE) in these patients, especially among those admitted to intensive care units (ICU) [5, 6]. In a previous meta-analysis, pooled incidence rates of pulmonary embolism (PE) and deep vein thrombosis (DVT) in COVID-19 were as high as 16.5% and 14.8%, respectively [7]. And although COVID-19's endothelial damage, persistent cellular inflammation and small vessel vascular thrombosis (microthrombi/thrombi) have been associated to a hypothetical risk of chronic pulmonary vascular sequelae, such as chronic thromboembolic pulmonary disease (CTED) and/or chronic thromboembolic pulmonary hypertension (CTEPH) [4, 8], few studies have investigated its prevalence upon follow-up, and whether persistent symptoms such as dyspnea, exercise intolerance and fatigue are exclusively related to residual pulmonary vascular obstruction in these cases.

Thus, we intended to retrospectively analyze possible risk factors of VTE during COVID-19 hospitalization, as well as to evaluate, specifically in those with PE, the persistence of dyspnea and its relation to possible residual pulmonary vascular obstruction.

2 | Methods

2.1 | Study Design and Population

The present study is a retrospective analysis of the REDCap database of the observational prospective COVID-19 Brazilian initiative, known as the FENIX Study (Brazilian Clinical Trials Registry ReBEC: RBR-8j9kqy - CEP/UNIFESP n: 1008/2020). This initiative evaluated clinical symptoms, respiratory, radiological, and metabolomic functions of previously hospitalized patients due to COVID-19. Medical charts of adult patients whose first outpatient visit after hospital discharge occurred between July 2020 and February 2022 in the post-COVID outpatient clinic of the Federal University of São Paulo (UNIFESP) were considered for review. Inclusion criteria were: (i) confirmed diagnosis of COVID-19 by reverse transcription polymerase chain reaction (RT-PCR) during hospitalization; (ii) diagnosis of VTE (DVT or PE) during hospitalization, and iii) presence of follow-up consultation between 3 and 6 months from hospital discharge (shown in Figure 1). During hospitalization, diagnosis of DVT was made through colored doppler ultrasound, and PE through chest computed tomography angiography (Chest CT-angiogram), in all cases.

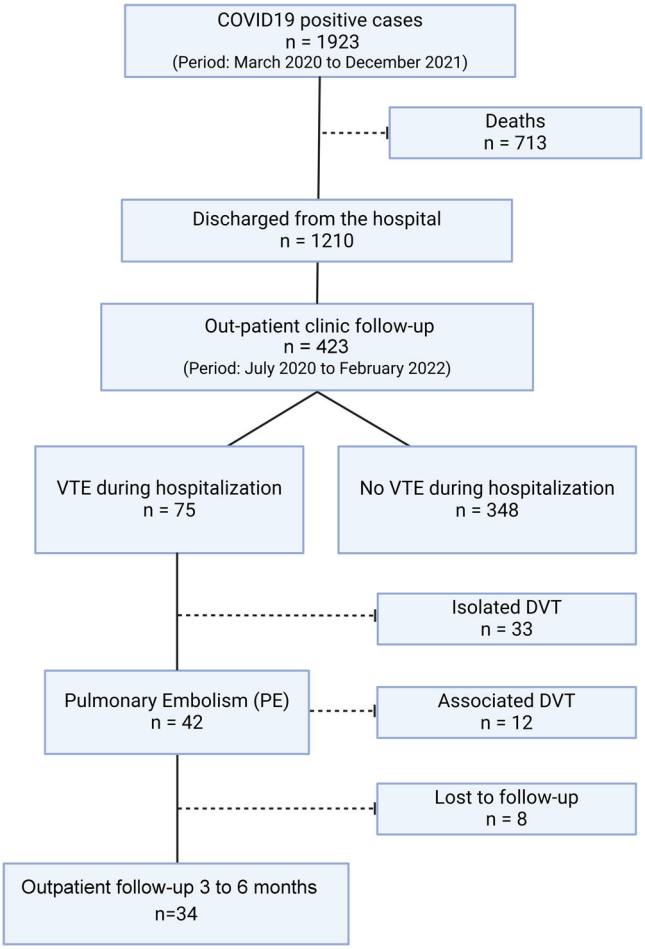

FIGURE 1 | Flow diagram illustrating the study design. Positive COVID-19 cases were compiled from the hospital of the Federal University of Sao Paulo with baseline evaluation during hospitalization. Patients with COVID-19-related PE were further assessed during follow-up up to 6 months after the acute event.

2.2 | Data Collection

Patient's medical charts contemplating baseline characteristics (sex, age, date of COVID-19), clinical comorbidities, hospitalization details (length of hospital stay, ICU admission, oxygen supplementation), and laboratory tests at admission (complete blood count, D-dimer, and C-reactive protein [c-RP]) were collected to compare patients with COVID-19-related VTE, and those without. Among those with VTE, patients with PE were identified and further assessed during follow-up at the post-COVID outpatient clinic. During follow-up, we focused on the persistence of dyspnea, alongside results from cardiopulmonary imaging and function tests performed (i.e., 6-min walk test, pulmonary function tests, chest computed tomography (CT), and/or chest CT-angiogram, ECHO, and cardiopulmonary exercise test [CPET]).

2.2.1 | Hospitalization

Chest imaging, including either chest CT or CT-angiogram, was performed at hospital admission for all patients suspected of COVID-19, according to clinical judgment, with a typical

appearance of peripheral, bilateral ground-glass opacities (GGO) with or without parenchymal consolidation [9]. At that time, grading of severity was based on the percentage of GGO and parenchymal involvement (categorized as $<$ or $\geq 50\%$). Chest CT-angiogram was prompted by clinical suspicion of acute PE. Transthoracic ECHO were performed within 48 h to assess PE risk stratification by cardiology specialists, primarily using visual estimation to assess the right ventricular (RV) function and when RV dysfunction was suspected, additional measurements of systolic pulmonary artery pressure (sPAP), tricuspid regurgitation velocity (TRV), and tricuspid annular plane systolic excursion (TAPSE) was attempted, however some exams were conducted under suboptimal conditions, as patients were often hemodynamically unstable and required bedside evaluations in the ICU. Values of sPAP >35 mmHg, TRV >2.8 mm/s, and TAPSE <17 mm were considered indirect signs of RV dysfunction and pulmonary hypertension.

2.2.2 | Follow-Up

During outpatient follow-up, the mMRC scale was used as a self-assessment tool, allowing patients to rate their breathlessness during daily activities on a scale of 0 to 4. Patients were subsequently categorized as symptomatic (mMRC ≥ 1) or asymptomatic (mMRC 0). As part of the FENIX Study, all patients underwent a chest CT/CT-angiogram between 3 and 6 months of acute infection, focusing on identifying parenchymal lung sequelae and persistence of GGO. A chest CT-angiogram was performed based on clinical judgment. Pulmonary function tests (PFTs) were also conducted during that time, including spirometry measurements (FVC, FEV1, FEV1/FVC), and when available, diffusing capacity of the lungs for carbon monoxide (DLCO and VA), using the Elite DX Body Plethysmography system (MedGraphics, MGC, St. Paul, MO, USA). Lastly, ECHO and CPET were indicated according to clinical judgement. ECHO was performed as previously stated. CPETs were conducted as a symptom-limited, ramp-incremental test on a cycle ergometer (ULTIMA CardioO2, MedGraphics, Saint Paul, MN, USA). Final reports were classified as normal or based on limitations: cardiocirculatory (e.g., low O_2 pulse, low oxygen consumption (VO_2)to work rate, early AT, high heart rate to VO_2 slope), ventilatory (e.g., low breathing reserve, low tidal volume, high respiratory rate), and gas exchange (e.g., exercise-induced hypoxemia, high alveolar-arterial oxygen gradient [P(A-a)O2], high dead space to tidal volume ratio [VD/VT]), or combined limitations.

2.3 | Data Analysis

Standard descriptive statistics, including mean and standard deviation or median and interquartile range, were calculated based on the distribution of the data. To assess differences between patients with and without VTE during hospitalization, as well as between symptomatic and asymptomatic patients during follow-up, Pearson's Chi-square test was employed for categorical variables. For continuous variables, *t*-tests or Mann–Whitney *U* tests were used, depending on the normality of the data. A p-value of less than 0.05 was considered statistically significant. Graphs and statistical analyses were conducted using SPSS™ for Windows, version 21.0 (Armonk, NY: IBM Corp).

3 | Results

In this analysis, 1923 positive cases of COVID-19 were admitted to the hospital of the Federal University of Sao Paulo between March 2020 and December 2021, with 713 deaths (37.1%) by all causes (data not shown). Among the referred survivors to the outpatient clinic, 423 patients (35%) were included in the COVID-19 FENIX Study with at least one clinical visit after discharge. These patients were further analyzed according to hospitalization and follow-up data (as shown in Figure 1).

3.1 | Hospitalization

Diagnosis of VTE was made in 75 of 423 patients, with a cumulative incidence of 17.7%. PE was present in 42 of those patients (9.9%), with associated DVT in 12 cases, affecting exclusively the lower limbs. PE was diagnosed in all cases by chest CT-angiogram at the time of admission. A comparison of COVID-19 patients with and without VTE showed no significant differences in age, sex, or comorbidities. However, patients with VTE had longer hospital stays, higher rates of ICU admission, and a tendency for extended ICU stays. Also, mechanical ventilation ($p = 0.002$) and need of prone position ($p = 0.008$) were higher among VTE patients compared to those without. Laboratory findings showed a higher white blood cell (WBC) count, with higher neutrophils, a higher neutrophil-to-leukocyte ratio, and a lower lymphocyte-to-leukocyte ratio (%). Higher serum levels of C-reactive protein (CRP) and D-dimer were also observed in VTE patients (as shown in Table 1).

Patients diagnosed with PE had a median of 15 [4–21] days between positive RT-PCR and PE diagnosis, a median of 20 [12–28] days of total hospital stay, and 26/42 patients (62%) were hospitalized in ICU settings. Acute-phase ECHO was performed in 30/42 patients (71%), with RV dysfunction and pulmonary hypertension indirect signs in 6/30 (20%) exams. Visual analysis of RV dysfunction by chest CT-angiogram was considered in cases where ECHO was not performed, and no additional cases of RV dysfunction were identified. PE patients were majorly classified as intermediate-low risk (74%), and all high-risk patients were treated with intravenous thrombolytic therapy at recommended dosage, and no bleeding or other adverse events occurred. During hospitalization, 33/42 patients (78.5%) received parenteral anticoagulation with either unfractionated heparin or enoxaparin, and anticoagulation therapy was maintained after discharge for all patients, indicated for at least 6 months (as shown in Table 2). After discharge, major bleeding events were reported in 2 patients (4.7%), both of whom experienced gastrointestinal bleeding and needed an emergency room (ER) consultation. In both cases, bleeding was resolved spontaneously, and oral anticoagulation therapy was resumed shortly thereafter.

3.2 | Follow-Up

Analysis of follow-up tests between 3 and 6 months after discharge was conducted exclusively in patients with previous PE.

TABLE 1 | Cohort baseline characteristics of COVID-19 patients with and without VTE during hospitalization.

	COVID-19 without VTE $n = 348$	COVID-19 with VTE $n = 75$	p value
Male Gender, %	189 (54)	47 (63)	0.126
Age, Years	56 ± 15	56 ± 15	0.605
Comorbidities/Risk Factors			
≥ 2 comorbidities, %	239 (68)	51 (68)	0.909
Systemic Hypertension	193 (55)	40 (55)	0.737
Ex-Smoker	97 (28)	23 (31)	0.626
COPD	26 (7)	4 (5)	0.513
Obesity	81 (23)	15 (20)	0.539
Diabetes	106 (30)	22 (30)	0.847
Asthma	28 (8)	4 (5)	0.420
Kidney Disease	43 (12)	4 (5)	0.079
Hospitalization			
Hospital Days	12 [7–21]	20 [12–31]	< 0.001
Patients in ICU	184 (53)	50 (68)	0.018
Days in ICU	9 [5-17]	13 [6-21]	0.053
Prone position	38 (11)	19 (25)	0.008
Chest CT (GGO ≥ 50%)	129 (37)	36 (48)	0.066
Oxygen Supplementation			
SpO_2, %	89 [86–92]	88 [83–91]	0.091
No supplementation	14 (4)	5 (7)	0.316
Nasal cannula or NRM	175 (51)	30 (40)	0.106
NIV or HFNC	83 (24)	11 (13)	0.083
Mechanical Ventilation	76 (22)	29 (39)	0.002
Laboratory Results at Admission			
Hb, g/dl	13.7 [12.4–14.8]	14.1 [12.8–15.1]	0.103
Platelets, $\times 10^3$	215 [165–275]	218 [174–264]	0.901
White Cell Count, ($\times 10^3$)	7.7 [5.7–10.2]	10.5 [7.1–13.0]	< 0.001
Neutrophil, %	78 [72–84]	81 [76–86]	0.037
Neutrophil,/μL($\times 10^3$)	6.0 [4.1–8.4]	8.2 [6.1–11.0]	< 0.001
Lymphocytes, %	13 [8–18]	11 [7–15]	0.008
Lymphocytes,/μL($\times 10^3$)	9.4 [6.4–13.0]	10.7 [5.9–15.0]	0.191
c-RP, nmol/L	99 [61–180]	146 [89–232]	0.001
D-dimer, μg/mL	1.1 [0.6–1.8]	2.5 [0.9–8.0]	< 0.001

Note: Data presented as an absolute value and percentage: *n* (%), mean ± standard deviation, and interquartile ratio median [25%-75%].
Abbreviations: Chest CT, chest computed tomography; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; GGO, ground-glass opacities; Hb, hemoglobin; HFNC, high-flow nasal cannula; ICU, intensive care unit; NIV, non-invasive ventilation; NRM, non-rebreathing mask; SpO_2, pulse oxygen saturation.

There were 34/42 patients (81%), while the remaining eight were excluded due to being lost to follow-up. Dyspnea (mMRC ≥ 1) unrelated to previous comorbidities was reported by 19/34 patients (56%), and fatigue (31%) was the second most common symptom. Dry cough (14.3%), myalgia (11.9%), and chest pain on exertion (7.1%) were also reported. Syncope or near-syncope was not reported. Regarding follow-up exams, all patients had undergone chest CT, and 15/34 (44.1%) presented significant parenchymal lung sequelae, described as either persistence of GGO ≥ 50% of parenchyma, diffuse septal thickening, and/or signs of fibrosis. Of those, 11/15 (73%) were symptomatic (mMRC ≥ 1). ECHO was performed in 27/34 (79.4%) patients, and no signs of RV dysfunction or pulmonary hypertension were found. Further comparison of symptomatic (mMRC ≥ 1) and asymptomatic (mMRC 0) post-PE patients (as shown in Table 3) revealed no difference in 6-min walk test (6MWT) distance or exercise-induced hypoxemia. However, pulmonary function tests (PFTs) showed lower FVC (L) and FEV1 (L) in those symptomatic (mMRC ≥ 1).

CPET was performed in 18/34 (53%) patients, of whom 13 (72%) demonstrated some form of exercise limitation. Among the

TABLE 2 | Baseline characteristics of COVID-19-related PE patients.

	COVID19-related PE patients $n = 42$
Male Gender, (%)	28 (66)
Age, Years	56 ± 16
ΔTime COVID RT-PCR to PE event	15 [4–21]
Hospitalization	
Hospital Days	20 [12–28]
Patients In ICU	26 (61)
Days In ICU	10 [7–19]
Prone position	10 (24)
sPESI ≥ 1	35 (83)
Troponin > 15	17 (41)
Acute-phase ECHO[†]	
TRV (m/s)	2.8 ± 0.5
sPAP (mmhg)	41 ± 16
TAPSE (mm)	22 ± 5
TAPSE/sPAP	0.66 ± 0.13
LVEF (%)	68 ± 4
PE risk stratification	
Low	7 (16.7)
Intermediate-low	31 (73.8)
Intermediate-high	1 (2.4)
High	3 (7.1)
Anticoagulation at discharge	
Rivaroxaban	33 (79)
Apixaban	3 (7)
Warfarin	6 (14)

Note: Data are presented as absolute values and percentages *n (%)*, or as mean ± standard deviation.
Abbreviations: ICU, intensive care unit; LVEF, left ventricular ejection fraction; PE, pulmonary embolism; RT-PCR, reverse transcription–polymerase chain reaction; sPAP, systolic pulmonary artery pressure; sPESI, simplified pulmonary embolism severity index; TAPSE, tricuspid annular plane systolic excursion; TRV, tricuspid regurgitation velocity.
[†]Acute-phase ECHO was performed in 30/42 patients, RV function was assessed through TRV in 6/30 ($n = 6$) exams, sPAP in 8/30 ($n = 8$) exams and TAPSE in 15/30 ($n = 15$) exams. TAPSE/sPAP ratio was obtained in 6/30 ($n = 6$) patients. In the absence of these variables, RV dysfunction was visually assessed by the cardiologist performing the exam. LVEF was performed in all exams.

symptomatic group (mMRC ≥ 1), patients were older and exhibited a lower absolute peak VO_2 (mL/kg/min). Additionally, an elevated VE/VCO_{2RCP} slope was found, with increased VD/VT ratio at peak exercise (shown in Table 4). In these patients, exercise-induced hypoxemia on 6MWT, lower DLCO, and significant parenchymal sequelae on chest CT were found. Chest CT-angiogram was performed in 7/34 patients (21%) by clinical judgement, and only one showed signs of residual vascular obstruction in the pulmonary circulation, in the segmental arteries of the right lower lobe, with normal ECHO and combined limitation in CPET.

4 | Discussion

In this observational retrospective report, COVID-19 survivors followed at a regional outpatient clinic presented a high cumulative incidence of VTE (17.7%) and PE (9.9%) events during hospitalization. However, persistence of dyspnea after 6 months of COVID-19-related PE was not solely related to residual pulmonary vascular obstruction, as only one patient presented residual clots in segmental arteries with no other signs of CTED/CTEPH on echocardiogram or CPET. Follow-up exams demonstrated no specific correlation with the persistence of dyspnea; however, symptomatic patients (mMRC ≥ 1) presented with lower FEV1 and FVC, as well as an increased peak VD/VT ratio and ventilatory inefficiency, along with a higher prevalence of pulmonary parenchymal alterations and exercise-induced hypoxemia. These findings corroborate that dyspnea and exercise intolerance in this population may be associated with pulmonary ventilatory impairment and/or pulmonary microcirculation injury. However, other pathophysiological mechanisms may also be present, including deconditioning, muscle weakness, altered peripheral O_2 extraction rate, and neuro-autonomic disorders (as shown in Figure 2).

According to the literature, the incidence of VTE during the acute-phase COVID-19 in early years could be as high as 25%, and a higher risk of events was related to male sex, older age, ICU-admission, mechanical ventilation, as well as higher CRP and D-dimer levels [7, 10]. In the present analysis, in accordance with reported literature, the cumulative incidence of VTE and PE in COVID-19 survivors was high, and VTE patients showed longer hospital stay, higher admission to ICUs, and a higher need for mechanical ventilation and prone positioning. However, although a predilection for males was noted, no other risk factors regarding age and/or comorbidities were found. Patients with VTE also presented more severe initial GGO parenchymal involvement (≥ 50%), as demonstrated by chest CT at admission. Laboratory findings also supported an exacerbated inflammatory response in patients with higher WBC counts and lower lymphocyte counts, as well as higher c-RP and D-Dimer levels. Increased WBC count, higher neutrophils [11], elevated ferritin and c-RP [12, 13] serum levels have all been implied as possible serological markers of thrombotic events during acute-phase COVID-19, with the latter also being reported as a marker of prognosis of PE [13, 14].

During follow-up, persistence of dyspnea in PE patients up to 6 months could not be solely explained by the presence of residual vascular obstruction of the pulmonary circulation, as only one (2%) patient presented segmental clots on chest CT-angiogram. The low incidence of CTED/CTEPH is supported by a recent Dutch cohort study by De Jong et al. (2023) [15], in which CTEPH was ruled out by noninvasive methods in all patients after COVID-19-associated PE, and other studies also showing significantly low incidence of CTED/CTEPH up until twelve months of acute event [16, 17]. Suggesting that CTED/CTEPH evolution in PE events related to COVID-19 does not exceed the general population risk, ranging from 2% to 3% [18].

Post-PE functional impairment (PPEI), as well as Long-COVID, may be considered as possible contributing causes of dyspnea, fatigue, and exercise intolerance in the present scenario, excluding CTED/CTEPH [18, 19]. In this population, severe acute-phase

TABLE 3 | Complementary exams of COVID-related PE at 6-month follow-up.

	Total $n = 34$	mMRC 0 $n = 15$	mMRC ≥ 1 $n = 19$	*P*
BMI (kg/m^2)	31.7 ± 5.8	31.2 ± 6.4	32.4 ± 5.3	0.586
ICU (%)	26 (61)	11 (78)	12 (60)	0.341
6MWT				
Distance, m	473 [438–532]	485 [449–580]	469 [395–517]	0.131
Baseline SpO_2, %	96 [94–98]	96 [96–97]	96 [93–98]	0.595
Peak SpO_2, %	93 [88–95]	94 [90-95]	91 [87–84]	0.160
ECHO[†]				
TRV (m/s)	2.54 ± 0.35	—	—	—
sPAP (mmhg)	33 ± 8	—	—	—
TAPSE (mm)	21 ± 3	20 ± 3	21 ± 4	0.493
TAPSE/sPAP	0.57 ± 0.08	—	—	—
LVEF (%)	65 ± 5	67 ± 3	64 ± 6	0.080
PFT[††]				
FVC (L)	3.3 ± 0.8	3.8 ± 0.7	3.1 ± 0.9	0.041
FVC, %	87 ± 13	89 ± 11	86 ± 15	0.296
FEV1 (L)	2.7 ± 0.8	3.2 ± 0.5	2.4 ± 0.8	0.016
FEV1, %	89 ± 15	92 ± 11	87 ± 17	0.339
FEV1/FVC	0.84 [0.79–0.86]	0.83 [0.78–0.85]	0.82 [0.79–0.87]	0.399
DLCO (%pred)[¶]	84 ± 19	84 ± 15	85 ± 23	0.834
Chest Image (CT/CTA)[§]				
Moderate-Severe (> 50%)	15 (44)	4 (27)	11 (58)	0.069

Note: Data presented as an absolute value and percentage: *n* (%), mean ± standard deviation, and interquartile ratio median [25%-75%].
Abbreviations: 6MWT, six-minute walk test; BMI, body mass index; DLCO, diffusing capacity of the lung for carbon monoxide; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; ICU, intensive care unit; LVEF, left ventricular ejection fraction; sPAP, systolic pulmonary artery pressure; SpO_2, pulse oxygen saturation; TAPSE, tricuspid annular plane systolic excursion; TRV, tricuspid regurgitation velocity.
[†]Follow-up ECHO was performed in 27/34 patients, RV function was assessed through TRV in 5/27 ($n = 5$) exams, sPAP in 6/27 ($n = 6$) exams and TAPSE in 22/27 ($n = 22$) exams. TAPSE/sPAP ratio was present in 6/27 ($n = 6$) exams. In the absence of these variables, RV dysfunction was visually assessed by the cardiologist performing the exam. LVEF was performed in all exams.
[††]Pulmonary function test was performed in 30/34 ($n = 30$),
[¶]DLCO analysis was present in 10/30 ($n = 10$).
[§]Chest CTA was performed in 7/34 ($n = 7$) cases, with only one presenting a minimal residual clot, and non-contrasted chest CT was performed in the remaining 27/34 ($n = 27$) cases.

disease, exacerbated and chronic inflammatory response, long bed-bound periods, neuro-muscular disorders, and parenchymal pulmonary sequelae may contribute to some extent to referred symptoms. In our cohort, the evaluation of 6MWT and PFP performed between symptomatic and asymptomatic patients post-PE revealed a mild reduction in absolute values of FVC and FEV1, and normal values of 6MWT distance. Normal 6MWT distance, even among symptomatic patients, is corroborated by similar previous reports of pulmonary hypertension patients within the Latin American population, in which patients seem to achieve longer distances despite their functional class. This phenomenon may be attributed to sociocultural and behavioral factors, including higher levels of incidental physical activity and lifestyle habits, increased use of public transportation and/or walking, as well as possible differing perceptions of exertion and symptom burden [20].

During the CPET evaluation, absolute peak VO_2 values were lower in the symptomatic group (mMRC ≥ 1) and cardiocirculatory evaluation revealed normal O_2 pulse with no difference between groups. Ventilatory and gas exchange analysis showed an increased VE/VCO2 slope at the respiratory compensation point and an increased peak VD/VT ratio among symptomatic patients, corroborating that pulmonary ventilatory impairment and/or pulmonary microcirculation injury may play a role in influencing aerobic capacity and dyspnea sensation in this population [21]. This finding is supported by the higher prevalence of chest CT parenchymal involvement and exercise-induced hypoxemia in symptomatic patients, even after 6 months of the acute COVID-19 infection.

No signs of cardiac complications related to COVID-19 or to previous PE were found in this cohort. However, patients may present a higher risk of new onset of cardiovascular disease of any type, including arrhythmias, as well as nonischemic and ischemic cardiomyopathy [22].

Although CPET is useful in inferring possible pathophysiological mechanisms of exercise intolerance, especially among cardiovascular and pulmonary diseases, in Long-COVID, patients may present normal aerobic capacity even in the setting of an impaired peripheral O2 extraction and abnormal cardiac and pulmonary hemodynamics [23–25]. Thus, a definite

TABLE 4 | Baseline characteristics and peak variable results from the cardiopulmonary exercise test (CPET).

CPET ($n = 18$)	mMRC 0 ($n = 10$)	mMRC ≥ 1 ($n = 8$)	p value
Sex, male	5	7	—
Age, yrs	46 ± 4	56 ± 5	0.132
BMI, kg/m²	31.1 ± 1.5	31.7 ± 1.3	0.749
VO_2 peak, ml/kg/min	22.0 ± 1.6	16.8 ± 0.8	0.016
RER peak	1.15 ± 0.02	1.04 ± 0.03	0.021
Peak O_2 Pulse, mL/beat	11.8 ± 0.8	11.2 ± 0.9	0.640
HR peak, % pred	94 ± 4	85 ± 3	0.103
VE/VCO_2 slope RCP	27.7 ± 0.6	32.5 ± 2.3	0.075
$\Delta P_{ET}CO_2$ (AT-rest)	5 ± 0.9	3 ± 0.7	0.093
Peak VD/VT[†]	0.22 ± 0.03	0.35 ± 0.04	0.050
Peak VE/MVV	0.54 ± 0.05	0.47 ± 0.04	0.328
REPORT			
Normal	3 (30)	2 (25)	—
Cardiocirculatory limitation	3 (30)	0 (0)	—
Ventilatory limitation	0 (0)	0 (0)	—
Gas-exchange alteration	2 (20)	3 (37.5)	—
Mixed limitation	2 (20)	3 (37.5)	—

Note: Data are presented as absolute values and percentages *n (%)*, as mean ± standard deviation, and as interquartile range (median [25–75%]).
Abbreviations: AT, anaerobic threshold; $ETCO_2$, end-tidal pressure of carbon dioxide; HR, heart rate; MVV, maximal voluntary ventilation; RER, respiratory exchange ratio; VCO_2, carbon dioxide output; VD/VT, dead-space/tidal volume ratio; VE, minute ventilation; VO_2, oxygen consumption.
[†]VD/VT ratio was present in 12/18 ($n = 12$) exams, when earlobe arterialized capillary blood gas analysis were performed.

exclusion of peripheral limitation and/or central cardiovascular abnormal response to exercise can only be obtained through an invasive CPET (iCPET) [24, 25].

Dyspnea, fatigue, and exercise limitation are major symptoms reported by long-COVID patients, with direct impact on quality of life and the healthcare system [26]. Pathophysiological mechanisms involved in long-COVID are theorized to arise from chronic immune-system dysregulation, endothelial dysfunction, cellular inflammation, and coagulopathies [27–30]. And multiorgan involvement is a common occurrence, with primary symptoms arising from respiratory, cardiovascular, and neurological (central and peripheral) dysfunction [27, 29–31]. In this context, previous studies have demonstrated possible associations between dyspnea and: i. central cardiocirculatory disorders, including myocardial infarction/fibrosis, inflammation (myocarditis and cardiomyopathy), and pulmonary vascular injury; ii. reduced peripheral muscle oxygen extraction [32, 33], sarcopenia and deconditioning [34, 35]; iii. restrictive pulmonary disease, dysfunctional breathing [32], and ventilatory responses such as hyperventilation [36]; and most recently, association with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) [25, 37]. It is important to consider that long-COVID is a complex disorders, with multiple and combined mechanisms, that may be partially explained by pulmonary radiological abnormalities, such as GGO and reticular alterations, as well as functional impairments seen in static exams (PFTs) or during exercise evaluation (CPET, 6MWT), especially up to 6 months of acute COVID-19 infection [17, 30, 36], but not for all patients, requiring further studies to better understand the complex dynamics of exercise intolerance and oxygenation in these patients pathway mechanics.

Therefore, the present data should be interpreted considering the study's limitations, of being a retrospective database analysis of a single Brazilian center, the lack of a standardized ECHO evaluation and assessment of cardiac parameters in acute-phase and follow-up exams, the low number of chest CT-angiogram and CPET performed, as well as the absence of right heart catheterization which is the gold standard exam for the diagnosis and exclusion of pulmonary hypertension [38]. However, findings of cumulative incidence of VTE and PE presented in our cohort are in accordance with recent literature and similar studies.

Thus, we emphasize the strength of these findings, as this is, to the best of our knowledge, the first Brazilian cohort to extensively evaluate COVID-19-related PE and assess potential complications up to 6 months after the following event. We conclude that patients with venous thromboembolism (VTE) during the acute phase exhibited more severe disease during hospitalization, and over 50% of patients with PE remained symptomatic after. However, dyspnea was not solely linked to residual vascular obstruction in the pulmonary circulation, as this condition was observed in only one patient. As a result, within 6 months of being diagnosed with PE during their hospital stay, COVID-19 patients do not seem to have a higher risk of developing CTED or CTEPH compared to the general population, as part of post-PE syndrome. And although PPEI may be considered a cause of dyspnea and exercise intolerance, the broad spectrum of symptoms within long-COVID appears to be multifactorial, with uncertain pathophysiological mechanisms. Patients may present with a combination of cardiovascular, respiratory, and muscular involvement,

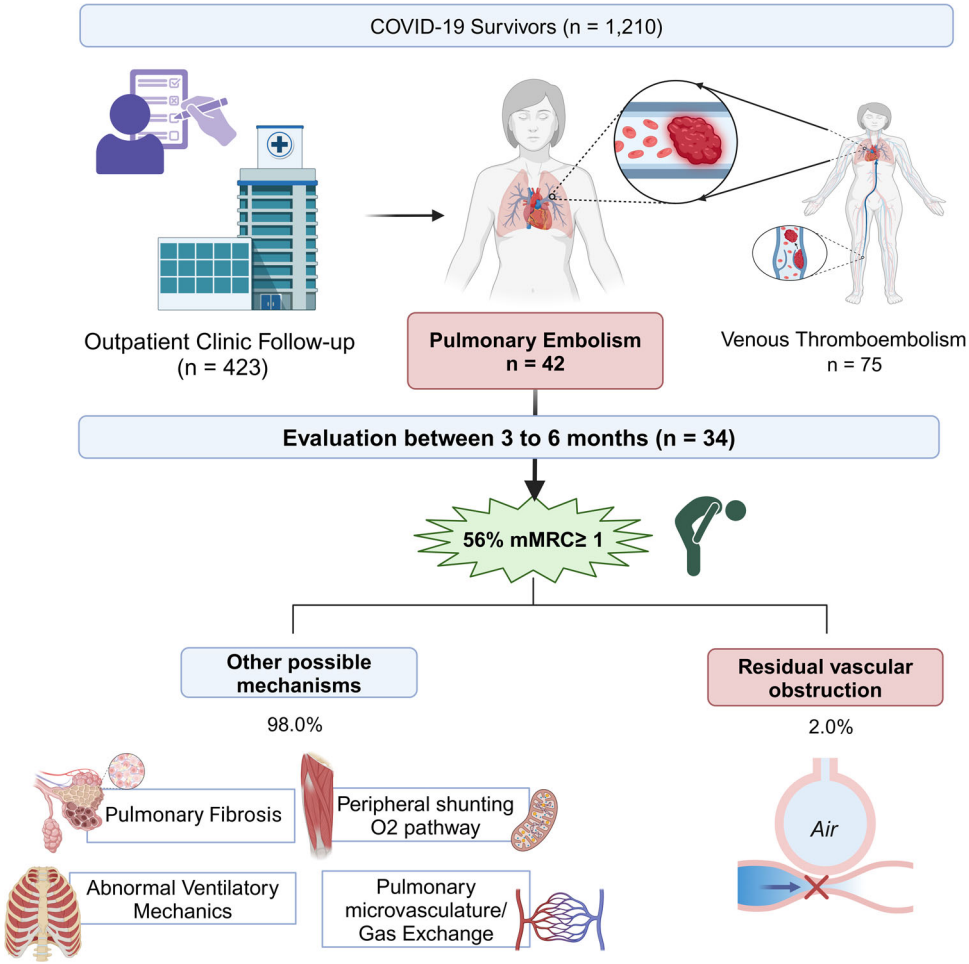

FIGURE 2 | Clinical and functional evaluation of symptomatic patients with PE up to 6 months after the acute event. Dyspnea was not exclusively related to residual vascular obstruction in the pulmonary circulation ($n = 1$), and other mechanisms were considered.

corroborating the need for further and invasive evaluation of this population.

Author Contributions

Authors Ana Carolina B. Duarte, Priscila A. Sperandio and Eloara V. M. Ferreira were responsible for the data analysis and drafting the contents of the article and reviewing the AI tool corrections. Data collection was done by Mariana L. Lafetá, Eloara V. M. Ferreira and Priscila A. Sperandio and imaging analysis by Carlos G. Y. Verrastro, Frederico J. Mancuso and Eloara V. M. Ferreira. Revision and final approval of the manuscript was done by Mariana L. Lafetá, Rudolf K. F. Oliveira, Jaquelina S.Ota-Arakaki and Eloara V. M. Ferreira.

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Ethics Statement

This study protocol was reviewed and approved by the Ethical Committee of Federal University of Sao Paulo (Ethical Review Board: CEP), approval number n:1008/2020.

Consent

Informed consent was obtained from participants (or their parent/legal guardian/next of kin) to participate in the study in compliance with the Helsinki Declaration.

Conflicts of Interest

The authors declare no conflicts of interest.

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