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COVID-19 in Lymphangioleiomyomatosis
An International Study of Outcomes and Impact of Mechanistic Target of Rapamycin Inhibition

To the Editor:
Lymphangioleiomyomatosis is a rare low-grade neoplastic lung disease that occurs sporadically in women or in people with tuberous sclerosis complex. Mechanistic target of rapamycin (mTOR) inhibitors are used for patients with progressive or severe pulmonary impairment or extrapulmonary manifestations. COVID-19 is associated with worse outcomes in patients with chronic pulmonary diseases. However, only a small number of patients with lymphangioleiomyomatosis and COVID-19 have been reported, and the outcomes and impact of mTOR inhibitors on lymphangioleiomyomatosis and COVID-19 infection are unclear. We conducted an international study to evaluate the consequences of COVID-19 in patients with lymphangioleiomyomatosis and the impact of mTOR inhibitors on outcomes after COVID-19.

Methods
We conducted a retrospective observational study that assessed patients with lymphangioleiomyomatosis receiving care at lymphangioleiomyomatosis clinics in Brazil, the United States, Europe, and Japan who contracted COVID-19 between December 1, 2019, and August 31, 2021. All local institutional ethical committees approved the study.

Demographic and clinical features associated with lymphangioleiomyomatosis, risk factors for poor outcomes resulting from COVID-19, pulmonary function tests closest to COVID-19, use of mTOR inhibitors, symptoms, details if hospitalized, treatments received, and outcomes related to COVID-19 were obtained through medical records and telephone follow-up. Long COVID-19 was defined as persisting symptoms or new supplemental oxygen use at least 6 weeks after the onset of symptoms. Normally and nonnormally distributed data are reported as mean ± SD and as median (interquartile range), respectively. Unpaired t tests or the Mann-Whitney U test was used to compare continuous variables, whereas the Fisher exact test or χ² test was used to compare categorical variables. A univariate and a forward stepwise multivariate logistic regression analysis were performed to identify the predictors of hospitalization or need for supplemental oxygen. P values of < .05 were considered significant. All analyses were performed using SigmaStat version 3.5 software (Systat Software, Inc.).

Results
Ninety-one women with lymphangioleiomyomatosis (77 with sporadic lymphangioleiomyomatosis, 14 with tuberous sclerosis complex and lymphangioleiomyomatosis) and COVID-19 were identified, with a mean age of 47 ± 12 years and a median time from diagnosis of lymphangioleiomyomatosis of 14 months (interquartile range, 6-78 months). FEV₁ and diffusing capacity of the lungs for carbon monoxide (DLCO) were 73 ± 23% predicted and 62 ± 23% predicted, respectively. Forty-seven patients (53%) were using mTOR inhibitors at the time of infection, and 16 patients (17.5%) had at least one comorbidity associated with severe COVID-19 (Table 1).

The most common COVID-19 symptom was asthenia. Corticosteroids were used in 26.4% of patients, antibiotics were used in 17.6% of patients, anticoagulants were used in 11% of patients, azithromycin was used in 7.7% of patients, and remdesivir was used in 5.5% of patients. Fifty-three patients (58.2%) received no specific drug treatment. Twenty-eight patients (31%) required hospital admission with a mean stay of 11 ± 8 days, two patients (2.2%) required noninvasive ventilation, and two patients (2.2%) required mechanical ventilation. One patient, 59 years of age with severe lymphangioleiomyomatosis, died (oxygen dependent with FEV₁ of 32% predicted). Twenty patients (22%) received a diagnosis of long COVID-19, mainly fatigue (Table 1). None of the patients were vaccinated against SARS-CoV-2 when they contracted COVID-19. Patients who were hospitalized or needed supplemental oxygen showed worse pulmonary function (FEV₁ % predicted: 63 ± 22% vs 79 ± 21%; P = .002; DLCO % predicted: 49...
### TABLE 1
Demographic, Clinical, and Functional Characteristics and Outcomes of Patients With Lymphangioleiomyomatosis Who Received a Diagnosis of COVID-19 (N = 91)

| Variable | Data |
|----------|------|
| **Demographic and clinical data** | |
| Country | |
| United States | 23 (25.3) |
| Brazil<sup>a</sup> | 20 (22) |
| Poland | 20 (22) |
| United Kingdom | 16 (17.5) |
| France | 6 (6.6) |
| Italy | 3 (3.3) |
| The Netherlands | 2 (2.2) |
| Japan | 1 (1.1) |
| **Age, y** | 47 ± 12 |
| **Race or ethnicity** | |
| White | 76 (83.5) |
| Black | 4 (4.4) |
| Hispanic | 8 (8.8) |
| Asian | 3 (3.3) |
| **Subtype of lymphangioleiomyomatosis** | |
| Sporadic | 77 (84.6) |
| Associated with TSC | 14 (15.4) |
| **Time from diagnosis of lymphangioleiomyomatosis, mo** | 14 (6-78) |
| **BMI ≥ 30 kg/m²** | 21 (23.1) |
| **Comorbidities** | |
| Diabetes | 6 (6.6) |
| Cancer | 3 (3.3) |
| Chronic kidney disease | 6 (6.6) |
| Heart failure, coronary artery disease, or cardiomyopathy | 0 |
| Sickle cell disease | 1 (1.1) |
| Previous organ transplantation | 0 |
| Current pregnancy | 0 |
| Smoking (former or current) | 14 (15.4) |
| **Use of mTOR inhibitors before COVID-19<sup>b</sup>** | 47 (52.8) |
| Sirolimus | 44 (49.4) |
| Everolimus | 3 (3.4) |
| Dose of sirolimus, mg | 2 (1-2) |
| Dose of everolimus, mg | 5 (5-8.75) |
| Duration of mTOR inhibitor use, mo | 44 (12-70) |

(Continued)

### TABLE 1 (Continued)

| Variable | Data |
|----------|------|
| **Pulmonary function tests** | |
| FEV₁, L | 2.13 ± 0.77 |
| FEV₁, % predicted | 73 ± 23 |
| FVC, L | 3.05 ± 0.82 |
| FVC, % predicted | 88 ± 21 |
| D<sub>LCO</sub>, mL/min/mm Hg | 7.84 (5.71-17.00) |
| D<sub>LCO</sub>, % predicted | 62 ± 23 |
| **COVID-19 diagnosis** | |
| RT-PCR swab | 87 (95.6) |
| COVID-19 seroconversion and clinical manifestations | 4 (4.4) |
| **Symptoms during COVID-19** | |
| Asthenia | 80 (87.9) |
| Fever | 64 (70.3) |
| Cough | 64 (70.3) |
| Anorexia | 48 (52.7) |
| Dyspnea | 43 (47.3) |
| Headache | 40 (44) |
| Anosmia | 38 (41.8) |
| Dysgeusia | 33 (36.3) |
| Diarrhea | 20 (22) |
| **Other**<sup>c</sup> | 10 (11) |
| **Hospital admission** | |
| Hospital admission | 28 (30.8) |
| Duration of hospital stay, d | 11 ± 8 |
| Supplemental oxygen use | 27 (29.7) |
| Duration of supplemental oxygen use, d | 7 (5-14) |
| Duration of mechanical ventilation, d | 14 (6-22) |
| **Suspension of mTOR inhibitors** | 21 (44.7) |
| **Outcomes** | |
| Death | 1 (1.1) |
| New or increased supplemental oxygen | 10 (11) |
| Pulmonary embolism | 1 (1.1) |
| Pneumothorax | 1 (1.1) |
| Long COVID-19<sup>d</sup> | 20 (22) |

Data are presented as No. (%), mean ± SD, or median (interquartile range). D<sub>LCO</sub> = diffusing capacity of the lungs for carbon monoxide; mTOR = mechanistic target of rapamycin; RT-PCR = reverse-transcription polymerase chain reaction; TSC = tuberous sclerosis complex.

<sup>a</sup>Partial information about six patients from Brazil was described in a previous report.<br>
<sup>b</sup>Two patients were enrolled in a double-blind placebo-controlled trial of sirolimus vs placebo, and therefore were not included in this analysis.<br>
<sup>c</sup>Other symptoms include nausea, chest pain, night sweats, myalgia, sore throat, and dysphonia.<br>
<sup>d</sup>The most common manifestation of long COVID-19 was fatigue.
± 21% vs 69 ± 20%; \( P < .001 \) than those treated at home without supplemental oxygen. No difference was found in the need for hospitalization or supplemental oxygen, nor in the duration of hospitalization, segregating the cohort on the basis of underlying BMI (≥ 25 kg/m² vs < 25 kg/m² or ≥ 30 kg/m² vs < 30 kg/m²; data not shown).

Patients using mTOR inhibitors demonstrated lower lung function, a higher frequency of dyspnea, and greater need for hospital admission and supplemental oxygen during the course of COVID-19 compared with untreated patients. Use of mTOR inhibitors had no effect on length of hospital stay or need for oxygen or ventilatory support (Table 2). In the univariate analysis, FEV₁ (% predicted; OR, 0.97; 95% CI, 0.95-0.99; \( P = .005 \)), DLCO (% predicted; OR, 0.95; 95% CI, 0.93-0.98; \( P = .001 \)), and use of mTOR inhibitors (OR, 3.23; 95% CI, 1.27-8.21; \( P = .01 \))

### TABLE 2  
Comparison of Patients Separated by mTOR Inhibitor Treatment (n = 89)ᵃ

| Variable | Patients Using mTOR Inhibitors (n = 47) | Patients Not Using mTOR Inhibitors (n = 42) | \( P \) Value |
|----------|----------------------------------------|----------------------------------------------|--------------|
| **Clinical and functional features** | | | |
| Age, y  | 47 ± 10 | 47 ± 13 | .96 |
| BMI ≥ 30 kg/m² | 9 (19.1) | 11 (26.2) | .59 |
| At least one comorbidityᵇ | 9 (19.1) | 7 (16.7) | .98 |
| Smoking (former or current) | 7 (14.9) | 7 (16.7) | .98 |
| Time from diagnosis of lymphangioleiomyomatosis, mo | 17 (6.25-96) | 13.5 (6-42) | .52 |
| FEV₁, % predicted | 66 ± 24 | 80 ± 18 | .004 |
| DLCO, % predicted | 55 ± 22 | 69 ± 20 | .005 |
| **Symptoms during COVID-19** | | | |
| Asthenia | 42 (89.4) | 36 (85.7) | .84 |
| Fever | 37 (78.7) | 25 (59.5) | .08 |
| Cough | 34 (72.3) | 29 (69) | .91 |
| Anorexia | 26 (55.3) | 20 (47.6) | .61 |
| Dyspnea | 28 (59.6) | 15 (35.7) | .04 |
| Headache | 22 (46.8) | 17 (40.5) | .70 |
| Anosmia | 20 (42.6) | 18 (42.9) | .85 |
| Dysgeusia | 16 (34) | 17 (40.5) | .68 |
| Diarrhea | 10 (21.3) | 9 (21.4) | .81 |
| **Hospital admission** | | | |
| Hospital admission | 20 (42.6) | 8 (19) | .03 |
| Supplemental oxygen use | 18 (38.3) | 9 (21.4) | .13 |
| Hospital admission or supplemental oxygen use | 22 (46.8) | 9 (21.4) | .02 |
| Duration of supplemental oxygen use, d | 7 (7-14) | 7 (3-15) | .57 |
| Noninvasive ventilation | 2 (4.3) | 0 | .50 |
| Mechanical ventilation | 2 (4.3) | 0 | .50 |
| Duration of hospital stay, d | 8 (5-12) | 12 (5-20) | .38 |
| **Outcomes** | | | |
| Death | 1 (2.1) | 0 | 1.00 |
| New or increased supplemental oxygen after COVID-19 | 7 (14.9) | 3 (7.1) | .32 |
| Pulmonary embolism | 0 | 1 (2.4) | .47 |
| Pneumothorax | 1 (2.1) | 0 | 1.00 |
| Long COVID-19 | 12 (25.5) | 8 (19) | .63 |

Data are presented as No. (%), mean ± SD, or median (interquartile range). Boldface indicates statistical significance. DLCO = diffusing capacity of the lungs for carbon monoxide; mTOR = mechanistic target of rapamycin.

ᵃTwo patients were enrolled in a double-blind placebo-controlled trial of sirolimus vs placebo, and therefore were not included in this analysis.
ᵇDiabetes, cancer, chronic kidney disease, heart failure, coronary artery disease or cardiomyopathy, and sickle cell disease.
were predictors of hospitalization or need for supplemental oxygen. However, in the multivariate analysis, only DLCO (% predicted; OR, 0.96; 95% CI, 0.93-0.99; \( P = .02 \)) was associated with the need for hospitalization or supplemental oxygen.

**Discussion**

To our knowledge, this is the largest study of COVID-19 in patients with lymphangioleiomyomatosis. The major findings are: (1) approximately one-third of the patients with lymphangioleiomyomatosis required hospitalization after COVID-19, with one death among 91 patients; (2) reduced DLCO was associated with the need for hospitalization and need for supplemental oxygen; and (3) the overall outcomes were similar in patients receiving mTOR inhibitors vs those not receiving mTOR inhibitors.

Multiple cohort studies have demonstrated an increased risk of severe COVID-19 and death in patients with pre-existing chronic lung diseases.\(^2\)-\(^4\) When comparing women with lymphangioleiomyomatosis with a general population of comparable age (30-59 years), need for hospitalization was greater (31% vs 9.5%), but no increase in mortality was found (1.1% vs 1.3%).\(^8\) suggesting that women with lymphangioleiomyomatosis may not be at an increased risk of poor outcomes after COVID-19. The younger age of women with lymphangioleiomyomatosis in our study in part may explain the better outcomes compared with patients with other chronic pulmonary diseases. The prevalence of persistent symptoms at 6 weeks after infection (long COVID-19) of 22% in this lymphangioleiomyomatosis cohort is also similar to that in the general population.\(^9\)

The impact of mTOR inhibitors on COVID-19 outcomes is not well understood. Although it is generally believed that patients with underlying immunosuppression are at increased risk of COVID-19-related complications,\(^7\) it has been speculated that mTOR inhibitors may have a beneficial impact in patients with COVID-19 owing to their in vitro inhibitory effects on viral replication and their potential to mitigate cytokine storm.\(^10\) In a small series from Brazil of six patients with lymphangioleiomyomatosis who received a diagnosis of COVID-19, half were using sirolimus, and all completely recovered from the infection.\(^1\) In the present study, the use of mTOR inhibitors was not associated with worse outcomes, despite these patients having poorer lung function than untreated patients, which should provide reassurance to patients with lymphangioleiomyomatosis and clinicians.

Our study has several limitations. The number of patients with lymphangioleiomyomatosis who received a diagnosis of COVID-19 may have been underestimated because of our criteria limiting inclusion to confirmed cases, which excluded asymptomatic patients and patients who were not tested. Most of the patients in our study contracted COVID-19 before the widespread availability of COVID-19 vaccines or the worldwide emergence of the delta variant, and the impact of these variables on outcomes after COVID-19 in patients with lymphangioleiomyomatosis remains unknown. Asthenia is experienced frequently by women with lymphangioleiomyomatosis and might have led to the overestimation of prevalence of long COVID-19 in our study. Other limitations include the lack of a control group or propensity score matching and the nonstandardized and evolving treatment paradigms for COVID-19 in different countries. Additionally, some of the results obtained may be explained by a type II error. However, these limitations are mitigated by the inclusion of data from multiple international centers and the relatively large sample size for a rare disease.

In conclusion, this multicenter study demonstrated that the risks of death and long COVID-19 after COVID-19 infection in women with lymphangioleiomyomatosis are similar to those of the general population and that mTOR inhibitor use is not associated with worse outcomes.

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