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Case Report

Ten-year follow-up of monozygotic twin sisters with TSC-LAM: A rare case report

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ABSTRACT

Lymphangioleiomyomatosis (LAM) is a rare systemic disease characterized by cystic lung destruction, renal angiomyolipomas (AMLs), and lymphangioleiomyomas. It is classified into tuberous sclerosis complex-associated LAM (TSC-LAM) and sporadic LAM based on the TSC mutations. We reported monozygotic twin sisters of TSC-LAM with sirolimus therapy for ten years. Both twins presented cystic lung involvement, renal AMLs, cerebral MRI alterations, and severe ventilatory impairment at baseline. During long-term treatment, lung function remained stable in both patients, although exercise capacity declined. Despite identical genetics, clinically relevant differences were observed: one twin exhibited earlier disease onset, irregular menstruation, higher VEGF-D and poorer exercise tolerance at baseline. During treatment, she experienced greater weight loss, fluctuating sirolimus concentrations, and earlier need for oxygen therapy. These findings highlight substantial phenotypic heterogeneity in TSC-LAM despite shared genetics and emphasize the importance of early diagnosis, individualized management, and therapeutic drug monitoring in this complex disease.

1. Introduction

Lymphangioleiomyomatosis (LAM) is a rare systemic disease characterized by cystic lung destruction, renal angiomyolipomas (AMLs) and lymphangioleiomyomas, mostly affecting women of reproductive age [1]. It is classified into tuberous sclerosis complex–associated LAM (TSC-LAM) and sporadic LAM (S-LAM), based on *TSC1/TSC2* mutations [2], and its clinical course can be modified by mTOR inhibitors. Treatment with sirolimus, originally known as rapamycin, has significantly improved clinical outcomes [3]. To date, one monozygotic twin pair has been described with LAM affecting a single twin due to a somatic mutation [4], while TSC twins have mainly reported with neurological or cardiac manifestations. Here we present a unique case of monozygotic twins with genetically confirmed TSC-LAM caused by *TSC2* mutation and provide a ten-year follow-up of their clinical course, highlighting phenotypic similarity and variability despite identical genetic backgrounds.

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2. Case report

Twin A (TA) experienced suspected seizures at 1-3 years old and underwent resection of a retroperitoneal neoformation with uncertain histology at age 27. From age 29 to 30 she suffered recurrent pneumothorax (PNX) requiring drainage, apicectomy, bullectomy and pleurectomy. At age 30, she exhibited multiple epileptic seizures controlled by levetiracetam and clonazepam. Twin B (TB) became symptomatic at age 21 and underwent right nephrectomy due to papillary renal neoplasm with extensive clear cell component associated with multiple angiomyolipomas (pT1N1Mx), followed by six months of interferon therapy. At age 23-25, she also suffered recurrent PNX requiring multiple interventions, including drainage, apicectomy, bullectomy, pleurectomy, thoracoscopy, and pleurodesis. At age 30, genetic tests in both twins showed heterozygous *TSC2* Exon 37 mutation (c.4842_4844delCAT p. Ile1614_Met1615delinsMet). The serum levels of vascular endothelial growth factor-D (VEGF-D) were markedly elevated (TA 2249 pg/ml; TB 1348 pg/ml; diagnostic threshold ≥800 pg/ml), leading to a diagnosis of TSC-LAM (Fig. 1). During the clinical course, no changes involving the skin, retina or cardiac system were identified. No other family members have reported a history of TSC.

Following diagnosis, both twins initiated sirolimus therapy, maintaining serum drug levels between 5 and 15 ng/ml (Fig. 2A). Clinical states, adverse effects, radiological characteristics, and functional capacity were monitored over ten years.

During the therapy, neither twin experienced PNX recurrence or other pulmonary complications. Psychiatric status remained stable throughout the follow-up period. No clinically significant adverse effects such as stomatitis, diarrhea, edema were reported. Routine laboratory tests showed normal blood cell counts, as well as normal hepatic, renal, and lipid profiles. Notably, TA experienced weight loss, with body mass index (BMI) decreasing from 22.9 to 20.8, while TB maintained a relatively stable BMI (24.2 to 23). TA reported irregular menstrual periods before and during sirolimus therapy and has been using Azalia (Desogestrel) for the past year. TB had regular menses before sirolimus therapy but developed irregularity during treatment.

For radiological findings, neither the original images nor formal radiology reports were available for review during the episodes of PNX. At the time of TSC diagnosis at age 30, thoracic computed tomography (CT) of TA revealed diffuse bilateral thin-walled cysts with a bullous cystic lesion (5.1*5.2 cm) in the superior right lung. TB exhibited similar cystic changes with a loculated PNX in the superior right lung. Follow-up CT scans at age 40 demonstrated progressive morphostructural distortion of the lung parenchymal with numerous cystic formations in both twins, consistent with widespread LAM (Fig. 3). Extrapulmonary manifestations included renal

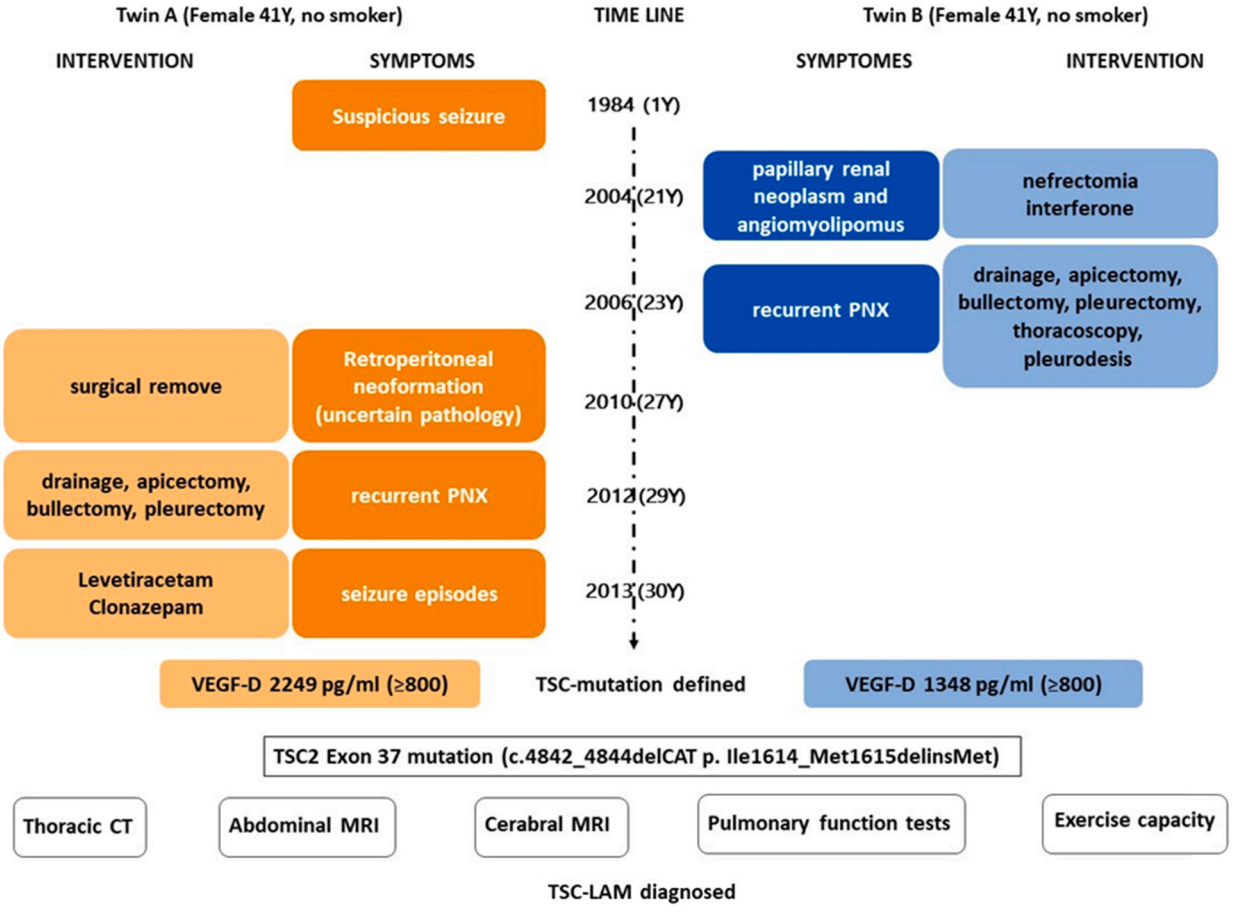

Fig. 1. Timeline of the clinical presentation of the twin sisters prior to diagnosis.

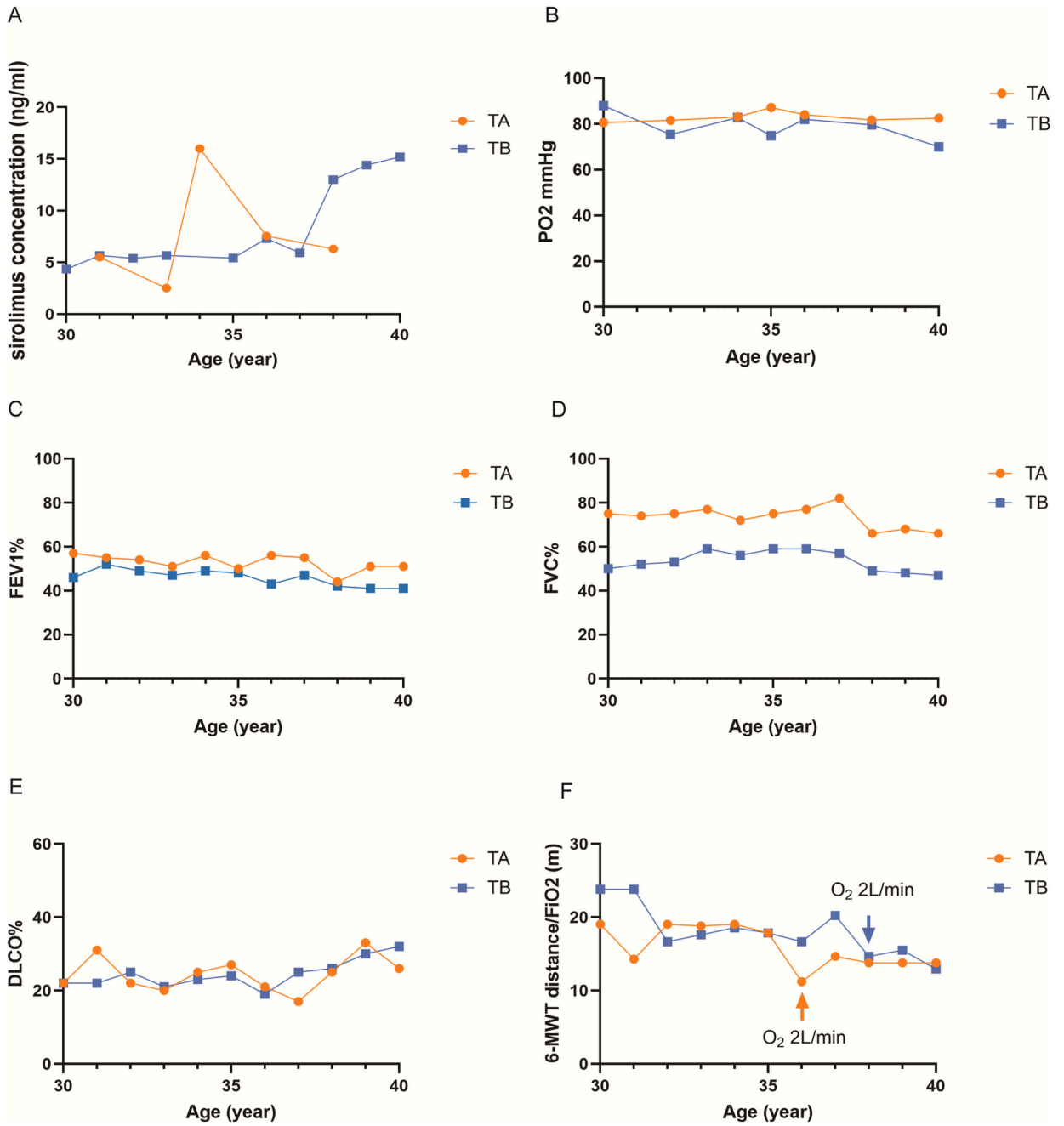

Fig. 2. The trends for ten years follow-up in (A) sirolimus concentration, (B) PO2 on room air, (C) FEV1% predicted, (D) FVC% predicted, (E) DLCO % predicted and (F) 6-MWT distance/FiO_2.
PO2, Partial Pressure of Oxygen in Arterial Blood, FEV1%, Forced Expiratory Volume in one Second % Predicted, FVC%, Forced Vital Capacity % Predicted, DLCO%, Diffusing Capacity of the Lung for Carbon Monoxide % Predicted, 6-MWT, Six-Minute Walking Test Distance, FiO_2, Fraction of Inspired Oxygen.

AMLs and cerebral alterations. Abdominal MRI of TA confirmed a 2.3 cm AML in the right kidney, whereas TB had at least eight AMLs lesions in the left kidney with the largest measuring 3.2 cm at diagnosis. Following treatment, the AMLs lesions decreased in size in both patients. On brain MRI at diagnosis, both patients exhibited subependymal nodules and multiple hyperintense lesions on long TR sequences in the frontal, temporale and parietal regions, affecting the cortex and cortico-subcortical junction bilaterally. TA showed more extensive involvement, which may explain the presence of epilepsy. The images remained stable during follow-up. The twins were also monitored via serial pelvic ultrasound for ovarian cystic lesions, with no progression observed during treatment.

For functional evaluation, resting Arterial Blood Gas analysis (ABG) remained within normal limits on room air throughout follow-

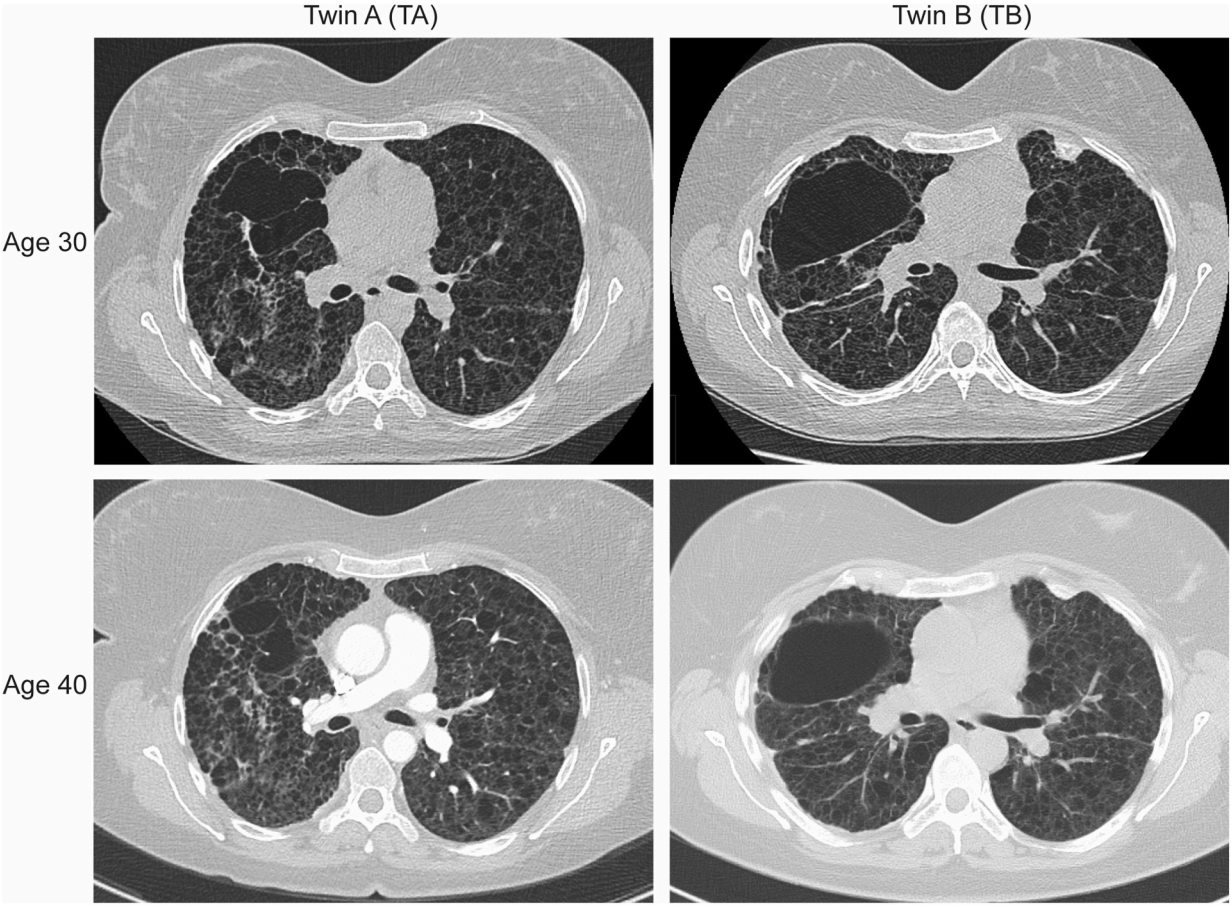

Fig. 3. Thoracic CT scan of the twins at diagnosis (age 30) and after ten years follow-up (age 40), respectively.

up (Fig. 2B). Spirometry revealed a gradual decline in forced expiratory volume in 1 s (FEV1) during treatment, with annual declines of 17ml/year (0.6% predicted) for TA and 15ml/year (0.5% predicted) for TB (Fig. 2C). Forced vital capacity (FVC) remained relatively stable in both twins, although TB had a lower baseline FVC value (TA 2.66L, 75% predicted vs. TB 1.6L, 50% predicted) (Fig. 2D). Both twins exhibited severe baseline diffusing capacity of the lung for carbon monoxide (DLCO) reduction but gained improvement under sirolimus (TA: 22% to 26% predicted; TB: 22% to 32% predicted) (Fig. 2E). Six-minute walking test (6-MWT) distance adjusted for fraction of inspired oxygen (FiO_2) declined in both twins. TA showed lower baseline performance (400 m vs. 500 m) and required supplemental oxygen earlier than TB (January 2022 vs. June 2023) (Fig. 2F).

3. Discussion

With identical *TSC2* mutations, the twin sisters demonstrated largely overlapping clinical courses. Both exhibited characteristic pulmonary involvement with diffuse thin-walled cysts, recurrent PNX, as well as renal AMLs and altered cerebral MRI signals. Baseline spirometry revealed mixed ventilatory impairment, marked by severely reduced DLCO and moderately-severely decreased FEV1. This disease severity was likely multifactorial: genetically, *TSC2* mutations, particularly large deletions, are associated with more aggressive LAM phenotypes, compared with *TSC1* mutations [5]. Clinically, delayed diagnosis and consequently postponed therapy further contributed to disease progression, as both patients experienced symptoms for over a decade prior to definitive diagnosis. Notably, both twin sisters lacked skin lesions, which are among the most common clinical features of TSC [6], potentially making the disease more difficult to recognize. This highlights a persistent challenge in real-world clinical practice and underscores the need for earlier recognition of LAM. Particularly in women with TSC aged over 18 years, screening for LAM is essential and should be incorporated into routine follow-up [7].

Despite shared genetic background, notable phenotypic differences were observed. Previous studies have shown substantial intrafamilial variability among patients carrying identical TSC mutations, reflecting the complexity of TSC manifestations and the influence of the “second-hit” mechanism [8]. In our report, TA exhibited earlier disease onset, menstrual irregularities, higher VEGF-D levels, and poorer exercise tolerance, all of which have been previously associated with unfavorable prognosis [9]. These factors likely contributed to her more rapid disease progression and earlier requirement for supplemental oxygen. Such difference emphasizes the

importance of individualized monitoring and consideration of earlier or more intensive therapeutic intervention in patients exhibiting adverse prognostic indicators.

Sirolimus is widely recognized as the first-line therapy for LAM, with demonstrated efficacy in stabilizing FEV1, DLCO and exercise capacity, largely independent of serum drug levels [10]. Treatment response is influenced by baseline CT scan grade, VEGF-D levels, and FEV1 [11]. In our study both sisters showed measurable improvement in spirometry parameters, accompanied by commonly reported adverse effects including menstrual disturbances and ovarian cysts. Notably, obvious weight loss was observed only in TA, potentially related to greater fluctuation in sirolimus levels and less consistent monitoring. Given the established association between sirolimus concentration and adverse effects [10], regular therapeutic drug monitoring remains essential to optimize efficacy while minimizing toxicity.

4. Conclusion

This case report offers unique insight into the shared and divergent clinical characteristics of monozygotic twin sisters with LAM, highlighting the importance of early diagnosis to prevent functional deterioration and the need for individualized monitoring and treatment based on specific disease phenotypes.

CRediT authorship contribution statement

Lu Fan: Writing – original draft, Conceptualization. **Davide Elia:** Writing – original draft, Conceptualization. **Roberto Cassandro:** Writing – review & editing. **Sergio Alfonso Harari:** Writing – review & editing.

Ethics statement and informed consent

The study was conducted in accordance with the principles of the declaration of Helsinki. Written informed consent for the publication of the case details and accompanying images was obtained from the patients.

Data availability statement

The data can be obtained from the corresponding author upon reasonable request.

Prior presentation

This case was orally presented under the title "Ten-year Follow-up of Monozygotic Twin Sisters with TSC-LAM: A Rare Case Report" at the 11th International meeting on pulmonary rare diseases and orphan drugs. Milan - 14 and 15 March 2025.

Declaration of generative AI and AI-assisted technologies in the manuscript preparation process

During the preparation of this work, the author(s) used ChatGPT (OpenAI) to assist with English-language editing (grammar, wording, and clarity) and to generate alternative phrasings of author-written text. No new scientific content, data analysis, or reference selection was generated by the tool. After using this tool, the author(s) reviewed and edited the content as needed and take full responsibility for the content of the published article.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: S. Harari reports grants or contracts from Boehringer Ingelheim; Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Ferrer, AstraZeneca, Aerovate, Boehringer Ingelheim, Jansen, Sanofi, Pulmovant; Support for attending meetings and/or travel from Dompè; and Participation on a Data Safety Monitoring Board or Advisory Board with Direction de la Recherche en Santé - France. L. Fan, D. Elia, R. Cassandro have nothing to disclose.

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Abbreviations

LAM: Lymphangioleiomyomatosis; AMLs: angiomyolipomas; TSC-LAM: tuberous sclerosis complex associated

lymphangioleiomyomatosis; S-LAM: sporadic lymphangioleiomyomatosis; TA: twin A; TB: twin B; PNX: pneumothorax; CT: computed tomography; MRI: magnetic resonance imaging; VEGF-D: vascular endothelial growth factor-D; BMI: body mass index; ABG: arterial blood gas analysis; FEV1: forced expiratory volume in 1 s; FVC: Forced vital capacity; DLCO: diffusing capacity of the lung for carbon monoxide; 6-MWT: six-minute walking test. FiO_2: fraction of inspired oxygen.

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