Two forced expiratory volume in 1 s trajectories with distinct prognoses in pulmonary Langerhans cell histiocytosis

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Shareable abstract (@ERSpublications)
Pulmonary function outcomes are favourable in most patients with PLCH. However, a subgroup of patients experiences a significant decline over time and has a poor prognosis. These patients warrant close monitoring for early therapeutic intervention. https://bit.ly/3XBpmXU

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Abstract

Background Lung function outcomes in pulmonary Langerhans cell histiocytosis (PLCH) patients are variable and difficult to predict. Our goal was to identify different forced expiratory volume in 1 s (FEV_1) trajectories in these patients during long-term follow-up.

Methods All newly diagnosed adult PLCH patients seen between January 2004 and April 2018 were eligible for inclusion in our prospective cohort. The primary end-point was the identification of FEV_1 trajectories using a joint latent class model for longitudinal and time-to-event data. Internal validation was performed *via* bootstrapping.

Results Among the 191 patients included (mean age of 39±12 years, 59% females, 96% current smokers), who were followed for a median of 5.1 years (interquartile range 3.2–6.0), two FEV_1 trajectories were identified. Patients with trajectory 1 (n=157, 82.2%) were characterised by a normal FEV_1 at diagnosis (mean predicted value (pred) of 95±3%) that remained stable over time (annual variation of 0.2% pred, 95% CI −0.8–0.4). Patients with trajectory 2 (n=34, 17.8%) had a decreased initial FEV_1 (63±7% pred) and an annual decrease of −1.8% pred (−3.4–−0.2). Trajectory 2 was associated with increased mortality (hazard ratio 9.46, 95% CI 1.24–72.2; p=0.03).

Conclusions FEV_1 remained stable in most PLCH patients, but the subgroup of patients that experienced a significant decrease in FEV_1 over time had a poorer prognosis. These patients should be closely monitored for early therapeutic intervention. These results need to be confirmed in an external validation cohort.

Introduction

The natural history of pulmonary Langerhans cell histiocytosis (PLCH) is variable and unpredictable [1, 2]. PLCH may spontaneously resolve, remain stable for several years or progress to obstructive respiratory failure with pulmonary hypertension, leading to lung transplantation or death [1, 2]. We have recently shown that the overall survival of patients is much more favourable than initially reported [3]. However, a minority of patients develop severe respiratory impairment within the 5 years following diagnosis [3]. Thus, identifying patients who are at risk of progression early in the course of the disease is crucial for appropriate management and early therapeutic intervention.

Given the difficulty in accurately predicting the prognosis of PLCH, patients are empirically followed-up with serial lung function evaluation [4–6]. Airway obstruction due to a decrease in FEV_1 is the salient

functional pattern observed in cases of disease progression [1, 7]. Two previous studies prospectively evaluated longitudinal lung function in small cohorts of PLCH patients during the first years after diagnosis. In one study, 77 newly diagnosed PLCH patients were followed for a median time of 3 years [8]. The proportion of patients with airflow obstruction increased from baseline to the end of study, but overall, the FEV_1 did not significantly change between the initial and last examinations [8]. We previously evaluated the natural history of 58 consecutive patients with newly diagnosed PLCH over a 2-year period [9]. Airflow obstruction was the predominant function profile observed in the entire study population and 20% of patients experienced FEV_1 deterioration (pre-defined as a decrease of least 15% in absolute value) at 24 months [9]. Smoking cessation reduced the risk of lung function deterioration. No reliable information is available concerning the longitudinal variations in FEV_1 over a longer period. Thus, there is an important need for long-term evaluation of FEV_1 outcomes in PLCH patients as well as, ideally, for reliable predictive factors that could help identify patients who are at risk of deterioration at the time of diagnosis.

To address these issues, we used our long-term prospective cohort of adult PLCH patients. Our main objective was to identify different trajectories of FEV_1 over time and assess the associations of these trajectories with survival. We also attempted to develop a trajectory prediction score.

Materials and methods

Study design

The data were obtained from the prospective cohort of the French National Reference Centre for Histiocytosis, which is a longitudinal registry-based study aimed at evaluating the long-term outcomes of all adult PLCH patients and registered with www.clinicaltrials.gov (NCT04665674).

The present study involved a cohort of PLCH patients who were newly diagnosed in adulthood between January 2004 and 15 April 2018, with recruitment ending on 31 October 2018 [3]. The study was approved by the Institutional Review Board of the French Institute of Medical Research and Health (IRB number 909207). All patients provided written informed consent for the use of their medical records for research.

Data collection

The data of interest for the present study were retrieved from the reference centre standardised dedicated prospective database, which gathers data of all patients referred to the French National Reference Centre for Histiocytosis. The lung function tests included spirometry, plethysmography and diffusion of carbon monoxide (D_{LCO}), which were performed according to the European standards [10]. The predictive values were determined as previously described [9]. Airway obstruction was defined by an FEV_1/forced vital capacity (FVC) ratio below the lower limit of normal, set at the fifth percentile [11, 12]. Restriction and air trapping were defined as previously described [9]. Patients were classified as having isolated PLCH or multisystem disease in the case of extrapulmonary involvement [3]. All lung high-resolution computed tomography (HRCT) scans performed at diagnosis were analysed by a radiologist (C.d.M.-M.) and two chest physicians (A.T. and A.B.) to determine the global nodular and cystic scores, as previously described [9].

End-points

The primary outcome was FEV_1 evolution from diagnosis up to 6 years or until the initiation of systemic treatment for Langerhans cell histiocytosis (LCH). The secondary outcomes were as follows: survival, defined as the time from diagnosis to lung transplantation or death from any cause; FVC; FEV_1/FVC; residual volume (RV); total lung capacity (TLC); and D_{LCO}.

Statistical analysis

Descriptive statistics are presented as the mean±standard deviation, median (interquartile range (IQR)) or percentages.

A joint latent class mixed model (JLCM) was used to identify groups of trajectories of FEV_1 over time. This model assumes that the population is heterogeneous and consists of subgroups of subjects called latent classes that share the same FEV_1 trajectory over time and a similar risk of death [13]. The longitudinal FEV_1 measurements were censored at 6 years after the PLCH diagnosis or earlier at the time systemic treatment for LCH was initiated.

The JLCM combines the following: 1) a latent class model to identify latent groups of subjects; 2) a mixed model to describe the mean trajectory of FEV_1 over time in each latent group; and 3) a survival model to correct for missing data due to death or lung transplantation and to explore the association between the

latent classes and the risk of death. The mixed model does not require the same number of FEV_1 measurements per patient or the same time-points of measurement.

In the mixed model of the JLCM, an I-spline with three nodes located at the quantiles of the marker distribution was used to describe the class-specific trajectories of FEV_1 without adjustment for baseline covariates. Covariates were first introduced separately in the class-membership model. All covariates with a p-value <0.20 were then included together in the mixed model of the JLCM. Age was adjusted for in the survival model as a class common effect. The model assigned each participant the latent trajectory to which they had the highest likelihood of belonging. A detailed description of the methodology is provided in the online data supplement (supplementary methods). The optimal number of latent classes was determined using the Bayesian information criterion and the Akaike information criterion, the measure of entropy, and by assessing the mean posterior probabilities of belonging to each latent class according to the final classification [14–16] (supplementary methods). A numerical resampling method (bootstrap) with 500 replications was used to evaluate model robustness. We compared the agreement in the assigned trajectories with those assigned by the original model by Cohen's kappa. A mixed model for repeated measures was used *a posteriori* to compare the changes in the other lung function parameters over time across the classes.

To assess the association between FEV_1 trajectories and clinical, functional and radiological parameters measured at diagnosis, we planned to use univariable and multivariable logistic regression and Firth's penalised likelihood approach if needed. Parameters associated with trajectories in the univariable analysis with a p-value <0.10 were thereafter included in the multivariable model.

Statistical analyses were performed using R (www.R-project.org) software. The JLCM estimation used the lcmm R package [17].

Results

Characteristics of the study population

After the exclusion of 15 patients with no baseline chest HRCT (n=10) or missing FEV_1 longitudinal measurements (n=5), 191 patients were included in the analysis. Table 1 displays the characteristics of the patients at diagnosis.

The median follow-up after PLCH diagnosis was 5.1 years (IQR 3.2–6.0). The total number of FEV_1 measurements was 1021 (5.3±3.4 measurements per patient). 12 patients received systemic treatment for LCH.

Identification of FEV_1 trajectories

Joint latent class mixed modelling identified two latent classes with the best fit regarding the observed evolution of FEV_1 over time (supplementary table S1 and figure S1). The two average FEV_1 trajectories are illustrated in figure 1. The largest class (trajectory 1) contained 157 (82.2%) patients. It was characterised by a normal FEV_1 at diagnosis (95±3% pred) that remained stable over time (annual variation of −0.2% pred, 95% CI −0.8–0.4) and −22 mL (−40–−5)). The second class (trajectory 2), which included the remaining 34 (17.8%) patients, had lower FEV_1 at diagnosis (63±7% pred) and declined with an annual rate of −1.8% pred (−3.4–−0.2) and −75 mL (−141–−10). The model showed good discrimination with adequate assignment of patients to specific trajectories (supplementary figure S2).

To reinforce these findings, we performed an internal validation of the model *via* bootstrapping and independently applied the JLCM on 500 bootstrap samples (supplementary figure S3). The agreement between class assignment according to joint models developed in bootstrap samples and the original class assignment was good (median kappa statistic 0.77, median observed agreement 97.3%), confirming the consistency of the two profiles identified in the cohort (supplementary figure S4).

The percentage of the cumulative duration patients spent as active smokers compared to the duration of their follow-up did not differ between the two FEV_1 trajectories (65.3±42.2% in trajectory 1 *versus* 57.9±45.2% in trajectory 2, p=0.38). Additionally, the proportion of patients who had quit smoking for at least 6 months at the end of their follow-up was also similar between the two groups (38.3% in trajectory 1 *versus* 44.8% in trajectory 2, p=0.51). However, there was an association between smoking status and variation in FEV_1 over time in the whole cohort without considering each trajectory separately. Thus, patients who had been smoke-free for at least 6 months had an average percentage predicted FEV_1 that was 1.9% (95% CI 0.8–3.0) greater than that of the other patients (p=0.0005). Conversely, for a 10% increase

TABLE 1 Characteristics of the study population at diagnosis

Characteristic	Value
Subjects, n	191
Age, years	38.9±12.5
Sex	
Female	113 (59)
Male	78 (41)
Smoking status	
Current smokers	183 (96)
Ex-smokers	7 (4)
Pack-years	21.9±16.7
Nonsmokers	1 (<1)
LCH extent	
Isolated PLCH	145 (76)
Multisystem PLCH[#]	46 (24)
Pneumothorax at diagnosis	16 (8)
HRCT score[¶]	
Nodular score	6.8±4.7
Cystic score	6.8±4.5
Lung function	
TLC % pred, n=146	102±16
RV % pred, n=141	124±34
RV/TLC % pred, n=141	117±26
FEV_1% pred, n=159	89±19
FVC % pred, n=149	95±18
FEV_1/FVC %, n=149	80±10
D_{LCO} % pred, n=122	63±17
Lung function patterns[+]	
Normal spirometry	95 (64)
Obstruction	23 (15)
Restriction	14 (10)
Air trapping	54 (38)
D_{LCO} <80% pred[§]	102 (84)

The data are expressed as the mean±SD or n (%). [#]: 46 patients (24%) had at least one extrarespiratory localisation at the time of diagnosis of pulmonary Langerhans cell histiocytosis (PLCH). [¶]: The maximal values for nodular and cystic scores are 18 and 24, respectively. [+]: Obstruction was defined as forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ratio <lower limit of normal (LLN), restriction as total lung capacity (TLC) <80% of the predicted values and air trapping as residual volume (RV)/TLC ratio >120% of the predicted values, normal spirometry as FEV_1/FVC ratio >LLN and FEV_1 >80% and FVC >80%. [§]: 67 patients had isolated decrease of diffusing capacity for carbon monoxide (D_{LCO}). HRCT: high-resolution computed tomography; LCH: Langerhans cell histiocytosis.

in the percentage of cumulative smoking duration compared to the duration of follow-up, the predicted FEV_1% was 0.2% (95% CI −0.3–−0.1) lower (p=0.0027) on average.

Evolution of the other lung function parameters according to FEV_1 trajectory

The evolution of the other lung function parameters in each trajectory of FEV_1 is provided in table 2. The annual decline of FEV_1 expressed in millilitres was greater in trajectory 2 (−76 (−141–−10) *versus* −22 (−40–−5), p=0.043). Similarly, the annual decline of percentage predicted D_{LCO} over time was steeper in trajectory 2 (−1.9% (−2.8–−0.9) *versus* −0.5% (−1.0–−0.1), p=0.026). The mean annual variation in percentage predicted FVC was significantly different between the two trajectories (p=0.02). These results reinforce the consistency of distinguishing the two trajectories of percentage predicted FEV_1 evolution.

Patient survival according to FEV_1 trajectories

10 patients died during the study period. The survival curves for each FEV_1 trajectory are shown in figure 1. The estimated survival rates at 5 years after PLCH diagnosis in trajectory 1 and trajectory 2 were 98.6% (95% CI 96.6–100.0) and 73.5% (95% CI 58.2–92.8), respectively. Thus, trajectory 2 was associated with a higher mortality (hazard ratio 9.46, (95% CI 1.24–72.2), p=0.03).

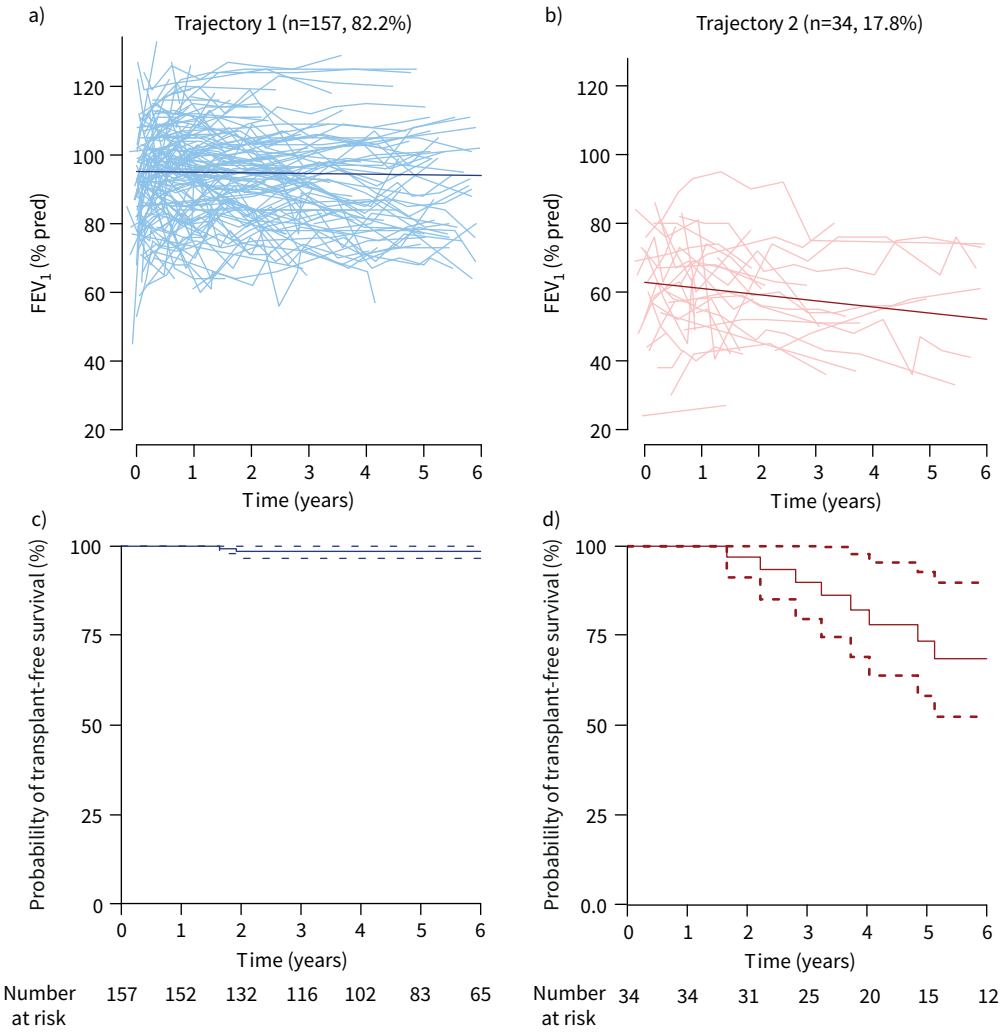

FIGURE 1 The two trajectories of forced expiratory volume in 1 s (FEV_1) and their corresponding survival. The two FEV_1 profiles identified with the joint latent class mixed model are shown. a) Trajectory 1 was composed of patients with a normal baseline FEV_1 that remained stable over time. b) Trajectory 2 was characterised by a decreased baseline FEV_1 (% pred) that declined over time. The Kaplan–Meier survival curve associated with each FEV_1 trajectory is shown in c) and d). The mortality rate was higher among patients with trajectory 2 (hazard ratio 9.46, 95% CI 1.24–72.2; p=0.03).

TABLE 2 Mean annual variation after diagnosis of lung function parameters in each forced expiratory volume in 1 s (FEV_1) trajectory[#]

Lung function parameter	Trajectory 1 (n=157)	Trajectory 2 (n=34)	p-value
FEV_1, mL·year^{-1}	−22 (−40–−5)	−76 (−141– −10)	0.043
FVC, mL·year^{-1}	13 (−8–34)	−46 (−126–34)	0.065
FVC, % pred·year^{-1}	1.0 (0.4–1.5)	−0.9 (−2.4–0.8)	0.020
FEV_1/FVC, %·year^{-1}	−1.0 (−1.3–−0.7)	−1.6 (−2.8–−0.4)	0.212
RV, % pred·year^{-1}	3.2 (1.9–4.6)	5.0 (−1–10.9)	0.564
RV/TLC, % pred·year^{-1}	1.0 (0.1–2.0)	2.3 (−1.3–6.0)	0.497
D_{LCO}, % pred·year^{-1}	−0.5 (−1.0–−0.1)	−1.9 (−2.8–−0.9)	0.026

[#]: Mean annual variations as estimated in mixed linear models with their 95% confidence intervals. D_{LCO}: diffusing capacity for carbon monoxide; FVC: forced vital capacity; RV: residual volume; TLC: total lung capacity.

Clinical, radiological and functional determinants of FEV_1 trajectory assessed at diagnosis

The results of the univariable analysis of patient characteristics at diagnosis according to assigned FEV_1 trajectory are detailed in table 3. The proportion of female patients was significantly higher in the trajectory 1 group (62%) than in the trajectory 2 group (44%) (p=0.049). The percentage of patients with a history pneumothorax was higher in the trajectory 2 group (32% *versus* 3%, p<0.001). Patients with trajectory 2 demonstrated significantly lower values for percentage predicted FEV_1 (p<0.001), TLC (p<0.001), RV/TLC (p<0.001), FVC (p<0.001), FEV_1/FVC (p=0.003) and D_{LCO} (p<0.001), and higher values of HRCT cystic score than patients with trajectory 1.

It was not possible to construct a reliable prediction model for trajectory from these variables because of sparse data bias. The obtained multivariable logistic regression model using five independent variables measured at diagnosis (FEV_1, age, sex, history of pneumothorax and HRCT cystic score) converged but produced extremely inflated estimated odds ratios. To address this bias, we used Firth's penalised regression, but similar results were obtained, which still indicated sparse data bias. The results are therefore not presented.

Discussion

In this large national prospective cohort, we identified two clearly distinct trajectories of FEV_1 at a median follow-up time of 5 years. Overall, the majority of patients had a normal FEV_1 at diagnosis that remained stable during follow-up. However, approximately one-fifth of the patients were characterised by lower initial FEV_1 that decreased over time, which had an important impact on their survival.

This is the first study prospectively evaluating the lung function outcomes of PLCH patients beyond the first years after diagnosis. In a previous study on the natural history of PLCH over 2 years after diagnosis, we estimated the cumulative incidence of FEV_1 outcomes (*i.e.* improvement *versus* deterioration, based on a pre-defined absolute variation) with the nonparametric Kaplan–Meier method [9]. A limitation of this approach is that the follow-up of a given patient is censored once his or her FEV_1 has improved or deteriorated. One of the strengths of the statistical approach used here is its ability to handle the heterogeneity of FEV_1 variations over time and thus more appropriately reflect the evolution of FEV_1 throughout the follow-up period. Furthermore, better phenotyping of PLCH was achieved by identifying a subgroup of patients at risk for FEV_1 decline who may require active management.

TABLE 3 Description of the patients in the two forced expiratory volume in 1 s (FEV_1) trajectories defined by the joint latent class analysis

Characteristic	Trajectory 1	Trajectory 2	p-value[#]
Patients, n	157	34	
Age, years	38±12	42±16	0.135
Female sex	98 (62)	15 (44)	0.049
Smoking status			
Current smokers	153 (97)	30 (88)	0.035
Pack-years	21±15	27±22	0.349
Multisystem LCH	39 (25)	7 (21)	0.599
Pneumothorax at diagnosis	5 (3)	11 (32)	<0.001
HRCT			
Nodular score	7.0±4.7	5.9±4.8	0.211
Cystic score	5.8±3.3	11.6±5.8	<0.001
Lung function			
FEV_1 % pred	93±16	59±15	<0.001
TLC % pred	104±15	91±16	<0.001
RV % pred	122±35	134±32	0.159
RV/TLC % pred	113±24	143±27	<0.001
FVC % pred	98±16	72±19	<0.001
FEV_1/FVC %	81±8	69±15	0.003
D_{LCO} % pred	66±15	40±13	<0.001

The data are expressed as the means±SD or n (%). [#]: Univariable analysis. The chi-squared test or Fisher's exact test were used for categorical variables and the t-test or the Mann–Whitney test were used for quantitative variables, as appropriate. D_{LCO}: diffusing capacity for carbon monoxide; FVC: forced vital capacity; HRCT: high-resolution computed tomography; LCH: Langerhans cell histiocytosis; RV: residual volume; TLC: total lung capacity.

An important factor in the validity of a joint latent class model is the identification of meaningful latent classes with clinical relevance. In the present study, there was a strong association between the two identified FEV_1 trajectories and mortality in each group of patients. Patients with trajectory 1 had an excellent prognosis with an estimated survival of more than 98% at 5 years. In contrast, trajectory 2 was associated with a substantial increase in mortality, with an estimated survival rate at 5 years of 73.5%. Interestingly, this result is comparable to the mortality rates reported by two previous retrospective studies that evaluated the long-term outcomes of PLCH [18, 19]. Notably, the mean predicted FEV_1 percentage at diagnosis of patients with trajectory 2 was also in a range similar to that of the PLCH patients included in these previous studies. Because these studies performed lung imaging mainly by standard chest radiography, there was most likely an inclusion bias toward more severe patients. The fact that we identified a subgroup of similar patients in our cohort emphasises the clinical relevance of the statistical model we used.

In our previous 2-year prospective study, smoking cessation for even 6 months was associated with a reduced risk of FEV_1 deterioration [9]. In the present study, when considering the entire cohort, patients' smoking habits also similarly influenced their FEV_1. Thus, patients who had ceased smoking for at least 6 months had significantly greater FEV_1 at the time of last follow-up. Smoking cessation is mandatory in PLCH patients due to a significant increased risk of lung cancer [3]. However, there was no difference in smoking habits between patients in the two FEV_1 trajectory groups. This finding highlights the fact that the two identified trajectories do not reflect two groups of PLCH patients defined only by different smoking habits but rather two distinct profiles of the disease.

Despite the impossibility of establishing a prediction model due to data structure limitations, our findings highlight several key factors associated with FEV_1 trajectories. Specifically, we observed significant differences in FEV_1 at diagnosis, sex, history of pneumothorax and HRCT cystic score between the two identified trajectories. Recognising patients at risk of following trajectory 2 could aid clinicians in identifying those at higher risk of disease progression early on, facilitating targeted monitoring and intervention strategies tailored to individual patient needs.

This study has several limitations. First, due to the rarity of PLCH, we were unable to test the validity of our results in an external validation cohort. We chose not to split our study sample into training and validation cohorts because of the relatively small number of patients and the recognised associated risk of losing power [20]. To overcome this limitation, we performed an internal validation of the model *via* bootstrapping, which confirmed the consistency of the two FEV_1 trajectories. Nevertheless, the lack of validation cohort limits the significance and generalisation of these findings. Given the limited event rate relative to the sample size study and the unbalanced structure of covariates, it was not possible to construct a reliable prediction model.

In summary, we identified two different trajectories of FEV_1 over time in this large cohort of PLCH patients, which had a substantial impact on prognosis. Overall, pulmonary function outcome was favourable in most patients. However, a subgroup of patients, comprising approximately one-fifth of the patients, was characterised by lower initial FEV1 that decreased over time. Patients in this group had a poorer prognosis with a higher risk of mortality. Our results provide important evidence that could improve the risk stratification of individual patients and ultimately lead to a better selection of patients for therapeutic intervention. These results need to be confirmed in an external validation cohort.

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Data availability: Requests for data supporting the results that are reported in the current study will be reviewed on an individual basis by the director of the hospital clinical trial unit and data will be available following publication.

This study is registered at www.clinicaltrials.gov with identifier number NCT04665674.

Ethics statement: The study was approved by the Institutional Review Board of the French Institute of Medical Research and Health (IRB number 909207).

Conflict of interest: A. Benattia reports travel grants from Boehringer Ingelheim, Asten Santé and Epione Santé, unrelated to the submitted work. R. Porcher has nothing to disclose. C. de Margerie-Mellon reports consulting fees from Bracco, Gilead Sciences, Boehringer Ingelheim and Pfizer, unrelated to the submitted work. E. Caradec has nothing to disclose. G. Lorillon reports travel grants from Vitalaire and Adep Assistance, unrelated to the submitted work. A. Tazi reports personal fees for lectures from Boehringer Ingelheim and travel grants from Vitalaire and Isis Medical, unrelated to the submitted work.

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