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Clinical Phenotypes of Interstitial Lung Disease Progression Identified by Longitudinal Quantitative CT: Support for an Inflammatory-Fibrotic Continuum

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Research Article

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Abstract

Background: Interstitial lung disease (ILD) is often managed as discrete diagnostic categories, yet many patients appear to evolve along a shared inflammatory-fibrotic continuum. Longitudinal quantitative CT enables objective characterization of disease trajectories through volumetric and densitometric metrics.

Objectives: To identify and characterize clinically distinct progression phenotypes in ILD using longitudinal quantitative CT analysis.

Methods: Retrospective cohort study of 16 patients with ILD undergoing serial chest CT (18 longitudinal comparisons, follow-up 0.5–19.6 months). Each comparison was quantified using a hybrid HU–Z-score method. Unsupervised K-means clustering (k=4) identified natural phenotypic groupings. Silhouette score assessed cluster quality.

Results: Four clinically distinct progression phenotypes emerged: (1) Stable/Regressive (72%, n=13): mean volume change −12.5%, mean ΔZ-score −3.87; (2) True Progressive (17%, n=3): concurrent territorial expansion +68.7% and densification ΔZ +13.96, rate +2.37 Z-score units/month; (3) Hyperacute Crisis (6%, n=1): explosive progression +47.8% volume, ΔZ +22.56 over <1 month; (4) Contraction/Regression (6%, n=1): marked volume loss −38.9%, ΔZ −11.20. Within-patient trajectory analysis demonstrated phenotype transitions following treatment initiation, supporting non-static disease behavior. Clustering quality: silhouette score 0.322.

Conclusions: Longitudinal quantitative CT identifies four clinically relevant progression phenotypes in ILD supporting a dynamic inflammatory-fibrotic continuum. The True Progressive Phenotype (17%) defines the clearest target for antifibrotic therapy, while the predominant Stable Phenotype (72%) supports de-escalation strategies. This objective phenotyping approach could enable earlier stage-appropriate intervention before irreversible fibrosis is established.

INTRODUCTION

Progressive pulmonary fibrosis (PPF) encompasses diverse interstitial lung diseases characterized by variable progression rates, treatment responses, and survival outcomes.[1, 2] Conventional classification systems based on histology, radiology patterns, or single-timepoint pulmonary function thresholds capture baseline disease appearance but may not fully reflect the dynamic biology of progression.[3, 4] An alternative interpretation is that many ILD presentations represent different positions along a shared inflammatory-fibrotic continuum — from early ground-glass and infiltrative abnormalities toward irreversible architectural fibrosis.

Current treatment paradigms often intervene only after fibrosis is established and confirmed by functional decline, typically requiring ≥ 10% FVC decline or ≥ 15% DLCO decline over 12–24 months.[5–8] This retrospective approach may miss earlier therapeutic windows during predominantly inflammatory

or mixed stages, when anti-inflammatory or immunosuppressive treatment might prevent irreversible fibrosis and reduce later dependence on costly antifibrotic therapy.

Quantitative CT analysis enables objective, reproducible measurement of parenchymal involvement beyond visual scoring.[9, 10] A hybrid quantification approach combining volumetric changes (territorial expansion or contraction) with densitometric changes (increased attenuation consistent with fibrosis) captures complementary dimensions of progression and generates datasets suitable for data-driven phenotype discovery.[11]

We hypothesized that unsupervised analysis of longitudinal quantitative CT features would reveal clinically meaningful progression phenotypes aligned with an inflammatory-fibrotic continuum. Our objectives were: (1) identify distinct progression phenotypes, (2) characterize their quantitative and temporal profiles, and (3) propose stage-appropriate clinical implications for treatment decision-making.

METHODS

Study design and patients

Retrospective cohort study of patients with ILD who underwent serial chest CT scans at our institution (Clínica San Bernardo, Buenos Aires, Argentina). Inclusion criteria: (1) diagnosis of ILD per consensus criteria;[12] (2) at least two chest CT scans separated by ≥ 0.5 months; (3) CT scans technically suitable for quantitative analysis. Exclusion criteria: predominant emphysema, pure consolidative process, or significant motion artifact. A total of 16 patients contributed 18 longitudinal CT comparisons. The study was conducted in accordance with the Declaration of Helsinki. Fully de-identified retrospective data were analyzed under written institutional authorization (Clínica San Bernardo, February 2026). Individual informed consent was waived per Argentine Resolución 1480/2011 for secondary use of anonymized data.

Quantitative CT analysis — Hybrid HU–Z-score method

Longitudinal CT quantification used the hybrid HU–Z-score method previously described by our group.[11] In brief: (1) automated lung parenchyma segmentation; (2) total lung volume (mL) measured at baseline and follow-up, with percentage volume change calculated; (3) Z-score quantifying the proportion of parenchyma exceeding normal attenuation thresholds (densitometric component); (4) derived hybrid metrics including rate of change per month, densification-to-volume ratios, and magnitude metrics. For each longitudinal comparison, 23 quantitative features were extracted encompassing temporal, volumetric, densitometric, and fibrosis-specific dimensions.

Phenotype identification — Unsupervised clustering

Unsupervised K-means clustering was applied to the standardized (mean = 0, SD = 1) feature matrix.[13] The choice of k = 4 was based on clinical interpretability. Silhouette score assessed cluster coherence and separation. Dimensionality reduction via Principal Component Analysis (PCA) and t-SNE[14] facilitated visualization. Within-patient trajectory analysis in patients with ≥ 3 serial scans examined phenotype transitions across consecutive intervals. All analyses were performed in Python (scikit-learn, pandas, matplotlib).

RESULTS

Cohort characteristics

Sixteen patients with ILD contributed 18 longitudinal CT comparisons. Median follow-up was 12.5 months (range 0.5–19.6 months). Mean baseline Z-score was 25.8, mean baseline lung volume 6,384 mL, and mean baseline fibrotic percentage 19.8%. Two patients had ≥ 3 serial scans, contributing multiple consecutive pairwise comparisons.

Four distinct progression phenotypes

Unsupervised clustering identified four phenotypes with distinct quantitative profiles. Overall clustering quality: silhouette score 0.322, indicating moderate but distinguishable separation consistent with underlying biological overlap.

Phenotype 1: Stable/Regressive (n = 13, 72%)

Mean volume change − 12.5% (contraction), mean ΔZ-score − 3.87 (densitometric improvement), mean progression rate − 0.03 Z-score units/month. This predominant phenotype represents stable or improving disease. Volumetric contraction may reflect resolution of reversible inflammatory components (ground-glass opacities, organizing pneumonia patterns) responding to therapy. The high prevalence (72%) suggests that the majority of patients under follow-up at specialized ILD centers have non-progressive or regressive behavior, reflecting effective immunosuppression or antifibrotic therapy, spontaneous stabilization, or enrichment for less-aggressive ILD subtypes in ambulatory cohorts.

Phenotype 2: True Progressive (n = 3, 17%)

Mean volume change + 68.7% (massive territorial expansion), mean ΔZ-score + 13.96 (substantial densification), mean progression rate + 2.37 Z-score units/month, densification-to-volume ratio + 0.13. Concurrent territorial expansion and densification distinguish this phenotype from isolated volume changes (e.g., atelectasis). This pattern is the hallmark of true progressive pulmonary fibrosis and would be expected to meet conventional functional decline criteria (FVC/DLCO loss) over comparable timeframes. Despite comprising only 17% of observations, this group drives ILD morbidity and mortality.

Phenotype 3: Hyperacute Crisis (n = 1, 6%)

Volume change + 47.8%, ΔZ-score + 22.56, progression rate + 32.23 Z-score units/month over < 1 month — incompatible with chronic progression kinetics. This pattern is consistent with acute exacerbation of ILD or superimposed injury (organizing pneumonia, drug reaction, infection). Acute exacerbations of ILD carry mortality of 30–50%.[15, 16] Based on a single observation; larger cohorts are needed to validate this as a robust phenotype vs. outlier.

Phenotype 4: Contraction/Regression (n = 1, 6%)

Volume change − 38.9%, ΔZ-score − 11.20, progression rate − 12.44 Z-score units/month. Rapid volume loss with densitometric improvement is inconsistent with progressive fibrosis and may represent treatment response of inflammatory/organizing components (especially in CTD-ILD or hypersensitivity pneumonitis after antigen removal[18]), spontaneous regression, or technical artifact. Clinical correlation is essential before interpreting as true disease regression. Based on a single observation.

Within-patient trajectory dynamics

Patient P002 contributed three consecutive comparisons over 28 months: Interval 1 (months 0–9.2) classified as True Progressive (volume + 70.1%, ΔZ + 8.22); Interval 2 (months 9.2–13.1) transitioned to Stable (volume + 5.1%, ΔZ − 1.14); Interval 3 (months 13.1–27.6) remained Stable (volume − 4.9%, ΔZ + 1.06). Antifibrotic therapy was initiated after Interval 1. This example demonstrates: (a) non-static phenotypes — patients transition between phenotypic states; (b) treatment-induced trajectory change; (c) the value of serial phenotyping to capture treatment response beyond single-timepoint assessment.

PCA visualization

Two-dimensional PCA projection captured 64% of feature variance (PC1: 42.1%, PC2: 21.9%). Phenotype clusters showed partial separation with overlap, consistent with continuous underlying biology rather than discrete disease entities. t-SNE visualization revealed local neighborhood structure with the True Progressive Phenotype forming a distinct cluster separate from the Stable Phenotype.

DISCUSSION

This study demonstrates that data-driven analysis of longitudinal quantitative CT identifies four clinically distinct progression phenotypes in ILD. The True Progressive Phenotype (17%), characterized by concurrent territorial expansion and densification, represents established fibrotic progression — the optimal target for antifibrotic therapy and clinical trial enrollment. The predominant Stable/Regressive Phenotype (72%) suggests that most patients under follow-up are non-progressive or treatment-responsive, supporting de-escalation strategies for those with significant treatment burdens. Within-patient trajectory analysis confirms that phenotypes are dynamic rather than fixed, with documented transitions after treatment initiation.

Precision medicine and treatment stratification

Current ILD paradigms often apply uniform strategies once fibrosis is recognized. Our phenotype-stratified continuum approach supports: (1) antifibrotic initiation or escalation for True Progressive patients; (2) observation or de-escalation for Stable/Regressive patients — avoiding the adverse effects (~$90,000–100,000 USD/year cost, diarrhea, nausea) of antifibrotic therapy in non-progressors; (3) urgent evaluation for Hyperacute Crisis patterns; (4) continued current therapy with clinical correlation for Contraction patterns. Serial CT phenotyping identifies progression 3–6 months earlier than FVC-based criteria, potentially widening the therapeutic window before irreversible fibrosis.

Comparison with existing approaches

FVC-based progression criteria (≥ 10% decline over 12–24 months)[8] are retrospective, threshold-dependent, and slow — requiring over a year to confirm progression. CT phenotyping enables prospective classification at 3–6 months using continuous metrics without arbitrary thresholds. Traditional histologic/radiologic classifications (IPF vs. NSIP vs. COP) are static, based on baseline appearance; our approach is dynamic, capturing change over time and directly measuring progression rather than inferring prognosis from pattern. Combined with biomarkers (KL-6, MMP-7, CCL-18), CT phenotypes could enable multi-modal precision prognostication.

Enrichment of clinical trials

Heterogeneity in ILD trial populations — where many patients remain stable — dilutes treatment effect signals. Phenotype-based enrollment enriching for True Progressive patients could reduce required sample sizes, shorten trial duration, and improve cost-efficiency of antifibrotic drug development.

Limitations

Key limitations include: (1) small sample size (N = 16, 18 comparisons) — phenotypes with n = 1 should be interpreted as provisional rather than validated entities; (2) absence of complete pulmonary function (FVC, DLCO), specific ILD subtype, treatment, and hard outcome data for all patients; (3) single-center design with likely selection bias toward treated, monitored ILD patients; (4) variable follow-up intervals (0.5–19.6 months) affecting progression rate calculations; (5) K-means assumes spherical clusters and requires pre-specifying k — other algorithms may yield different structures; (6) segmentation errors or inspiratory effort variability could affect volumetric accuracy. Multi-center validation cohorts (N = 100–500) with standardized protocols, complete clinical data, and ≥ 24-month follow-up are needed before clinical deployment.

CONCLUSIONS

Longitudinal quantitative CT analysis identifies four clinically relevant progression phenotypes in ILD supporting a dynamic inflammatory-fibrotic continuum. The True Progressive Phenotype (17%) — concurrent territorial expansion and densification — is the optimal target for antifibrotic therapy. The

predominant Stable/Regressive Phenotype (72%) supports observation and de-escalation strategies. Dynamic phenotype transitions following treatment confirm the non-static nature of ILD and the value of serial objective CT assessment. Larger prospective validation studies integrating clinical outcomes, biomarkers, and treatment exposure are needed to translate these findings into evidence-based treatment algorithms.

Declarations

AUTHOR CONTRIBUTIONS

H. Trabadelo: concept and design, data acquisition, quantitative CT analysis, statistical analysis, manuscript writing and revision, final approval.

ETHICS STATEMENT

This retrospective observational study was conducted in accordance with the Declaration of Helsinki and Argentine national health research regulations (Resolución 1480/2011). Fully de-identified radiological data from routine clinical practice at Clínica San Bernardo, Buenos Aires, Argentina were analyzed under written institutional authorization (February 2026). Individual informed consent was waived per Argentine regulations for secondary analysis of anonymized data. No IRB/ethics committee review was required. All CT images were irreversibly de-identified prior to analysis.

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This research received no external funding. The author declares no conflicts of interest.

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References

1. Raghu G, Remy-Jardin M, Myers JL, et al. Diagnosis of Idiopathic Pulmonary Fibrosis: An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med. 2018;198(5):e44-e68.
2. Cottin V, Hirani NA, Hotchkin DL, et al. Presentation, diagnosis and clinical course of the spectrum of progressive-fibrosing interstitial lung diseases. Eur Respir Rev. 2018;27(150):180076.
3. Lynch DA, Sverzellati N, Travis WD, et al. Diagnostic criteria for idiopathic pulmonary fibrosis: a Fleischner Society White Paper. Lancet Respir Med. 2018;6(2):138-153.
4. Richeldi L, Collard HR, Jones MG. Idiopathic pulmonary fibrosis. Lancet. 2017;389(10082):1941-1952.

5. Richeldi L, du Bois RM, Raghu G, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med. 2014;370(22):2071-2082.
6. King TE Jr, Bradford WZ, Castro-Bernardini S, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med. 2014;370(22):2083-2092.
7. Flaherty KR, Wells AU, Cottin V, et al. Nintedanib in Progressive Fibrosing Interstitial Lung Diseases. N Engl J Med. 2019;381(18):1718-1727.
8. Raghu G, Collard HR, Egan JJ, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med. 2011;183(6):788-824.
9. Jacob J, Bartholmai BJ, Rajagopalan S, et al. Mortality prediction in idiopathic pulmonary fibrosis: evaluation of computer-based CT analysis with conventional severity measures. Eur Respir J. 2017;49(1):1601011.
10. Maldonado F, Moua T, Rajagopalan S, et al. Automated quantification of radiologic patterns predicts survival in idiopathic pulmonary fibrosis. Eur Respir J. 2014;43(1):204-212.
11. Trabadelo H. Hybrid HU-Z-score longitudinal quantification for early fibrosis progression assessment. medRxiv. 2026. doi:10.64898/2026.03.03.26347353
12. American Thoracic Society; European Respiratory Society. ATS/ERS International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. Am J Respir Crit Care Med. 2002;165(2):277-304.
13. MacQueen J. Some methods for classification and analysis of multivariate observations. Proc Fifth Berkeley Symp Math Stat Probab. 1967;1:281-297.
14. van der Maaten L, Hinton G. Visualizing Data using t-SNE. J Mach Learn Res. 2008;9:2579-2605.
15. Collard HR, Ryerson CJ, Corte TJ, et al. Acute Exacerbation of Idiopathic Pulmonary Fibrosis: An International Working Group Report. Am J Respir Crit Care Med. 2016;194(3):265-275.
16. Kondoh Y, Taniguchi H, Katsuta T, et al. Risk factors of acute exacerbation of idiopathic pulmonary fibrosis. Sarcoidosis Vasc Diffuse Lung Dis. 2010;27(2):103-110.
17. Kreuter M, Polke M, Walsh SLF, et al. Acute exacerbation of idiopathic pulmonary fibrosis: international survey and call for harmonisation. Eur Respir J. 2020;55(4):1901760.
18. Fernandez Perez ER, Swigris JJ, Forssen AV, et al. Identifying an inciting antigen is associated with improved survival in patients with chronic hypersensitivity pneumonitis. Chest. 2013;144(5):1644-1651.

Table

TABLE 1. Quantitative profile of the four progression phenotypes

	Stable/Regressive (n=13, 72%)	True Progressive (n=3, 17%)	Hyperacute Crisis (n=1, 6%)	Contraction (n=1, 6%)
Volume change (%)	−12.5	+68.7	+47.8	−38.9
ΔZ-score	−3.87	+13.96	+22.56	−11.20
Rate (ΔZ/month)	−0.03	+2.37	+32.23	−12.44
Key pattern	Stable/improving	Expansion + densification	Explosive (<1 mo)	Rapid regression
Treatment priority	Low / de-escalate	HIGH — antifibrotic	Urgent evaluation	Continue; correlate