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**Clinical Assessment and Outcomes Across
Respiratory Diseases**



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ABOUT

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Editorial



Clinical Assessment and Outcomes Across Respiratory Diseases

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Clinical assessment of respiratory disease should establish the cause of symptoms, define functional impairment and inform management. These aims often require more than one measure. This issue brings together seven original studies on pulmonary function testing, rehabilitation, patient-reported outcomes and prognosis. The papers span airway disease, stem cell transplantation, chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF), pneumonia and other interstitial lung diseases (ILD).

Subacute cough is conventionally defined as lasting three to eight weeks, but duration alone does not establish its etiology.¹ In "Pulmonary Function Test Abnormalities in Subacute Cough: A Neglected Tool," Yüksel and İlgar Akelma² compared 156 adults with subacute cough with 156 healthy controls. The cough group had lower spirometric indices, including mid-expiratory flow; postinfectious cough accounted for 37.8% of diagnoses and asthma for 25%.² These findings suggest that spirometry can identify functional abnormalities in some patients presenting during this interval. The retrospective, selected sample does not establish that all patients with subacute cough require spirometry, and an isolated forced expiratory flow at 25–75% of the pulmonary volume (FEF_{25–75}) result is not a specific diagnosis. European Respiratory Society/American Thoracic Society (ERS/ATS) interpretation standards require lung function results to be considered with the patient's history, test quality, reference range and pretest probability.³

In the asthma study, 63 of 98 adults (64.3%) had oscillometry-defined small airway dysfunction, accompanied by poorer control, worse quality of life and more exacerbations. The quality-of-life association persisted after spirometric adjustment, whereas the association with asthma control was attenuated.⁴ A 2025 ATLANTIS analysis found that R5–R20-defined dysfunction was associated with future exacerbations in patients with well controlled asthma, after adjustment for established risk factors, including forced expiratory volume in one second (hazard ratio 2.26; 95% confidence interval 1.05–4.85).⁵ Small airway measurements may therefore contribute to risk assessment even when symptoms appear controlled. Differences between oscillometry indices and thresholds need to be considered when comparing studies or applying their findings.

The study of 83 hematopoietic stem cell transplantation recipients illustrates the difference between association and predictive performance. Reduced pretransplant FEF_{25–75} was associated with a composite of post-transplant complications, including nonpulmonary events, but its standalone area under the receiver operating characteristic curve was only 0.578.⁶ The 2024 ERS/European Society for Blood and Marrow Transplantation guideline on pulmonary chronic graft-versus-host disease supports pretransplant baseline lung function assessment and subsequent physiological monitoring.⁷ Further work should establish whether small airway measurements improve prediction of specific complications beyond conventional indices and clinical risk factors.

The COPD exercise study evaluated a culturally adapted program of repeated floor-to-stand movements. Seven of 15 participants completed the nine-week program; improvements were mainly in symptoms and disease impact, without

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consistent changes in functional tests or peripheral muscle outcomes.⁸ The 2023 ATS guideline strongly recommends pulmonary rehabilitation for stable COPD and after hospitalization for an exacerbation.⁹ Evidence for this particular floor-to-stand program remains preliminary. A 2024 study found that the standardized one-minute sit-to-stand test reflected exercise capacity and responded to rehabilitation,¹⁰ but that chair-based assessment differs from floor-to-stand training. For the proposed program, larger controlled studies should assess adherence and determine whether symptom improvement is accompanied by better daily function.

The Turkish adaptation of the IPF-specific St George's Respiratory Questionnaire (SGRQ-I) was evaluated in 180 patients, with good-to-excellent test-retest reliability and moderate correlations with physiological and walking measures.¹¹ This extends previous validation of the 34-item SGRQ-I in IPF.¹² A validated Turkish version allows health status to be assessed using an instrument developed for this population. Its measurement properties must remain central to the interpretation of scores in clinical practice and research.

The King's Brief Interstitial Lung Disease (K-BILD) questionnaire is another established measure of health status in ILD. Its 15 items cover breathlessness and activities, chest symptoms and psychological impact.¹³ In a 2024 Finnish cohort of 245 patients with IPF, lower baseline K-BILD scores were associated with poorer survival.¹⁴ These observational findings do not establish K-BILD as a standalone prognostic rule. A 2025 analysis of 736 participants in the IPF-PRO Registry found only weak relationships between changes in lung function and changes in patient-reported outcomes.¹⁵ Health status therefore needs to be measured directly alongside physiology. The choice between SGRQ-I and K-BILD should take account of the intended population, questionnaire burden, measurement properties and availability of a validated language version.

In the pneumonia study, adding computed tomography (CT) severity to CURB-65 improved discrimination for intensive care admission ($P = 0.003$) among 456 adults with CT-confirmed community-acquired pneumonia. The improvement for 30-day mortality was not statistically significant ($P = 0.081$).¹⁶ A 2025 cohort comparison also supported the performance of pneumonia-specific severity scores.¹⁷ The recent ATS guideline conditionally accepts lung ultrasound as an alternative to chest radiography where appropriate expertise exists.¹⁸ The choice of diagnostic imaging and the value of imaging for prognosis need to be assessed separately. The combined CT model requires external validation, calibration assessment and evidence of improved triage before wider adoption. Results from a CT-selected cohort do not justify routine CT solely for risk scoring.

Uchiyama et al.¹⁹ studied 443 patients with ILD, of whom 158 developed an acute exacerbation. Median survival after exacerbation was two months, and older age and selected comorbidities were associated with worse outcomes. A 2026 multicentre UK study of 938 ILD-related admissions also documented high mortality, with age, preadmission oxygen use and neutrophilia associated with mortality in its acute

exacerbation subgroup.²⁰ Differences in case definitions and populations limit direct comparison of survival estimates. The age threshold of 80 years reported by Uchiyama et al.¹⁹ should not be treated as a universal threshold for individual care. Prognostic information should be considered together with disease severity, comorbidities and the patient's preferences when discussing treatment and supportive care.

These studies address practical questions about the use of familiar tests and the assessment of outcomes that matter to patients. They also show why the purpose of measurement must be explicit. An index associated with complications may discriminate poorly between individual patients, while a physiological change may not reflect a change in health status. For the proposed predictive measures, the next step is to test their added value in other populations. For rehabilitation programs and patient-reported measures, further work should examine their use over time and their effect on clinical decisions. Evidence that an assessment changes management and improves outcomes will be needed to establish its place in routine care.

Footnotes

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Original Article



Pulmonary Function Test Abnormalities in Subacute Cough: A Neglected Tool

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ABSTRACT

OBJECTIVE: Subacute cough is often considered a benign and self-limiting condition, and pulmonary function tests (PFTs) are not routinely performed during this period. This study aimed to evaluate PFT findings in patients with subacute cough compared with those in healthy controls.

MATERIAL AND METHODS: This retrospective, cross-sectional study included adults with subacute cough who underwent standardized spirometry, along with age- and sex-frequency matched healthy controls. Forced expiratory volume in one second (FEV₁), forced vital capacity (FVC), and forced expiratory flow at 25–75% of the pulmonary volume (FEF_{25–75}) were recorded as absolute values and z-scores. Between-group comparisons were performed using analysis of covariance to adjust for age, sex, and height.

RESULTS: A total of 156 patients with subacute cough and 156 controls were analyzed. Patients with subacute cough demonstrated significantly lower FEV₁ and FVC z-scores, and lower FEF_{25–75} values and z-scores (all $P < 0.001$). After adjustment, group differences remained significant for FVC, FEV₁ z-score, and FEF_{25–75} (both absolute and z-score). Post-infectious cough was the most common diagnosis (37.8%), followed by asthma (25%); interstitial lung diseases (ILD) were also detected. FVC z-scores, absolute FEF_{25–75}, and FEF_{25–75} z-scores were lower in the obstructive airway disease and ILD subgroups than in the post-infectious cough group. FEF_{25–75} z-scores showed the greatest discriminatory ability across diagnostic categories.

CONCLUSION: Subacute cough encompasses a heterogeneous group of underlying diseases and should not be considered solely post-infectious. Patients with subacute cough may exhibit impaired PFTs, especially FEF_{25–75} z-scores. PFTs may provide additional information for the evaluation of subacute cough.

KEYWORDS: Asthma, COPD, interstitial lung disease, pulmonary function tests

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INTRODUCTION

Cough is one of the most common symptoms prompting outpatient visits to pulmonary medicine services and represents a significant clinical and socioeconomic burden. Based on symptom duration, cough is classified as acute (<3 weeks), subacute (3–8 weeks), or chronic (>8 weeks).^{1,2} While subacute cough is frequently considered a benign and self-limiting condition, most often following an upper respiratory tract infection (URTI), accumulating evidence suggests that it may also represent an early manifestation of underlying airway disease in a subset of patients.³ The etiological spectrum of subacute cough includes post-infectious cough, upper airway cough syndrome, cough variant asthma (CVA), non-asthmatic eosinophilic bronchitis, atopic cough, and gastroesophageal reflux-related cough. Several of these conditions may present without overt airflow limitation on conventional spirometry, resulting in under-recognition during the subacute phase. These conditions may present with normal pulmonary function tests (PFTs), making early identification difficult without more sensitive functional assessments. The forced expiratory flow at 25–75% of the pulmonary volume (FEF_{25–75}) or maximal mid-

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expiratory flow) is a marker of small airway function. Previous studies have demonstrated significantly lower FEF_{25-75} values in CVA patients compared to healthy controls or those with post-infectious cough.⁴ Although conventional spirometry may be within normal limits, early small airway dysfunction can still be present and measurable through these indices. Identifying subtle physiological changes during the subacute phase may enable earlier diagnosis and treatment, especially with inhaled corticosteroids (ICS), and potentially prevent progression to chronic cough and improve patient outcomes.⁵

In clinical practice, patients presenting with subacute cough are frequently managed conservatively, and PFT is not routinely performed unless symptoms persist beyond eight weeks. This “wait-and-see” approach may delay the recognition of airway hyperresponsiveness or an obstructive defect in a subset of patients. Therefore, further data are needed to evaluate the role of PFT in this clinical context.

In this context, evaluating PFT findings in patients presenting with subacute cough may provide valuable insights into subclinical airway dysfunction. Therefore, we hypothesized that patients with subacute cough would have abnormal z-score-based spirometric parameters compared with healthy controls.

MATERIAL AND METHODS

Study Design and Population

This retrospective, cross-sectional, observational study was conducted at an academic hospital. Medical records of adult patients (≥ 18 years) who presented between January and June 2025 with a subacute cough lasting 3–8 weeks and who underwent standardized spirometry were reviewed. A control group consisting of age- and sex-frequency matched individuals without known pulmonary disease was selected from subjects who underwent spirometry during the same period for pre-employment, periodic health assessment, or routine check-up. Active or ex-smokers, patients with known chronic respiratory diseases [including asthma, chronic obstructive pulmonary disease, bronchiectasis, or interstitial lung disease (ILD)], acute upper or lower respiratory tract infection, pulmonary infection (such as pneumonia or tuberculosis), abnormal chest

radiography or computed tomography (CT) findings, pregnancy, or inability to perform acceptable spirometry maneuvers were excluded. Patients with a previously established diagnosis of asthma, COPD, bronchiectasis, or ILD before the study evaluation were excluded. However, patients who were newly diagnosed with these conditions during the diagnostic work-up were not excluded and were reported in the results. The current study protocol was approved by the Local Ethics Committee of TOBB University of Economics and Technology (date: 22.10.2025; number: 34), and the study was performed in accordance with the ethical standards laid down in the Declaration of Helsinki. All data were anonymized prior to analysis.

Data Collection and Pulmonary Function Testing

Demographic data, including age, sex, and body mass index (BMI), were obtained from the hospital electronic information system. PFT parameters extracted from the laboratory database included forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), FEV_1/FVC ratio, and forced expiratory flow between 25% and 75% of FVC (FEF_{25-75}). All spirometric measurements were performed using the same calibrated spirometer in accordance with the American Thoracic Society and the European Respiratory Society (ERS) standards.⁶ Absolute values and corresponding z-scores were recorded for analysis. Spirometric z-scores were calculated using the Global Lung Function Initiative reference equations.

Definition of Etiologic Diagnoses

Etiologic diagnoses were determined based on clinical evaluation, spirometric findings, radiologic evaluation, or multidisciplinary evaluation. Asthma was defined as the presence of compatible respiratory symptoms with either documented bronchodilator reversibility (increase in $FEV_1 \geq 12\%$ and ≥ 200 mL after bronchodilator administration) or a prior physician diagnosis supported by treatment response to the ICS with or without long-acting beta-agonists. Chronic obstructive pulmonary disease (COPD) was defined by spirometric criteria demonstrating persistent airflow limitation (post-bronchodilator $FEV_1/FVC < 0.70$) and/or radiological findings in the context of a compatible clinical history. ILDs were identified based on radiologic findings on chest CT and/or pathological findings, as determined by multidisciplinary evaluation. Gastroesophageal reflux disease (GERD)-related cough was defined based on compatible symptoms and multidisciplinary evaluation with or without ongoing anti-reflux therapy. Post-infectious cough was defined as cough persisting for 3–8 weeks following an URTI in the absence of alternative identifiable etiologies.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences, version 22 (IBM, Armonk, NY, USA). The distribution of continuous variables was assessed using the Kolmogorov–Smirnov test. Normally distributed continuous variables are presented as mean $\pm$ standard deviation (SD), while categorical variables are expressed as number and percentage (%). Between-group comparisons were performed using the Student’s t-test for normally distributed continuous variables and the chi-square test for categorical variables. In

Main Points

- Subacute cough is commonly managed conservatively, yet a substantial proportion of patients have clinically relevant airway or parenchymal lung disease.
- Small airway dysfunction is a key physiological abnormality in subacute cough and is best captured by forced expiratory flow at 25–75% of the pulmonary volume (FEF_{25-75}) particularly the z-score.
- FEF_{25-75} z-scores outperform forced expiratory volume in one second in differentiating between obstructive airway diseases during the subacute cough phase.
- Routine spirometry in patients with subacute cough may challenge the “wait-and-see” approach and enable earlier, etiology-driven diagnostic and therapeutic decisions.

addition, analysis of covariance (ANCOVA) was conducted to evaluate group differences in pulmonary function parameters after adjustment for age, sex, height, and BMI. Group-effect *P* values and partial eta-squared (η^2) were reported for adjusted analyses. A two-sided *P* value of <0.05 was considered statistically significant for all analyses.

RESULTS

Baseline Characteristics

A total of 312 individuals were included in the analysis, consisting of 156 patients with subacute cough and 156 healthy controls. Baseline demographic characteristics are presented in Table 1. Age and BMI were not statistically different between subacute cough group and healthy controls (50.4±1.2 vs. 53.4±1.6 years, *P* = 0.099; 27.4±0.35 vs. 27.2±0.44 kg/m², *P* = 0.292; respectively). Sex distribution differed significantly between groups, with a higher proportion of males in the subacute cough group (*P*=0.041). Among the 156 patients with subacute cough, post-infectious cough (37.8%, n = 59) was the most frequent etiology; asthma was the second most common definitive diagnosis (25%, n = 39). GERD (7.1%, n = 11) and COPD (7.1%, n = 11) were tied for the third most prevalent causes of subacute cough (Figure 1). All definite diagnoses and their prevalence are presented in Supplementary Table 1.

Pulmonary Function Test Results

PFT results are summarized in Table 2. Absolute FEV₁ and FVC values were comparable between the subacute cough and control groups (FEV₁: 2.83±0.07 L vs. 2.69±0.08 L, *P* = 0.225;

FVC: 3.40±0.09 L vs. 3.59±0.10 L, *P* = 0.149). In contrast, z-score-based spirometric indices demonstrated significant differences. The subacute cough group had significantly lower FEV₁ z-scores (−1.05±0.09 vs. −0.37±0.10, *P* < 0.001) and FVC z-scores (−1.30±0.09 vs. 0.24±0.10, *P* < 0.001). The FEV₁/FVC z-score was significantly higher in the subacute cough group compared with controls (*P* < 0.001). Small airways function was significantly impaired in patients with subacute cough. Both absolute FEF_{25–75} values (2.36±0.14 L/s vs. 3.06±0.10 L/s, *P* < 0.001) and FEF_{25–75} z-scores (−1.12±0.76 vs. −0.18±0.09, *P* < 0.001) were significantly lower than those observed in the control group.

Among the 136 patients with subacute cough who underwent bronchodilator reversibility testing, 31 (22.8%) showed a positive bronchodilator response. In the subacute cough group, the mean ± SD serum eosinophil count was 210±17 cells/μL. Serum eosinophil levels were significantly higher in the reversible group compared with the irreversible group (327±56 vs. 188±15 cells/μL, respectively; *P* = 0.009). No significant correlation was observed between serum eosinophil counts and FEF_{25–75} values.

Adjusted Analysis

Results of ANCOVA adjusted for age, sex, height, and BMI are shown in Table 3. After adjustment, statistically significant group effects persisted for FVC, FVC z-score, FEV₁ z-score, FEV₁/FVC z-score, and FEF_{25–75} (absolute and z-score values; all *P* < 0.001). No significant group effect was observed for absolute FEV₁ values (*P* = 0.319). The largest effect sizes were observed for FVC z-score (partial η^2 = 0.283) and FEV₁/FVC

Table 1. Demographic characteristics

	Subacute cough group (n = 156)	Control group (n = 156)	<i>P</i>
Age (mean ± SD)	50.4±1.2	53.4±1.6	0.099
Gender, n (%)			
Female	73 (46.8%)	91 (58.3%)	0.041*
Male	83 (53.2%)	65 (41.7%)	
Body mass index (mean ± SD)	27.4±0.35	27.2±0.44	0.292

**P* < 0.05
SD: standard deviation

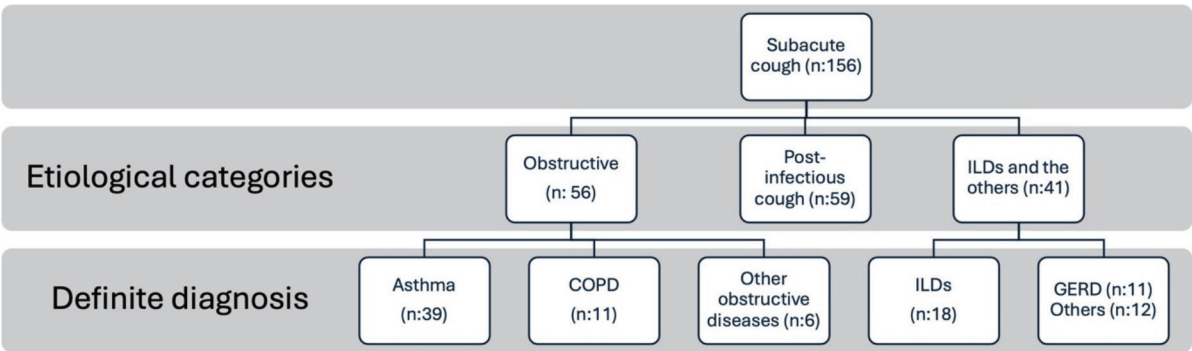


Figure 1. Diagnostic categories and most common final diagnoses of patients with subacute cough
COPD: chronic obstructive pulmonary disease, GERD: gastroesophageal reflux disease, ILDs: interstitial lung diseases

z-score (partial $\eta^2 = 0.200$), followed by FEF_{25-75} z-score (partial $\eta^2 = 0.168$).

PFT results were evaluated according to three main diagnostic categories comprising post-infectious cough, obstructive lung diseases (asthma, COPD, bronchiectasis), and ILDs and the others (GERD, etc.) (Figure 1); significant differences were observed in FEV_1 z-scores, FEF_{25-75} absolute values, and FEF_{25-75} z-scores across groups (Figure 2 and Supplementary Table 2). Overall comparisons demonstrated a statistically significant effect of diagnosis on FEV_1 z-scores ($P < 0.05$), with post-hoc analyses revealing significantly lower (more negative) FEV_1 z-scores in the obstructive disease groups compared with the post-infectious cough group (Figure 2B). Similarly, FEF_{25-75} absolute values differed significantly among diagnostic groups ($P < 0.05$), showing a wider dispersion and lower central tendency in diagnoses characterized by small airway involvement (Figure 2C). FEF_{25-75} z-scores showed the most significant intergroup differences (overall $P < 0.001$). Post-hoc analyses indicated that obstructive ventilatory pattern diagnoses such as asthma had significantly lower FEF_{25-75} z-scores compared with other diagnostic categories (Figure 2D), even in cases where FEV_1 z-scores remained within normal limits.

DISCUSSION

This study demonstrates that subacute cough should not be presumed to be post-infectious by default, as our cohort exhibited a broad range of underlying conditions. Post-infectious cough was the most frequent etiology, while asthma

(25%) represented the second most common etiology; GERD and COPD each accounted for 7.1% of etiologies. Importantly, a subset of patients was also diagnosed with ILDs, underscoring that clinically meaningful parenchymal pathology may be encountered even within a 3–8-week symptom window.

Although post-infectious cough was the most common etiology in our cohort, accounting for only 37.8% of cases, a substantial proportion of patients were diagnosed with asthma, other obstructive lung diseases, and ILDs. This finding is consistent with the study by Kwon et al.⁵, who demonstrated that while post-infectious cough is common in the subacute phase, asthma-related phenotypes constitute a significant proportion of cases and are frequently under-recognized early in the disease course. Importantly, both the CHEST and ERS cough guidelines emphasize that symptom duration alone is insufficient to define etiology and that structural or inflammatory lung diseases may manifest before the chronic cough threshold is reached.^{1,7}

A key physiological finding of this study is that z-score-based spirometric indices identified abnormalities that were not apparent on absolute spirometric volumes alone. Absolute FEV_1 and FVC values were comparable between the subacute cough and control groups, whereas FEV_1 and FVC z-scores were significantly lower in the subacute cough group. In addition, small airway function was consistently impaired, as reflected by lower FEF_{25-75} values (both absolute and z-scores) in the subacute cough group. Collectively, these results indicate that deviation from predicted normative values (z-scores) may be more informative than absolute volumes in this clinical

Table 2. Pulmonary function tests results

	Subacute cough group (n = 156)	Control group (n = 156)	P
FEV_1 (L) [95% CI]	2.826±0.072 [2.683 – 2.969]	2.693±0.081 [2.531 – 2.855]	0.225
FEV_1 z-score [95% CI]	-1.054±0.087 [-1.227 – -0.882]	-0.367±0.096 [-0.556 – -0.177]	<0.001*
FVC (L) [95% CI]	3.399±0.086 [3.227 – 3.570]	3.587±0.096 [3.396 – 3.777]	0.149
FVC z-score [95% CI]	-1.300±0.931 [-1.485 – -1.116]	0.240±0.096 [0.045 – 0.435]	<0.001*
FEV_1/FVC z-score [95% CI]	0.615±0.110 [0.398 – 0.833]	-0.503±0.570 [-0.617 – 0.190]	<0.001*
FEF_{25-75} (L/s) [95% CI]	2.360±0.139 [2.145 – 2.576]	3.062±0.103 [2.856 – 3.266]	<0.001*
FEF_{25-75} z-score [95% CI]	-1.116±0.760 [-1.267 – -0.964]	-0.177±0.086 [-0.349 – -0.006]	<0.001*

* $P < 0.05$. Results are given as mean ± standard deviation with corresponding 95% confidence intervals (CI)

FEF_{25-75} : forced expiratory flow between 25% and 75% of FVC, FEV_1 : forced expiratory volume in one second, FVC: forced vital capacity, CI: confidence interval

Table 3. Adjusted group effects on spirometric parameters in subacute cough compared with healthy controls

	Group effect (F)	P value	Partial η^2
FVC (L)	24.038	<0.001*	0.073
FVC z-score	121.247	<0.001*	0.283
FEV_1 (L)	0.995	0.319	0.003
FEV_1 z-score	25.784	<0.001*	0.077
FEV_1/FVC z-score	76.628	<0.001*	0.200
FEF_{25-75} (L/s)	18.082	<0.001*	0.056
FEF_{25-75} z-score	61.910	<0.001*	0.168

* $P < 0.05$. ANCOVA adjusted for age, sex, height and BMI

ANCOVA: analysis of covariance, BMI: body mass index, FEF_{25-75} : forced expiratory flow between 25% and 75% of FVC, FEV_1 : forced expiratory volume in one second, FVC: forced vital capacity

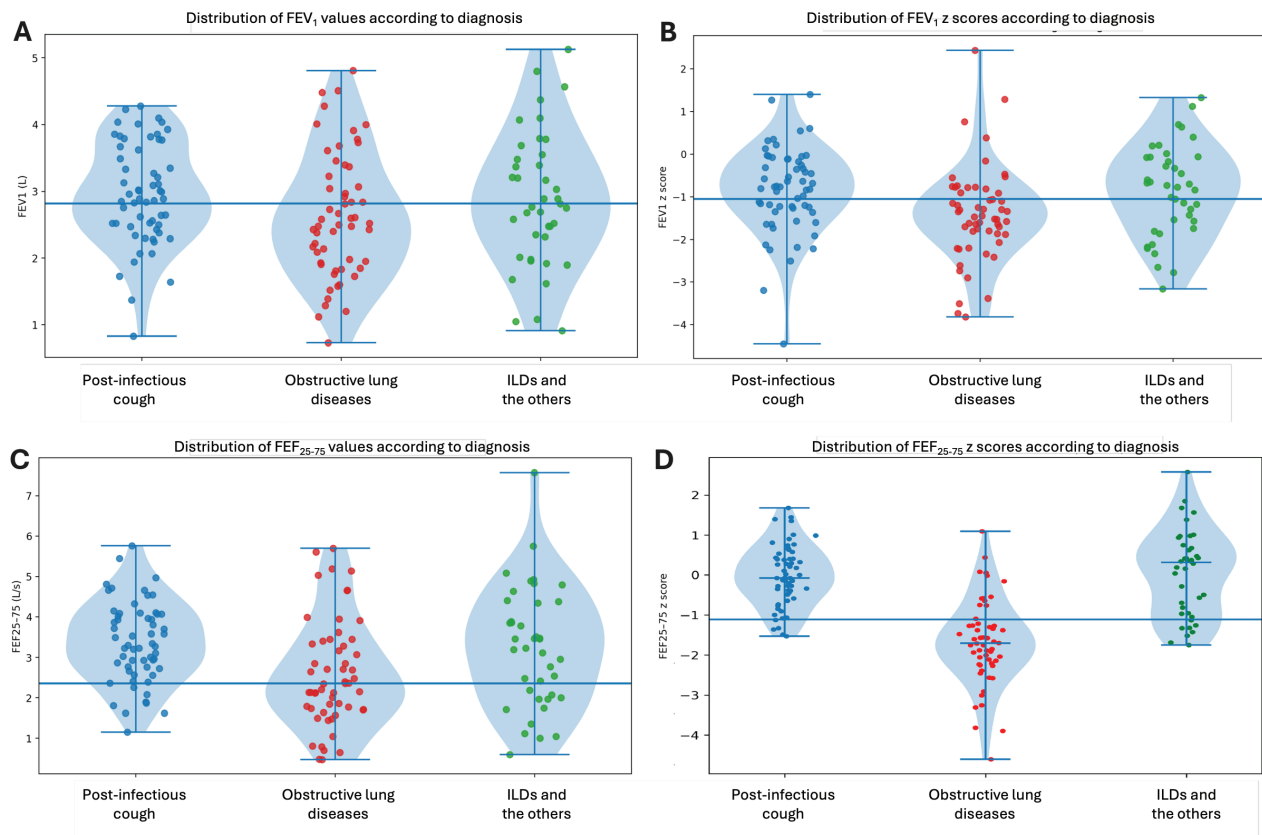


Figure 2. Distribution of spirometric parameters according to diagnosis. Violin plots illustrate the distribution of spirometric parameters across diagnostic groups, with overlaid dots representing individual patient measurements. (A) Distribution of FEV_1 values (L), (B) distribution of FEV_1 z-scores, (C) distribution of FEF_{25-75} values (L/s), and (D) distribution of FEF_{25-75} z-scores according to diagnosis. Horizontal reference lines indicate the mean value for each parameter across the patient population. Diagnostic categories include post-infectious cough, obstructive lung diseases, interstitial lung diseases and the others. Violin width reflects the kernel density of the distribution. Each dot represents an individual patient. Reference lines correspond to the cohort mean values

FEF_{25-75} : forced expiratory flow between 25% and 75% of forced vital capacity, FEV_1 : forced expiratory volume in 1 second, ILDs: interstitial lung diseases, L: liter, L/s: liters per second

context. The discriminatory value of small-airway indices was further supported by adjusted analyses. After controlling for age, sex, height, and BMI, significant group effects persisted for FVC, FVC z-score, FEV_1 z-score, FEV_1 /FVC z-score, and FEF_{25-75} (absolute and z-score), whereas no significant group effects were observed for absolute FEV_1 . The largest effect sizes were observed for the FVC z-score and the FEV_1 /FVC z-score, followed by the FEF_{25-75} z-score; this indicates that the most robust between-group separation was captured by standardized indices rather than raw volumes.

Beyond case-control comparisons, we observed that spirometric profiles differed across major diagnostic categories (post-infectious cough, obstructive lung diseases, and ILDs and the others (including GERD)). Specifically, FEV_1 z-scores, FEF_{25-75} absolute values, and FEF_{25-75} z-scores varied significantly across these categories. Post-hoc testing indicated that obstructive disease categories had lower (more negative) FEV_1 z-scores than the post-infectious cough category, and that FEF_{25-75} z-scores showed the most prominent intergroup differences, with obstructive-pattern diagnoses exhibiting significantly lower values than other diagnostic categories. These findings suggest that small airway indices, particularly FEF_{25-75} z-scores, may provide incremental discriminatory value beyond FEV_1 for

identifying subtle obstructive physiology during the subacute cough stage. These results are consistent with prior evidence indicating that mid-expiratory flow parameters are sensitive markers of early airway dysfunction.^{4,5,8,9} In one study, patients with normal FEV_1 but positive bronchial hyperresponsiveness demonstrated significantly reduced FEF_{25-75} values compared with patients without airway hyperresponsiveness, suggesting that small airway involvement precedes overt airflow limitation.⁸ Similarly, a study reported that FEF_{25-75} was superior to FEV_1 in differentiating CVA from other causes of chronic cough,¹⁰ supporting the concept that small airway dysfunction plays a central role in cough-predominant obstructive phenotypes.⁸⁻¹¹ The recent study by Li et al.⁴, evaluating PFTs in CVA with or without GERD, similarly demonstrated that combined assessment of spirometric indices improves diagnostic sensitivity. Together with our data, these findings suggest that reliance on FEV_1 alone may lead to underdiagnosis of obstructive disease in patients presenting with subacute cough. Our findings extend these observations to the subacute cough phase, indicating that FEF_{25-75} abnormalities are detectable earlier than previously appreciated.

A noteworthy finding of this study is the identification of ILDs among patients presenting with a subacute cough. Although

ILDs are traditionally associated with chronic respiratory symptoms, cough is increasingly recognized as a common and sometimes early manifestation of these disorders. Cough may precede dyspnea in several ILD subtypes and can be a dominant presenting symptom, even in the absence of advanced radiologic disease.¹² Our findings support this observation and suggest that subtle reductions in FEF₂₅₋₇₅ and FVC z-scores during the subacute phase may warrant further evaluation for underlying parenchymal lung disease. Current clinical practice often adopts a conservative approach to subacute cough, deferring extensive evaluation until symptoms persist beyond eight weeks. However, early diagnosis is associated with a better prognosis in ILDs. Our results provide objective evidence that spirometry performed during the subacute phase can uncover both obstructive and restrictive physiological abnormalities, facilitating earlier diagnosis and targeted management. Early identification of asthma may allow timely initiation of inhaled anti-inflammatory therapy, while recognition of a potential ILD can prompt appropriate imaging and specialist referral.

Study Limitations

Several limitations should be acknowledged. The retrospective, single-center design introduces the potential for selection bias, as only patients who underwent spirometry were included in the analysis. In routine clinical practice, spirometry is not systematically performed in all patients presenting with subacute cough and is often reserved for those with persistent symptoms or clinical suspicion of underlying airway disease. Consequently, the study population may represent a subgroup of patients in whom clinicians had already suspected physiological abnormalities, potentially resulting in an overrepresentation of pulmonary function abnormalities. Therefore, the results should be interpreted with caution and may not fully reflect the broader population of patients with subacute cough presenting in general clinical settings. The cross-sectional nature of the analysis precludes inference regarding prognosis, including whether early abnormalities in z-scores or FEF₂₅₋₇₅ predict persistence of cough or progression to chronic airway disease. While FEF₂₅₋₇₅ provided discriminatory information in our cohort, mid-expiratory flows can demonstrate greater variability than primary spirometric indices and should be interpreted in conjunction with the overall clinical context. Additionally, the study did not systematically incorporate tests of airway inflammation or hyperresponsiveness (fractional exhaled nitric oxide, induced sputum eosinophils, bronchial provocation) for all patients. Although ILDs were detected among the identified etiologies, the present dataset does not permit granular inferences about specific ILD subtypes.

CONCLUSION

These findings challenge a purely conservative “wait-and-see” approach for subacute cough. Our data indicate that performing spirometry during the subacute phase can uncover subtle obstructive physiology (captured particularly by FEV₁ z-score and FEF₂₅₋₇₅) and also raise suspicion for restrictive or parenchymal processes when patterns, such as lower FVC z-scores, are present. Consequently, spirometry may serve as an early, accessible tool to guide targeted diagnostic evaluation and earlier disease-specific management for patients who

might otherwise be reassured that they have an uncomplicated post-infectious cough.

Ethics

Ethics Committee Approval: The current study protocol was approved by the Local Ethics Committee of TOBB Economics and Technology University (date: 22.10.2025; number: 34), and the study was performed in accordance with the ethical standards laid down in the Declaration of Helsinki.

Informed Consent: This retrospective study was conducted using previously collected clinical data and pulmonary function test results. All data were anonymized prior to analysis, and no additional interventions were performed. The requirement for informed consent was waived by the Ethics Committee due to the retrospective nature of the study.

Footnotes

Authorship Contributions

Concept: A.Y., Design: A.Y., C.İ.A., Data Collection or Processing: A.Y., Analysis or Interpretation: A.Y., C.İ.A., Literature Search: A.Y., C.İ.A., Writing: A.Y., C.İ.A.

Conflict of Interest: No conflict of interest was declared by the authors.

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Supplementary Tables 1, 2 Link: <https://d2v96fxpocvxx.cloudfront.net/f6118de3-f656-440d-95f2-50c620149951/content-images/2ef38bb2-a0a7-4584-918d-5b6fd5b3e8a2.pdf>

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Original Article



Small Airway Dysfunction in Asthma: Associations with Control and Quality of Life

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ABSTRACT

OBJECTIVE: Small airway dysfunction (SAD) is an important but frequently underrecognized component of asthma. This study aimed to determine the prevalence of SAD in asthma, as assessed by impulse oscillometry (IOS), and to evaluate its association with clinical outcomes.

MATERIAL AND METHODS: This cross-sectional study, with a 12-month prospective follow-up, included adult patients with asthma. SAD was defined by IOS as $R5-R20 \geq 0.07$ kPa·s·L⁻¹. The asthma control test (ACT) and the asthma quality of life questionnaire (AQLQ) were administered. Exacerbations were prospectively recorded during the 12 months after enrollment. Patients were stratified according to the presence of SAD. Clinical and functional parameters were compared between groups.

RESULTS: SAD was identified in 63 of 98 participants (64.3%). SAD prevalence differed significantly across the five Global Initiative for Asthma treatment steps ($P < 0.001$). Patients with SAD had significantly lower ACT scores ($P = 0.021$), poorer quality of life (AQLQ, $P = 0.002$), and more frequent exacerbations ($P < 0.001$) than those without SAD. In multivariable regression analyses, higher $R5-R20$ was independently associated with a lower AQLQ score ($\beta = -0.18$, 95% confidence interval -0.30 to -0.07 ; $P = 0.002$) and higher odds of being in a worse asthma control category (odds ratio 1.33, $P = 0.010$).

CONCLUSION: SAD is common among patients with asthma and is associated with poorer asthma control, lower quality of life, and an increased exacerbation burden. Higher $R5-R20$ remained associated with poorer quality of life after adjustment for spirometry, whereas its association with asthma control was attenuated and became non-significant after adjustment for forced expiratory volume in the first second. These findings support further evaluation of IOS-defined SAD as a potentially clinically relevant trait in asthma.

KEYWORDS: Asthma, small airway dysfunction, impulse oscillometry, asthma control, quality of life

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INTRODUCTION

Asthma is a chronic inflammatory airway disease characterized by variable respiratory symptoms and airflow limitation. Spirometry is recommended as the primary tool for diagnosing and assessing airflow obstruction in routine clinical practice.¹ However, growing evidence indicates that conventional spirometric indices, particularly forced expiratory volume in the first second (FEV₁), may inadequately reflect symptom burden, asthma control, and health-related quality of life.^{2,3} Previous real-world and cohort studies have demonstrated a significant discordance between spirometric measurements and patient-reported outcomes, suggesting that clinically relevant disease may persist despite normal or near-normal spirometric values.²⁻⁴

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Small airways, defined as airways with an internal diameter of ≤ 2 mm, have gained increasing attention in asthma pathophysiology. Although they contribute minimally to total airway resistance under normal conditions, inflammation and structural remodeling of small airways may lead to ventilation heterogeneity, air trapping, and persistent symptoms.^{2,5,6} Histopathological studies have demonstrated inflammatory involvement of the distal airways even in patients with mild or well-controlled asthma, suggesting that small airway dysfunction (SAD) may be present despite apparently preserved lung function.^{7,8}

Spirometry remains the cornerstone of asthma diagnosis and follow-up; however, it has well-recognized limitations in detecting small airway involvement. Parameters such as forced expiratory flow between 25% and 75% of forced vital capacity (FEF_{25-75}) are often used as indirect markers of distal airway function, yet they are highly effort-dependent and show substantial variability. Importantly, spirometric indices may remain within normal ranges in patients with clinically relevant small airway impairment, limiting their ability to accurately reflect disease burden and symptom severity.^{9,10}

Impulse oscillometry (IOS) is a non-invasive, effort-independent technique that assesses respiratory system impedance during tidal breathing. By applying pressure oscillations at different frequencies, IOS allows the separate evaluation of central and peripheral airway mechanics. Parameters such as resistance at 5 Hz (R5), frequency-dependent resistance (R5–R20), reactance at 5 Hz (X5), and reactance area (AX) have been proposed as sensitive indicators of SAD. Several studies have suggested that IOS may detect distal airway abnormalities in asthmatic patients even when spirometric measurements are normal.^{11,12}

Although the clinical relevance of SAD in asthma has been increasingly recognized, data regarding its prevalence and association with asthma control and quality of life remain limited and inconsistent, particularly in real-world clinical settings. Moreover, studies integrating IOS-derived small

airway indices with validated patient-reported outcomes are scarce.^{2,13,14}

Therefore, the primary aim of this study was to determine the prevalence of SAD, assessed by IOS, in adult patients with asthma. The secondary aim was to investigate the relationship among IOS-defined SAD, asthma control, measured by the asthma control test (ACT), and health-related quality of life, assessed using the asthma quality of life questionnaire (AQLQ).

MATERIAL AND METHODS

Study Design and Setting

This study was designed as a cross-sectional investigation with a 12-month prospective follow-up. Patients with asthma were recruited from the Chest Diseases Clinic of Mersin University Hospital, Türkiye, between June 1, 2019, and November 1, 2019. All participants were intended to undergo a 12-month follow-up. Complete questionnaire and follow-up data were available for 74 participants, who constituted the longitudinal analysis cohort. Therefore, the overall follow-up period was completed on November 1, 2020. A convenience sampling method was employed. Individuals who met the inclusion criteria, did not meet any exclusion criteria, and provided written informed consent were enrolled. The study protocol was approved by the Mersin University Clinical Research Ethics Committee (decision no: 2019/199, dated: 08.05.2019) and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The study was registered on ClinicalTrials.gov (NCT04375995).

Study Groups

A total of 105 participants with asthma were included. Patients were excluded if they had experienced an exacerbation within the past 4 weeks, had a coexisting pulmonary condition, had a history of lung surgery, had severe comorbidities (e.g., unstable cardiovascular disease, malignancy), or were unable to complete the required functional assessments.

Participants with a diagnosis of asthma for at least one year were included based on Global Initiative for Asthma (GINA) 2019 criteria, which require at least one of the following: a positive reversibility test (defined as an increase in FEV_1 $>12\%$ and >200 mL within 10–15 minutes after 400 μ g salbutamol via a metered-dose inhaler), a positive methacholine bronchial provocation test, peak expiratory flow variability $>10\%$, or documented reversibility after four weeks of maintenance therapy.

Procedures

Demographics and clinical characteristics were recorded. Spirometry and IOS were performed in all 105 participants. However, technically acceptable R5–R20 measurements suitable for SAD classification were available for 98 participants. Reliable R5–R20 values could not be obtained for seven participants because the IOS measurements did not meet technical acceptability criteria. In patients who agreed to complete the questionnaires and who provided complete responses ($n = 74$), asthma control and health-related quality of life were assessed using the ACT and the AQLQ. This subgroup was followed prospectively for 12 months to record exacerbation outcomes,

Main Points

- Small airway dysfunction (SAD) assessed by impulse oscillometry (IOS) is highly prevalent (64.3%) in adult patients with asthma and is also observed in patients with preserved spirometry.
- Higher R5–R20 was independently associated with reduced quality of life, with this association persisting after additional spirometric adjustment. Its association with asthma control was attenuated after adjustment for spirometric indices.
- Significant discordance exists between preserved spirometric indices and IOS-defined impairment, indicating that IOS-defined impairment may not be fully reflected in conventional spirometric indices.
- IOS may provide complementary information on small airway involvement beyond conventional spirometry, while the therapeutic implications of IOS-defined SAD require further investigation in prospective interventional studies.

including attacks requiring systemic corticosteroids, emergency department visits, unscheduled outpatient visits, and asthma-related hospitalizations. Patients who declined to complete the questionnaire or did not complete follow-up assessments were not included in the longitudinal analyses.

Pulmonary Function Tests

All participants underwent spirometry and IOS. Spirometry was performed using the MasterScreen™ PFT (CareFusion, Hoechberg, Germany) in accordance with American Thoracic Society (ATS)/European Respiratory Society (ERS) 2019 standards.¹⁵ A post-bronchodilator test was conducted 15 minutes after administration of 400 µg salbutamol via a metered-dose inhaler. For comparative analyses, spirometric small-airway impairment was defined as $FEF_{25-75}\%$ <60%.¹⁶

IOS was performed using the Jaeger Vyntus IOS (CareFusion, Germany), with at least five valid trials per participant. Recorded parameters included R5, R20, X5, Fres, AX, and R5–R20.

SAD was primarily defined using an R5–R20 threshold of ≥ 0.07 kPa·s·L⁻¹, because this parameter reflects frequency-dependent resistance and is widely used as a clinically applicable IOS marker of peripheral airway dysfunction.^{4,17,18} Other IOS indices, including X5 and AX, were also evaluated as complementary parameters in descriptive and correlation analyses.

Fractional Exhaled Nitric Oxide (FeNO)

FeNO levels were measured in patients with asthma using the Bedfont NObreath® device (England) in accordance with ATS/ERS 2011 recommendations.¹⁹

Assessment of Asthma Control, Quality of Life, and Exacerbations

Asthma Control Test

Asthma symptom control was assessed using the validated Turkish version of the ACT.²⁰ The questionnaire was administered to the 74 participants who had complete responses. The ACT consists of five items, each scored on a 5-point Likert scale, yielding a total score ranging from 5 to 25. Based on the total score, asthma control was categorized as well controlled (20–25), partially controlled (16–19), or uncontrolled (5–15).¹

Asthma Quality of Life Questionnaire

Health-related quality of life was evaluated using the validated Turkish version of the AQLQ.²¹ The questionnaire includes 32 items across four domains: symptoms, activity limitation, emotional function, and environmental stimuli. Each item is scored on a 7-point scale ranging from 1 (severe impairment) to 7 (no impairment). In accordance with the conventional AQLQ scoring method, domain scores and the overall AQLQ score were calculated as means of the relevant item scores, yielding scores ranging from 1 to 7, with higher scores indicating better asthma-related quality of life.^{21,22}

Assessment of Asthma Exacerbations

Asthma exacerbations were recorded prospectively over a 12-month follow-up period. Exacerbations were defined as events requiring systemic corticosteroid therapy and/or resulting in emergency department visits, unscheduled outpatient visits, or hospitalizations related to asthma.

Statistical Analysis

The sample size was calculated based on an expected SAD prevalence of 70%, a 95% confidence level, and an absolute precision of approximately 10.5%, resulting in a minimum required sample size of 73 patients.² Continuous variables were expressed as mean $\pm$ standard deviation or median (interquartile range), while categorical variables were presented as counts and percentages. Between-group comparisons were performed using the independent samples t-test or Mann-Whitney U test for continuous variables and the chi-square test or Fisher's exact test for categorical variables.

For comparisons involving more than two groups, one-way analysis of variance was used for normally distributed continuous variables, whereas the Kruskal-Wallis test was used for non-normally distributed variables. Associations between continuous variables were assessed using Spearman's rank correlation coefficient. To determine independent associations with clinical outcomes, multivariable regression models were constructed. Multiple linear regression, with HC3 heteroskedasticity-consistent robust standard errors, was used for the AQLQ total score, and ordinal logistic regression was used for the ACT control categories. Models were adjusted for age, sex, body mass index (BMI), and smoking exposure (pack-years). Further sensitivity analyses were conducted by separately adding spirometric indices ($FEV_1\%$ and $FEF_{25-75}\%$) to these models.

To assess potential selection bias due to missing questionnaire data, baseline characteristics of participants included in multivariable analyses ($n = 74$) were compared with those of participants not included ($n = 31$) (Supplementary Table S1). All analyses were performed using IBM SPSS Statistics, version 26.0 (IBM Corp., Armonk, NY, USA); a P value < 0.05 was considered statistically significant.

RESULTS

Study Population

The cohort consisted of 105 patients with asthma, of whom 78 (74.3%) were female. The mean age was 49.04 ± 13.00 years. Smoking status was available for 104 participants, of whom 73 (70.2%) were never-smokers, 17 (16.3%) were active smokers, and 14 (13.5%) were ex-smokers. The mean BMI was 27.76 ± 5.02 kg/m². Baseline demographic and clinical characteristics are summarized in Table 1.

Prevalence of Small Airway Dysfunction

SAD was identified by IOS in 63 (64.3%) patients with asthma. SAD status differed significantly across the five individual GINA

treatment steps ($P < 0.001$; Table 1). In a separate analysis that grouped patients into GINA steps 1–3 and 4–5, SAD was more frequent in the higher treatment-step group ($P < 0.001$).

Asthma Control and Small Airway Dysfunction

Mean ACT scores were significantly lower among patients with SAD than among those without dysfunction ($P = 0.021$). When patients were categorized according to ACT-defined asthma control levels (uncontrolled, partially controlled, and well-controlled), symptom control status was significantly associated with the presence of SAD ($P = 0.041$). Notably, SAD was present in 25 (92%) of the 27 patients with uncontrolled asthma. As shown in Table 2, asthma control assessed by the ACT was significantly associated with both oscillometry- and spirometry-derived indices of small airway function. Among IOS parameters, R5–R20 showed a moderate negative correlation

with ACT scores ($r = -0.366$), indicating poorer asthma control with increasing peripheral airway resistance. In contrast, the spirometric small airway index FEF_{25-75} demonstrated a weaker positive correlation with ACT scores ($r = 0.291$). These findings suggest that both methods reflect small airway involvement, but oscillometry-derived parameters are more strongly associated with symptom control.

Quality of Life Assessment

Health-related quality of life, assessed using the AQLQ, was significantly impaired in patients with SAD. Patients with SAD had lower mean AQLQ total scores than those without SAD (4.34 ± 1.27 vs. 5.43 ± 1.14 , $P = 0.002$) (Figure 1). As detailed in Table 3, patients with SAD also demonstrated significantly lower scores across multiple AQLQ subdomains, including symptoms, activity limitation, and emotional function,

Table 1. Baseline demographic, clinical, and pulmonary function characteristics of asthma patients

Demographic data	SAD present (R5–R20 ≥ 0.07) n = 63	SAD absent (R5–R20 < 0.07) n = 35	P value
Age, years, mean $\pm$ SD	53.90 $\pm$ 10.05	41.74 $\pm$ 13.60	<0.001
Sex, n (%), female	51 (81%)	21 (60%)	0.044
BMI, kg/m ² , mean $\pm$ SD	28.90 $\pm$ 5.11	26.02 $\pm$ 4.41	0.005
Smoking exposure, pack-years, mean $\pm$ SD	20.40 $\pm$ 10.89 (n = 12)	13.44 $\pm$ 8.40 (n = 10)	0.194
Cardiovascular comorbidities, n (%)	20/62 (32.3%)	8/35 (22.9%)	0.454
GINA treatment step, n (%)			
1	1/7 (14.3%)	6/7 (85.7%)	<0.001
2	4/14 (28.6%)	10/14 (71.4%)	
3	12/24 (50.0%)	12/24 (50.0%)	
4	20/26 (76.9%)	6/26 (23.1%)	
5	26/27 (96.3%)	1/27 (3.7%)	
FeNO, ppb, median (IQR)	18.00 (9.50–31.50) (n = 43)	19.50 (11.25–40.75) (n = 26)	0.264
Blood eosinophil count, $10^3/\mu\text{L}$ median (IQR)	0.37 (0.15–0.58)	0.30 (0.15–0.59)	0.648
Spirometry			
FVC % predicted	92.63 $\pm$ 19.16 (n = 62)	102.50 $\pm$ 17.24 (n = 31)	0.008
FEV ₁ % predicted	77.40 $\pm$ 21.09 (n = 62)	93.74 $\pm$ 16.36 (n = 31)	<0.001
FEV ₁ /FVC (%), median (IQR)	72.57 (64.00–77.91) (n = 62)	77.52 (72.59–79.52) (n = 31)	0.004
FEF ₂₅₋₇₅ % predicted, median (IQR)	44.00 (22.25–63.75) (n = 62)	66.00 (47.50–76.00) (n = 30)	0.002
Impulse oscillometry			
R5, mean $\pm$ SD	0.81 $\pm$ 0.33 (n = 63)	0.43 $\pm$ 0.12 (n = 32)	<0.001
R20, mean $\pm$ SD	0.46 $\pm$ 0.11 (n = 63)	0.38 $\pm$ 0.12 (n = 32)	0.002
AX, mean $\pm$ SD	4.98 $\pm$ 4.33 (n = 56)	1.16 $\pm$ 1.69 (n = 32)	<0.001
R5–R20, mean $\pm$ SD	0.34 $\pm$ 0.25 (n = 63)	0.05 $\pm$ 0.02 (n = 35)	<0.001
Fres, mean $\pm$ SD	30.92 $\pm$ 11.88 (n = 58)	19.63 $\pm$ 7.86 (n = 32)	<0.001
X5, mean $\pm$ SD	–0.46 $\pm$ 0.51 (n = 60)	–0.12 $\pm$ 0.15 (n = 32)	<0.001

Continuous variables are presented as mean $\pm$ standard deviation or median (interquartile range), according to data distribution. Categorical variables are presented as n (%). Numerical values are reported using decimal points. For variables with missing data, the number of available observations (n) is indicated. SAD classification based on R5–R20 ≥ 0.07 kPa-s-L⁻¹ was available for 98 of 105 participants (SAD present, n = 63; SAD absent, n = 35). Variable-specific denominators are reported where data were unavailable. Percentages were calculated using the number of participants with available data for each variable. Between-group P values are based on participants with available SAD classification and available data for the respective variable. Normally distributed continuous variables were compared using the independent-samples t -test, whereas non-normally distributed variables, including FEV₁/FVC and FEF₂₅₋₇₅, were compared using the Mann-Whitney U test. IOS parameters are reported according to device output units: R5, R20, R5–R20, and X5 in kPa-s-L⁻¹; Fres in Hz; and AX in kPa/L.

SAD: small airway dysfunction, BMI: body mass index, FeNO: fractional exhaled nitric oxide, FVC: forced vital capacity, FEV₁: forced expiratory volume in the first second, FEF₂₅₋₇₅: forced expiratory flow between 25% and 75%, AX: reactance area, R5–R20: difference between resistances at 5 and 20 Hz, Fres: resonant frequency in Hz, X5: reactance at 5 Hz, SD: standard deviation, IQR: interquartile range, GINA: Global Initiative for Asthma, IOS: impulse oscillometry

indicating an association between SAD and poorer patient-reported quality of life.

Exacerbation and Small Airway Dysfunction

During the 12-month prospective follow-up, exacerbations requiring systemic corticosteroids, emergency department visits, unscheduled outpatient visits, and asthma-related hospitalizations were recorded. Patients with IOS-defined SAD experienced more emergency department visits and a greater total exacerbation burden over 12 months than those without dysfunction ($P < 0.001$) (Table 3).

Inflammatory Biomarkers

FeNO levels and blood eosinophil counts were not significantly associated with IOS-defined SAD.

Independent Associations of SAD with Clinical Outcomes

Multivariable analyses were conducted to determine whether SAD was independently associated with asthma outcomes. R5–R20 was significantly associated with patient-reported outcomes after multivariable adjustment (Table 4). When modeled as a continuous variable, elevated R5–R20 values were independently associated with worse health-related quality of life. For each 0.1 kPa·s·L⁻¹ increase in R5–R20, the mean AQLQ score decreased by 0.18 points after adjustment for age, sex, BMI, and smoking history [$\beta = -0.18$; 95% confidence interval

(CI) -0.30 to -0.07 ; $P = 0.002$]. This association persisted in sensitivity analyses that additionally controlled for spirometric indices (FEV₁% and FEF₂₅₋₇₅%), whereas spirometric parameters themselves did not show statistically significant independent associations with AQLQ.

For asthma control, higher R5–R20 values were associated with poorer ACT-defined control categories in the adjusted ordinal logistic regression model (Table 4). Each 0.1 kPa·s·L⁻¹ increase in R5–R20 increased the odds of being in a worse control category by 33% [odds ratio (OR) 1.33; 95% CI 1.07 to 1.66; $P = 0.010$]. This association remained directionally consistent in models additionally adjusted for spirometric parameters, and reached borderline significance when FEF₂₅₋₇₅% was included (OR 1.26; 95% CI 1.00 to 1.58; $P = 0.049$), whereas it was attenuated after adjustment for FEV₁% predicted (OR 1.25; 95% CI 0.99 to 1.58; $P = 0.057$).

DISCUSSION

In the present study, SAD assessed by IOS was highly prevalent among adult patients with asthma and was significantly associated with poorer asthma control and reduced health-related quality of life. The association between R5–R20 and quality of life remained significant after additional adjustment for conventional spirometric indices, whereas the association with asthma control was attenuated after spirometric adjustment. These findings suggest that assessment of distal airway function

Table 2. Correlation between asthma control test scores and spirometric and impulse oscillometric parameters					
Impulse oscillometric parameters		Asthma control test	Spirometric parameters		Asthma control test
R5	r	−0.373	FEV ₁	r	0.178
	P	0.001		P	0.129
	n	74		n	74
R20	r	−0.237	FVC	r	0.135
	P	0.042		P	0.251
	n	74		n	74
R5–R20	r	−0.366	FEV ₁ /FVC	r	0.239
	P	0.001		P	0.040
	n	74		n	74
X5	r	0.236	FEF ₂₅₋₇₅ %	r	0.291
	P	0.043		P	0.012
	n	74		n	74
Fres	r	−0.138	FEF ₅₀ %	r	0.286
	P	0.249		P	0.014
	n	72		n	74
AX	r	−0.200			
	P	0.095			
	n	71			
Correlation analyses were performed using available paired data. ACT data were available for 74 patients; Fres values were missing in 2 patients and AX values in 3 patients, resulting in n = 72 for Fres and n = 71 for AX. IOS parameters are reported according to device output units: R5, R20, R5–R20, and X5 in kPa·s·L ^{−1} ; Fres in Hz; and AX in kPa/L					
FVC: forced vital capacity, FEV ₁ : forced expiratory volume in the first second, FEF ₂₅₋₇₅ : forced expiratory flow between 25% and 75%, AX: reactance area, R5–R20: difference between resistance at 5 Hz and 20 Hz, Fres: resonant frequency in Hz, X5: reactance at 5 Hz, ACT: asthma control test, IOS: impulse oscillometry, FEF50: forced expiratory flow at 50% of forced vital capacity					

may provide complementary clinical information not fully captured by conventional spirometry.

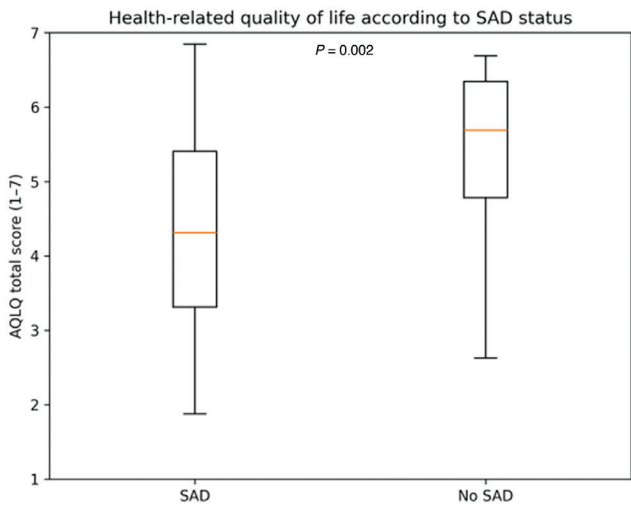


Figure 1. Health-related quality of life according to small airway dysfunction status. Boxplot showing total asthma quality of life questionnaire (AQLQ) scores in patients with and without small airway dysfunction defined by impulse oscillometry ($R5-R20 \geq 0.07$ kPa·s·L⁻¹). Patients with small airway dysfunction had significantly lower AQLQ total scores compared with those without dysfunction ($P = 0.002$)

SAD: small airway dysfunction

The high prevalence of SAD (64.3%) observed in our cohort is consistent with recent large-scale and real-world studies demonstrating that small airway abnormalities are pervasive across the asthma severity spectrum. Notably, the ATLANTIS study established that SAD represents a distinct and measurable trait, frequently present even in patients with preserved FEV₁ and minimal airflow limitation on spirometry.² This aligns with histopathological and physiological evidence suggesting that inflammation and remodeling of the distal airways contribute to ventilation heterogeneity and air trapping, often occurring independently of large airway obstruction.^{5,6}

Our results show that SAD is significantly associated with clinical status, with patients exhibiting an increased likelihood of poor asthma control. This finding aligns with growing evidence that oscillometry-derived parameters correlate more closely with symptom burden than conventional spirometry.^{9,23} Crucially, we observed that FEV₁ was preserved in many patients despite significant distal airway impairment, whereas FEF₂₅₋₇₅ showed substantial overlap between groups. These discrepancies highlight the “silent zone” in the lungs, where inflammation may persist undetected by routine flow-volume loops. The observation that elevated R5–R20 values were associated with worse asthma control in the primary adjusted model (although this association was attenuated after additional adjustment for spirometric indices) and with greater exacerbation burden suggests that SAD may reflect greater disease burden. Although SAD has been proposed as a potential treatable trait, our observational findings do not establish whether specifically targeting the distal airways improves clinical outcomes, and this

	According to IOS-defined small airway dysfunction status		P value
	SAD n = 57	No SAD n = 17	
Number of hospitalizations in 1 year* Median [IQR]	0 [0–0]	0 [0–0]	0.079
Number of emergency department visits in 1 year* Median [IQR]	1 [0–3]	0 [0–0]	<0.001
Total number of exacerbations in 1 year* Median [IQR]	3 [2–5]	2 [0–2]	<0.001
Asthma control test score**, mean ± SD	16.79±5.36	20.12±4.84	0.021
AQLQ symptoms**, mean ± SD	4.64±1.37	5.51±1.18	0.019
AQLQ activity limitation**, mean ± SD	4.44±1.29	5.51±1.21	0.006
AQLQ emotional function**, mean ± SD	3.97±1.68	5.82±1.40	<0.001
AQLQ environmental stimuli**, mean ± SD	3.58±1.70	4.44±1.80	0.069
AQLQ total score**, mean ± SD	4.34±1.27	5.43±1.14	0.002

Analyses in this table were restricted to patients with complete ACT, AQLQ, and 12-month follow-up data (n = 74). SAD was defined as R5–R20 ≥ 0.07 kPa·s·L⁻¹

*Mann-Whitney U test, **Independent-samples t-test

IOS: impulse oscillometry, SAD: small airway dysfunction, ACT: asthma control test, AQLQ: asthma quality of life questionnaire, IQR: interquartile range, SD: standard deviation

Table 4. Independent association of IOS-derived small airway dysfunction (R5–R20) with asthma control and health-related quality of life

Model	R5–R20 effect	Added spirometry term
Panel A. outcome: AQLQ total (OLS)		
Primary	−0.18 (−0.30 to −0.07); <i>P</i> = 0.002	−
+ FEV ₁ % predicted	−0.18 (−0.31 to −0.06); <i>P</i> = 0.004	−0.000 (−0.017 to 0.017); <i>P</i> = 0.987
+ FEF _{25–75} % predicted	−0.16 (−0.29 to −0.04); <i>P</i> = 0.010	0.006 (−0.012 to 0.024); <i>P</i> = 0.491
Panel B. outcome: ACT control category (ordinal logit)		
Primary	1.33 (1.07 to 1.66); <i>P</i> = 0.010	−
+ FEV ₁ % predicted	1.25 (0.99 to 1.58); <i>P</i> = 0.057	0.98 (0.96 to 1.01); <i>P</i> = 0.141
+ FEF _{25–75} % predicted	1.26 (1.00 to 1.58); <i>P</i> = 0.049	0.98 (0.95 to 1.00); <i>P</i> = 0.096

R5–R20 was modeled as a continuous predictor, scaled per 0.1 kPa·s·L^{−1} increase. Models adjusted for age, sex, BMI, and smoking exposure (pack-years). Spirometric indices were added separately (sensitivity analyses). Panel A reports β coefficients with 95% confidence intervals and *P* values (HC3 robust standard errors). The β coefficient represents the change in the mean AQLQ total score associated with a 0.1 kPa·s·L^{−1} increase in R5–R20. Panel B reports odds ratios (ORs) for being in a worse ACT control category with 95% confidence intervals and *P* values (ordinal logistic regression, logit link). Higher OR indicates poorer control. Note: FEV₁% and FEF_{25–75}% were entered in separate sensitivity models to avoid collinearity when both spirometric indices are included simultaneously. The AQLQ total score was calculated as the mean of the 32 item scores and ranges from 1 to 7, with higher scores indicating better asthma-related quality of life. Sample size: *n* = 74 for Panel A; *n* = 74 for Panel B

ACT: asthma control test, AQLQ: asthma quality of life questionnaire, BMI: body mass index, IOS: impulse oscillometry, OLS: ordinary least squares, FEV₁: forced expiratory volume in the first second, FEF_{25–75}: forced expiratory flow between 25% and 75%, HC3: heteroskedasticity-consistent standard error estimator type 3

question requires confirmation in prospective interventional studies.

Health-related quality of life was also significantly impaired in patients with SAD. Previous studies have reported weak or inconsistent associations between spirometric parameters and quality of life in asthma.²⁴ In contrast, recent investigations using IOS have demonstrated meaningful relationships between distal airway mechanics and patient-reported outcomes.^{12,14} Our findings suggest that SAD may contribute to limitations in daily activities, affect symptom perception, and impair emotional well-being—domains that are not adequately captured by conventional lung function tests and may therefore explain the observed dissociation between spirometric measurements and quality of life. Higher R5–R20 values were independently associated with lower health-related quality of life. Specifically, each 0.1 kPa·s·L^{−1} increase in R5–R20 was associated with an estimated 0.18-point decrease in the conventional 1–7 AQLQ score. Although this association was statistically significant, its magnitude was below the established minimal clinically important difference of 0.5 points and should therefore be interpreted cautiously in terms of clinical relevance.²⁵ The association remained significant after additional adjustment for FEV₁% predicted and FEF_{25–75}% predicted, suggesting that IOS-derived SAD may capture aspects of asthma-related burden not fully reflected by conventional spirometric indices.

In this study, we defined SAD based on a fixed cut-off value for R5–R20 (≥ 0.07 kPa·s·L^{−1}), rather than relying on percent predicted values.^{2,4,18} This fixed R5–R20 threshold was selected based on its use in the ATLANTIS study as an IOS measure of SAD in asthma.² While percent-predicted values are theoretically ideal, they are often limited by the variability of available reference equations across different populations. In contrast, a fixed cut-off offers a pragmatic advantage in routine clinical settings: it provides a standardized, easily applicable metric that does not require complex software calculations that depend on specific reference sets. The observed association between this threshold and patient-reported outcomes supports its potential clinical utility, although further validation in larger cohorts is warranted.

In our cohort, patients with IOS-defined SAD were older, were more often female, and had a higher BMI. Because these findings were derived from unadjusted group comparisons, they should be interpreted cautiously. Nevertheless, they may indicate that demographic and anthropometric factors influence peripheral airway mechanics and the clinical expression of SAD. These observations are consistent with the concept that SAD represents a heterogeneous and clinically relevant trait in asthma.^{2,17} Further studies are needed to determine whether these factors independently contribute to IOS-defined SAD.

Study Limitations

Several limitations of this study should be acknowledged. Although exacerbation outcomes were assessed prospectively during a 12-month follow-up period, the baseline analysis was cross-sectional; therefore, causal inference between SAD and clinical outcomes remains limited. In addition, ACT and AQLQ data were available only for a subset of the study cohort. SAD was more frequent among participants included in the questionnaire-based analyses than among those not included. Furthermore, R5–R20 classification was unavailable in seven participants, all of whom belonged to the latter group. These differences indicate some degree of selection affecting the availability of complete data and may have influenced the observed prevalence of SAD. Accordingly, the prevalence estimate should be interpreted in the context of the available R5–R20 data and should be confirmed in larger cohorts with more complete IOS measurements. This selection may also have influenced the observed associations between SAD and patient-reported outcomes, and may limit the generalizability of these analyses. Detailed information on maintenance treatment for asthma and treatment adherence was not systematically available; therefore, treatment heterogeneity and non-adherence may have contributed to residual confounding. Because poor adherence to maintenance therapy may influence asthma control, exacerbation risk, quality of

life, and IOS-derived airway mechanics, future studies should incorporate standardized adherence assessment to better clarify the independent relationship between IOS-defined SAD and clinical outcomes. Although R5–R20 was selected as the primary IOS index for defining SAD, other IOS parameters, including X5 and AX, were evaluated and may provide complementary information on peripheral airway reactance and elastic properties. Future studies using composite IOS-based definitions may further improve the characterization of SAD in asthma. Nevertheless, the use of validated patient-reported outcome measures and standardized IOS assessment based on contemporary guidelines strengthens the validity of our findings.

CONCLUSION

This study demonstrates that SAD is a frequent feature of asthma. Higher R5–R20 was independently associated with poorer quality of life; this association remained significant after additional adjustment for conventional spirometric indices. Higher R5–R20 was also associated with poorer asthma control in the primary adjusted model, although this association was attenuated after additional spirometric adjustment. Additionally, IOS-defined SAD was associated with a greater exacerbation burden during follow-up. These findings suggest that IOS may provide complementary information on small airway involvement.

Ethics

Ethics Committee Approval: The study protocol was approved by the Mersin University Clinical Research Ethics Committee (decision no: 2019/199, dated: 08.05.2019) and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Informed Consent: Individuals who met the inclusion criteria, did not meet any exclusion criteria, and provided written informed consent were enrolled.

Footnotes

Authorship Contributions

Surgical and Medical Practices: D.P.Y., S.N., E.S.Ö., C.Ö., Concept: D.P.Y., S.N., E.S.Ö., C.Ö., Design: D.P.Y., S.N., B.T., E.S.Ö., C.Ö., Data Collection or Processing: D.P.Y., S.N., B.T., Analysis or Interpretation: D.P.Y., S.N., B.T., Literature Search: D.P.Y., S.N., B.T., Writing: D.P.Y., S.N., B.T., E.S.Ö., C.Ö.

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Supplementary Table: <https://d2v96fxpocvxx.cloudfront.net/a2440bda-5c5c-4e7b-8a75-abf1691c9260/content-images/1d7c7d34-d0aa-451b-b23d-9b08f28f63e2.pdf>

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Original Article



Pretransplant Small-airway Dysfunction is Associated with Posttransplant Complications in Adult HSCT Recipients

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ABSTRACT

OBJECTIVE: Pulmonary function testing is routinely performed before hematopoietic stem cell transplantation (HSCT), but conventional parameters may not capture subtle airway abnormalities. This study evaluated the association of pretransplant forced expiratory flow between 25% and 75% of forced vital capacity (FEF₂₅₋₇₅) with post-HSCT complications in adults.

MATERIAL AND METHODS: This retrospective single-center cohort included 83 adults who underwent HSCT between 2016 and 2023. Reduced FEF₂₅₋₇₅ was defined as <75% predicted. The primary outcome was a composite of post-HSCT complications. Multivariable logistic regression models were adjusted for age, sex, ever-smoking status, HSCT type, and reduced forced expiratory volume in 1 second (FEV₁). Discrimination was assessed using receiver operating characteristic analysis.

RESULTS: Overall, 32 patients (38.6%) experienced post-HSCT complications. Complications occurred in 50.0% of patients with reduced FEF₂₅₋₇₅ versus 28.9% of those with FEF₂₅₋₇₅ ≥75% predicted ($P = 0.049$). Reduced FEF₂₅₋₇₅ was independently associated with higher odds of complications [odds ratio (OR): 3.58, 95% confidence interval (CI): 1.28–10.04; $P = 0.015$]. Reduced FEV₁ showed an inverse association (OR: 0.12, 95% CI: 0.02–0.71; $P = 0.019$). FEF₂₅₋₇₅ showed poor standalone discrimination (area under the curve: 0.578, 95% CI: 0.450–0.705).

CONCLUSION: Reduced pretransplant FEF₂₅₋₇₅ was independently associated with post-HSCT complications, but showed poor standalone discrimination. These hypothesis-generating findings suggest that FEF₂₅₋₇₅ may provide information complementary to FEV₁, but they do not support its use as an independent predictive test. Larger prospective studies are required.

KEYWORDS: Hematopoietic stem cell transplantation, small-airway disease, FEF₂₅₋₇₅, pulmonary complications, FEV₁, DLCO

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INTRODUCTION

Pulmonary complications remain a leading source of morbidity after hematopoietic stem cell transplantation (HSCT). Conventional pretransplant assessment prioritizes diffusing capacity of the lung for carbon monoxide (DLCO) and forced expiratory volume in 1 second (FEV₁), yet these parameters may not capture subtle airway abnormalities that precede overt ventilatory limitation.

Small-airway disease (SAD) is now recognized as a pivotal “silent zone” in early airflow impairment, often undetectable by standard spirometric indices.^{1,2} Mid-expiratory flow parameters, such as forced expiratory flow (FEF₂₅₋₇₅), are used as functional markers of peripheral airway impairment. Although variability exists, reductions in FEF₂₅₋₇₅ have been shown to precede measurable reductions in FEV₁ and correlate with markers of airway inflammation and early functional impairment across various pulmonary diseases.^{3,4} Although FEF₂₅₋₇₅ has been associated with pulmonary complications in pediatric pretransplant cohorts and with bronchiolitis obliterans syndrome (BOS) in early posttransplant adult assessments, evidence regarding its association with subsequent post-HSCT morbidity in adults remains limited.⁵⁻⁹

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Therefore, this study aimed to evaluate the association between pretransplant FEF_{25-75} and post-HSCT complications in an adult cohort and to compare its relationship with outcomes to that of conventional pulmonary function parameters. We hypothesized that reduced FEF_{25-75} would be associated with posttransplant complications and might identify functional abnormalities not fully captured by conventional FEV_1 thresholds.

MATERIAL AND METHODS

Study Design and Population

This retrospective cohort study included adult patients who underwent HSCT at the Marmara University Bone Marrow Transplantation Unit (İstanbul, Türkiye) between January 2016 and December 2023.

A total of 120 patients were screened; 83 patients with complete pretransplant pulmonary function test (PFT) data and follow-up records were included in the final analysis.

Demographic data, underlying hematologic diagnoses, transplant type (autologous or allogeneic), and comorbidity profiles were retrieved from institutional electronic medical records. Baseline comorbidity burden was evaluated using a validated transplantation-specific comorbidity scoring system.¹⁰ Follow-up duration was calculated from the date of HSCT to death or the administrative censoring date (January 1, 2024), whichever occurred first.

Smoking history (ever-smoking status and cumulative pack-years) and physician-diagnosed asthma or chronic obstructive pulmonary disease were retrieved from the electronic medical records when available, and were included in the baseline characteristics. Because information on obstructive airway disease was unavailable for a subset of patients, the number of available observations was reported.

Ethics Approval and Informed Consent

This study was conducted in accordance with the Declaration of Helsinki and approved by the Marmara University Faculty

of Medicine Clinical Research Ethics Committee (decision no.: 09.2023.669, date: 05/05/2023).

Because of the retrospective study design, the Ethics Committee waived the requirement for informed consent. All patient data were anonymized prior to analysis.

Pulmonary Function Testing

All pretransplant PFTs were performed at the Marmara University Respiratory Physiology Laboratory in accordance with the American Thoracic Society and the European Respiratory Society technical standards. DLCO was measured using the single-breath technique.^{11,12}

PFT included FEV_1 , forced vital capacity (FVC), the FEV_1/FVC ratio, and FEF_{25-75} (forced expiratory flow between 25% and 75% of FVC). Gas transfer function was assessed using DLCO and DLCO per unit of alveolar volume. Pulmonary function parameters were expressed as percentages of predicted values, where applicable, using the reference equations employed by the laboratory.¹³

Reduced FEF_{25-75} was operationally defined as <75% of predicted. Although no universally accepted diagnostic threshold exists for FEF_{25-75} , this cut-off was selected a priori based on previous evidence identifying values of approximately 75% predicted as thresholds associated with airway hyperresponsiveness in individuals with otherwise preserved conventional spirometric indices.¹⁴ Accordingly, FEF_{25-75} <75% predicted was used as an operational research definition of reduced mid-expiratory flow rather than an established clinical lower limit of normal.

For categorical analyses, reduced FEV_1 and FVC were defined as <80% predicted, airflow obstruction as FEV_1/FVC <0.70, and reduced DLCO as <80% predicted.¹⁵ These thresholds were used for analytical categorization and were not intended to substitute for comprehensive physiologic interpretation.

Definition of Outcomes

Clinical outcomes were extracted from standardized transplant follow-up records. Early complications were defined as events occurring within 100 days post-HSCT, whereas late complications were defined as those occurring after day 100, until the end of follow-up. All-cause mortality was recorded as a major endpoint. Complications included infectious, pulmonary, hepatic, gastrointestinal, and graft-related events. Diagnostic consistency was ensured through review by hematologists and pulmonologists.

Statistical Analysis

All statistical analyses were performed using Jamovi software.¹⁶ The distribution of continuous variables was assessed using the Shapiro-Wilk test. Continuous variables were summarized as mean $\pm$ standard deviation or median [interquartile range (IQR)], as appropriate, and categorical variables as frequencies and percentages. Between-group comparisons were performed using Student's t-test or the Mann-Whitney U test for continuous variables and the χ^2 test or Fisher's exact test for categorical variables, as appropriate.

Main Points

- Pretransplant small-airway dysfunction may represent an early marker of pulmonary vulnerability in hematopoietic stem cell transplantation (HSCT) candidates.
- Reduced forced expiratory flow between 25% and 75% of forced vital capacity (FEF_{25-75}) was associated with increased post-transplant pulmonary morbidity despite largely preserved conventional spirometric indices.
- Conventional parameters such as forced expiratory volume in 1 second and carbon monoxide may fail to detect subtle pretransplant physiologic impairment.
- Small-airway evaluation using FEF_{25-75} can be obtained from routine spirometry without additional cost or procedural burden.
- Pretransplant pulmonary risk assessment in HSCT may benefit from incorporating small-airway-focused functional markers.

Given the limited number of events, a parsimonious multivariable logistic regression model was used to evaluate factors associated with any post-HSCT complication. The final model included age, sex, ever-smoking status, HSCT type (autologous vs. allogeneic), reduced FEV₁ (<80% predicted), and reduced FEF₂₅₋₇₅ (<75% predicted). Adjusted odds ratios (OR) with 95% confidence intervals (CI) were reported. Overall model significance was assessed using the likelihood-ratio χ^2 test. Multicollinearity among included covariates was evaluated using variance inflation factors (VIFs) and tolerance values, and model calibration was assessed using the Hosmer-Lemeshow goodness-of-fit test.

Receiver operating characteristic (ROC) curve analysis was used to assess the discriminatory performance of individual pretransplant pulmonary function parameters in predicting any post-HSCT complication, with results reported as area under the curve (AUC) and 95% CIs.

No missing data were imputed. Analyses used the available data, and the multivariable model was based on complete cases (82/83 patients). All tests were two-sided, and *P* values <0.05 were considered statistically significant.

RESULTS

Patient Characteristics

Of the 120 patients screened, 83 met the inclusion criteria and were included in the analysis, as shown in the study flow

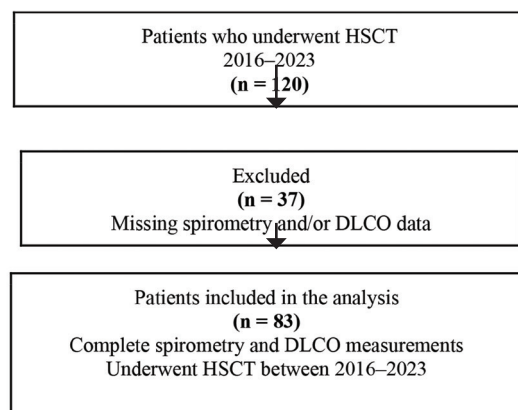


Figure 1. Study flow diagram

HSCT: hematopoietic stem cell transplantation, DLCO: diffusing capacity of the lung for carbon monoxide

Table 1. Distribution of hematological diagnoses in the study population

Diagnosis	n	%
Acute lymphoblastic leukemia	4	4.8
Acute myeloid leukemia	12	14.5
Hodgkin lymphoma	10	12.0
Multiple myeloma	39	47.0
Non-Hodgkin lymphoma	17	20.5
Myelofibrosis	1	1.2
Total	83	100.0

diagram (Figure 1). The median follow-up duration was 1,527 days (IQR: 889–1,911 days), with a range of 5–2,532 days. The mean age of the cohort was 49.0±14.3 years, and 57.8% were male. Multiple myeloma was the most common indication for HSCT (47.0%), followed by lymphomas (32.5%) (Table 1).

Most patients underwent autologous HSCT (79.5%). Baseline pulmonary function was generally preserved, with mean FEV₁ and FVC values of approximately 96% predicted, while mean FEF₂₅₋₇₅ was 78.9±24.7% predicted (Table 2).

Early complications (≤100 days after HSCT) occurred in 27.7% of patients. Baseline FEF₂₅₋₇₅ and DLCO did not significantly differ according to early complication status, whereas time to neutrophil recovery differed significantly (*P* = 0.014) (Supplementary Table 1).

Table 2. Baseline demographic, clinical, and pulmonary function characteristics of the study population (n = 83)

Variable	Value
Demographic characteristics	
Male sex, n (%)	48 (57.8)
Age, years	49.0±14.3
Body mass index, kg/m ²	28.5±5.2
Ever smoker, n (%)	31 (37.3)
Smoking exposure among ever smokers, pack-years†	20 (20–30)
Pre-existing obstructive airway disease‡, n (%)	4 (4.8)
Baseline comorbidity	
HCT-CI risk group	
• Low (=0)	48 (57.8)
• Intermediate (1–2)	26 (31.3)
• High (≥3)	9 (10.8)
Pulmonary function parameters	
FEV ₁ , % predicted	95.7±19.7
FVC, % predicted	96.8±20.6
FEF ₂₅₋₇₅ *, % predicted	78.9±24.7
DLCO, % predicted	76.1±19.9
DLCO/VA, % predicted	92.3±17.8
Transplant characteristics and outcomes	
Autologous HSCT, n (%)	66 (79.5)
Time to neutrophil recovery, days	10.7±3.5
Early HSCT complication, n (%)	23 (27.7)
Late HSCT complication, n (%)	12 (16.7)
Any HSCT complication, n (%)	32 (38.6)
All-cause mortality, n (%)	10 (12.1)

Values are presented as mean ± standard deviation, median (interquartile range), or number (percentage), as appropriate

†Smoking exposure is presented only for ever-smokers

‡Includes physician-diagnosed asthma or chronic obstructive pulmonary disease

HCT-CI: hematopoietic cell transplantation–comorbidity index, FEV₁: forced expiratory volume in one second, FVC: forced vital capacity, FEF₂₅₋₇₅: forced expiratory flow between 25% and 75% of forced vital capacity, DLCO/VA: diffusing capacity of the lung for carbon monoxide adjusted for alveolar volume, HSCT: hematopoietic stem cell transplantation

During follow-up, all-cause mortality was 12.1%. No baseline spirometric or diffusion parameter, including FEF_{25-75} , was significantly associated with mortality (Supplementary Table 2).

Association Between FEF_{25-75} and Post-HSCT Complications

Conventional pulmonary function parameters, including FEV_1 , FVC, and DLCO, did not differ significantly between patients with and without post-HSCT complications (all $P > 0.05$) (Table 3).

Complications occurred in 19 of 38 patients (50.0%) with reduced FEF_{25-75} (<75% predicted), compared with 13 of 45 patients (28.9%) with $FEF_{25-75} \geq 75\%$ predicted (χ^2 : 3.88, $P = 0.049$) (Table 4).

Overall Complications

Among the 83 HSCT recipients, 32 (38.6%) experienced at least one posttransplant complication during follow-up. These included 14 episodes of pneumonia, 7 pulmonary thromboembolic events, 6 episodes of neutropenic fever, 4 graft-versus-host disease (GVHD) events, and 4 non-infectious complications (3 thrombophlebitis and 1 posterior reversible encephalopathy syndrome). Because some patients experienced more than one complication, the total number of events exceeded the number of patients with complications.

Multivariable Analysis

In the multivariable logistic regression model adjusted for age, sex, ever-smoking status, HSCT type, and reduced FEV_1 , reduced

Table 3. Comparison of clinical and pulmonary parameters between patients with and without any HSCT complication

Variable	Without complication (n = 51) mean $\pm$ SD	With complication (n = 32) mean $\pm$ SD	P value
Age (years)	47.7 $\pm$ 15.4	51.0 $\pm$ 12.2	0.443
Smoking (pack-years)	7.4 $\pm$ 13.6	13.5 $\pm$ 17.0	0.062
BMI (kg/m ²)	28.6 $\pm$ 5.0	28.3 $\pm$ 5.7	0.796
FEV_1 /FVC (%)	82.9 $\pm$ 8.0	81.3 $\pm$ 6.8	0.362
FEV_1 (%)	95.7 $\pm$ 21.7	95.7 $\pm$ 16.3	0.998
FVC (%)	96.6 $\pm$ 21.3	97.2 $\pm$ 19.9	0.910
FEF_{25-75} (%)	80.6 $\pm$ 24.5	76.1 $\pm$ 25.1	0.238
Dysanapsis ratio (FEF_{25-75} /FVC)	0.88 $\pm$ 0.42	0.81 $\pm$ 0.29	0.477
DLCO _{SB} (%)	76.3 $\pm$ 22.1	75.8 $\pm$ 16.0	0.914
DLCO/VA (%)	91.4 $\pm$ 14.9	93.8 $\pm$ 21.8	0.562
Neutrophil recovery (days)	11.4 $\pm$ 3.8	9.8 $\pm$ 2.6	0.058

HSCT: hematopoietic stem cell transplantation, SD: standard deviation, BMI: body mass index, FEV_1 : forced expiratory volume in one second, FVC: forced vital capacity, FEF_{25-75} : forced expiratory flow between 25% and 75% of forced vital capacity, DLCO_{SB}: single-breath diffusing capacity of the lung for carbon monoxide, DLCO/VA: diffusing capacity of the lung for carbon monoxide adjusted for alveolar volume

Table 4. Association between reduced FEF_{25-75} (< 75%) and any post-HSCT complication

FEF_{25-75} group	No complication (n = 51)	Any complication (n = 32)	Total (n = 83)
$\geq 75\%$ predicted	32 (62.7%)	13 (40.6%)	45 (54.2%)
<75% predicted	19 (37.3%)	19 (59.4%)	38 (45.8%)
Total	51	32	83

χ^2 : 3.88, df = 1, $P = 0.049$

FEF_{25-75} : forced expiratory flow between 25% and 75% of forced vital capacity, HSCT: hematopoietic stem cell transplantation, χ^2 : chi-square, df: degrees of freedom

Table 5. Multivariable logistic regression analysis of factors associated with any post-HSCT complication

Predictor	OR (95% CI)	P value
Age, per year	1.00 (0.97–1.05)	0.827
Male sex	1.32 (0.45–3.89)	0.609
FEF_{25-75} <75% predicted	3.58 (1.28–10.04)	0.015
Autologous HSCT	1.67 (0.40–6.95)	0.483
FEV_1 <80% predicted	0.12 (0.02–0.71)	0.019
Ever smoker	1.57 (0.53–4.63)	0.410

Model fit: Deviance = 95.0; AIC = 109; McFadden R^2 = 0.134; overall likelihood-ratio $\chi^2(6)$ = 14.7, $P = 0.023$; Hosmer-Lemeshow $\chi^2(8)$ = 13.74, $P = 0.089$.

Note: Estimates represent the odds of developing any post-HSCT complication (1 = complication)

HSCT: hematopoietic stem cell transplantation, OR: odds ratio, CI: confidence interval, FEF_{25-75} : forced expiratory flow between 25% and 75% of forced vital capacity, FEV_1 : forced expiratory volume in one second, AIC: Akaike information criterion, χ^2 : chi-square

FEF₂₅₋₇₅ (<75% predicted) was independently associated with higher odds of any post-HSCT complication (OR: 3.58, 95% CI: 1.28–10.04; $P = 0.015$). Reduced FEV₁ (<80% predicted) showed an inverse association (OR: 0.12, 95% CI: 0.02–0.71; $P = 0.019$), whereas age, sex, ever-smoking status, and HSCT type were not significantly associated with the outcome (Table 5).

The overall model was statistically significant [likelihood-ratio $\chi^2(6) = 14.7$, $P = 0.023$]. The Hosmer-Lemeshow test showed no significant lack of fit [$\chi^2(8) = 13.74$, $P = 0.089$]. No problematic multicollinearity was detected among the covariates (VIF range: 1.13–1.36; Supplementary Table 3).

Discriminative Performance (ROC Analysis)

ROC analysis demonstrated poor standalone discriminatory ability of pretransplant pulmonary function parameters for predicting any post-HSCT complication (Supplementary Table 4). FEF₂₅₋₇₅ had an AUC of 0.578 (95% CI: 0.450–0.705), while FEV₁, FVC, and DLCO had AUCs of 0.504, 0.506, and 0.495, respectively. None demonstrated statistically significant discrimination (all $P > 0.05$).

DISCUSSION

This single-center study identified an association between reduced pretransplant FEF₂₅₋₇₅ and the composite endpoint of post-HSCT complications. After adjustment for age, sex, ever-smoking status, HSCT type, and reduced FEV₁, FEF₂₅₋₇₅ <75% predicted remained independently associated with higher odds of complications. However, its standalone discriminative performance was poor (AUC: 0.578), indicating that the observed association should not be interpreted as evidence of clinical predictive utility. Reduced FEV₁ was unexpectedly inversely associated with complications. Collinearity diagnostics did not indicate problematic multicollinearity between FEF₂₅₋₇₅ and FEV₁, but this finding should be interpreted with caution because of the small number of patients with reduced FEV₁ and the small number of outcome events.

FEF₂₅₋₇₅ in the Context of Previous HSCT Studies

FEF₂₅₋₇₅ reflects expiratory flow during the middle portion of forced expiration and has been used as a functional marker of the small airways, where abnormalities may occur before conventional spirometric indices become impaired.¹⁷⁻²¹ However, the clinical significance of FEF₂₅₋₇₅ in the transplant setting remains incompletely established.

Our findings are consistent with previous pediatric evidence. Srinivasan et al.⁵ demonstrated that children who subsequently developed pulmonary complications had significantly lower pretransplant FEF₂₅₋₇₅ values. Although differences in age, underlying diseases, and outcome definitions limit direct comparison, our primary endpoint was a broader composite comprising pulmonary and non-pulmonary complications. Therefore, the observed association should not be interpreted as evidence of a direct mechanistic relationship between reduced FEF₂₅₋₇₅ and individual components of the composite.

Evidence from adult HSCT studies also supports the relevance of assessing the small airways, although previous investigations

have focused predominantly on posttransplant pulmonary outcomes. Jamani et al.⁶ reported that early posttransplant reductions in FEF₂₅₋₇₅ were associated with subsequent BOS. Similarly, Yang et al.⁷ associated pretransplant pulmonary function abnormalities with chronic pulmonary GVHD after allogeneic HSCT, while Walter et al.⁹ linked pulmonary function abnormalities with long-term posttransplant outcomes. In contrast, our study evaluated pulmonary function before transplantation and used overall post-HSCT complications; therefore, pulmonary-specific findings cannot be directly extrapolated to non-pulmonary complications.

Parimon et al.⁸ demonstrated the prognostic importance of conventional pretransplant pulmonary function, particularly FEV₁ and DLCO, for respiratory failure and mortality after HSCT. Our findings should not be interpreted as evidence that FEF₂₅₋₇₅ replaces established pulmonary function parameters. Whether the observed association reflects pulmonary-specific vulnerability or residual confounding cannot be determined.

Although the association was not restricted to pulmonary complications, potential links between impaired respiratory health and systemic outcomes have been described. Chronic inflammatory lung diseases have been associated with venous thromboembolism, with inflammation, coagulation activation, and immunothrombotic pathways proposed as links between pulmonary diseases and thrombotic events.²² However, this literature provides biological context rather than evidence that reduced FEF₂₅₋₇₅ is mechanistically related to thrombotic events. Such mechanisms were not evaluated in our study and remain speculative.

Interpretation of the FEV₁ Findings

The inverse association with reduced FEV₁ should be interpreted cautiously and should not be considered evidence of a protective effect. FEV₁ and FEF₂₅₋₇₅ represent related but distinct aspects of expiratory function. Reduced FEV₁ and FEF₂₅₋₇₅ were significantly associated ($\chi^2 = 7.29$, $P = 0.007$); however, substantial discordance between the measures was observed. Among 38 patients with FEF₂₅₋₇₅ <75% predicted, 27 (71.1%) had preserved FEV₁ ($\geq 80\%$ predicted), indicating that reduced mid-expiratory flow frequently occurred despite preserved FEV₁. Collinearity diagnostics showed low VIFs for FEF₂₅₋₇₅ (VIF: 1.13) and FEV₁ (VIF: 1.25), indicating no problematic multicollinearity (Supplementary Table 3).

FEV₁ did not differ by complication status in unadjusted analyses, whereas reduced FEV₁ showed an inverse association with complication status after multivariable adjustment. Given that only 14 patients had FEV₁ <80% predicted, this unexpected association may reflect small-sample instability, categorization effects, or residual confounding rather than a protective effect (Supplementary Table 5).

These findings suggest that reductions in FEF₂₅₋₇₅ and FEV₁ may provide different information in this cohort; however, the association for FEF₂₅₋₇₅ should not be interpreted as evidence of superior predictive performance, particularly given its poor standalone discrimination.

Clinical Implications

The present findings suggest that FEF_{25-75} may provide complementary information during pretransplant pulmonary assessment, particularly when FEV_1 remains preserved. Because FEF_{25-75} is derived from standard spirometry, it can be evaluated without additional testing.^{23,24} However, its poor standalone discriminative performance (AUC: 0.578) indicates that FEF_{25-75} should not be considered an independent clinical decision-making tool or a replacement for established pretransplant risk assessment. Rather, reduced FEF_{25-75} may represent a candidate functional marker warranting further investigation within broader risk-assessment approaches. Prospective studies are needed to determine whether FEF_{25-75} provides incremental prognostic information beyond established risk factors.

Strengths and Limitations

This study has several strengths. To our knowledge, it is the first adult HSCT cohort to specifically evaluate pretransplant FEF_{25-75} in relation to overall posttransplant complications, extending previous observations from pediatric cohorts and adult studies focused on pulmonary outcomes. Standardized pretransplant PFT allowed direct comparison of FEF_{25-75} with conventional spirometric and diffusion parameters. The relatively long follow-up enabled the assessment of complications beyond the early posttransplant phase. The multivariable analysis accounted for age, sex, smoking history, and transplant type; multicollinearity and model calibration were formally assessed.

Several limitations should be considered. First, the retrospective, single-center design introduces selection bias and limits generalizability. The cohort was small; only 32 patients experienced complications, which constrained multivariable adjustment. Although a parsimonious model was used, overfitting and model instability cannot be excluded, and the findings require validation in larger independent cohorts.

Second, the cohort was heterogeneous with respect to underlying hematologic diagnoses and transplant types. Autologous and allogeneic HSCT differ in their complication profiles, particularly with respect to GVHD, and the small size of the allogeneic subgroup limited transplant-specific analyses. Although transplant type was included in the multivariable model, complications specific to allogeneic transplants could not be adequately analyzed. Detailed transplant-related variables, particularly conditioning regimens and CMV serostatus, had substantial missing data and could not be reliably incorporated. GVHD-related risk factors and immunosuppressive treatments were not comprehensively accounted for. Consequently, residual confounding by disease-, transplant-, and treatment-related factors remains possible.

Third, although pretransplant PFT was standardized, FEF_{25-75} exhibits greater variability than conventional spirometric indices and is influenced by lung volumes and expiratory effort. The <75% predicted threshold was an operational research definition and should not be interpreted as a universally

established diagnostic threshold for SAD. Imaging correlates were not systematically available, precluding physiologic-radiologic validation.

Fourth, information on chronic respiratory medications, including bronchodilators and inhaled corticosteroids, was not consistently available. Although smoking history was included in the multivariable model and physician-diagnosed obstructive airway disease was assessed, these data were unavailable for a subset of patients. Therefore, residual confounding related to baseline respiratory characteristics cannot be excluded.

Fifth, the primary outcome was a clinically heterogeneous composite of pulmonary and non-pulmonary complications. This heterogeneity limits mechanistic and organ-specific interpretation.

Although the Hosmer-Lemeshow test showed no significant lack of fit and collinearity diagnostics did not identify problematic multicollinearity, these diagnostics do not eliminate the possibility of model instability arising from the modest sample size and limited number of events. Moreover, the poor discriminative performance of FEF_{25-75} (AUC: 0.578) indicates that it should not be considered a clinically useful standalone predictive marker. Prospective, multicenter studies with larger cohorts, comprehensive transplant-specific covariates, standardized respiratory characterization, and external validation are needed.

CONCLUSION

Reduced pretransplant FEF_{25-75} was independently associated with the composite endpoint of post-HSCT complications after adjustment for relevant clinical factors, including reduced FEV_1 . However, its poor discriminative performance (AUC: 0.578) indicates that FEF_{25-75} should not be considered a standalone predictive test or used to guide clinical decision-making. Reduced FEF_{25-75} was frequently observed despite preserved FEV_1 , suggesting that these measures may provide different information. These findings are hypothesis-generating, and larger prospective studies that incorporate comprehensive transplant-specific covariates and include external validation are needed to determine its clinically meaningful incremental prognostic information.

Ethics

Ethics Committee Approval: This study was conducted in accordance with the Declaration of Helsinki and approved by the Marmara University Faculty of Medicine Clinical Research Ethics Committee (decision no.: 09.2023.669, date: 05/05/2023).

Informed Consent: Because of the retrospective study design, the Ethics Committee waived the requirement for informed consent. All patient data were anonymized prior to analysis.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: C.Ç., A.M.Y., Concept: C.Ç., Z.M., C.Y., I.A., S.E.E., Design: C.Ç., Z.M., T.T., S.K., Data Collection or Processing: C.Ç., A.M.Y., C.Y., Analysis or Interpretation: C.Ç., Literature Search: C.Ç., A.M.Y., Writing: C.Ç., A.M.Y., Z.M.

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Supplementary Tables 1-5 Link: <https://d2v96fxpocvxx.cloudfront.net/1dda20c2-8b22-466b-a98e-85ecfb39ceaf/content-images/bb8ee4a8-8b88-401f-93bd-cbbdb0b051da.pdf>

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Original Article



Culturally Adapted Floor-to-Stand Exercises for COPD: A Quasi-experimental Study

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ABSTRACT

OBJECTIVE: Conventional pulmonary rehabilitation remains difficult to access in many low-resource settings because of practical, geographic, and sociocultural barriers. Accordingly, floor-to-stand exercises (FSE) were developed as an equipment-free program centered on repeated floor-to-stand transitions that are commonly performed in daily life in North Africa. The main objective of the present study was to estimate program completion rates, identify predictors of non-completion, and describe clinical, functional, and peripheral muscle outcomes in chronic obstructive pulmonary disease (COPD) outpatients with documented difficulty rising from the floor.

MATERIAL AND METHODS: In this prospective, quasi-experimental pilot study, COPD outpatients participated in the 9-week progressive FSE program. Completion was defined as ≥ 22 floor-to-stand transitions/day during weeks 7-9. Assessments were performed at baseline and at day 63, and outcomes were compared between completers and non-completers.

RESULTS: Fifteen COPD outpatients were included; the completion rate was 46.7% (7/15). Completers had lower baseline Borg CR10 scores (6.0 vs. 7.5; $P = 0.047$) and higher 6-minute walk distance (330 vs. 261 m; $P = 0.037$). On day 63, completers improved on the modified Medical Research Council Dyspnea Scale (-2.0 ; $P = 0.015$), Borg CR10 (-3.0 ; $P = 0.011$), and COPD assessment test (-8.0 ; $P = 0.008$), whereas non-completers improved only on the Borg CR10 (-2.0 ; $P = 0.020$). Functional tests and peripheral muscle outcomes showed no consistent changes overall.

CONCLUSION: The FSE was feasible and safe in this study, with improvements primarily in symptoms and disease impact. Larger controlled studies are needed to confirm the effectiveness and optimize adherence. Trial registration: ClinicalTrials.gov NCT07277855.

KEYWORDS: COPD, exercise training, pulmonary rehabilitation and chronic care, cultural characteristics, pulmonary diseases

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterized by systemic manifestations, notably skeletal muscle dysfunction, which contribute to a self-perpetuating cycle of dyspnea, inactivity, deconditioning, and progressive functional decline.^{1,2} Pulmonary rehabilitation (PR) is the cornerstone intervention recommended by the Global Initiative for Chronic Obstructive Lung Disease (GOLD), aiming to improve symptoms, functional capacity, and quality of life while reducing healthcare costs.^{3,4}

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Conventional PR programs, such as treadmill or track walking, cycling and resistance training, are well established and endorsed by major societies (American College of Sports Medicine, American Thoracic Society, European Respiratory Society).^{5,6} However, their accessibility remains critically limited, with only 1.2% of eligible symptomatic COPD patients participating worldwide,⁷ mainly due to socioeconomic, infrastructural, and cultural barriers.^{8,9} These limitations have prompted the development of culturally adapted PR approaches, such as yoga in India, tai chi in China, and dance-based programs in specific countries, all showing promising results.¹⁰⁻¹² Culturally contextualized strategies may therefore be relevant not only in settings where PR access is limited, but also as complementary options for populations with habitual daily movement patterns.

In North Africa, culturally tailored PR strategies are scarcely evaluated. Daily life commonly includes floor sitting¹³ and repeated floor-to-stand movements. Moreover, a widely practiced daily religious routine in this predominantly Muslim region involves repeated transitions between floor-level and standing postures. Considering the 17 obligatory prayer units together with five commonly practiced additional units, a pragmatic target of 22 daily floor-to-stand transitions was selected.¹⁴⁻¹⁶ This context suggests that a structured rehabilitation model based on familiar floor-rising movements, performed either within daily routines or as a stand-alone exercise, may improve acceptability and adherence.

A floor-to-stand exercise (FSE) program was developed, centered on repeated floor-to-stand transitions commonly performed in daily life across North African communities. The FSE is proposed as a progressive, equipment-free program requiring minimal space and limited assistance, delivered over nine weeks in three phases. The program culminated in a target of 22 daily floor-to-stand transitions, distributed in clusters

throughout the 24-hour period. Completion was defined as achieving the target of 22 floor-to-stand transitions/day during weeks 7 to 9.

The main objective of the present study was to estimate program completion, identify predictors of non-completion, and describe clinical, functional, and peripheral muscle outcomes¹⁷⁻¹⁹ in COPD outpatients with documented difficulty rising from the floor.

MATERIAL AND METHODS

Study Design and Setting

This prospective, quasi-experimental study used a single-arm interventional design. The intervention and study assessments were conducted at the coordinating study site in Laghouat; four specialized respiratory care centers served to identify potentially eligible patients, as described below. Week 9 (day 63) outcomes, including clinical, functional, and muscle performance measures, were compared between completers and non-completers, and the prespecified completion endpoints were reported.

Participants

Eligible participants were adult outpatients diagnosed with COPD according to GOLD criteria⁴ [post-bronchodilator forced expiratory volume in one second (FEV1)/forced vital capacity <0.7 and compatible clinical symptoms such as dyspnea or chronic cough] and reporting muscle dysfunction that limited their ability to rise from a kneeling position. Exclusion criteria were ischemic heart disease, stroke, or COPD exacerbation requiring systemic corticosteroids, each occurring within the preceding two months. Early termination criteria consisted of predefined serious adverse events occurring after protocol initiation, including major cardiovascular, respiratory, or neurological complications that compromise safe participation; acute intercurrent illness; clinically significant cognitive decline impairing adherence; and withdrawal of consent.

Potentially eligible patients presenting for routine COPD consultation at the four specialized respiratory care centers in Laghouat, Algeria, between 01 December 2024 and 28 February 2025 were identified by the consulting respiratory physicians and referred to the coordinating study site for eligibility assessment. Sixteen individuals were initially recorded administratively. One did not proceed to the study baseline evaluation after a very early cardiological assessment identified clinically significant heart failure with recurrent pulmonary edema, making participation in the exercise program unsafe. The clinical study cohort therefore comprised 15 participants. All participants included in the clinical study cohort received guidance on the structured FSE rehabilitation program and provided written informed consent before study procedures.

Data Collection and Measurement Tools

Assessments were conducted in person at baseline (day 0) and post-intervention (day 63). Mid-intervention monitoring on days 21 and 42 was performed via structured telephone calls focusing on adherence and adverse events. An adverse event

Main Points

- Floor-to-stand exercises represent an equipment-free, culturally grounded, predominantly home-based pulmonary rehabilitation strategy based on repeated floor-to-stand transitions and designed for resource-limited settings.
- In this 9-week study, 46.7% of chronic obstructive pulmonary disease (COPD) outpatients with floor-rising difficulty achieved the predefined completion target (≥22 floor-to-stand transitions/day during weeks 7–9).
- Lower baseline perceived exertion (Borg CR10) and higher baseline exercise capacity [6-minute walk distance (6MWD)] were associated with completion, suggesting identifiable profiles for targeted support.
- Completers showed statistically significant and clinically relevant improvements in dyspnea (mMRC) and health status (CAT), while objective functional tests [6MWD, 1-minute sit-to-stand (STS), timed up and go (TUG), fingertip-to-floor distance (FFD)] did not significantly change in this small sample.
- Peripheral muscle performance assessed by force-sensor dynamometry with belt-stabilized testing showed no consistent improvement over the 9-week study period.

was defined as any untoward medical occurrence temporally associated with study participation, whether or not it was considered related to the intervention. A serious adverse event was defined as any adverse event that results in death, is life-threatening, requires inpatient hospitalization or prolongs existing hospitalization, results in persistent or significant disability or incapacity, or constitutes an important medical event requiring intervention to prevent such outcomes. Event seriousness and relationship to the intervention were assessed separately by the investigators.

To minimize measurement variability, clinical questionnaires, functional tests, and standardized peripheral muscle tests were administered in a fixed sequence at each in-person visit. The fixed sequence was as follows: symptom- and health-status questionnaires [modified Medical Research Council Dyspnea Scale (mMRC), perceived exertion Borg CR10, and health status COPD assessment test (CAT)]; functional tests [6-minute walking distance (6MWD), 1-minute sit-to-stand (STS), timed up and go (TUG), and fingertip-to-floor distance (FFD)]; and peripheral muscle testing. Standardized rest intervals were planned; additional recovery time was allowed, when clinically required, to safely complete symptom-limited testing.

Socio-demographic and medical history data were collected at baseline. COPD diagnosis was confirmed by post-bronchodilator spirometry, with disease stage categorized according to GOLD ABE classification.⁴

Clinical assessment included dyspnea, measured using the mMRC (0–4; 0= dyspnea only with strenuous exercise; 4= too dyspneic to leave the house), and perceived exertion/dyspnea during FSE, measured using the modified Borg CR10 scale (0–10; 0= no dyspnea; 10= maximal dyspnea). Disease impact was evaluated with CAT (0–40; higher scores indicate greater disease impact). Functional evaluation focused on mobility (TUG, in seconds); flexibility (FFD, in cm); and exercise capacity (6MWD, in meters, and 1-min STS, number of repetitions). Prognosis was assessed using the body mass index (BMI), airflow obstruction, dyspnea, and exercise index (BMI, predicted post-bronchodilator FEV1 %, mMRC, and 6MWD).

Peripheral muscle performance was assessed on the right side using a portable force-sensor dynamometer with standardized positioning and belt-stabilized testing, consistent with published recommendations and reliability data in COPD.^{17–19} Testing followed a fixed sequence. Lower-limb tests were performed first and included seated knee flexion and knee extension, with the ankle strap positioned above the malleoli. Upper-limb tests were then performed; they included standing shoulder flexion and seated pectoral press, with the pectoral press performed last. For each task, the assessment followed a standardized progression from maximal isometric strength to isometric endurance and, when applicable, to isotonic endurance, each at 50% of maximal force. Outcomes were maximal isometric strength (kg), isometric endurance at 50% of maximal force (hold time maintaining $\geq 50\%$ of maximal force, s), and isotonic endurance at 50% of maximal force (repetitions completed in 1 minute).

Program adherence and adverse events were assessed during structured telephone calls on days 21 and 42, and on day 63

clinical, functional, and muscle assessments were repeated, and program completion was documented.

Intervention: The Floor-to-Stand Exercise

All participants were invited to undertake the FSE, a progressive 9-week training structured into three phases with daily targets accumulated across brief, distributed sessions. The program was equipment-free, required minimal space, and combined home practice with brief supervised sessions during the initial phase. Each floor-to-stand transition begins in standing, transitions to a floor position, and ends in standing; daily targets refer to completed floor-to-stand cycles. Participants could integrate the practice into their daily routine, including during their religious prayers, or perform it in separate exercise sessions; in both cases, repetitions corresponded to completed cycles, as defined above.

Assistance during FSE was categorized as human assistance (a caregiver or family member), environmental support (chair or wall), or independent execution (Figure 1). Assistance was adapted to individual needs and progressively reduced when safe and feasible, rather than being rigidly linked to a specific phase.

The goal of the initial phase (weeks 1–3) was to achieve 7–15 floor-to-stand transitions per day and to restore the ability to rise from the floor. The training combined home practice with biweekly supervised sessions at the study hospital. Assistance was provided at the hospital with a chair, the wall, a family member, or a caregiver to ensure safety until basic ability was regained. Once patients reached this stage, hospital sessions were discontinued, and training continued at home. During supervised sessions, staff provided hands-on support as needed to help participants safely manage body weight during the transition and adjusted the level of support according to the participants' dyspnea, balance, and tolerance.

Family members/caregivers who would assist at home were also trained to provide safe support (positioning, grip, and timing of assistance) to enable home practice and progressively reduce assistance when possible.

In the intermediate phase (weeks 4–6), the goal was increased to 15–22 floor-to-stand transitions/day, to be performed at home. At this stage, patients were encouraged to practice partially independently, using support only when needed (chair, wall, or family assistance), providing stability and reassurance while progressively reducing reliance on help. Progression was symptom-guided: participants increased repetitions gradually within the prescribed range and assistance was reduced only when the cycle could be completed safely without pain or undue dyspnea.

The consolidation phase (weeks 7–9) aimed to maintain 22 floor-to-stand transitions per day, performed independently, without assistance, and exclusively at home.

For the analysis, completion was defined as the consistent achievement of 22 floor-to-stand transitions per day during the consolidation phase, as reported by the patient and corroborated whenever possible through interim phone calls.

This target was chosen because it reflects the 22 daily prayer units described above in Muslims' daily religious prayers (salat), thereby providing a culturally familiar and attainable benchmark for use within or outside a spiritual routine.

To ensure safety, patients were instructed to discontinue the exercise in case of acute pain, dizziness, syncope, falls, or respiratory deterioration and to promptly contact the clinical team. Participants were advised to "listen to their body", to progress gradually, to "push their limits but never through pain", and to adjust the number of sessions and the level of assistance according to day-to-day symptom tolerance.

For participants with severe dyspnea, balance impairment, or musculoskeletal limitations, the protocol allowed slower progression and the continued use of chair or wall support, with or without caregiver supervision, until the movement could be performed safely.

Ethical Considerations

The study was conducted in accordance with the Declaration of Helsinki. The protocol was approved by the Ethics Committee of the Faculty of Medicine, Laghouat University (protocol no.: 12/2024; decision date: 20 November 2024). Confidentiality was ensured through anonymization and secure data handling.

The intervention was delivered in a culturally sensitive manner

and designed to be compatible with participants' personal beliefs and practices, without promoting or discouraging religious or spiritual views.

Trial registration: ClinicalTrials.gov NCT07277855. The trial registration record was first publicly posted after completion of the nine-week assessment period.

Statistical Analysis

Analyses were performed using R software version 4.5.1 (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was set at $P < 0.05$. Qualitative variables were summarized as frequencies and percentages, and quantitative variables as medians with interquartile ranges. Group comparisons were made using chi-square test or Fisher's exact test for categorical variables and the Mann-Whitney U test for continuous variables.

The analysis addressed program completion rate, predictors of non-completion, and post-intervention changes. Predictors were explored by comparing baseline socio-demographic, medical, clinical, and functional characteristics between completers and non-completers. Within-group changes from baseline were assessed using the Wilcoxon signed-rank test (one-sided, according to the expected direction of improvement: higher scores for 6MWD and 1-min STS repetitions, and lower scores for mMRC score, Borg CR10 scale, CAT total score, TUG test,

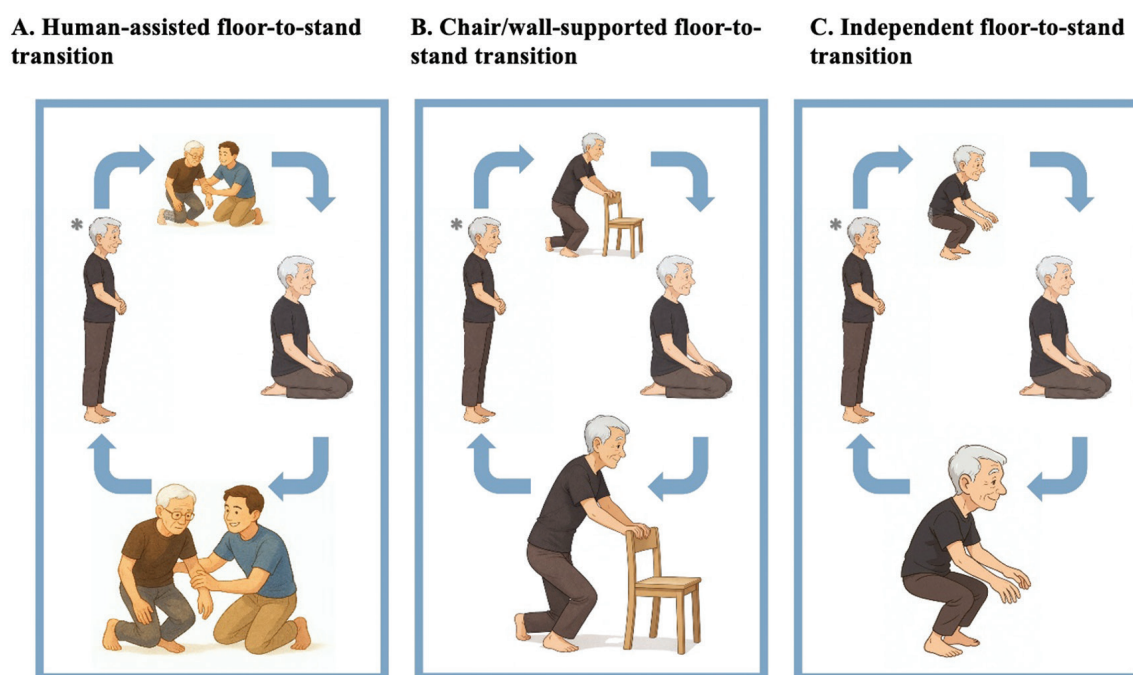


Figure 1. Categorized assistance modalities for floor-to-stand transitions

*Starting and finishing position of a complete floor-to-stand transition

Each panel depicts one complete floor-to-stand cycle, from standing to a floor position and back to standing. Panel A shows a transition performed with caregiver or family-member assistance. Panel B shows a transition performed with chair or wall support. Panel C shows an independent floor-to-stand transition without external assistance. These assistance modalities were used pragmatically according to patient capacity, symptom tolerance, and safety considerations, rather than being rigidly assigned to a specific phase of the program. The intervention followed a 9-week progressive schedule, with daily targets increasing from 7–15 to 15–22 and then 22 floor-to-stand transitions/day, accumulated in distributed daily sessions. Exercise was discontinued in case of acute pain, dizziness, syncope, falls, or respiratory worsening. The final target was selected as a culturally familiar benchmark; repetitions could be performed as separate exercise clusters or, if the participant wished, integrated into daily routines, including salat-related floor-to-stand transitions

and FFD). Between-group differences in median change scores were tested with the Mann–Whitney U test. Median changes in completers were further interpreted relative to minimal clinically important difference thresholds to evaluate clinical relevance, as follows: ≥ 1 -grade reduction for mMRC,²⁰ ≥ 2 -point reduction for CAT,²¹ ≥ 1 -point reduction for Borg CR10,²² ≥ 30 m for 6MWD,²³ ≥ 3 repetitions for 1-min STS,²⁴ and ≥ 0.9 – 1.4 s for TUG.²⁵

Muscle outcomes were analyzed using the same non-parametric framework (within-group Wilcoxon signed-rank tests and between-group comparisons of change scores), with one-sided tests applied in the prespecified direction of improvement (higher maximal strength and endurance).

RESULTS

Fifteen outpatients with difficulty rising from the floor were included. Most participants had symptomatic COPD at baseline: 9/15 (60.0%) were classified as GOLD group B and 5/15 (33.3%) as group E. No participant was receiving long-term oxygen therapy or non-invasive ventilation. Cardiometabolic comorbidities (hypertension and type 2 diabetes) were common, whereas musculoskeletal disorders were present in a minority of participants; one participant had inflammatory myopathy (Table 1; Supplementary Table S1). Overall, 7/15 participants (46.7%) met the completion criterion, consistently achieving the target of 22 floor-to-stand transitions per day during weeks 7–9. Among non-completers (8/15, 53.3%), four had 0–6 transitions/day, two had 7–14/day, and two had 15–21/day.

Predictors of Non-completion

Baseline socio-demographic, respiratory, and clinical characteristics were broadly comparable between completers and non-completers (Table 2). Baseline peripheral muscle performance is presented in Supplementary Table S2. In addition to lower perceived exertion and higher exercise capacity (Borg CR10 and 6MWD), completers showed higher baseline lower-limb muscle performance as measured by selected dynamometry measures. Functional and clinical profiles were otherwise generally similar. Musculoskeletal disorders were observed only among non-completers, without reaching statistical significance ($P = 0.244$).

Post-intervention Outcomes (Clinical, Functional, and Muscle Performance)

By day 63, completers showed statistically significant improvements in mMRC, Borg CR10, and CAT, with changes meeting clinically important thresholds. Non-completers showed a statistically significant improvement only in Borg CR10. No significant changes were observed in functional tests (6MWD, 1-min STS, TUG, and FFD) in either group (Table 3). Peripheral muscle performance outcomes did not show systematic changes over the study period; only pectoral press isometric endurance increased in non-completers (Table 4). During in-person assessments, some participants required recovery periods longer than the standardized rest intervals to complete symptom-limited testing safely, particularly during the final upper-limb muscle tasks.

Table 1. Baseline clinical, respiratory, and functional characteristics of the study population (n = 15)

Variable	Value
Demographics	
Age (years)	67.0 [62.5, 74.5]
Male sex, n (%)	13 (86.7)
Weight, kg	68.0 [50.2, 88.5]
BMI, kg/m ²	22.5 [18.6, 30.9]
Socio-economic and access to care	
Distance home–hospital, km	2.3 [1.9, 3.6]
Transportation barrier, n (%)	10 (66.7)
Lack of social support, n (%)	6 (40.0)
Socioeconomic status, n (%)	
Low	2 (13.3)
Middle	11 (73.3)
High	2 (13.3)
Smoking history	
Current smoker, n (%)	2 (13.3)
Former smoker, n (%)	11 (73.3)
Pack-years index	40.0 [24.0, 55.0]
Smoking cessation, years	4.0 [2.0, 6.0]
COPD severity and symptoms	
Post-bronchodilator FEV1, % predicted	33.0 [26.5, 55.0]
mMRC score	3.0 [2.0, 4.0]
Borg CR10 scale	6.0 [6.0, 7.5]
CAT total score	21.0 [17.0, 24.5]
GOLD ABE classification, n (%)	
Group A	1 (6.7)
Group B	9 (60.0)
Group E	5 (33.3)
Comorbidities	
Cardiovascular disorders, n (%)	6 (40.0)
Metabolic disorders, n (%)	3 (20.0)
Musculoskeletal disorders, n (%)	3 (20.0)
Other disorders, n (%)	1 (6.7)
Functional tests and prognosis	
6MWD, m	300.0 [236.0, 332.5]
1-min STS repetitions	11.0 [10.0, 14.0]
TUG test, s	12.5 [12.0, 16.1]
FFD, cm	1.0 [0.0, 10.1]
BODE index	4.0 [3.0, 7.0]

Values are expressed as median [interquartile range] or n (%), as appropriate. Pack-years index was calculated as packs/day $\times$ years smoked. Other disorders included one case of dermatomyositis

BMI: body mass index, FEV1: forced expiratory volume in one second, mMRC: modified Medical Research Council, Borg CR10: borg category-ratio scale, CAT: COPD assessment test, GOLD: Global Initiative for Chronic Obstructive Lung Disease, 6MWD: 6-minute walk distance, STS: sit-to-stand, TUG: timed up and go, FFD: fingertip-to-floor distance, BODE: body mass index, airflow obstruction, dyspnea, and exercise capacity index, kg: kilogram, m: meter, min: minute, cm: centimeter, s: seconds

Table 2. Baseline clinical, respiratory, and functional characteristics and their univariate differences between FSE completers and non-completers

Variable	Completers (n = 7)	Non-completers (n = 8)	P
Demographics			
Age (years)	67.0 [62.0, 71.0]	68.0 [64.8, 76.8]	0.562
Male sex, n (%)	7 (100.0)	6 (75.0)	0.509
Weight, kg	70.0 [59.5, 92.7]	65.0 [48.0, 88.0]	0.487
BMI, kg/m ²	23.6 [21.5, 30.0]	21.9 [16.3, 28.0]	0.643
Socio-economic and access to care			
Distance home–hospital, km	3.2 [2.2, 3.9]	2.1 [1.7, 3.4]	0.417
Transportation barrier, n (%)	5 (71.4)	5 (62.5)	1.000
Lack of social support, n (%)	2 (28.6)	4 (50.0)	0.751
Socioeconomic status			0.988
Low, n (%)	1 (14.3)	1 (12.5)	
Middle, n (%)	5 (71.4)	6 (75.0)	
High, n (%)	1 (14.3)	1 (12.5)	
Medical history and comorbidities			
Cardiovascular disorders, n (%)	4 (57.1)	2 (25.0)	0.460
Musculoskeletal disorders, n (%)	0 (0.0)	3 (37.5)	0.244
Metabolic disorders, n (%)	2 (28.6)	1 (12.5)	0.897
Other disorders, n (%)	0 (0.0)	1 (12.5)	1.000
Smoking history			
Current smoker, n (%)	1 (14.3)	1 (12.5)	1.000
Former smoker, n (%)	6 (85.7)	5 (62.5)	0.668
Pack-years index	45.0 [32.0, 57.5]	27.5 [21.2, 40.5]	0.391
Smoking cessation, years	2.0 [1.2, 12.0]	4.5 [2.5, 5.8]	0.773
COPD severity and baseline symptoms			
Post-bronchodilator FEV1, % predicted	41.0 [26.5, 46.0]	33.0 [27.2, 62.2]	0.817
mMRC score	3.0 [2.0, 3.0]	3.5 [2.5, 4.0]	0.334
Borg CR10 scale	6.0 [5.5, 6.5]	7.5 [6.0, 8.2]	0.047
CAT total score	19.0 [15.0, 23.0]	23.0 [18.8, 24.8]	0.324
GOLD ABE classification			0.535
Group A, n (%)	1 (14.3)	0 (0.0)	
Group B, n (%)	4 (57.1)	5 (62.5)	
Group E, n (%)	2 (28.6)	3 (37.5)	
Functional tests and prognosis			
6MWD, m	330.0 [317.5, 357.5]	261.0 [172.5, 288.8]	0.037
1-min STS repetitions	12.0 [11.0, 16.5]	10.5 [8.8, 12.0]	0.114
TUG test, s	12.0 [10.5, 13.8]	14.5 [12.0, 17.4]	0.199
FFD, cm	8.0 [0.0, 9.6]	0.5 [0.0, 12.0]	1.000
BODE index	4.0 [3.0, 6.0]	5.0 [3.5, 7.5]	0.521

Values are expressed as median [interquartile range] or n (%), as appropriate. Between-group comparisons were performed using Fisher's exact test or chi-square test for categorical variables and the Mann–Whitney U test for continuous variables. Pack-years index was calculated as packs/day × years smoked. Other disorders included one case of dermatomyositis

FSE: floor-to-stand exercises, BMI: body mass index, FEV1: forced expiratory volume in one second, mMRC: modified Medical Research Council, Borg CR10: borg category-ratio scale, CAT: COPD assessment test, GOLD: Global Initiative for Chronic Obstructive Lung Disease, 6MWD: 6-minute walk distance, STS: sit-to-stand, TUG: timed up and go, FFD: fingertip-to-floor distance, BODE: body mass index, airflow obstruction, dyspnea, and exercise capacity index, kg: kilogram, m: meter, min: minute, cm: centimeter, s: seconds

Table 3. Baseline-to-post-intervention changes in clinical and functional outcomes: completers vs. non-completers

Outcome	Completers Δ (n = 7)	P within	Non-completers Δ (n = 8)	P within	P between
mMRC score	-2.0 [-2.0, -1.0]	0.015	-1.0 [-1.3, 0.0]	0.197	0.178
Borg CR10 scale	-3.0 [-3.0, -2.0]	0.011	-2.0 [-3.0, -0.8]	0.020	0.227
CAT total score	-8.0 [-11.5, -5.0]	0.008	-4.0 [-8.5, 0.8]	0.075	0.147
6MWD, m	-10.0 [-72.5, 19.5]	0.711	-16.0 [-43.8, 40.6]	0.663	0.728
1-min STS repetitions	0.0 [-1.5, 3.0]	0.262	-0.5 [-1.5, 3.0]	0.534	0.769
TUG test, s	-0.9 [-2.1, 2.7]	0.751	0.6 [-0.5, 1.4]	0.824	0.728
FFD, cm	0.0 [-4.6, 0.0]	0.181	0.0 [-1.5, 0.0]	0.292	0.714

Values are expressed as median change from baseline to day 63 [interquartile range]. Within-group changes were assessed using one-sided Wilcoxon signed-rank tests in the prespecified direction of improvement. Between-group comparisons of change scores were assessed using the Mann-Whitney U tests

Δ : change from baseline to day 63, mMRC: modified Medical Research Council, Borg CR10: modified borg category-ratio scale, CAT: COPD assessment test, 6MWD: 6-minute walk distance, STS: sit-to-stand, TUG: timed up and go, FFD: fingertip-to-floor distance, m: meters, s: seconds, cm: centimeters, IQR: interquartile range, min: minute

Table 4. Baseline-to-post-intervention changes in peripheral muscle performance: completers vs. non-completers

Variable	Completers Δ (n = 7)	P within	Non-completers Δ (n = 8)	P within	P between
Knee flexion					
Max isometric strength, kg	-1.2 [-14.3, 1.5]	0.864	-2.8 [-3.6, -1.1]	0.971	0.685
Isometric endurance at 50% max force, s	5.3 [-10.9, 15.0]	0.534	11.6 [4.5, 21.0]	0.054	0.385
Knee extension					
Max isometric strength, kg	-4.3 [-9.4, 3.2]	0.777	-2.8 [-4.5, -1.4]	0.962	0.862
Isometric endurance at 50% max force, s	-7.7 [-29.2, -4.7]	0.925	13.8 [-10.8, 31.2]	0.147	0.224
Isotonic endurance at 50% max force, reps/1 min	-8.0 [-18.0, 8.0]	0.866	2.0 [-5.0, 7.0]	0.336	0.296
Shoulder flexion					
Max isometric strength, kg	3.0 [-2.3, 6.7]	0.136	0.5 [-0.2, 2.1]	0.181	0.325
Isometric endurance at 50% max force, s	1.5 [-11.0, 14.0]	0.336	-4.8 [-11.0, 6.1]	0.824	0.728
Isotonic endurance at 50% max force, reps/1 min	-2.0 [-5.0, 1.0]	0.800	-2.5 [-6.0, 4.0]	0.802	0.954
Pectoral press					
Max isometric strength, kg	-1.8 [-5.1, 5.8]	0.664	-3.1 [-4.5, 1.7]	0.819	0.908
Isometric endurance at 50% max force, s	-7.6 [-13.9, 9.7]	0.777	16.5 [8.4, 23.3]	0.015	0.024

Values are expressed as median change from baseline to day 63, with interquartile range [IQR] shown below the median. Positive values indicate increased muscle performance, whereas negative values indicate decreased performance. P within refers to the within-group change assessed using a one-sided Wilcoxon signed-rank test in the prespecified direction of improvement. P between refers to the between-group comparison of change scores assessed using the Mann-Whitney U test. Peripheral muscle performance outcomes were maximal isometric strength, isometric endurance at 50% of maximal force, and isotonic endurance at 50% of maximal force

Δ : change from baseline to day 63; IQR: interquartile range, Reps: repetitions, min: minute, s: seconds, kg: kilogram, Max: maximum

Safety Profile and Motivational Barriers

Telephone follow-up at days 21 and 42 was completed for 14 of 15 participants (7/7 completers and 7/8 non-completers). A small amount of additional item-level information was missing, so available-case denominators were 13 or 14 depending on the variable; percentages at these interim assessments were calculated using the number of participants with available data for each item. Day-63 assessments were available for all 15 participants. Effort-related musculoskeletal complaints were infrequent on day 21 (14.3% vs. 28.6%, $P = 1.000$) and on day 42 (one case in each group, $P = 1.000$). By day 63, no completer reported symptoms, whereas 50.0% of non-completers did (P

$= 0.110$). Four COPD exacerbations occurred during follow-up; one required hospitalization and was therefore classified as a serious adverse event. In the investigators' judgment, these exacerbations were related to the underlying course of COPD and not to the intervention. No comorbidity decompensation was reported on days 21 or 42; one inflammatory myopathy flare occurred on day 63. Mental fatigue was common but consistently less frequent among completers, although these differences were not statistically significant (day 21: 28.6% vs. 71.4%, $P = 0.285$; day 42: 42.9% vs. 57.1%, $P = 1.000$; day 63: 28.6% vs. 75.0%, $P = 0.201$).

DISCUSSION

In this 9-week, equipment-free FSE program, 46.7% of participants achieved the predefined completion target (22 floor-to-stand transitions/day). Completers had a better baseline functional status and showed clinically meaningful improvements in dyspnea and health status, whereas functional performance and peripheral muscle outcomes changed minimally.

Determinants of Program Completion and Adherence

Nearly half of participants achieved program completion, defined as performing 22 daily floor-to-stand repetitions. Although modest, this rate supports the feasibility of the protocol in a setting with limited rehabilitation infrastructure. Importantly, even non-completers demonstrated substantial engagement, with half achieving over seven daily repetitions, indicating overall acceptability.

Completion was associated with better baseline functional status, as completers exhibited lower Borg CR10 scores and higher 6MWD. This contrasts with findings by Boutou et al.²⁶, who reported higher completion among patients with lower baseline performance, likely reflecting differences in program structure and completion definitions. Socio-demographic characteristics and smoking status were not associated with adherence, suggesting that commonly reported barriers such as cost, distance, and transportation²⁷⁻²⁹ were effectively mitigated by the program's design.

Social support appeared influential, with a higher prevalence among completers, consistent with evidence highlighting the facilitating role of caregivers in rehabilitation participation.^{8,30} Conversely, musculoskeletal pain and psychological factors, including fatigue and low motivation, may have limited adherence, in line with previous reports identifying these as under-recognized barriers in COPD rehabilitation.³¹⁻³³ These findings emphasize that adherence reflects an interplay of physical, psychological, and social determinants rather than physiological capacity alone.

Interpretation of Post-intervention Changes

Completers showed clinically meaningful improvements in dyspnea, exertional effort, and disease impact, whereas the only statistically significant change among non-completers was in perceived exertion. This pattern suggests that the main short-term benefit of sustained FSE practice was symptomatic rather than physiological. The improvement in CAT among completers is particularly relevant, because CAT is known to be responsive to rehabilitation-related change and is widely used to capture patient-perceived benefit in COPD.²¹

These results should be interpreted in the context of conventional center-based PR, which remains the reference intervention when accessible. Conventional PR is usually delivered as a supervised, multidisciplinary program combining endurance training (such as cycle ergometry) with resistance training, often including lower-limb strengthening. In randomized controlled trials, such programs have produced clinically meaningful improvements in exercise tolerance, dyspnea, and health-related quality of life compared with usual care.^{34,35} In

this respect, the direction of change observed with the FSE is consistent with the rehabilitation literature regarding symptom burden and health status, but the magnitude and breadth of benefit appear to be narrower than typically expected from conventional PR.

This difference is also helpful for interpreting the functional outcomes. In conventional PR, improvements in exercise tolerance are commonly reflected by gains in 6MWD and related endurance outcomes.^{34,35} In the present study, the absence of consistent signals for 6MWD and 1-min STS suggests that FSE did not provide sufficient aerobic or endurance stimuli to induce broader physiological adaptations over 9 weeks. Rather, the intervention seems to have primarily affected confidence in movement, symptom perception, and task-specific functional tolerance. The numerically favorable change in TUG among completers may still be of interest because repeated floor-to-stand transitions plausibly train balance, transitional mobility, and lower-limb control; however, this signal remains modest and should be interpreted cautiously given the small pilot sample.

The muscle results follow the same logic. Peripheral muscle outcomes remained largely unchanged over 9 weeks, suggesting that the FSE program did not provide a sufficiently strong resistance stimulus to produce consistent gains in dynamometric testing. This contrasts with COPD training studies showing that resistance-containing rehabilitation programs can improve peripheral muscle force, including lower-limb strength, and that combined endurance-plus-strength approaches may produce greater gains in quadriceps strength than endurance training alone.^{36,37} The discrepancy is plausible: FSE is a pragmatic, low-resource, functional-transition program, whereas conventional PR and structured resistance training use more controlled loading, progression, and repetition schemes. Furthermore, in the present study, the muscle assessments relied on isolated, standardized measures, whereas FSE is likely to have a greater influence on task-specific movement efficiency and confidence than on maximal force generation.

Finally, the present findings remain coherent with the literature on culturally adapted rehabilitation modalities such as Tai Chi and yoga, which often show stronger effects on symptoms, health status, and functional confidence than on isolated physiological or muscle endpoints.^{10,12,38-40} Overall, FSE should not be viewed as equivalent to conventional PR. Rather, it appears to be a pragmatic, culturally contextualized strategy that may provide meaningful symptomatic benefit when conventional PR is unavailable or difficult to access.

Cultural Relevance and External Validity

A major strength of the FSE program is its alignment with local cultural practices and daily routines. Exercises could be performed safely at home with minimal supervision, thereby reducing travel and cost burdens that participants frequently reported. The floor-based movements reflect functional activities embedded in North African daily life,¹³ potentially enhancing familiarity and adherence. Program flexibility further allowed adaptation to personal and religious schedules without imposing cultural constraints.

These features suggest that FSE could be transferable across North Africa, where shared lifestyle patterns and familial structures provide a common framework.¹⁴ However, heterogeneity in healthcare infrastructure and patient education across urban and rural areas warrants cautious extrapolation.⁴¹ Broader validation will require multicenter studies in diverse settings.

Limitations and Implications for Future Research

The absence of randomization limits causal inference, although it is ethically justified in this context. Sample size and attrition reduced statistical power, and self-reported home practice may have introduced information bias. COPD-related fatigue and psychological comorbidities further complicated sustained participation, underscoring the need for individualized rehabilitation strategies. In addition, the clinically necessary extension of recovery time beyond standardized rest intervals may have increased measurement variability in late-session measures of muscle strength and endurance. Future studies should plan more conservative rest windows and consider recording actual recovery times to support sensitivity analyses.

Despite these limitations, clinically meaningful improvements were observed in key outcomes, supporting further evaluation of the FSE in larger, randomized trials. Future research should assess long-term effects on falls, quality of life, and disease burden, as well as optimal integration within existing rehabilitation pathways.

CONCLUSIONS

In a resource-limited North African setting, a culturally adapted, equipment-free, floor-to-stand rehabilitation program proved feasible and safe, with nearly half of participants achieving full adherence. Completers consistently obtained statistically significant improvements in dyspnea, tolerance to exertion, and disease impact, whereas non-completers showed limited benefits. Peripheral muscle testing did not show systematic gains over 9 weeks. Musculoskeletal comorbidities, mental fatigue and limited social support emerged as potential barriers to adherence, underscoring the role of both physical and psychosocial determinants in rehabilitation success. The socio-cultural adaptability of the protocol further supports its relevance for similar populations across North Africa. These findings should not be interpreted as supporting equivalence between the FSE and conventional center-based PR, which remains the reference intervention when accessible. Rather, they support further controlled evaluation of the FSE as a pragmatic, low-resource, culturally acceptable option that may complement existing rehabilitation pathways or extend access to rehabilitation where conventional PR cannot be delivered.

Ethics

Ethics Committee Approval: The study protocol was approved by the Ethics Committee of the Faculty of Medicine, Laghouat University (protocol no.: 12/2024; decision date: 20 November 2024). All procedures were conducted in accordance with institutional and ethical standards and the Declaration of Helsinki.

Informed Consent: Informed written consent was obtained from all participants.

Footnotes

Authorship Contributions

Surgical and Medical Practices: R.S.A.B., H.M.F., A.Z., L.L., F.H., A.L., Concept: R.S.A.B., H.M.F., A.Z., L.L., M.S.B., F.H., A.L., M.O.S., Design: R.S.A.B., M.B., H.M.F., A.Z., L.L., M.S.B., F.H., M.O.S., Data Collection or Processing: M.B., H.M.F., A.Z., L.L., M.S.B., Analysis or Interpretation: R.S.A.B., H.M.F., A.Z., L.L., F.H., A.L., M.O.S., Literature Search: R.S.A.B., M.B., H.M.F., A.Z., L.L., M.S.B., Writing: R.S.A.B., M.B., H.M.F., A.Z., L.L., M.S.B., F.H., A.L., M.O.S.

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Original Article



Translation, Cultural Adaptation, and Validation of the Turkish Version of the St George's Respiratory Questionnaire for Idiopathic Pulmonary Fibrosis (SGRQ-I)

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ABSTRACT

OBJECTIVE: Idiopathic pulmonary fibrosis (IPF) substantially impairs health-related quality of life (HRQoL). The IPF-specific St George's Respiratory Questionnaire (SGRQ-I) is not available in Turkish. This study aimed to translate, culturally adapt, and validate the SGRQ-I for Turkish-speaking patients with IPF.

MATERIAL AND METHODS: Following international guidelines, the SGRQ-I underwent forward translation, reconciliation, back translation, developer review, and cognitive debriefing. Adult patients with IPF were consecutively recruited. Validity was assessed against the Turkish SGRQ and by examining associations with forced vital capacity (FVC), diffusing capacity for carbon monoxide (DLCO), the six-minute walk test (6MWT), gender-age-physiology (GAP) stage, modified Medical Research Council (mMRC) grade, and long-term oxygen therapy (LTOT) status. Test-retest reliability was assessed over seven days in clinically stable patients.

RESULTS: One hundred eighty patients were included (mean age 66.3±10.0 years; 36% male). Agreement with the SGRQ was excellent for the activities, impact, and total scores [intraclass correlation coefficients (ICC) >0.90] and moderate for the symptoms score. The SGRQ-I total score was significantly correlated with FVC% ($r = -0.476$), DLCO% ($r = -0.406$), and 6MWT distance ($r = -0.462$, all $P < 0.001$). SGRQ-I scores differed significantly across groups stratified by DLCO%, GAP stage, mMRC grade, and LTOT status ($P < 0.01$). Test-retest reliability was good to excellent, with ICCs ranging from 0.891 to 0.962.

CONCLUSION: The Turkish SGRQ-I is a valid and reliable instrument for assessing HRQoL in IPF, supporting its use in clinical practice and multinational research.

KEYWORDS: Idiopathic pulmonary fibrosis, quality of life, SGRQ, validation, reliability, translation

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INTRODUCTION

Health-related quality of life (HRQoL) is a pivotal endpoint in chronic respiratory diseases, as clinical stabilization does not always reflect the full impact of the disease on patients' daily functioning and overall well-being. The St George's Respiratory Questionnaire (SGRQ), originally devised for chronic airflow limitations,¹ has gained widespread adoption due to its robust

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psychometric properties and has been successfully translated into multiple languages^{2,3}—including Turkish⁴—while maintaining its validity and reliability.

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive interstitial lung disorder characterized by ongoing fibrosis of the lung parenchyma, leading to impaired gas exchange, persistent breathlessness, and markedly limited exercise capacity. The median life expectancy following diagnosis is generally reported to be around 3–5 years.⁵ In comparison with other long-term respiratory conditions such as chronic obstructive pulmonary disease (COPD), patients with IPF usually experience a faster deterioration in functional ability and HRQoL.⁵

To address this disease-specific burden, the St George's Respiratory Questionnaire for idiopathic pulmonary fibrosis (SGRQ-I) was developed to capture IPF's unique symptomatology and functional impairments.⁶ Despite its demonstrated utility in IPF populations, no Turkish version of the SGRQ-I existed prior to our work. Ensuring conceptual equivalence and cultural relevance through a rigorous translation and adaptation process is essential for preserving the validity of patient-reported outcome (PRO) instruments.⁷

The goal of this study was to translate, culturally adapt, and psychometrically validate the SGRQ-I into Turkish for use among patients with IPF. A linguistically and culturally validated version of the SGRQ-I may facilitate standardized assessment of HRQoL among Turkish-speaking patients with IPF and support their inclusion in multinational research. The aim of this study was to translate and culturally adapt the SGRQ-I into Turkish and evaluate the validity and reliability of the Turkish version in patients with IPF.

MATERIAL AND METHODS

Study Design

This methodological, prospective study aimed to translate, culturally adapt, and validate the Turkish version of the SGRQ-I. Authorization to translate and validate the questionnaire was obtained from the original developer (Prof. J. Yorke).

The study protocol was approved by the Clinical Research Ethics Committee of University of Health Sciences Türkiye, Yedikule Chest Diseases and Thoracic Surgery Training and Research

Hospital (approval no: 2020-52, date: 03.12.2020). The study was registered at ClinicalTrials.gov (Identifier: NCT05147597). Written informed consent was obtained from all participants prior to enrollment.

Translation and Cultural Adaptation Process

This multi-step translation and cultural adaptation process—including developer permission, independent forward translations, reconciliation, blind back translation, developer review, and patient cognitive debriefing—aligns with established best practice guidelines in the field of PRO measures.^{8,9} The procedures performed are described below in a stepwise manner.

1. Permission and Preparation

Prior to translation, formal permission for adaptation was obtained from the questionnaire developer. The original English version of the SGRQ-I served as the reference text.

2. Forward Translation

Two independent native Turkish-speaking translators (translators 1 and 2) each produced a Turkish translation of the original questionnaire. The translations were performed one week apart to minimize recall bias.

3. Reconciliation

The two forward translations were compared in detail by the principal investigator, and a reconciled Turkish draft was produced through consensus. Differences in terminology, phrasing, and cultural relevance were discussed and resolved.

4. Back Translation

An independent bilingual translator, a native English speaker fluent in Turkish (translator 3), produced a back translation of the reconciled Turkish version into English. To ensure objectivity, this translator had no prior knowledge of the questionnaire.

5. Developer Review

The back-translated version and a reconciliation report were sent to the original questionnaire developer (Prof. J. Yorke) for review. Feedback from the developer was incorporated into revisions to ensure conceptual equivalence.

6. Pilot Testing (Cognitive Debriefing)

The pre-final Turkish version was administered to 10 patients diagnosed with IPF. Participants completed the questionnaire and were then interviewed using structured questions.

- “Did you understand this item?”
- “What does this mean to you?”
- “Can you explain it in your own words?”
- “Would you suggest an alternative wording?”

Based on patient feedback, minor modifications were made to improve clarity and cultural relevance.

Main Points

- A Turkish version of the St George's Respiratory Questionnaire for idiopathic pulmonary fibrosis (SGRQ-I) was developed through a standardized cross-cultural adaptation process.
- The Turkish SGRQ-I demonstrated strong validity and excellent test-retest reliability.
- SGRQ-I scores were associated with physiological impairment, exercise capacity, dyspnea, and disease severity.
- The instrument can be used confidently in clinical practice and research involving Turkish-speaking patients with idiopathic pulmonary fibrosis.

7. Proofreading and Finalization

The final Turkish version was formatted identically to the source version. Two independent proofreaders (proofreader 1 and proofreader 2) sequentially reviewed the document for spelling, grammar, typography, and consistency. The corrected version was sent to the developer for final endorsement.

Participants

The study population consisted of patients diagnosed with IPF who were consecutively recruited from the University of Health Sciences Türkiye, Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital. The diagnosis of IPF was established in accordance with the international American Thoracic Society (ATS)/European Respiratory Society (ERS)/Japanese Respiratory Society/Latin American Thoracic Association diagnostic guidelines and on the basis of compatible clinical findings, high-resolution computed tomography findings, and multidisciplinary evaluation. Histopathological findings were considered when clinically indicated and available.¹⁰ Eligible participants were adults over 18 years of age who were literate in Turkish and had a confirmed diagnosis of IPF. Patients were excluded if they had experienced an acute exacerbation within the preceding six weeks, had comorbid conditions limiting ambulation, or exhibited cognitive impairment that could interfere with questionnaire completion.

In scale development studies, it is generally recommended to include at least five participants for each item, resulting in a sample size equal to at least five times the number of items.^{11,12} Since the original questionnaire contained 36 items, a total of 180 patients were included in the present study.

Outcome Measures and Data Collection

Participants were prospectively recruited between January 2022 and January 2026. At the baseline visit, demographic and clinical characteristics were recorded, pulmonary function and functional exercise capacity were assessed, and the Turkish SGRQ-I and the validated Turkish SGRQ were completed by participants. The SGRQ-I was re-administered seven days later for assessment of test-retest reliability. Demographic data and clinical characteristics were recorded for all participants. Pulmonary function was assessed by forced vital capacity (FVC, % predicted) and diffusing capacity of the lung for carbon monoxide (DLCO, % predicted), measured according to ATS/ERS guidelines.¹³ Long-term oxygen therapy (LTOT) status (yes/no) was also documented. Functional exercise capacity was evaluated using the six-minute walk test (6MWT),¹⁴ expressed in meters.

Dyspnea severity was evaluated with the modified Medical Research Council (mMRC) dyspnea scale,¹⁵ while overall disease severity was classified using the gender-age-physiology (GAP) index. The GAP model is a multidimensional staging tool designed for prognostic assessment in IPF. It integrates four routine clinical variables: sex, age, and two lung function parameters (FVC, % predicted, and DLCO, % predicted). Each component is assigned a point value according to predefined cut-offs, producing a cumulative score between 0 and 8. Based on this score, patients are categorized into stage I (0–3 points),

stage II (4–5 points), or stage III (6–8 points). Advancing GAP stage is associated with poorer survival, with approximate 1-year mortality rates of 6%, 16%, and 39% for the three stages, respectively. This model is frequently applied in both clinical care and research as a prognostic indicator, for patient counseling, and for risk stratification in therapeutic studies.¹⁶ Participants completed both the Turkish version of the SGRQ-I and the validated Turkish version of the SGRQ during routine visits. To test reproducibility, the SGRQ-I was re-administered to all patients after a 7-day interval. Clinical stability during the 7-day test-retest interval was defined as the absence of acute exacerbation, hospitalization, or clinically relevant change in treatment.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, NY, USA). Concurrent validity of the SGRQ-I was evaluated by analyzing its agreement with SGRQ by Bland-Altman analysis and intraclass correlation coefficients (ICC). Pearson correlation analysis was used to analyze the relationship between SGRQ-I and the clinical variables. Known-groups validity of SGRQ-I was explored by comparing it across patient groups stratified by DLCO% (<40% vs. ≥40%), GAP score, mMRC grade, and LTOT status (yes vs. no), using independent-samples t-test or one-way ANOVA test depending on the number of patient groups. SGRQ-I was administered twice, at a 7-day interval, to assess test-retest reliability. A paired-samples t-test was used to compare the test and retest scores for any meaningful difference. ICCs were calculated for each domain score and for the total score of SGRQ-I. ICC values were interpreted according to the thresholds proposed by Koo and Li¹⁷, with values <0.50 indicating poor, 0.50–0.75 moderate, 0.75–0.90 good, and >0.90 excellent reliability.

RESULTS

The final cohort included 180 patients, with no missing data. Demographic and clinical characteristics of the participants, together with SGRQ-I and SGRQ scores, are presented in Table 1.

Agreement between SGRQ-I and SGRQ, as measured by ICCs, was excellent for the activity and impact domain scores and the total score, whereas it was moderate for the symptoms domain, as shown in Table 2. The Bland-Altman analysis presented in Figure 1 also supported agreement between the questionnaires, demonstrating that the mean differences between SGRQ-I and SGRQ scores were close to zero for the activity, impact, and total scores, with most observations lying within the 95% limits of agreement. However, patients tended to score higher on the SGRQ-I, especially if they had a higher symptom burden. Correlations of the domain and total scores of the SGRQ-I with clinical variables, including FVC%, DLCO%, and 6MWT, were statistically significant, further supporting the concurrent validity of the SGRQ-I. However, correlations between the symptoms domain and clinical variables were relatively weaker than those for the other domains, as shown in Table 3.

Each domain score and the total score of the SGRQ-I differed significantly among patients when stratified by DLCO% (<40%

Table 1. Demographic and clinical characteristics	
	Mean ± SD or n (%)
Age (years)	66.33±10.04
Female sex, n (%)	115 (64%)
DLCO, % predicted	53.88±19.27
FVC, % predicted	65.92±20.47
LTOT, n (%)	32 (17%)
6MWT (m)	435±140
SGRQ-I	
Symptoms	47.22±27.51
Activities	60.21±25.97
Impact	27.92±28.27
Total	40.26±24.74
SGRQ	
Symptoms	38.13±21.14
Activities	56.80±26.65
Impact	27.77±25.81
Total	38.29±22.86

SD: standard deviation, DLCO: diffusing capacity of the lung for carbon monoxide, FVC: forced vital capacity, LTOT: long-term oxygen therapy, 6MWT: six-minute walk test, SGRQ-I: St George's Respiratory Questionnaire for idiopathic pulmonary fibrosis, SGRQ: St George's Respiratory Questionnaire

Table 2. Agreement between SGRQ-I and SGRQ	
SGRQ-I domain	ICC (95% CI)
Symptoms	0.580 (0.474–0.669)
Activities	0.906 (0.876–0.929)
Impact	0.923 (0.898–0.942)
Total	0.940 (0.920–0.955)

SGRQ-I: St George's Respiratory Questionnaire for idiopathic pulmonary fibrosis, SGRQ: St George's Respiratory Questionnaire, ICC: intraclass correlation coefficient, CI: confidence interval

Table 3. Association of SGRQ-I with clinical variables		FVC %	DLCO %	6MWT
SGRQ-I symptoms	r	−0.304	−0.269	−0.216
	P	<0.001	<0.001	0.007
SGRQ-I activities	r	−0.466	−0.395	−0.462
	P	<0.001	<0.001	<0.001
SGRQ-I impact	r	−0.451	−0.381	−0.452
	P	<0.001	<0.001	<0.001
SGRQ-I total	r	−0.476	−0.406	−0.462
	P	<0.001	<0.001	<0.001

SGRQ-I: St George's Respiratory Questionnaire for idiopathic pulmonary fibrosis, FVC: forced vital capacity, DLCO: diffusing capacity of the lung for carbon monoxide, 6MWT: six-minute walk test

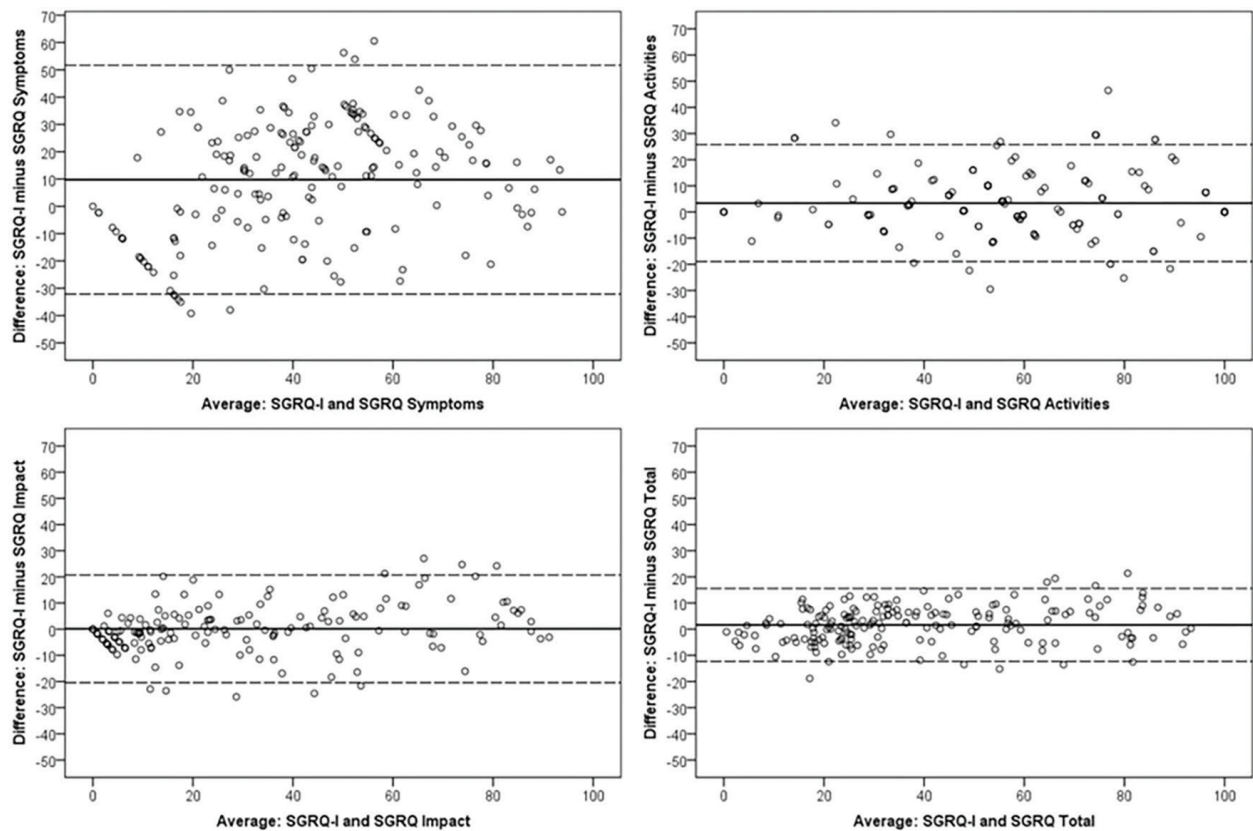


Figure 1. Bland-Altman plots showing agreement between SGRQ-I and SGRQ scores for the symptoms, activities, impact, and total domains. The solid horizontal line represents the mean difference between the two instruments, and the dashed lines represent the upper and lower 95% limits of agreement (mean difference ± 1.96 SD)

SGRQ-I: St George's Respiratory Questionnaire for idiopathic pulmonary fibrosis, SGRQ: St George's Respiratory Questionnaire, SD: standard deviation

vs. $\geq 40\%$), GAP stage, mMRC grade, and LTOT status (yes vs. no) ($P < 0.01$). A comparison of the total SGRQ-I scores across patient groups is presented in Figure 2.

The final analysis included 180 participants with complete data. The SGRQ-I was re-administered seven days after the baseline assessment for test-retest reliability. Test-retest reliability was good to excellent, with ICCs ranging from 0.891 to 0.962 across the domains and the total score; corresponding 95% confidence intervals are presented in Table 4. Paired-samples t-tests showed no significant differences between test and retest scores (all $P > 0.05$).

DISCUSSION

The Turkish version of the SGRQ-I demonstrated strong concurrent validity with the original Turkish SGRQ. ICCs were excellent for the activities, impact, and total scores (ICC > 0.90)

and moderate for the symptoms domain, closely mirroring the patterns observed in the original English validation¹⁸ and derived version studies.¹⁹ Bland-Altman analysis confirmed the agreement between the two instruments, with mean differences near zero for most domains. Similar domain-specific variability, particularly lower correlations for symptoms, has been reported in other adaptations,^{8,20} suggesting that symptom perception may be influenced by disease-specific and cultural factors.

The SGRQ-I effectively discriminated between patient groups stratified by DLCO%, GAP stage, mMRC grade, and LTOT status, with all comparisons reaching statistical significance. Patients with more advanced disease, worse gas exchange, or greater dyspnea burden had significantly higher (worse) SGRQ-I scores. These findings are consistent with prior work demonstrating the sensitivity of SGRQ-I to clinically relevant differences in disease severity in IPF populations.^{18,21,22}

Test-retest analysis over a 7-day interval in clinically stable patients revealed no significant differences between repeated administrations, and ICCs indicated good-to-excellent reliability. These values align with previous validations, including the Brazilian-Portuguese⁸ and Spanish²⁰ versions, which reported ICCs above 0.88.

Our psychometric findings parallel those of the Spanish²⁰ and Brazilian-Portuguese⁸ adaptations, both of which demonstrated high internal consistency (Cronbach $\alpha > 0.90$), strong test-

Table 4. Test-retest reliability of SGRQ-I

SGRQ-I domain	ICC (95% CI)
Symptoms	0.891 (0.857–0.918)
Activities	0.936 (0.915–0.952)
Impact	0.952 (0.936–0.964)
Total	0.962 (0.949–0.972)

SGRQ-I: St George's Respiratory Questionnaire for idiopathic pulmonary fibrosis, ICC: intraclass correlation coefficient, CI: confidence interval

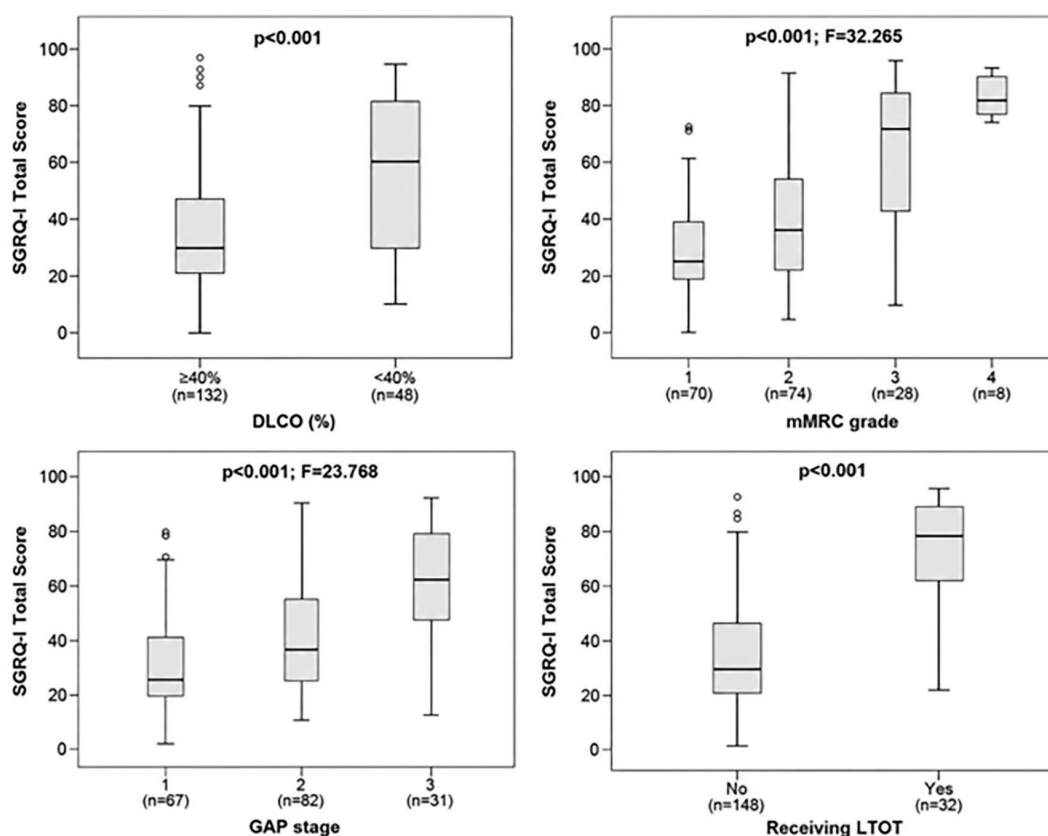


Figure 2. Total SGRQ-I scores according to DLCO%, GAP stage, mMRC grade, and LTOT status. Group comparisons were performed using independent-samples t-tests or one-way analysis of variance (ANOVA), depending on the number of groups, as described in the statistical analysis section

SGRQ-I: St George's Respiratory Questionnaire for idiopathic pulmonary fibrosis, DLCO: diffusing capacity of the lung for carbon monoxide, GAP: gender-age-physiology, mMRC: modified Medical Research Council, LTOT: long-term oxygen therapy

retest reliability, and robust construct validity. Cross-cultural adaptations have consistently shown that SGRQ-I retains its measurement properties across diverse settings.

Reliability coefficients were consistently high across all domains, supporting the instrument's stability for repeated measurements. The slightly lower reliability in the symptoms domain has also been noted in the original validation¹⁸ and may reflect day-to-day symptom variability in IPF.

Several PRO measures are employed to evaluate HRQoL in IPF, each with unique strengths and limitations. The King's Brief Interstitial Lung Disease (K-BILD) questionnaire is a concise, ILD-specific instrument validated for IPF, offering reduced respondent burden compared to longer tools.²³ However, it lacks direct comparability with COPD cohorts or the extensive historical datasets available for the SGRQ.^{1,7,18,24} The original SGRQ, though psychometrically robust, was developed for obstructive lung diseases and may not fully capture IPF-specific symptomatology and functional limitations.^{7,24} Swigris et al.²⁴ reviewed SGRQ's performance in IPF populations, affirming its utility, but emphasized that the disease-specific modifications in the SGRQ-I improve responsiveness and interpretability.^{7,21}

Other instruments have also been explored in IPF. The COPD assessment test, while originally developed for COPD, has demonstrated significant correlations with SGRQ scores and physiological parameters in IPF patients, indicating its validity as a measure of health status in this group.²⁵ The Leicester Cough Questionnaire addresses the impact of chronic cough—a cardinal feature in IPF—but focuses solely on cough-related domains and does not encompass broader HRQoL constructs. Other tools, such as the Needs Assessment Tool: Progressive Disease–Interstitial Lung Disease, target supportive care and palliative needs rather than HRQoL per se;²⁶ further illustrating the complementary value of the SGRQ-I, which captures both respiratory-specific health status and functional impairment in a disease-sensitive manner.

In our study, SGRQ-I scores were significantly correlated with DLCO%, 6MWT distance, and symptom burden, consistent with previous evidence. Amin et al.²⁷ demonstrated in a heterogeneous ILD cohort (including IPF) that DLCO% predicted was strongly associated with both 6MWT distance and SGRQ total score. In contrast, FVC% predicted showed no significant correlation with SGRQ, suggesting that DLCO may be a more sensitive physiological marker of HRQoL than FVC in ILD populations. Our findings in a cohort composed solely of IPF patients are consistent with these results, reinforcing the notion that reduced gas exchange capacity more closely reflects functional limitation and HRQoL impairment than do spirometric measures alone. In larger IPF-specific cohorts, higher GAP stage, reduced FVC and DLCO, and shorter 6MWT distances have been linked to poorer HRQoL outcomes. For example, in the IPF-PRO registry cohort ($n = 829$), each 10% decrease in DLCO% predicted corresponded to a significant increase in SGRQ total score—specifically, by 5.0 points.²⁸ This underscores the profound connection between physiological decline in gas exchange and deteriorating HRQoL in IPF.²⁸ Additionally, components of the SGRQ-I—across activity,

impact, and total scores—have shown moderate to strong correlations with FVC%, DLCO%, and mMRC dyspnea grade in validation studies.²⁹ These findings underscore the central role of dyspnea in HRQoL impairment. The alignment of SGRQ-I scores with functional capacity, gas exchange, dyspnea severity, and GAP staging affirms its clinical relevance in capturing the multidimensional burden of IPF.

While tools such as the K-BILD have also been validated in IPF,²³ SGRQ-I offers the advantage of direct comparability with COPD cohorts and large historical datasets, while preserving IPF-specific sensitivity.^{18,19}

Strengths of the Study

This study benefits from a robust translation and cultural adaptation process that adheres to international guidelines, and from the direct involvement of the original questionnaire developer. The sample size was larger than in some prior adaptations,^{8,20} enhancing the precision of the validity and reliability estimates.

Study Limitations

Due to its cross-sectional design, the study could not assess responsiveness to change; therefore, the longitudinal validity of the instrument remains to be determined. Furthermore, the single-center design may limit the generalizability of the findings to the broader Turkish IPF population. The relatively low proportion of male participants in the study cohort should be considered when interpreting the representativeness and generalizability of the findings. Although concurrent validity was assessed using the validated Turkish SGRQ and associations with relevant clinical measures were examined, the inclusion of an additional ILD-specific PRO measure, such as the K-BILD, could have strengthened the assessment of convergent validity. Additionally, subtle cultural differences may influence symptom reporting, warrant exploration in multicenter cohorts.

CONCLUSION

The findings of this study suggest that the Turkish version of the SGRQ-I is a valid and reliable instrument for assessing HRQoL in Turkish-speaking patients with IPF. The instrument may be useful for HRQoL assessment in clinical practice and facilitate the inclusion of Turkish-speaking patients in multinational studies using standardized PRO. Further multicenter, longitudinal studies are warranted to confirm its generalizability and to determine its responsiveness and the minimal clinically important difference.

Ethics

Ethics Committee Approval: The study protocol was approved by the Clinical Research Ethics Committee of University of Health Sciences Türkiye, Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital (approval no: 2020-52, date: 03.12.2020). The study was registered at ClinicalTrials.gov (Identifier: NCT05147597).

Informed Consent: Written informed consent was obtained from all participants prior to enrollment.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: E.P., Z.B.Ö., C.K., F.S.K., R.E., B.D., U.İ., H.Ç., E.Ç., Concept: E.P., Design: E.P., Data Collection or Processing: E.P., Z.B.Ö., C.K., F.S.K., R.E., B.D., U.İ., Analysis or Interpretation: M.Z., Literature Search: E.P., R.E., B.D., U.İ., Writing: E.P., M.Z., H.Ç., E.Ç.

Conflict of Interest: No conflict of interest was declared by the authors.

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Permission to Reproduce Material from Other Sources:

Permission to translate and culturally adapt the St George's Respiratory Questionnaire for Idiopathic Pulmonary Fibrosis (SGRQ-I) was obtained from the original developer, Prof. J. Yorke.

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Original Article



Integration of CURB-65 and CT Severity Score for Prognostic Prediction in Community-acquired Pneumonia

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ABSTRACT

OBJECTIVE: This study compared confusion, urea, respiratory rate, blood pressure, age ≥ 65 years (CURB-65) and computed tomography severity score (CTSS) for predicting 30-day mortality, intensive care unit (ICU) admission, and length of hospital stay in patients with community-acquired pneumonia (CAP) and assessed whether CTSS added prognostic value to CURB-65.

MATERIAL AND METHODS: This retrospective study included 456 adults with CT-confirmed CAP. CURB-65 and CTSS were calculated. Multivariable logistic regression and receiver operating characteristic analyses were performed for 30-day mortality and ICU admission, and area under the curve (AUC) values were compared using the DeLong test.

RESULTS: For mortality prediction, the AUC values were 0.894 for CURB-65, 0.762 for mean CTSS, and 0.909 for the combined mortality model. The combined model did not significantly outperform CURB-65 ($P = 0.081$). For ICU admission, the AUC values were 0.851, 0.716, and 0.881, respectively; the combined ICU model significantly outperformed CURB-65 ($P = 0.003$). The mean CTSS was independently associated with mortality and ICU admission, but was not associated with length of hospital stay.

CONCLUSION: CURB-65 remained a strong and practical predictor of mortality and ICU admission in CAP. Mean CTSS provided additional prognostic information for mortality and ICU admission, but not for length of hospital stay. The combined mortality model did not significantly improve discrimination compared with CURB-65 alone, whereas the combined ICU model did significantly improve discrimination in predicting ICU admission.

KEYWORDS: Community-acquired pneumonia, CURB-65, CT severity score, mortality, intensive care, ROC analysis

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INTRODUCTION

Lower respiratory tract infections, particularly pneumonia, remain a major cause of morbidity and mortality worldwide despite a decline in prevalence over the past three decades.¹ Because pneumonia has a broad clinical spectrum, accurate risk stratification at diagnosis is critical for determining the site of care and predicting prognosis.² Several prognostic scoring systems have therefore been developed and are widely used in clinical practice.

Confusion, urea, respiratory rate, blood pressure, age ≥ 65 years (CURB-65) is one of the most widely used and easily applied scoring systems. It includes confusion, urea level, respiratory rate, blood pressure, and age ≥ 65 years.³ CURB-65 is commonly used for mortality prediction and is included in international guidelines.^{2,4}

However, CURB-65 has several limitations for prognostication. The score was primarily developed to predict 30-day mortality, and its age component may substantially influence the score in older patients. In younger patients, reliance on clinical findings that may appear later, such as hypotension and confusion, may lead to early misclassification of some potentially severe cases as low risk.^{5,6} Its sensitivity for predicting intensive care unit (ICU) need is also limited, and it may not always provide adequate discrimination for critical patient triage.^{7,8} The absence of factors that may influence disease

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course, such as hypoxemia and radiological extent, may further limit its prognostic performance.⁹

In recent years, thoracic computed tomography (CT) has played an increasingly important role in assessing the severity and prognosis of pneumonia. The CT severity score (CTSS), a semiquantitative assessment method, enables objective evaluation of the extent and severity of lung involvement.¹⁰ Although CT-based severity scoring was widely studied during the coronavirus disease-2019 (COVID-19) pandemic,¹¹ lobar-based assessment of parenchymal involvement may also provide clinically relevant prognostic information in non-COVID community-acquired pneumonia (CAP).¹²⁻¹⁴

Clinical scores primarily reflect the systemic physiological response and clinical severity, whereas radiological scores reflect the anatomical extent of lung involvement. Therefore, these two approaches may provide complementary information. However, studies evaluating CURB-65 together with CTSS and investigating the additional prognostic contribution of combined models remain limited.¹³

Based on this complementary framework, we hypothesized that CTSS would provide prognostic information beyond CURB-65 by capturing the radiological disease burden. Therefore, this study aimed to compare the performance of CURB-65 and CTSS in predicting 30-day mortality, ICU admission, and length of hospital stay in patients with CAP, and to evaluate the additional prognostic contribution of CTSS to CURB-65.

MATERIAL AND METHODS

This retrospective study included patients aged 18 years or older who presented to the emergency department or the pulmonology outpatient clinic with CAP and who had pneumonia-compatible findings on thoracic CT between July 2023 and July 2025. This study was approved by the Ethics Committee of University of Health Sciences Türkiye, İzmir Tepecik Training and Research Hospital before data extraction and analysis (approval date: September 11, 2025; approval number: 2025/08-09), and all patient data were anonymized.

Main Points

- Confusion, urea, respiratory rate, blood pressure, age ≥ 65 years (CURB-65) was a strong predictor of 30-day mortality and intensive care unit (ICU) admission in patients with community-acquired pneumonia.
- Computed tomography severity score was independently associated with mortality and ICU admission, but its discriminative performance was lower than that of CURB-65.
- The combined mortality model did not significantly improve mortality discrimination over CURB-65 alone, whereas the combined ICU model significantly improved discrimination for ICU admission.
- The findings support the central role of scores that reflect systemic clinical response in the prognosis of pneumonia.

During the study period, 3,712 thoracic CT examinations were performed. The radiology database was retrospectively searched for thoracic CT reports obtained at presentation to the emergency department or pulmonology outpatient clinic that contained at least one of the predefined terms “consolidation,” “infiltration,” or “pneumonia.” This search identified 1,176 potentially eligible CT reports. Medical records were then reviewed to confirm CAP and determine eligibility according to the predefined criteria. After excluding patients with bilateral pleural effusion, severe acute respiratory syndrome coronavirus 2 positivity, absence of CT at initial presentation, repeated CT within the same clinical episode, trauma-related CT, insufficient data for CURB-65 calculation or outcome assessment, or alternative diagnoses, the final study population consisted of 456 patients. The detailed patient selection process and exclusion numbers are summarized in Figure 1.

During the study planning stage, the minimum required sample size was estimated to be 200 patients, based on previously reported 30-day mortality rates of approximately 10% for CAP, assuming 80% statistical power and a two-sided alpha level of 0.05 for logistic regression analysis. No sampling was performed; all eligible patients during the study period were included, and the final sample size exceeded the prespecified minimum requirement.

Demographic information, comorbidities, vital signs, and laboratory values were recorded, and CURB-65 scores were calculated for all patients. Radiological assessment was based exclusively on thoracic CT images obtained at presentation; chest radiographs were not evaluated. All CT examinations were independently evaluated by two radiologists, one with ≤ 5 years and the other with >10 years of radiology experience. Both radiologists were blinded to patients’ clinical and laboratory data, CURB-65 scores, ICU admission, mortality outcomes,

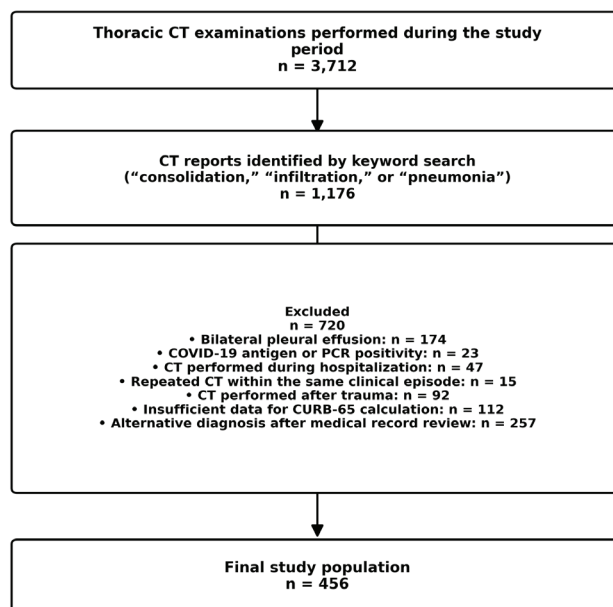


Figure 1. Flowchart showing the selection of the study population from thoracic CT examinations performed during the study period and the reasons for exclusion

CT: computed tomography, COVID-19: coronavirus disease-2019

and each other's assessments. CTSS was graded according to the percentage of parenchymal involvement in each lung lobe as follows: 0 = no involvement, 1 = <5%, 2 = 5–25%, 3 = 26–50%, 4 = 51–75%, and 5 = >75%. The total score, calculated by summing the scores of the five lobes, ranged from 0 to 25. The arithmetic mean of the scores assigned by the two radiologists was used as the final CTSS value in all statistical analyses.

For each outcome, separate multivariable logistic regression models were constructed: CURB-65-based, mean CTSS-based, and combined. The combined models included CURB-65, mean CTSS, and candidate covariates retained for multivariable analysis. For each patient, the predicted probability generated by the corresponding combined model was saved and used as the combined-model test variable in receiver operating characteristic (ROC) analyses.

Statistical Analysis

All data were analyzed using IBM SPSS Statistics for Windows, version 27.0 (IBM Corp., Armonk, NY, USA), and Python version 3.13.5 (Python Software Foundation, Wilmington, DE, USA) with NumPy 2.3.5, SciPy 1.17.0, and scikit-learn 1.8.0. Continuous variables were presented as mean $\pm$ standard deviation, and categorical variables were presented as numbers and percentages.

For binary outcomes, univariate logistic regression analysis was first performed to identify candidate predictors. Variables showing an association at $P < 0.20$ in univariate analyses were included as candidate variables in multivariable logistic regression models. Multivariable analysis results were reported as odds ratios (OR) with 95% confidence intervals (CI). The predicted probability from each combined multivariable model was used as the combined-model test variable in the ROC analysis. Non-parametric area under the curve (AUC) estimates, 95% CIs, optimal cutoffs based on the Youden index, and paired comparisons between ROC curves were calculated. AUC differences were evaluated using the DeLong method. For logistic regression models, the model fit was evaluated using the Omnibus test, -2 log likelihood, and Cox-Snell and Nagelkerke pseudo- R^2 values; calibration was assessed using the Hosmer-Lemeshow goodness-of-fit test.

The length of hospital stay was logarithmically transformed because it had a non-normal distribution. Correlations between log-transformed length of stay and prognostic scores were evaluated using Spearman correlation, and independent associations were assessed using multivariable linear regression.

To assess coefficient stability and potential overfitting in the combined models, a bootstrap robustness analysis was performed using 1,000 simple bootstrap samples. Bias-corrected and accelerated (BCa) 95% CIs and two-sided bootstrap P values were calculated for the regression coefficients.

Interobserver reliability for CTSS between the two radiologists was assessed using the intraclass correlation coefficient based on a two-way mixed-effects model, an absolute-agreement definition, and the mean of two measurements. Intraclass correlation coefficient (ICC) values were reported with 95% CIs.

A P value of < 0.05 was considered statistically significant for all tests.

RESULTS

A total of 456 patients were included in the study. Of the patients, 46.3% were female, and the mean age was 66.40 ± 17.67 years. The most common comorbidity was hypertension (40.1%). The mean CURB-65 score was 1.37 ± 1.12 , and the mean CTSS was 4.99 ± 3.29 . A total of 221 patients (48.5%) were hospitalized, 74 (16.2%) were admitted to the ICU, and the 30-day mortality rate was 11.0% (Table 1). Interobserver reliability for CTSS between the two radiologists was excellent (average-measures ICC: 0.981; 95% CI: 0.977–0.984; $P < 0.001$).

In the mortality analyses, variables showing an association at $P < 0.20$ in univariate analysis were included as candidate variables in multivariable models. To avoid conceptual overlap and overadjustment, age and the number of involved lobes were

Table 1. Demographic and clinical characteristics

Parameter	Number/percentage of cases
Sex/female	211 (46.3%)
Age, years, mean $\pm$ SD	66.40 $\pm$ 17.67
Comorbidities	
Hypertension	183 (40.1%)
Diabetes mellitus	95 (20.8%)
COPD	74 (16.2%)
Coronary artery disease	28 (6.1%)
Alzheimer's disease	93 (20.4%)
Congestive heart failure	37 (8.1%)
Atrial fibrillation	32 (7.0%)
Asthma	32 (7.0%)
Other	42 (9.2%)
CURB-65 score	
0	128 (28.1%)
1	119 (26.1%)
2	142 (31.1%)
3	48 (10.5%)
4–5	19 (4.2%)
Number of affected lobes	
1	131 (28.7%)
2	141 (30.9%)
3	103 (22.6%)
4	43 (9.4%)
5	38 (8.3%)
ICU admission	74 (16.2%)
Invasive mechanical ventilation requirement	33 (7.2%)
Mortality	50 (11.0%)

Data are presented as mean $\pm$ standard deviation for normally distributed continuous variables and as n (%) for categorical variables

COPD: chronic obstructive pulmonary disease, ICU: intensive care unit, CURB-65: confusion, urea, respiratory rate, blood pressure, age ≥ 65 years, SD: standard deviation

not included in the CURB-65-based and mean CTSS-based models, respectively. All mortality models were statistically significant and showed acceptable calibration. The Omnibus $\chi^2(6)$ values were 122.998, 81.106, and 132.205 for the CURB-65-based, mean CTSS-based, and combined mortality models, respectively; all with $P < 0.001$. The corresponding Nagelkerke R^2 values were 0.474, 0.326, and 0.504, respectively. Hosmer-Lemeshow goodness-of-fit tests indicated acceptable calibration for all three models: CURB-65-based model, $\chi^2(8) = 9.111$, $P = 0.333$; mean CTSS-based model, $\chi^2(8) = 5.080$, $P = 0.749$; and combined mortality model, $\chi^2(8) = 5.839$, $P = 0.665$.

In the CURB-65-based mortality model, CURB-65 was independently associated with 30-day mortality (OR: 5.380; 95% CI: 3.369–8.591; $P < 0.001$). In the mortality model based on mean CTSS, age (OR: 1.043; 95% CI: 1.013–1.073; $P = 0.004$), Alzheimer's disease (OR: 3.701; 95% CI: 1.690–8.105; $P = 0.001$), and mean CTSS (OR: 1.349; 95% CI: 1.221–1.490; $P < 0.001$) were independently associated with 30-day mortality. In the combined mortality model, both CURB-65 (OR: 4.496; 95% CI: 2.854–7.084; $P < 0.001$) and mean CTSS (OR: 1.206; 95% CI: 1.073–1.355; $P = 0.002$) remained independently associated with 30-day mortality, whereas asthma, Alzheimer's disease, congestive heart failure, and pleural effusion were not significantly associated with 30-day mortality (Table 2).

In the bootstrap robustness analysis of the combined mortality model, CURB-65 (bootstrap $P = 0.001$; BCa 95% CI for B, 1.005–2.395) and mean CTSS (bootstrap $P = 0.002$; BCa 95% CI

for B, 0.064–0.327) retained statistically significant coefficients. The BCa CIs for asthma, Alzheimer's disease, congestive heart failure, and pleural effusion included zero. The asthma estimate was unstable across bootstrap samples, consistent with sparse-data effects.

In ROC analysis for mortality prediction, the AUC values were 0.894 for CURB-65 (95% CI: 0.852–0.936; $P < 0.001$), 0.762 for mean CTSS (95% CI: 0.689–0.834; $P < 0.001$), and 0.909 for the combined mortality model (95% CI: 0.870–0.949; $P < 0.001$) (Figure 2). In paired DeLong comparisons, the combined mortality model did not significantly outperform CURB-65 (AUC difference: 0.015; 95% CI: -0.002 to 0.033; $P = 0.081$). CURB-65 significantly outperformed mean CTSS (AUC difference: 0.132; 95% CI: 0.059–0.206; $P = 0.0004$), and the combined mortality model significantly outperformed mean CTSS (AUC difference: 0.148; 95% CI: 0.085–0.210; $P < 0.001$).

At the Youden-optimal thresholds, CURB-65 ≥ 3 showed a sensitivity of 72.0% and specificity of 92.4% for mortality prediction. For mean CTSS, the optimal threshold was ≥ 8 , with a sensitivity of 52.0% and specificity of 86.7%. For the combined mortality model, the optimal predicted-probability threshold was ≥ 0.20768 , with a sensitivity of 74.0% and specificity of 92.1%. Thus, the combined mortality model provided only a limited numerical improvement over CURB-65, but did not show statistically significant superiority.

Table 2. Independent predictors of 30-day mortality

Model	Variable	B	S.E.	Wald	P	OR	95% CI lower	95% CI upper
Model 1 CURB-65	Number of lobes	0.152	0.165	0.854	0.355	1.165	0.843	1.609
	Asthma	-0.704	1.178	0.357	0.550	0.495	0.049	4.978
	Alzheimer's disease	0.586	0.415	1.995	0.158	1.797	0.797	4.053
	CHF	0.561	0.515	1.189	0.275	1.753	0.639	4.808
	CURB-65	1.683	0.239	49.644	<0.001*	5.380	3.369	8.591
	Effusion	0.337	0.418	0.651	0.420	1.400	0.618	3.174
Model 2 Mean CTSS	Age	0.042	0.015	8.165	0.004*	1.043	1.013	1.073
	CHF	0.591	0.503	1.378	0.240	1.805	0.673	4.841
	Alzheimer's disease	1.309	0.400	10.711	0.001*	3.701	1.690	8.105
	Effusion	0.344	0.375	0.842	0.359	1.411	0.676	2.943
	Asthma	-0.828	1.084	0.583	0.445	0.437	0.052	3.660
	Mean CTSS	0.299	0.051	34.775	<0.001*	1.349	1.221	1.490
Model 3 CURB-65 + mean CTSS	Asthma	-0.607	1.181	0.264	0.607	0.545	0.054	5.516
	Alzheimer's disease	0.719	0.430	2.801	0.094	2.053	0.884	4.765
	CHF	0.596	0.528	1.272	0.259	1.814	0.644	5.106
	Effusion	0.313	0.422	0.552	0.457	1.368	0.599	3.127
	CURB-65	1.503	0.232	41.994	<0.001*	4.496	2.854	7.084
	Mean CTSS	0.187	0.059	9.934	0.002*	1.206	1.073	1.355

Multivariable logistic regression analysis

* $P < 0.05$

CHF: congestive heart failure, CTSS: computed tomography severity score, CI: confidence interval, OR: odds ratio, CURB-65: confusion, urea, respiratory rate, blood pressure, age ≥ 65 years, S.E.: standard error

In the ICU admission analyses, variables showing an association at $P < 0.20$ in univariate analysis were included as candidates in multivariable models. To avoid conceptual overlap and overadjustment, age was not included in the CURB-65-based model, and the number of involved lobes was not included in

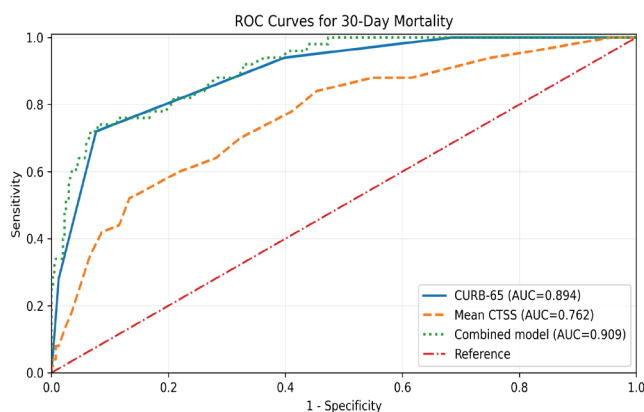


Figure 2. Comparison of ROC curves for CURB-65, mean CTSS, and the combined mortality model in predicting 30-day mortality. ROC curves for CURB-65, mean CTSS, and the combined mortality model based on predicted probability; AUCs were 0.894, 0.762, and 0.909, respectively

ROC: receiver operating characteristic, CURB-65: confusion, urea, respiratory rate, blood pressure, age ≥ 65 years, CTSS: computed tomography severity score, AUC: area under the curve

the mean CTSS-based model. All ICU admission models were statistically significant and showed acceptable calibration. The Omnibus $\chi^2(6)$ values were 135.121 for the CURB-65-based model, 83.792 for the mean CTSS-based model, and 139.623 for the combined ICU model, all with $P < 0.001$. The corresponding Nagelkerke R^2 values were 0.436, 0.285, and 0.449, respectively. Hosmer–Lemeshow goodness-of-fit tests indicated acceptable calibration for all three models: the CURB-65-based model ($\chi^2(8) = 8.236$, $P = 0.411$); the mean CTSS-based model ($\chi^2(8) = 10.482$, $P = 0.233$); and the combined ICU model ($\chi^2(8) = 8.549$, $P = 0.382$).

In the CURB-65-based model for ICU admission, CURB-65 (OR: 4.022; 95% CI: 2.762–5.855; $P < 0.001$), Alzheimer's disease (OR: 2.717; 95% CI: 1.347–5.478; $P = 0.005$), and pleural effusion (OR: 2.091; 95% CI: 1.066–4.100; $P = 0.032$) were independently associated with ICU admission. In the model based on mean CTSS, Alzheimer's disease (OR: 5.761; 95% CI: 2.893–11.469; $P < 0.001$), pleural effusion (OR: 2.049; 95% CI: 1.109–3.788; $P = 0.022$), age (OR: 1.024; 95% CI: 1.002–1.046; $P = 0.031$), and mean CTSS (OR: 1.239; 95% CI: 1.138–1.347; $P < 0.001$) were independently associated with ICU admission. In the combined ICU model, Alzheimer's disease (OR: 3.062; 95% CI: 1.495–6.271; $P = 0.002$), pleural effusion (OR: 2.080; 95% CI: 1.058–4.088; $P = 0.034$), CURB-65 (OR: 3.504; 95% CI: 2.424–5.065; $P < 0.001$), and mean CTSS (OR: 1.113; 95% CI: 1.009–1.227; $P = 0.033$) were independently associated with ICU admission (Table 3).

Table 3. Independent predictors of ICU admission

Model	Variable	B	S.E.	Wald	P	OR	95% CI lower	95% CI upper
Model 1 CURB-65	Asthma	−0.360	0.876	0.169	0.681	0.697	0.125	3.885
	Alzheimer's disease	0.999	0.358	7.803	0.005*	2.717	1.347	5.478
	CHF	−0.070	0.472	0.022	0.882	0.932	0.369	2.352
	Effusion	0.737	0.344	4.605	0.032*	2.091	1.066	4.100
	Number of lobes	0.009	0.137	0.004	0.947	1.009	0.772	1.319
	CURB-65	1.392	0.192	52.732	<0.001*	4.022	2.762	5.855
Model 2 Mean CTSS	Asthma	−0.576	0.807	0.509	0.476	0.562	0.116	2.735
	Alzheimer's disease	1.751	0.351	24.840	<0.001*	5.761	2.893	11.469
	CHF	0.214	0.457	0.219	0.640	1.238	0.505	3.035
	Effusion	0.718	0.313	5.243	0.022*	2.049	1.109	3.788
	Age	0.024	0.011	4.627	0.031*	1.024	1.002	1.046
	Mean CTSS	0.214	0.043	24.782	<0.001*	1.239	1.138	1.347
Model 3 CURB-65 + Mean CTSS	Asthma	−0.335	0.871	0.148	0.700	0.715	0.130	3.944
	Alzheimer's disease	1.119	0.366	9.366	0.002*	3.062	1.495	6.271
	CHF	−0.060	0.480	0.016	0.901	0.942	0.367	2.414
	Effusion	0.732	0.345	4.508	0.034*	2.080	1.058	4.088
	CURB-65	1.254	0.188	44.483	<0.001*	3.504	2.424	5.065
	Mean CTSS	0.107	0.050	4.569	0.033*	1.113	1.009	1.227

Multivariable logistic regression analysis

* $P < 0.05$

CHF: congestive heart failure, CTSS: computed tomography severity score, CI: confidence interval, CURB-65: confusion, urea, respiratory rate, blood pressure, age ≥ 65 years, S.E.: standard error, ICU: intensive care unit

In the bootstrap robustness analysis of the combined ICU model, Alzheimer’s disease, pleural effusion, and CURB-65 retained statistically significant coefficients, whereas the mean CTSS coefficient was borderline significant (bootstrap $P = 0.051$; BCa 95% CI for B, -0.012 to 0.219). Asthma and congestive heart failure were not significantly associated.

In the ROC analysis for ICU admission, the AUC values were 0.851 for CURB-65 (95% CI: 0.800–0.901; $P < 0.001$), 0.716 for mean CTSS (95% CI: 0.653–0.779; $P < 0.001$), and 0.881 for the combined ICU model based on the predicted probability (95% CI: 0.836–0.926; $P < 0.001$) (Figure 3). In paired DeLong comparisons, the combined ICU model significantly outperformed CURB-65 (AUC difference: 0.030; 95% CI: 0.010–0.050; $P = 0.0028$). Both CURB-65 and the combined ICU model significantly outperformed the mean CTSS: AUC difference: 0.135; 95% CI: 0.062–0.208; $P = 0.0003$ for CURB-65, and AUC difference: 0.165; 95% CI: 0.099–0.231; $P < 0.001$ for the combined ICU model.

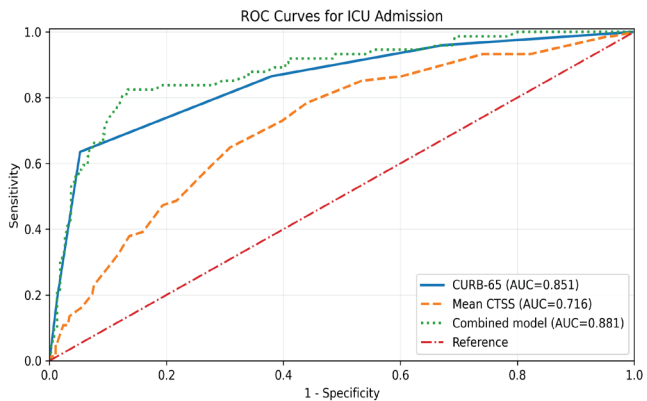


Figure 3. Comparison of ROC curves for CURB-65, mean CTSS, and the combined ICU model in predicting ICU admission. ROC curves for CURB-65, mean CTSS, and the combined ICU model based on predicted probability; AUCs were 0.851, 0.716, and 0.881, respectively

ROC: receiver operating characteristic, CURB-65: confusion, urea, respiratory rate, blood pressure, age ≥ 65 years, CTSS: computed tomography severity score, ICU: intensive care unit, AUC: area under the curve

At the Youden-optimal thresholds, CURB-65 ≥ 3 showed a sensitivity of 63.5% and specificity of 94.8% for ICU admission. For mean CTSS, the optimal threshold was ≥ 4.5 , with a sensitivity of 78.4% and specificity of 56.0%. For the combined ICU model, the optimal predicted-probability threshold was ≥ 0.20878 , with a sensitivity of 82.4% and specificity of 86.6%. A summary of ROC analyses, including AUC values, optimal cut-offs, sensitivity, specificity, Youden indices, and DeLong comparisons, is presented in Table 4.

Among hospitalized patients ($n = 221$), the length of hospital stay was not normally distributed; therefore, a logarithmic transformation was applied before analysis. In a Spearman correlation analysis, log-transformed length of stay showed a weak positive correlation with CURB-65 ($\rho = 0.230$; $P < 0.001$), whereas its correlation with CTSS was not statistically significant ($\rho = 0.110$; $P = 0.103$). In multivariable linear regression analysis, CURB-65 ($B = 0.096$; 95% CI: 0.023–0.170; $P = 0.010$), pleural effusion ($B = 0.269$; 95% CI: 0.082–0.456; $P = 0.005$), and congestive heart failure ($B = -0.295$; 95% CI: -0.570 to -0.019 ; $P = 0.036$) were independently associated with length of hospital stay. In contrast, CTSS was not independently associated with length of hospital stay ($P = 0.797$).

DISCUSSION

In this study, CURB-65 and CTSS were compared in their ability to predict 30-day mortality, ICU admission, and length of hospital stay in patients with CAP, and the performance of combined multivariable models was evaluated. CURB-65 showed strong discrimination for both mortality and ICU admission. Mean CTSS provided additional prognostic information for mortality and ICU admission in conventional multivariable models; however, its standalone discriminative performance was lower than that of CURB-65. The combined mortality model did not significantly improve discrimination over CURB-65 alone; however, the combined ICU model did significantly improve discrimination in predicting ICU admission.

In this study, the discriminatory power of CURB-65 for predicting mortality was high. This finding is consistent with previous studies reporting CURB-65 as a reliable tool for assessing pneumonia severity.^{3,15} However, CURB-65 may

Table 4. Summary of ROC analyses for 30-day mortality and ICU admission

Outcome	Model	AUC	95% CI	Optimal cut-off	Sensitivity (%)	Specificity (%)	Youden J
30-day mortality	CURB-65	0.894	0.852–0.936	≥ 3	72.0	92.4	0.644
	Mean CTSS	0.762	0.689–0.834	≥ 8	52.0	86.7	0.387
	Combined mortality model	0.909	0.870–0.949	≥ 0.20768	74.0	92.1	0.661
ICU admission	CURB-65	0.851	0.800–0.901	≥ 3	63.5	94.8	0.583
	Mean CTSS	0.716	0.653–0.779	≥ 4.5	78.4	56.0	0.344
	Combined ICU model	0.881	0.836–0.926	≥ 0.20878	82.4	86.6	0.691

The combined models were based on predicted probabilities derived from the corresponding multivariable logistic regression models. For CURB-65, the ROC-derived threshold of >2 corresponds to a clinical cut-off of ≥ 3 because CURB-65 is an integer-based score. In DeLong comparisons for 30-day mortality, the combined mortality model did not significantly outperform CURB-65 (AUC difference = 0.015; 95% CI: -0.002 to 0.033 ; $P = 0.081$), whereas CURB-65 significantly outperformed mean CTSS ($P = 0.0004$) and the combined mortality model significantly outperformed mean CTSS ($P < 0.001$). For ICU admission, the combined ICU model significantly outperformed CURB-65 (AUC difference = 0.030; 95% CI: 0.010–0.050; $P = 0.0028$), CURB-65 significantly outperformed mean CTSS ($P = 0.0003$), and the combined ICU model significantly outperformed mean CTSS ($P < 0.001$)

AUC: area under the curve, CI: confidence interval, CTSS: computed tomography severity score, ICU: intensive care unit, ROC: receiver operating characteristic, CURB-65: confusion, urea, respiratory rate, blood pressure, age ≥ 65 years

be insufficient in some patient groups because it includes a limited number of variables and does not directly incorporate hypoxemia, radiological extent, or broader markers of acute physiological reserve.^{5,6} Because CURB-65 includes age and parameters reflecting systemic physiological deterioration, its prognostic performance may be particularly strong in cohorts characterized by older age and greater clinical severity. Therefore, the high discriminative performance observed in our study may be partly related to the clinical characteristics and CT-selected nature of the patient population.

Although much of the available evidence on CT-based severity scoring originates from the COVID-19 era,¹⁰ CT-based quantification of parenchymal involvement may also be relevant in non-COVID CAP.¹²⁻¹⁴ Nevertheless, disease-specific differences in radiological patterns, clinical courses, and prognoses should be considered when extrapolating COVID-19 CTSS findings to non-COVID CAP. In the present study, CTSS was evaluated as a semiquantitative marker of anatomical disease burden rather than as a replacement for clinical severity assessment. The excellent interobserver reliability in the present study supports the reproducibility of this semiquantitative approach and is consistent with previous validation studies of CT scoring systems.^{16,17}

Although the AUC of the combined mortality model was numerically highest, the increase was not statistically significant compared with that of CURB-65. At the Youden-optimal thresholds, the combined mortality model provided slightly higher sensitivity and had specificity similar to that of CURB-65, whereas the mean CTSS alone provided lower sensitivity and specificity. These findings suggest that radiological disease burden may complement clinical severity assessment, but it does not meaningfully replace or substantially outperform CURB-65 for mortality prediction in this cohort.

For ICU admission, CURB-65 retained strong discriminative performance, but the combined ICU model achieved a statistically significant increase in AUC. The combined model also showed a more balanced sensitivity-specificity profile than either CURB-65 or mean CTSS alone. This finding suggests that integrating radiological extent with the clinical score and selected clinical covariates may improve discrimination in ICU triage, particularly in patients who are already undergoing thoracic CT for diagnostic clarification. However, this potential role should be interpreted cautiously because external validation is required before routine clinical application.¹⁸

The bootstrap findings further qualified the ICU results. CURB-65, Alzheimer's disease, and pleural effusion retained stable associations with ICU admission, whereas the mean CTSS coefficient was borderline in the bootstrap analysis. Thus, the incremental ICU discrimination provided by the combined model should not be attributed solely to a robust CTSS effect. Rather, it likely reflects the combined contribution of clinical severity, radiological extent, and selected clinical covariates.

Length-of-stay analyses also supported the limited contribution of CTSS. Log-transformed length of stay showed a weak positive correlation with CURB-65, whereas its correlation with CTSS was not statistically significant. In multivariable

linear regression analysis, CURB-65, pleural effusion, and congestive heart failure were independently associated with length of stay, whereas CTSS was not independently associated. These findings suggest that hospital stay may be more closely related to systemic clinical status and comorbidity burden than to radiological extent alone.¹⁹

From a practical perspective, CTSS should not be considered a routine replacement for bedside clinical scores because CT availability, cost, radiation exposure, and the need for radiological expertise may limit its universal use. Its potential role may be more appropriate in selected patients who are already undergoing CT for diagnostic clarification, or in those whose ICU triage remains uncertain after initial clinical assessment.

The relatively high AUC values observed for CURB-65 should be interpreted in the context of a CT-selected cohort rather than the broader CAP population. Although the mean CURB-65 score indicated a low-to-intermediate clinical risk profile, 45.8% of patients had a CURB-65 score ≥ 2 , nearly half of the cohort was hospitalized, and a substantial proportion required ICU admission. Because thoracic CT is more likely to be performed in patients with greater clinical concern, atypical presentation, diagnostic uncertainty, or relevant comorbidities, milder CAP cases managed without CT may have been underrepresented. This spectrum effect may have increased the apparent discriminative performance of CURB-65 and may limit the direct generalizability of the findings to all patients with CAP.²⁰

One of the strengths of this study is that CURB-65 and CTSS were evaluated both separately and in predicted-probability models based on logistic regression. This approach allowed comparison of the independent and combined contributions of clinical and radiological variables to prognostic prediction in the same study population. In addition, CTSS was assessed independently by two blinded radiologists, and interobserver reliability was excellent.

Study Limitations

This study has several limitations. Its retrospective and single-center design limits generalizability. In addition, the CT-selected design may have shifted the patient spectrum toward more clinically complex or severe cases and contributed to overestimation of model performance. Patients with CAP who did not undergo thoracic CT were not included; therefore, the findings may not be directly applicable to milder CAP cases managed without CT. Although a bootstrap robustness analysis was performed to assess coefficient stability, potential overfitting cannot be completely excluded because of the number of candidate predictors relative to outcome events. The bootstrap procedure evaluated the stability of regression coefficients but did not provide optimism-corrected AUC estimates, calibration slopes, or Brier scores; therefore, it should not be interpreted as a complete internal validation of model performance. In addition, sparse events in patients with asthma resulted in unstable bootstrap estimates. External validation in an independent cohort remains necessary.

CONCLUSION

In patients with CAP, CURB-65 was a strong predictor of 30-day mortality and ICU admission. Mean CTSS was independently associated with 30-day mortality and ICU admission in conventional multivariable analyses, but showed lower standalone discrimination than CURB-65 and was not independently associated with length of hospital stay. The combined mortality model did not significantly improve discrimination over CURB-65 alone, whereas the combined ICU model significantly improved discrimination for ICU admission. These findings suggest that radiological extent may provide complementary prognostic information in selected CT-assessed patients, particularly when ICU triage is being considered.

Ethics

Ethics Committee Approval: The approval was obtained from University of Health Sciences Türkiye, İzmir Tepecik Training and Research Hospital before data extraction and analysis (approval date: September 11, 2025; approval number: 2025/08-09).

Informed Consent: Patient consent was not obtained because of the retrospective design and use of anonymized data.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Ö.G., Concept: Ö.G., Design: Ö.G., Data Collection or Processing: Ö.G., O.Ö., İ.A., Analysis or Interpretation: Ö.G., O.Ö., İ.A., Literature Search: Ö.G., Writing: Ö.G., O.Ö., İ.A.

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Original Article



Clinical Significance of Age and Coexisting Lifestyle-related Diseases in ILD Patients with Acute Exacerbation

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ABSTRACT

OBJECTIVE: As the population ages, the impact of aging and comorbid lifestyle-related diseases on the prognosis of interstitial lung disease (ILD) has not been fully investigated. Therefore, we investigated the impact of age and comorbidities on the prognosis of patients with ILD who experienced acute exacerbations (AEs).

MATERIAL AND METHODS: We retrospectively reviewed the medical records and chest computed tomography scans of all consecutive ILD patients, with or without AE, between May 2015 and July 2025. The survival times of cases with and without AE were investigated.

RESULTS: Median survival time (MST) for 443 ILD cases was 10 years, while the MST for the 158 cases who developed AE was 2 months. The prognosis of cases who developed AE at age 80 years or older was significantly poorer than that of cases younger than 80 years. Among cases younger than 80 years, the survival curve for those who survived 3 months after the onset of AE plateaued. Favorable factors among cases who developed AE were age younger than 80 years and absence of comorbidities such as hypertension, diabetes mellitus, and malignancy.

CONCLUSION: For ILD patients who developed AE, “80 years of age” was the threshold age distinguishing good from poor prognosis. Some patients, particularly those with ILD who were diagnosed early, appeared likely to have an improved prognosis. Some AE patients, particularly younger patients, could be expected to have a good long-term prognosis if they survive a certain period of time.

KEYWORDS: Interstitial lung disease, acute exacerbation, age, comorbidities

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INTRODUCTION

Interstitial lung diseases (ILDs) are a variety of diverse entities that cause inflammation and fibrosis of the lung parenchyma.¹ ILDs, whether idiopathic pulmonary fibrosis (IPF) or connective tissue disease (CTD)-associated ILD,² can lead to acute exacerbations (AEs) characterized by the appearance of new pulmonary infiltrates in both lung fields and rapid progression of respiratory failure.³ There is a generally accepted, very pessimistic view that the prognosis of ILD patients is poor.^{4,5} Many studies have reported that the median survival time (MST) for patients who developed AEs was 1 to 4 months,⁸⁻¹⁰ and for patients who did not develop AEs, it was only several years.⁴⁻⁷ However, when assessing the prognosis of ILD, patient background factors such as age and comorbidities, as well as disease severity, should be considered. These results might be used to improve prognosis.

In developed countries, the population is aging, and as a result, changes are being observed in the onset of many diseases and the composition of patients.¹¹ These changes might also be occurring in ILD patients.^{4,12-19} In general, the elderly have a high prevalence of lifestyle diseases,¹¹ which might reduce their ability to resist sudden onset and their tolerance to the

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side effects of ILD treatment. Although it is assumed that such a situation also exists in ILD patients, the impact of aging and coexisting lifestyle-related diseases on prognosis has not been thoroughly investigated.

Against this background, we conducted a study to investigate the influence of age and comorbidities on the prognosis of ILD patients with AE, aiming to characterize the current situation and clarify issues in ILD clinical practice.

MATERIAL AND METHODS

Patients

We retrospectively reviewed medical records and chest computed tomography (CT) scans from May 2015 to July 2025. First, we extracted data on patients diagnosed with ILD from the medical records at our two institutions during the study period. ILDs included usual interstitial pneumonia (UIP)/idiopathic interstitial pneumonia,^{1,20-23} pleuroparenchymal fibroelastosis (PPFE),²¹ combined pulmonary fibrosis and emphysema (CPFE)²² and CTD-ILDs.² Patients with occupational ILDs, iatrogenic ILDs (e.g., drug-induced ILDs), sarcoidosis, pulmonary alveolar proteinosis, or lymphangioleiomyomatosis were excluded from this study. Additionally, patients with acute interstitial pneumonia were excluded due to their acute clinical course. Characteristics of CTD-ILD patients, such as age and gender, differed from those of idiopathic ILD patients; therefore, these characteristics were shown separately in the patient characteristics section. The chest CT images of the extracted patients were reinterpreted by chest physicians according to the diagnostic criteria of ATS.¹ For example, the presence of ground-glass opacities, traction bronchiectasis, and honeycombing was considered a UIP pattern, whereas the absence of these characteristics was considered a non-specific interstitial pneumonia (NSIP) pattern, PPFE pattern and CPFE pattern.^{1,20-22} Chest CT images of CTD-ILD patients were also reinterpreted to determine whether they exhibited UIP or NSIP patterns.^{1,20} Only patients whose images matched the imaging patterns of IPF, NSIP, CPFE, and PPFE were included in this study. In accordance with the ERS/ATS Statement 2025, an analysis of survival and prognosis was conducted for all ILD patients.²³ In addition, a sub-analysis of survival and prognosis in UIP patients, the most common type of idiopathic ILD, was performed based on morphologic patterns assessed by pathology and imaging.

Severity grading of ILD was determined according to the Japanese IPF disease severity classification; stage I: PaO₂ at rest ≥80 Torr, stage II: PaO₂ at rest = 70–80 Torr, and SpO₂ ≥93%

during a 6-min walk test, stage III: PaO₂ at rest = 60–70 Torr (SpO₂ = 90–93% at rest), and stage IV: PaO₂ at rest <60 Torr (SpO₂ <90% at rest).^{24,25}

The definition of AE was based on the diagnostic criteria for AE-IPF by Collard et al.³ According to the definition used in this study, an AE was considered present if the following conditions were met: ILD was diagnosed at the time of the AE or had been previously diagnosed; acute progression of dyspnea occurred within the previous month; CT revealed new ground-glass opacities and/or infiltrates; and deterioration was not explained by heart failure or excess fluid accumulation alone. In analyses of survival time after the onset of AE, several cut-off values such as 30 days, 60 days, and 90 days have been used in some previous reports.^{26,27} In the uni- and multivariate analyses of this study, survival or death at 30 days after the onset of AE was used as the cut-off period. In this study, if an ILD patient experienced two or more AEs, they were counted as two or more AE cases. For example, a patient who developed two AEs and was saved at least once was treated as two cases and analyzed.

This study investigated the impact of comorbidities that might affect the prognosis of ILD and its AEs, particularly major lifestyle-related diseases such as hypertension, diabetes, cardiovascular and cerebrovascular disorders, and malignant diseases.²⁸⁻³⁴

This study was reviewed and approved by the Institutional Ethics Committee of University of Tsukuba Hospital, Mito Medical Center (approval number: NO 25-47, date: June 2, 2025).

Statistical Analysis

In the statistical analysis of this study, the Mann-Whitney U test, a non-parametric test, was used to compare variables, including age, maximum primary tumor diameter, and clinical test values, between the two groups. The time at which ILD was confirmed by chest CT was used as the starting point, and survival status at the end of the study period was examined. For patients who were alive at the end of the study period, the observation period ran from the starting point. For patients who died during the study period or who were transferred to another hospital, the observation period extended from the starting point to the last follow-up. In this study, based on previous studies,²⁸⁻³⁰ patients who survived for more than 30 days after the onset of AE were defined as “patients who could be saved,” and patients who died within 30 days were defined as “patients who could not be saved.” Comparisons between groups were made using the chi-square test and the Mann-Whitney U test. Survival analysis was performed using the log-rank test and the Cox proportional hazards model. A *P* value of <0.05 indicated a significant difference.

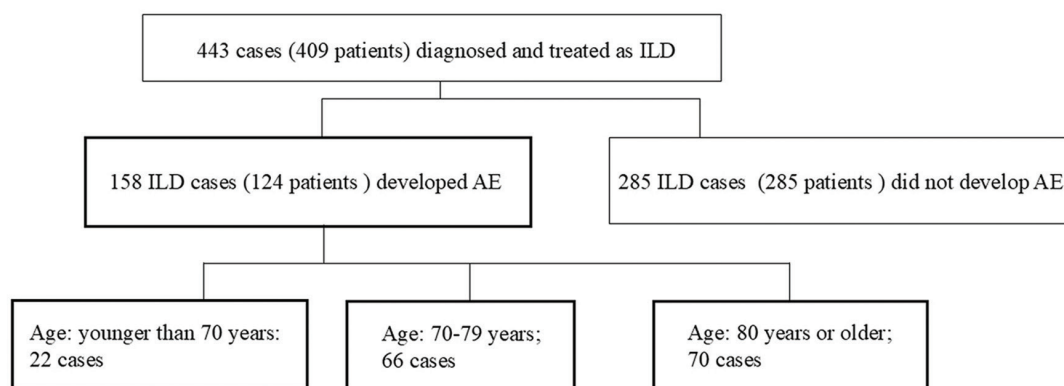
RESULTS

Characteristics of all the Interstitial Lung Disease Patients

Figure 1 shows the study flowchart for ILD patients. During the study period, 409 patients were diagnosed with ILD. Of these, 124 patients developed 158 AEs (26 patients had 34 AEs: 23 patients had 2 AEs, 1 patient had 3 AEs, 1 patient had 5 AEs, and 1 patient had 6 AEs). The median follow-up for all patients

Main Points

- For interstitial lung disease (ILD) patients who develop acute exacerbations (AEs), the age of 80 is the border between a better or poorer outcome.
- There are some patients, particularly those with ILD who are diagnosed early, who might achieve an improved outcome.
- Some patients with AE, particularly younger patients, can expect to have a good long-term prognosis if they can survive a certain period after AE onset.

**Figure 1.** Study flow chart

ILD: interstitial lung disease, AE: acute exacerbation

was 48 months (range: 1–360 months). Among 443 cases in 409 ILD patients (including 26 patients with 34 AEs), 178 were male, and the median age at the time of ILD diagnosis was 73 years (range: 20–97 years). Smoking history was current in 37 cases, former in 241, never in 162, and unknown in 3. The comorbidities were as follows: 167 cases of hypertension, 128 of diabetes mellitus, 108 of cerebrovascular disease (including past and coexisting conditions), and 91 of malignant tumors (including past and coexisting conditions). ILD was classified as UIP in 286 cases, as NSIP and other conditions in 88 cases, and as collagen disease-related in 69 cases. The severity classification at the time of ILD diagnosis was I: 330 cases, II: 39 cases, III: 60 cases, and IV: 14 cases.

Characteristics of Interstitial Lung Disease Patients who Developed Acute Exacerbation

The median age at AE onset was 78 years (range: 54–97 years). By age group, 22 (13.9%) cases were under 70 years old, 66

(41.8%) were in their 70s, and 70 (44.3%) were 80 years or older. Patient characteristics by age are shown in Table 1. The older the patient group, the higher the proportion of men, patients with cardiovascular disease, and patients with a history of smoking. The median time from AE onset to consultation was 2 days (range: 1–15 days).

Do Not Attempt Resuscitation Acquisition and Treatment Details for Patients with Acute Exacerbation

Table 2 shows the rate of DNAR submission by patients with AEs and their families, as well as the treatment outcomes for AEs. There were no significant differences between age groups in the rates of “do not attempt resuscitation (DNAR)” submission or of treatment administered for AEs.

Survival in all 443 Interstitial Lung Disease Cases

During the follow-up period, 161 of the 443 cases died. The causes of death were respiratory failure in 143 cases and other

Table 1. Clinical characteristics of cases by age at onset of acute exacerbation

	Patient groups by age		P value
	Younger than 80 years	80 years or older	
Number of cases	88	70	
Gender, male : female	74 ; 14	35 : 35	0.001
Comorbid diseases			
Hypertension	37	41	0.039
Diabetes	33	21	0.324
Cardio-cerebrovascular	17	17	0.450
Malignancy	18	13	0.767
Smoking habit, never : former : current	16 : 59 : 13	38 : 32 : 0	0.001
ILD			
Idiopathic ILD			0.820
UIP	57	45	
NSIP or others	15	10	
Collagen disease-related ILD	16	15	
ILD grade			
I : II : III : IV	57 : 11 : 17 : 3	36 : 6 : 20 : 8	0.080
ILD: interstitial lung disease, UIP: usual interstitial pneumonia, NSIP: non-specific interstitial pneumonia			

ILD: interstitial lung disease, UIP: usual interstitial pneumonia, NSIP: non-specific interstitial pneumonia

causes in 18 cases (cancer in 10 cases, unknown in 6 cases, and cardiovascular in 2 cases).

The survival curves for the 443 cases are shown in Figure 2A. The MST for these cases was 120 months. Figure 2B shows survival time by severity of ILD at diagnosis. The MST for each group was 121 months for stage I, 120 months for stage II, 73 months for stage III, and 44 months for stage IV. There was a significant difference in survival time among these four groups ($P = 0.0001$).

Survival of Patients with and Without Acute Exacerbation

The MST for the 158 cases of AE was 2.0 months. Sixty-five cases died within 30 days of an AE, 25 died between 30 and 90

days, and 68 survived more than 90 days. The survival curves for patients by age at AE onset are shown in Figures 3A and 3B. The survival curves for patients under 70 years of age and for those in their 70s were nearly identical, whereas survival times for patients aged 80 years or older were worse than those for the other age groups. A statistically significant difference in survival times was observed between cases younger than 80 years and those 80 years or older ($P = 0.0012$).

Forty-seven cases died during the follow-up period without developing an AE. Causes of death in these cases were respiratory failure (36 cases), cancer (10 cases), and other (arrhythmia) (1 case).

Table 2. Comparison of treatments for AEs in cases stratified by age				
A. Comparison of three case groups aged 70 and 80 years				
	Patient groups by age			P value
	Younger than 70 years	70-79 years	80 years or older	
Number of cases	22	66	70	
Confirmation of intention not to receive life-sustaining treatment				
Present : absent	15 : 7	52 : 14	60 : 10	0.1786
Treatment administered				
Steroid pulse therapy	19	48	44	0.0926
NPPV	1	7	9	0.5469
Ventilator management	2	8	3	0.2482
B. Comparison of two case groups: younger than 80 vs. 80 years or older				
	Patient groups by age		P value	
	Younger than 80 years	80 years or older		
Number of cases	88	70		
Confirmation of intention not to receive life-sustaining treatment				
Present : absent	67 : 21	60 : 10		0.1321
Treatment administered				
Steroid pulse therapy	67	44		0.0697
NPPV	8	9		0.4479
Ventilator management	10	3		0.0744
AE: acute exacerbation, NPPV: non-invasive positive pressure ventilation				

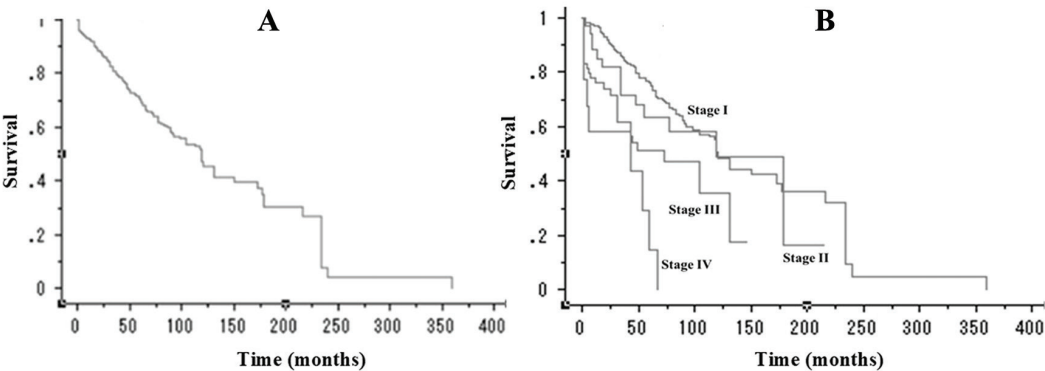


Figure 2. The survival curves for 443 interstitial lung disease (ILD) cases (A). The median survival time (MST) for these cases was 120 months. Survival curves according to the severity of ILD at the time of diagnosis (B). The MST for each group was 121 months for stage I, 120 months for stage II, 73 months for stage III, and 44 months for stage IV. There was a significant difference in survival time among these four groups ($P = 0.0001$)

Impact of Comorbidities on Prognosis

We investigated the impact of comorbidities on cases of AE (Table 3). Univariate analysis revealed that “younger than 80 years at the time of AE onset,” “no concurrent hypertension,” “no concurrent diabetes mellitus,” “no concurrent malignant disease,” and “imaging findings other than UIP” were significant factors; however, only the first four—excluding “imaging findings other than UIP”—were associated with a favorable prognosis.

Subgroup Analyses

Subgroup analyses were conducted in 102 patients with UIP (two-thirds of all cases), divided into two groups: those younger than 80 years and those 80 years or older. In univariate analysis, diabetes ($P = 0.0057$), malignant disease ($P = 0.0249$), and age 80 years or older ($P = 0.0271$) were found to be poor prognostic factors after the onset of AE. In multivariate analysis, only the presence of diabetes ($P = 0.0284$) was a significant poor prognostic factor, whereas the presence of malignant disease ($P = 0.0719$) and being 80 years or older ($P = 0.0555$) showed a trend toward a poor prognosis.

DISCUSSION

The present study included 443 ILD cases, including 158 with median ages of 73 years at ILD diagnosis and 78 years at AE onset, and yielded the following results: the MST for all ILD cases was 10 years, while the MST for AE-onset cases was 2 months. Elderly AE-onset cases were more likely to be male, to have comorbid hypertension, and to have a history of smoking. There were no age-related differences in requests for DNAR or in treatment administered for AE. However, the prognosis for cases in which AE developed at age 80 years or older was significantly poorer than for cases younger than 80 years. The survival curve for cases who survived 3 months after onset of AE plateaued. An age at onset of AE of 80 years or older and comorbidities such as hypertension, diabetes mellitus, and malignant disease were significant predictors of poor prognosis.

In developed countries, as the population ages, the median age at diagnosis for many diseases is changing. Even for ILDs, the median age at diagnosis is shifting to the 70s.^{4,12-15} Although it is unclear whether this change is due to the aging of patients, the age at which AEs occur is also increasing, with recent reports showing a median age of AE onset of the mid-70s.¹⁶⁻¹⁹ Takagi et

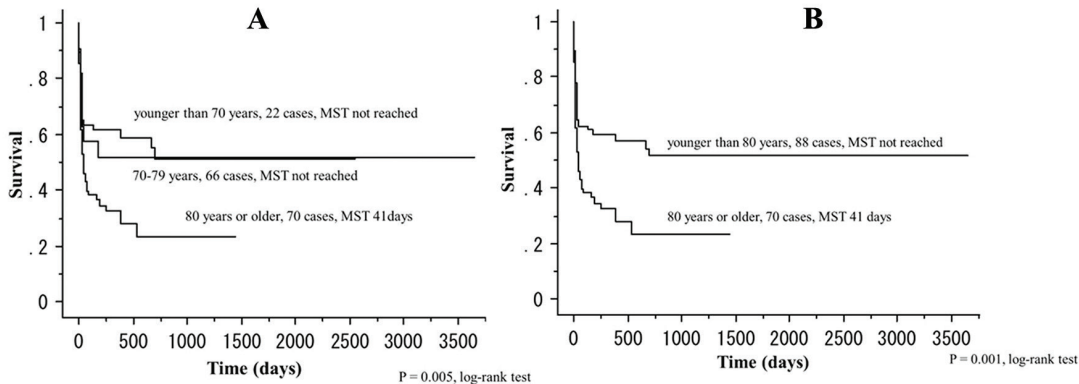


Figure 3. The survival curves by age at the time of acute exacerbation (AE) onset for cases younger than 70 years, 70–79 years, and 80 years or older (A). The survival curves for patients under 70 years of age and in their 70s were nearly identical, while survival times for those 80 years or older were worse than those for these age groups. There was a statistically significant difference among the three age groups ($P = 0.0050$). The survival curves by age at the time of AE onset for cases younger than 80 years and 80 years or older (B). There was a statistically significant difference between survival times for cases younger than 80 years and those 80 years or older ($P = 0.0012$)

Table 3. Univariate and multivariate analysis of clinicopathological factors and survival after AE in ILD patients

Variables	Univariate	Multivariate		
	<i>P</i> value	HR	95% CI	<i>P</i> value
Female gender	0.3443			
Age, younger than 80 years	0.0012	1.788	1.145–2.791	0.0106
Never smoker	0.1323			
Comorbid, without hypertension	0.0298	1.715	1.089–2.700	0.0200
Comorbid, without diabetes	0.0043	0.473	0.283–0.791	0.0043
Comorbid, without cardio-cerebrovascular diseases	0.8218			
Comorbid, without malignancy	0.0164	1.817	1.116–2.959	0.0164
ILD type, other types than UIP	0.0288	1.563	0.987–2.474	0.0567
ILD grade I at the time of diagnosis	0.7742			
Therapy with anti-fibrotic drug	0.7804			

AE: acute exacerbation, ILD: interstitial lung disease, UIP: usual interstitial pneumonia, HR: hazard ratio, CI: confidence interval

al.¹⁹ reported a study in which the median age at AE onset was 80 years old. In our study, the median age at ILD diagnosis and the age at onset of AE were 73 and 78 years, respectively. It was unclear how this aging affected the results. However, the results contained three notable findings, which we discuss below.

The first notable finding concerned the survival time of ILD patients. The results might have differed depending on the inclusion criteria used when conducting the survey, such as limiting ILD to IPF, limiting it to patients with UIP on imaging, or including CTD-ILD. However, regardless of the pathology or etiology of ILD, studies published within the last few years have also indicated that the MST from diagnosis for ILD patients was around 2 to 5 years.⁴⁻⁶ Our current study, comprising 158 cases, showed that the MST from ILD diagnosis was 10 years. Furthermore, according to the Japanese IPF disease severity classification, the MST was 10 years for stages I and II, 6 years for stage III, and 3 years for stage IV. We compared our results with those of one of the most impactful studies, the Hokkaido study,⁷ which included 553 IPF patients with a median age of 70 years at diagnosis. In this large-scale study, the cause of death in 40% of patients was respiratory failure due to AEs, and the overall MST was 35 months. The proportions of patients classified by the grading mentioned above were stage I, II, III, and IV, with 33.7%, 28.6%, 22.2%, and 15.7%, respectively.⁷ The severity classification percentages of our cases were 58.9%, 10.8%, 23.4%, and 7.0% for stage I, II, III, and IV, respectively. The percentages of patients in stages I and II were 62.3% and 69.7%, respectively, indicating that our cases had a significantly higher proportion of patients in stages I and II. Notably, MST could vary greatly depending on patient grading. As mentioned above, previous studies, including the Hokkaido study, generally indicate that the prognosis for ILD is approximately 2–4 years from diagnosis.⁶ However, it may be important to consider severity classification when evaluating MST, and our results suggest that, despite the advanced age of ILD patients, some patients, particularly those with less severe disease, may be expected to survive long-term. Therefore, early diagnosis and elimination of currently known risk factors, such as smoking, remain important. From this perspective, antifibrotic drug treatment³¹ for patients with stage I or II ILD might also contribute to improving the prognosis. Additionally, it would be necessary to carry out activities to raise widespread awareness of these matters.

The second notable finding was the Kaplan-Meier survival curves for patients who developed AE. Cases aged 80 years or older had a poor prognosis, which was significantly different from that of cases younger than 80 years. We speculated that this result was not due to a significant difference in the proportion of comorbid conditions between those in the two age groups, but rather to a decline in the ability to cope with acutely progressive conditions, such as AEs. Notably, the prognosis curve for cases younger than 80 years who developed AE declined rapidly until approximately 3 months and then leveled off. This suggested that patients who survived up to 3 months after the onset of AE might include a subgroup expected to survive long-term.

The third notable result concerned factors affecting the prognosis of AE. In this study, the factors that affected the prognosis were older age; lifestyle diseases, such as diabetes

mellitus and hypertension; and malignant diseases, such as lung cancer. Previous reports have highlighted the importance of lifestyle diseases such as these.³²⁻³⁴ The metabolism and side effects associated with the administration of corticosteroids and immunosuppressants might affect prognosis. Further elucidation of the pathogenesis of AE and establishment of standard treatments are needed.

Study Limitations

We acknowledge that our study had some limitations. First, when interpreting the results, the retrospective nature of the study and the inclusion of heterogeneous ILD subtypes should be explicitly emphasized. The study period was long, allowing for an extended follow-up. While progress was made in the diagnosis and treatment of ILD during that time, it remained possible that these clinical advances were not fully taken into account. Second, the GAP scoring system is the most commonly used tool for predicting survival,³⁵ but it requires patient effort and assessment of diffusing capacity. In contrast, the severity classification used in this study used oxygen saturation measurement, a non-invasive assessment method, and this classification was originally developed for IPF.^{24,25} The cohort in this study included a diverse group of ILD patients, including those with less severe disease. One limitation of this study is that this severity classification system has not been validated in ILD patient populations other than IPF. Third, we analyzed recurrent AEs as independent events. This might have introduced bias into the results. If an AE recovered to pre-onset levels and the interval between the onset and the next AE was at least several months, it was interpreted as a separate AE. However, it is unclear whether this interpretation was optimal, and future studies should consider optimal strategies for handling multiple AEs. Despite the limitations mentioned above, we believe we were able to provide results that more closely reflect actual clinical practice. The results of this study might indicate that many ILD patients aged 80 years or older have a decline in biological functions that cannot currently be quantified, such as the ability to tolerate and recover from acute illness.^{36,37} However, this is beyond our current knowledge and will need to be addressed in future research.

CONCLUSION

As the population ages, both the age at ILD diagnosis and the age at onset of AE appear to be becoming older. The stage of ILD should be considered when assessing its prognosis. Among ILD cases who developed AE, 80 years of age was the threshold distinguishing good from poor prognosis. Among cases with AE onset before age 80, those who survive for a certain period may be expected to have a favorable long-term prognosis. In addition to aging, comorbid lifestyle diseases may influence the prognosis of ILD cases who develop AE, and managing these comorbidities during AE treatment may also be important.

Ethics

Ethics Committee Approval: This study was reviewed and approved by the Institutional Ethics Committee of University of Tsukuba Hospital, Mito Medical Center (approval number: NO 25-47, date: June 2, 2025).

Informed Consent: Comprehensive informed consent was obtained from each patient at the time of the diagnostic workup of ILD.

Footnotes

Authorship Contributions

Concept: H.S., R.H., Design: M.U., K.M., H.S., R.H., Data Collection or Processing: M.U., K.M., Y.M., N.K., S.O., H.S., Analysis or Interpretation: M.U., K.M., S.O., H.S., Literature Search: M.U., H.S., Writing: M.U., H.S.

Conflict of Interest: No conflict of interest was declared by the authors.

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