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Factors associated with pulmonary function decline of patients in the cystic fibrosis registry of Turkey: A retrospective cohort study

Nagehan Emiralioğlu MD[1] | Banu Çakır MD[2] | Ahmet Sertçelik MD[2] | Ebru Yalçın MD[1] | Nural Kiper MD[1] | Velat Şen MD[3] | Derya Ufuk Altıntaş MD[4] | Mahir Serbes MD[4] | Haluk Çokuğraş MD[5] | Ayşe Ayzıt Kılınç MD[5] | Azer Kılıç Başkan MD[5] | Evrim Hepkaya MD[5] | Hakan Yazan MD[6] | Özden Türel MD[6] | Hale Molla Kafi MD[6] | Aslı İmran Yılmaz MD[7] | Gökçen Ünal MD[7] | Tuğçe Çağlar MD[7] | Ebru Damadoğlu MD[8] | İlim Irmak MD[8] | Esen Demir MD[9] | Gökçen Öztürk MD[9] | Ayşen Bingöl MD[10] | Erdem Başaran MD[10] | Nihat Sapan MD[11] | Ayşe Tana Aslan MD[12] | Pelin Asfuroğlu MD[12] | Koray Harmancı MD[13] | Mehmet Köse MD[14] | Melih Hangül MD[14] | Ali Özdemir MD[15] | Gökçen Tuğcu MD[16] | Sanem Eryılmaz Polat MD[16] | Gizem Özcan MD[17] | Zeynep Gökçe Gayretli MD[18] | Özlem Keskin MD[19] | Sevgi Bilgiç MD[19] | Hasan Yüksel MD[20] | Şebnem Özdoğan MD[21] | Erdem Topal MD[22] | Gönül Çaltepe MD[23] | Demet Can MD[24] | Pervin Korkmaz Ekren MD[25] | Mehmet Kılıç MD[26] | Ayşe Süleyman MD[27] | Tuğba Şişmanlar Eyüboğlu MD[12] | Güzin Cinel MD[16] | Sevgi Pekcan MD[7] | Nazan Çobanoğlu MD[17] | Erkan Çakır MD[28] | Uğur Özçelik MD[1] | Deniz Doğru MD[1]

Correspondence
Nagehan Emiralioğlu, MD, Department of Pediatric Pulmonology, Ihsan Dogramaci Children's Hospital, Hacettepe University Faculty of Medicine, 06230 Ankara, Turkey.
Email: drnagehan@yahoo.com

Abstract

Background: The decline in pulmonary function is a predictor of disease progression in patients with cystic fibrosis (CF). This study aimed to determine the decline rate of percent predicted forced expiratory volume in 1 s (ppFEV1) based on the data of the CF Registry of Turkey. The secondary aim was to investigate the risk factors related to the decline in ppFEV1.

Methods: A retrospective cohort study of CF patients over 6 years old, with pulmonary function data over at least 2 years of follow-up was extracted from the national CF registry for years 2017–2019. Patients were classified according to

For affiliations refer to page 2965.

Part of this study has been presented as a poster at 45th ECFS 2022 in Rotterdam.

disease severity and age groups. Multivariate analysis was used to predict the decline in ppFEV1 and to investigate the associated risk factors.

Results: A total of 1722 pulmonary function test results were available from 574 patients over the study period. Mean diagnostic age was older and weight for age, height for age, and body mass index *z* scores were significantly lower in the group of ppFEV1 < 40, while chronic *Pseudomonas aeruginosa* ($p < .001$) and mucoid *P. aeruginosa* colonization ($p < .001$) were significantly higher in this group ($p < .001$). Overall mean annual ppFEV1 decline was −0.97% (95% confidence interval [CI] = −0.02 to −1.92%). The mean change of ppFEV1 was significantly higher in the group with ppFEV1 ≥ 70 compared with the other (ppFEV1 < 40 and ppFEV1: 40–69) two groups ($p = .004$). Chronic *P. aeruginosa* colonization (odds ratio [OR] = 1.79 95% CI = 1.26–2.54; $p = .01$) and initial ppFEV1 ≥ 70 (OR = 2.98 95% CI = 1.06-8.36), $p = .038$) were associated with significant ppFEV1 decline in the whole cohort.

Conclusions: This data analysis recommends close follow-up of patients with normal initial ppFEV1 levels at baseline; advocates for early interventions for *P. aeruginosa*; and underlines the importance of nutritional interventions to slow down lung disease progression.

KEYWORDS

cystic fibrosis, FEV1, pulmonary function test, *Pseudomonas aeruginosa*

1 | INTRODUCTION

Cystic fibrosis (CF) is a multisystemic genetic disease, caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. Pulmonary involvement in CF is the most important determinant of mortality and morbidity.[1,2] Lung function decline is an important predictor for the severity of lung disease and prognosis depends on many disease-related factors. Despite improvements in general health and life expectancy, lung function continues to deteriorate during adolescence and early adult life. Decline in pulmonary function may be prevented if risk factors can be identified to slow the progression of lung disease.[3,4]

CF registries provide important data about the longitudinal course of pulmonary function in patients with CF. Registry systems of different countries have so far revealed a variety of risk factors affecting the progression of lung disease.[5–7] Recent literature indicated that genotype alone may not fully explain the lung function decline and other covariates including age, female sex, forced expiratory volume in 1 s (FEV1) levels, low body mass index (BMI), positive respiratory cultures for *Pseudomonas aeruginosa*, and a history of multiple previous exacerbations should be investigated for predicting clinical prognosis of CF.[8,9] Year to year change in lung function presents a large variability and further evidence is warranted to explain this variability in countries with high genetic heterogeneity, like Turkey.[8] National CF Registry of Turkey collects annual demographic and clinical data from all diagnosed patients, similar to other CF registries, to disclose significant variabilities and their potential effects on disease progression.[10]

This study aimed to determine the decline rate of percent predicted FEV1 (ppFEV1) according to disease severity and age groups, based on the data of the CF Registry of Turkey. The secondary aim was to investigate the risk factors related to the decline in ppFEV1.

2 | METHODS

2.1 | Study design and study population

A retrospective multicentric longitudinal cohort study of CF patients aged 6 years and over, with pulmonary function data over at least 2 consecutive years was extracted from the registry, for years 2017–2019 (the most recent data available at the time of the analysis). Patients without pulmonary function test (PFT) results were excluded from the data set. This study was performed in line with the principles of the Declaration of Helsinki and it was approved by the local institutional ethical committee (Hacettepe University Ethics Board, reference number: GO 2021/04-64, dated 23 February 2021). Other centers in this study have signed a formal reliance agreement with Hacettepe University. Written informed consent from parents or caregivers and assent from study participants if older than 12 years were obtained from the registry.

2.2 | Demographic and clinical variables

Data were obtained for demographic variables (age and gender), clinical variables (including, age at diagnosis, genetic results, weight *z*-score, height *z*-score, BMI *z*-score, pancreatic insufficiency status), laboratory variables (including, ppFEV1, ppFVC, sputum growth results, chronic microorganism colonizations), medications, oxygen requirement, use of non-invasive mechanical ventilation and CF related complications. Body weight *z* score, height *z* score, and BMI *z* scores were calculated for each patient, according to Centers for Disease Control and Prevention reference values.[11] Chronic *P. aeruginosa* infection was defined as >50% of the airway samples are positive for *P. aeruginosa* collected during the last 12 months (at least four samples collected) according to modified Leeds criteria. Chronic infection with other Gram-negative or Gram-positive bacteria was also described according to these criteria with the European CF Patient Registry Report (ECFSPR) reference.[12] None of these patients were using CFTR modulator treatment, due to nonreimbursement of these drugs in the study period.

For statistical analyses, ages were categorized as 6.0–9.9, 10.0–14.9, 15.0–19.9, 20.0–24.9 years, and 25 years and over, with the ECFSPR reference.[12]

2.3 | PFT

The primary outcome of this study was the decline in lung function expressed as the absolute change over time in ppFEV1, using the Global Lung Initiative calculations.[13] PFTs were performed for all patients in the registry using standardized American Thoracic Society/European Respiratory Society spirometry guidelines.[14] In our national registry, annual best values for PFT results are recorded and for the purposes of this study, the best values of the given year were used for ppFEV1, ppFVC like ECFSPR variables. Patients were categorized into three groups according to their baseline ppFEV1: such that ppFEV1 of 70% and above was defined as "mild"; 40%–69% as "moderate"; and below 40% as "severe" disease.[15] Baseline PFT was defined as the first ppFEV1 and ppFVC recorded during the eligibility period.

2.4 | Mutation classification

Genetic mutations of the patients were categorized into four groups as: severe mutations in both alleles, mild mutations in both alleles, severe and mild mutations together, and other unknown mutations. CFTR mutation classes 1–3 were defined as severe mutations, while classes 4–6 were defined as mild mutations.[16] The most common mutations were deltaF508, N1303K, 1677delTA, 2183AA->G, G542X, 2789+5G>A, E92K, and G85E in this cohort. Other unknown mutations were CFTR mutations that were unidentified in the CFTR2 database.

2.5 | Statistical analysis

Data were analyzed with a statistical software package (SPSS version 22.0; SPSS). Normally distributed continuous variables were summarized as mean, with standard deviation (SD) or 95% confidence intervals (CI). Nonnormally distributed variables were presented as median (with 25th–75th percentile). Categorical variables were summarized as frequency (percentage). χ^2 test and the Kruskal–Wallis or one-way analysis of variance tests were used for categorical and numerical variables, respectively. We evaluated the change in ppFEV1 by years, with repeated measures analysis of variance. The annual decline in ppFEV1 was calculated based on the baseline FEV1 value (in liters) for each patient. A multivariable logistic regression model was constructed to model lung function decline, based on baseline predictors (age at first FEV1, age at CF diagnosis, gender, genotype, BMI, weight for age, height for age *z* score), presence of *P. aeruginosa* infection, and CF-related complications. Statistical significance was accepted at a two-sided *p* value of less than .05.

3 | RESULTS

A total of 1722 PFT results were available from 574 patients over three consecutive years. The flowchart of this study is shown in Figure 1.

Of the 574 children, the median age was 12 (interquartile range [IQR] = 9–16) years and 47% (*n*: 270) of them were females. Median age for CF diagnosis was 0.58 (IQR = 0.25–5.00) years. Table 1 presents the baseline demographic and clinical characteristics of study participants. Baseline ppFEV1 values were <40 in 7.1% (*n* = 41), 40–69 in 19.2% (*n* = 110), and ≥70 in 73.7% (*n* = 423) of these patients.

3.1 | Comparison of patients according to baseline ppFEV1 values and age groups

Median age at diagnosis and baseline evaluation were older in the group with ppFEV1 < 40 (all $p < .001$), compared to the groups with better ppFEV1 values. Table 2 presents distribution of patient characteristics based on the baseline disease severity. Weight for age, height for age, BMI, and *z* scores were significantly lower (all $p < .001$); while chronic *P. aeruginosa* ($p < .001$) and mucoid *P. aeruginosa* colonization ($p < .001$) were significantly higher among those with poor ppFEV1 at baseline. Presence of allergic bronchopulmonary aspergillosis (ABPA), CF-related diabetes mellitus (CFRD), osteopenia, and osteoporosis were significantly associated with disease severity (all $p < .001$). Also prescription of airway treatments including inhaled hypertonic saline ($p = .003$), inhaled mannitol, antibiotic, bronchodilator, steroid, oxygen, noninvasive ventilation (all $p < .001$), long term azithromycin ($p = .003$), and gastrointestinal system treatments including multivitamines ($p = .04$), proton pump inhibitor (PPI) ($p = .003$), and oral enteral nutrition ($p < .001$) were significantly associated with disease severity.

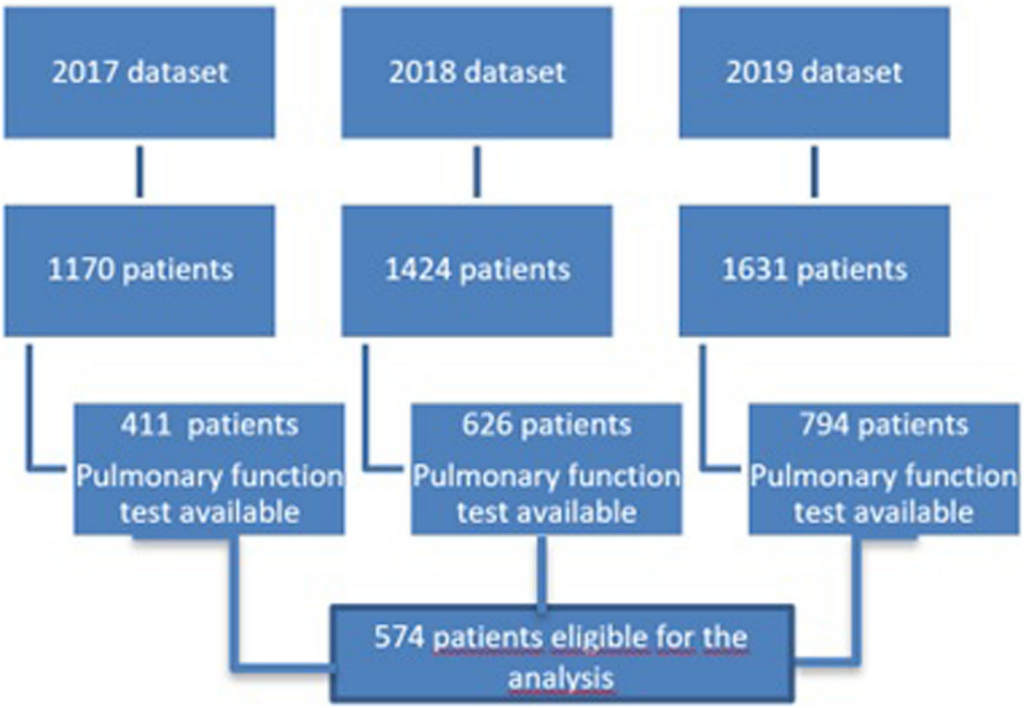


FIGURE 1 Flowchart of the study.

The mean annual ppFEV1 and ppFVC values were analyzed according to age groups: Mean (SD) ppFEV1 declined from 69.4% (22.8) to 68.4% (23.9) in the age group of 20–24 years (*n*: 29, $p = .01$), despite the increasing trends in the other age groups (Figure 2). Increased annual ppFVC values were observed in all age groups, over the study period.

3.2 | Risk factors for patients with severe disease

Delayed diagnosis and initially low *z* scores of body weight, height, and BMI were found to be significantly associated with disease severity risk factors. Similarly, presence of chronic *P. aeruginosa* and mucoid *P. aeruginosa* colonization, together with ABPA, diabetes mellitus, osteoporosis, osteopenia, and PPI use were all positively associated with severe disease. Table 3 shows the factors associated with severe disease in the study cohort.

3.3 | Evaluation of annual ppFEV1 decline and related factors

Overall mean annual ppFEV1 decline was calculated as −0.97% (95% CI = −0.02 to −1.92) in the study cohort. Although the mean annual ppFEV1 decline was higher in patients with pancreatic insufficiency (−0.35, 95% CI = −1.72 to 1.01) compared with patients with pancreatic sufficiency (2.82, 95% CI = −2.28 to 7.92), it was not statistically significant between the groups ($p = .170$). Difference of annual ppFEV1 change was not significant across age groups: annual differences were calculated as 0.1% (95% CI = −2.2 to 2.5); 0.4% (95% CI = −1.7 to 2.5); 0.6% (95% CI = −2.2 to 3.6); −5.7% (95% CI = −12.4 to 1); −1.3% (95% CI = −7.9 to 5.1) for patients in age groups of 6.0–9.9, 10.0–14.9, 15.0–19.9, 20.0–24.9, and 25 years or older, respectively ($p = .380$). The mean annual decline of ppFEV1 was calculated as −1.4% (95% CI = −0.2 to −2.6) that is significantly higher in the group with ppFEV1 ≥ 70 compared with the other groups with lower initial ppFEV1 (group with ppFEV1 < 40 and group with ppFEV1: 40%–69%, ppFEV1 ranges from 19% to 69%) values ($p = .004$) (Figure 3).

Presence of chronic *P. aeruginosa* colonization (OR = 1.79 95% CI = 1.26–2.54; $p = .01$) and initial ppFEV1 ≥ 70 (OR = 2.98 95% CI = 1.06–8.36; $p = .038$) were associated with a significant ppFEV1 decline in the whole cohort after adjusting for age. Type of pathogenic mutations as mild or severe on the genetic analysis, gender, age at diagnosis, low *z* scores of weight for age, height for age and BMI, disease-related complications were not statistically significant predictors of ppFEV1 decline (Table 4).

4 | DISCUSSION

Multiple factors including poor nutrition, inflammation in the lower airways, and infections with specific microorganisms such as *P. aeruginosa*, *Staphylococcus aureus*, *Aspergillus*, and acute pulmonary exacerbations can affect progression of lung disease in CF.[17–20] Analyses based on the Turkish national CF registry data revealed that pulmonary function decline was most prominent among patients between 20 and 24 years old and for those with normal initial

TABLE 1 Baseline demographic and clinical characteristics of patients in the cohort.

Patient characteristics	*N* = 574
Age at the study time (years), median (IQR)	12 (9–16)
Age range at the study time (years), *n* (%)	
6.0–9.9	160 (27.9)
10.0–14.9	226 (39.4)
15.0–19.9	129 (22.5)
20.0–24.9	29 (5.1)
25.0 or older	30 (5.2)
Age at diagnosis (year), median (IQR)	0.58 (0.25–5.00)
Gender (female), *n* (%)	270 (47)
Genotype (mutation per allele), *n* (%)	
Severe/severe	262 (45.6)
Severe/mild	62 (10.8)
Mild/mild	88 (15.3)
Other	152 (28.2)
Pancreatic insufficiency, *n* ((%)	518 (90.2)
Weight for age *z* score, median (IQR)	−0.83 (−1.35 to −0.26)
Height for age *z* score, median (IQR)	−0.74 (−1.53 to −0.07)
Body mass index *z* score, median (IQR)	−0.64 (−1.08 to 0)
Baseline ppFEV1, *n* (%)	
<40	41 (7.1)
40–69	110 (19.2)
70 or higher	423 (73.7)
ppFEV1 (mean) (95% CI)	
First year	84.1 (80.9-87.2)
Second year	84.5 (82.3-86.7)
Third year	85.0 (82.5-87.4)
ppFVC (mean) (95% CI)	
First year	81.4 (78.6-84.2)
Second year	84.1 (82.1-86.1)
Third year	84.6 (82.5-86.7)
Sputum colonization, *n* (%)	
Chronic *Pseudomonas aeruginosa*	200 (34.8)
Mucoid *P. aeruginosa*	97 (16.9)
Chronic *Staphylococcus aureus*	235 (40.9)
Methicillin-resistant *S. aureus*	57 (9.9)
Chronic liver disease, *n* (%)	99 (17.2)
Allergic bronchopulmonary aspergillosis, *n* (%)	25 (4.4)
CF-related diabetes mellitus, *n* (%)	19 (3.3)
Osteopenia, *n* (%)	83 (14.5)
Osteoporosis, *n* (%)	34 (5.9)
Airway treatments use, *n* (%)[a]	
Dornase alpha	549 (95.6)
Inhaled hypertonic saline	92 (16.0)
Inhaled mannitol	67 (11.7)
Inhaled antibiotic	184 (32.1)
Inhaled bronchodilator	152 (26.5)
Inhaled steroid	118 (20.6)
Inhaled long-term beta-agonist and steroid combination	46 (8.0)
Long-term azithromycin	56 (9.8)
Gastrointestinal system treatment use, *n* (%)[a]	
Pancreatic enzyme	518 (90.2)
Ursodeoxycholic acid	153 (26.7)
Multivitamins	460 (80.1)
Proton pump inhibitor	108 (18.8)
Oral enteral nutrition	365 (63.6)

Abbreviations: CF, cystic fibrosis; CI, confidence interval; IQR, interquartile range; ppFEV1, percent predicted forced expiratory volume in 1 s; ppFVC, percent predicted forced vital capacity.

[a]Percentages were calculated out of total number of patients, do not round up to 100.0%.

ppFEV1 levels. The association between chronic *P. aeruginosa* colonization and lung disease progression calls attention to early interventions for *P. aeruginosa*.

Progressive decline in pulmonary function is one of the important predictors of respiratory failure in CF; indicating the role of routine ppFEV1 monitoring in clinical practice for predicting disease progression.[21] In this study, the mean annual ppFEV1 decline was found to be 0.97% and was in line with the findings of other national registries. The mean annual decline in ppFEV1 was 1.01% (95% CI: 0.85–1.17) in a previous report by Cogen et al.[7] Canadian CF registry reported a decline in ppFEV1 as 1%–2% per year,[22] where, the UK CF registry data from 2015 to 2017 revealed an overall annual rate of decline in ppFEV1 as −1.52% and −0.55%, for patients with pancreatic insufficiency or sufficiency, respectively.[23] We found a higher nonsignificant ppFEV1 decline in patients with pancreatic insufficiency suggesting a possible type 2 error.

In CF, rapid decline in pulmonary function often occurs between adolescence and early adulthood. The specific timing of rapid decline, however, varies across studies. For example, Szczesniak et al. reported that the timing of the most rapid FEV1 decline was prominent between 7.8 and 19.2 years, and the maximal predicted FEV1 loss ranged from 2.7% to 5.7% per year.[24] Previous data also indicated that adolescents are at higher risk for lung function decline than younger patients or adults.[6] In contrary, Vandenbranden et al. found the highest decline during early adulthood.[25] Our results

TABLE 2 Distribution of demographic characteristics and clinical findings by baseline disease severity.

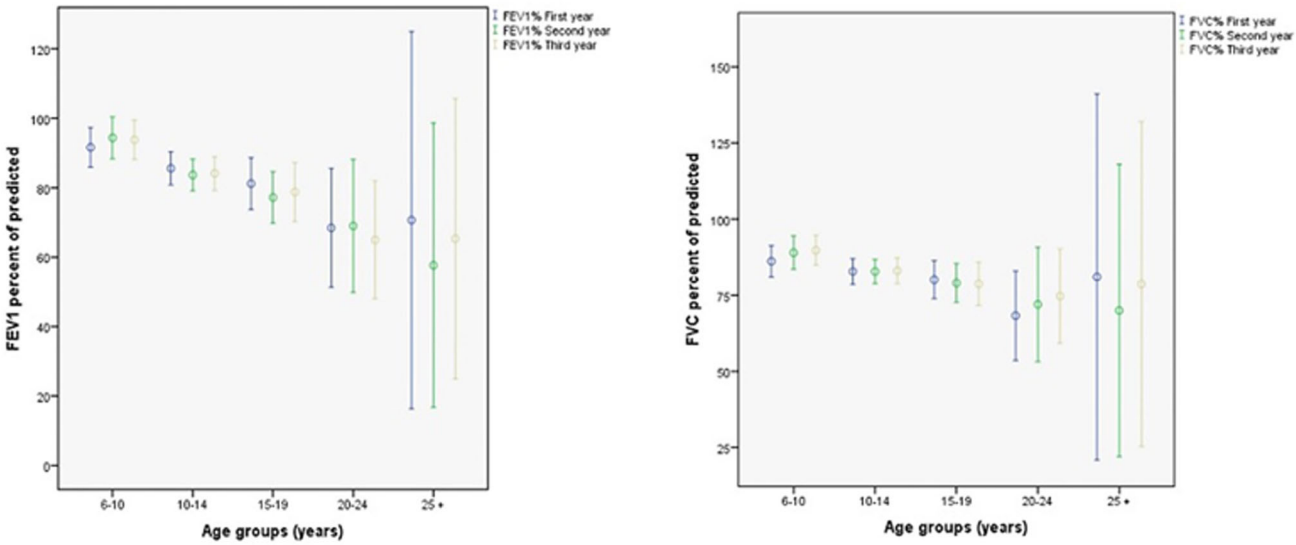
Variables	ppFEV1 <40, *n* = 41	40–69, *n* = 110	≥70, *n* = 423	*p* Value
Age at the study time (year), median (IQR)	17 (13–24)	13 (10–17)	11 (8–15)	<.001
Age range at the study time (years), *n* (%)				<.001
6.0–9.9	4 (9.8)	23 (20.9)	133 (31.4)	
10.0–14.9	9 (22.0)	43 (39.1)	174 (41.1)	
15.0–19.9	15 (36.6)	29 (26.4)	85 (20.1)	
20.0–24.9	3 (7.3)	10 (9.1)	16 (3.8)	
25.0 or older	10 (24.4)	5 (4.5)	15 (3.5)	
Age at diagnosis (year), median (IQR)	4 (0.42-9)	0.92 (0.25-6)	0.5 (0.25-3)	.003
Gender (female), *n* (%)	22 (53.6)	54 (49)	194 (45.8)	.56
Genotype *n* (%)				.69
Severe/severe	20 (48.8)	52 (47.3)	190 (44.9)	
Severe/mild	5 (12.2)	8 (7.3)	49 (11.6)	
Mild/mild	4 (9.8)	21 (19.1)	63 (14.9)	
Other	12 (29.3)	29 (26.4)	121 (28.6)	
Pancreatic insufficiency, *n* (%)	38 (95)	103 (93.6)	377 (89.5)	.26
Weight for age *z* score, median (IQR)	−1.88 (−2.39 to −1.23)	−1.20 (−1.71 to −0.64)	−0.67 (−1.16 to −0.07)	<.001
Height for age *z* score, median (IQR)	−1.66 (−2.40 to −0.56)	−0.95 (−1.98 to −0.31)	−0.56 (−1.35 to 0.07)	<.001
Body mass index *z* score, median (IQR)	−1.34 (−2.05 to −0.72)	−0.92 (−1.31 to −0.31)	−0.52 (−0.98 to 0.10)	<.001
Sputum colonization, *n* (%)				
Chronic *Pseudomonas aeruginosa*	34 (85.0)	59 (53.6)	107 (25.6)	<.001
Mucoid *P. aeruginosa*	13 (68.4)	31 (45.6)	53 (18.9)	<.001
Chronic *Staphylococcus aureus*	19 (47.5)	40 (36.4)	176 (42.0)	.40
Methicillin-resistant *S. aureus*	3 (16.7)	8 (11.8)	46 (16.4)	.63
Chronic liver disease, *n* (%)	6 (14.5)	27 (24.5)	66 (15.6)	.13
Allergic bronchopulmonary aspergillosis, *n* (%)	5 (12.5)	9 (8.2)	11 (2.6)	.001
CF-related diabetes mellitus, *n* (%)	5 (12.5)	7 (6.4)	7 (1.7)	<.001
Osteopenia, *n* (%)	19 (47.5)	33 (30.0)	31 (7.5)	<.001
Osteoporosis, *n* (%)	11 (27.5)	16 (14.8)	7 (1.7)	<.001
Treatment modalities				
Airway treatments use, *n* (%)				
Dornase alpha	40 (100.0)	106 (96.4)	403 (95.7)	.40
Inhaled hypertonic saline	9 (23.1)	28 (25.5)	55 (13.1)	.003
Inhaled mannitol	11 (27.5)	25 (22.7)	31 (7.4)	<.001
Inhaled antibiotic	30 (75)	61 (55.5)	93 (22.2)	<.001
Inhaled bronchodilator	22 (55)	43 (39.1)	87 (20.7)	<.001
Oxygen treatment	15 (37.5)	7 (6.4)	–	<.001
Noninvasive ventilation	7 (17.5)	13 (11.8)	3 (0.7)	<.001
Inhaled steroid	10 (25.0)	37 (33.6)	71 (16.9)	<.001
Long-term beta-agonist and steroid combination	12 (30.0)	13 (11.9)	21 (5.0)	<.001

(Continues)

TABLE 2 (Continued)

Variables	ppFEV1 <40, *n* = 41	40–69, *n* = 110	≥70, *n* = 423	*p* Value
Long-term azithromycin	8 (20.0)	17 (15.5)	31 (7.4)	.003
Gastrointestinal system treatment use, *n* (%)				
Pancreatic enzyme	38 (95.0)	103 (93.6)	377 (89.5)	.26
Ursodeoxycholic acid	11 (27.5)	35 (31.8)	107 (25.5)	.41
Multivitamins	38 (95.0)	91 (83.5)	331 (79.2)	.04
Proton pump inhibitor	14 (35.0)	27 (24.5)	67 (15.9)	.003
Oral enteral nutrition	30 (75.0)	81 (74.3)	254 (60.7)	<.001

Abbreviations: CF, cystic fibrosis; IQR, interquartile range; ppFEV1, percent predicted forced expiratory volume in 1 s.



Age	FEV1 Mean (SD) First year	FEV1 Mean (SD) Second year	FEV1 Mean (SD) Third year	FVC Mean (SD) First year	FVC Mean (SD) Second year	FVC Mean (SD) Third year
• 6-10 years	90.7(21.1)	93.5(23)	92.2(23.6)	85(19.4)	88.8(21.2)	88.6(21.1)
• 10-14 years	83.7(24)	85.3(24.9)	87.2(25.2)	81.5(22.1)	84.7(23)	85.9(22.7)
• 15-19 years	79.7(29.2)	79.6(29)	80.1(32.4)	78.7(24.6)	80.6(26.5)	80.5(28.1)
• 20-24 years	69.4(22.8)	70.5(25.2)	68.4(23.9)	72.9(20.9)	79.3(24.5)	79(23.5)
• Over 25 years	59.5(33.6)	63.8(30.1)	65.1(29.5)	67.2(36.2)	72.4(27.2)	75.4(28.2)

FIGURE 2 Pulmonary function follow-up of patients according to age groups (mean and SD results were reported). FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity.

showed that pulmonary function decline is most prominent in patients over 20 years, although it did not reach statistical significance. Despite the standardized treatment regimens across the country, this finding could be explained by transitioning to adult centers as patients get older, increasing life responsibilities, and/or decline in compliance with physical rehabilitation practices over time.

It is known that patients with early-stage CF lung disease are at risk for increased rates of lung function decline. De Boeck and Zolin reported that a year-to-year decline in FEV1 was the most prominent finding in patients with baseline ppFEV1 of above 90%.[8] Our results confirmed this finding, with a significantly high ppFEV1 decline among those with baseline ppFEV1 values of ≥70. Lower treatment compliance rates among those with mild disease and/or more aggressive inhaler treatment use for severe disease could explain this discrepancy. In previous studies, higher FEV1, airway infection with *P. aeruginosa*, female sex, and poorer nutritional status are among those factors associated with higher rates of FEV1 decline in CF.[26] Baseline low FEV1 levels are also associated with lower pulmonary function decline rate in those previous studies. The main reason for this lower pulmonary function decline in patients with

severe disease may be related to the prescription of intensive treatments in patients with low baseline FEV1 levels similar to our cohort. Dasenbrook et al. also reported that CF adults with early-stage lung disease in the youngest age group, between 18 and 21 years, had the most rapid decline in PFTs compared to those aged ≥22 years.[27] This is compatible with previous findings in other patient registries.[8,23] Despite some inconclusive negative effects of female sex on pulmonary function decline, gender was not associated with a decline in our cohort.[4,7,23]

Poor nutritional status is known to be associated with lower pulmonary function, long-term morbidity, and mortality in CF. In a recent report, pancreatic insufficiency was found to be associated with an annual rate of decline in lung function, with an effect size of three.[23] A recent study from the Australian CF registry also confirmed this finding.[28] Psoter et al. investigated the early life growth trajectories in CF patients and reported that trajectories that met CF Foundation nutritional guideline recommendations were associated with higher ppFEV1 at the age of six.[29] Our data revealed that weight, height, and BMI *z* scores were lower in patients with severe disease, suggesting a potential association between nutrition (as measured by growth parameters) and pulmonary function pointed out that early precautions for nutritional problems could be beneficial to slow the progression of pulmonary function in CF.

Successful *P. aeruginosa* eradication therapy is associated with improved long-term pulmonary function due to the potential negative impact of early acquired *P. aeruginosa* on morbidity and mortality among children with CF.[30] Our cohort showed that chronic *P. aeruginosa* colonization is a significant risk factor predicting pulmonary function decline from childhood through adolescence, as reported earlier by Kerem et al.[4] Female gender, lower FEV1 and BMI, more frequent acute exacerbations, *Burkholderia cepacia* followed by methicillin-resistant *S. aureus* and *P. aeruginosa* were all reported as risk factors for rapid lung function decline in a previous cohort of CF Foundation registry. However, there was no statistical association with ABPA and nontuberculous mycobacteria infections, also CFRD status and pancreatic enzyme use were not statistically significant predictors for lung function decline.[24] Australian CF registry data reported that age at baseline, BMI *z* score, age interaction with lung transplantation, insulin-dependent diabetes, cirrhosis/portal hypertension, pancreatic insufficiency, *P. aeruginosa* infection as significant predictors of ppFEV1.[28] The ECFSPR results

TABLE 3 Effect size of potential risk factors on severe disease.[a]

Variable of interest	Odds ratio (95% CI)	*p* Value
Age at diagnosis (year)	0.9 (0.8–0.97)	.001
Genotype		
Severe/severe	1.0 (0.5–2.2)	.93
Severe/mild	1.0 (0.4–3.2)	.86
Mild/mild	0.6 (0.2–1.9)	.38
Other (reference)	1.0	
Weight for age *z* score < 2	5.2 (3.2–8.5)	<.001
Height for age *z* score < 2	1.7 (1.3–2.2)	<.001
Body mass index *z* score < 2	3.8 (2.2–6.2)	<.001
Chronic *Pseudomonas aeruginosa* colonization	12.3 (5–30)	<.001
Mucoid *P. aeruginosa* growth	6.8 (2.5–18.4)	<.001
Allergic bronchopulmonary aspergillosis	3.6 (1.3–10.3)	.02
CF-related diabetes mellitus	5.2 (1.8–15.4)	.003
Osteopenia	6.4 (3.2–12.6)	<.001
Osteoporosis	8.2 (3.7–18.5)	<.001
Proton pump inhibitor use	2.5 (1.3–5)	.01

Abbreviations: CF, cystic fibrosis; CI, confidence interval; ppFEV1, percent predicted forced expiratory volume in 1 s.

[a]Severe disease: Patients with baseline ppFEV1 < 40.

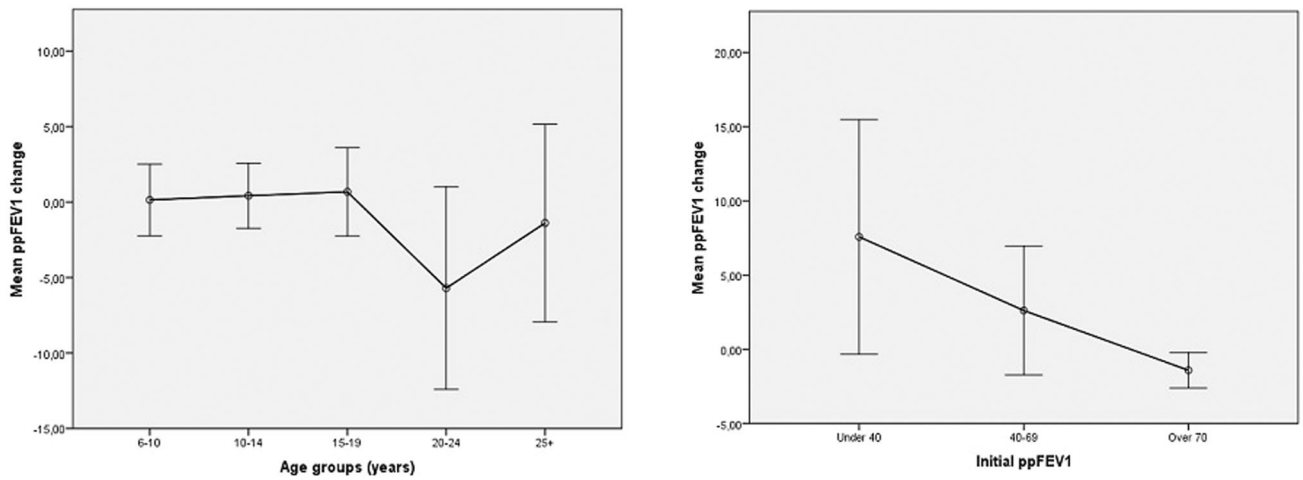


FIGURE 3 ppFEV1 change of CF patients according to age groups and initial ppFEV1 (mean and 95% CI results were reported). CF, cystic fibrosis; CI, confidence interval; ppFEV1, percent predicted forced expiratory volume in 1 s.

TABLE 4 Risk factors in patients with ppFEV1 decline.

	Odds ratio (95% CI)	*p* Value
Age at diagnosis (year)	0.98 (0.95–1.02)	.40
Age range at the study time (years)		
6.0–9.9	1.08 (0.49–2.37)	.83
10.0–14.9	1.34 (0.62–2.87)	.45
15.0–19.9	1.31 (0.59–2.91)	.50
20.0–24.9	0.80 (0.28–2.25)	.68
25 or older (reference)	1.00	
Gender		.5
Female	1.10 (0.79–1.53)	
Male	1.00	
Genotype (per allele)		
Severe/severe	0.83 (0.56–1.23)	.36
Severe/mild	1.45 (0.58–1.89)	.85
Mild/mild	1.07 (0.87–2.5)	.14
Other (reference)	1.00	
Weight for age *z* score	1.11 (0.94–1.31)	.21
Height for age *z* score	1.13 (0.98–1.3)	.08
Body mass index *z* score	1.03 (0.87–1.22)	.68
Chronic *P. aeruginosa* colonization	1.79 (1.26–2.54)	.01
Mucoid *P. aeruginosa* growth	1.45 (0.91–2.31)	.11
Chronic liver disease	1.20 (0.78–1.85)	.40
Allergic bronchopulmonary aspergillosis	1.61 (0.71–3.65)	.25
CF-related diabetes mellitus	1.46 (0.58–3.70)	.41
Osteopenia	1.16 (0.73–1.85)	.52
Osteoporosis	1.54 (0.76–3.12)	.22
Proton pump inhibitor use	1.11 (0.73–1.69)	.60

Note: Results were obtained after adjusting for age.

Abbreviations: CF, cystic fibrosis; CI, confidence interval; ppFEV1, percent predicted forced expiratory volume in 1 s.

also revealed that BMI, chronic infection with *P. aeruginosa*, pancreatic status, and CFRD had a statistically significant and clinically relevant effect on ppFEV1 adjusting for age.[6] Altogether, directed efforts for eradication of *P. aeruginosa* at first isolation are essential to suppress infection to prevent chronic colonization.

Disease severity and rate of disease progression vary among CF patients in accordance with the type of CFTR mutation. We have categorized the genetic results of our patients as mild and severe mutations based on previous reports and genotype per se, however, did not add on to clinically relevant effect on FEV1 decline in our cohort study, confirming preceding registry findings in other populations.[4,8,9]

Previous studies found an association between respiratory exacerbations and lung function decline during childhood and adolescence.[3,7,20] Begum et al. reported that pulmonary exacerbations in early age are related with hospitalization requirement due to an accelerated loss of pulmonary function from childhood to adolescence.[31] Such a causality analysis is beyond the scope of our work, yet, treating acute pulmonary exacerbations of CF may promptly reduce lung function decline and could be important study question for future research.

CFRD is known to be associated with lung function decline and increased risk of respiratory failure in previous studies.[4] Similar findings in our cohort suggest an association between CFRD and low lung function measures at baseline. CFRD is not preventable, yet, close follow-up of patients with routine screening tests may slow down the decline in PFTs.[32] Similar to the Danish CF registry report, we did not find any significant association between CFRD and the lung function decline over time.[2] Presence of CF complications is apparently more common among those with severe disease and osteopenia and osteoporosis were significantly associated with disease severity, though, in opposition to earlier reports.[4,7] This may, at least partially, be explained by the relatively low nutritional status of our patients compared to the populations of other CF registries. We recommend close monitoring for CF-related osteopenia and osteoporosis.

The use of PPI was associated with disease severity in our cohort, with no prominent effect on pulmonary function decline. PPIs are often recommended in CF patients due to concomitant gastroesophageal reflux and are also used with pancreatic enzyme replacement to increase fat absorption and reduce gastrointestinal symptoms in CF patients. The consistent evidence for an association between PPI use and an increased risk of respiratory tract infections among non-CF patients has not been proven among CF patients, though.[33] Van Horck et al. revealed PPI use as a risk factor for pulmonary exacerbations and decline in PFTs.[3] Our finding of a significant association with CF severity in our cohort could be due to the low nutritional status of patients with severe disease, necessitating more frequent use of PPIs to control gastrointestinal symptoms.

Our study has several strengths and novelties. First, national data from 26 centers enabled us to reach a large study population. This is the first study evaluating the degree of FEV1 decline in a longitudinal cohort, besides the analytical investigation of potential risk factors of CF prognosis in the Turkish population. Identification of significant risk factors is the first step for effective interventions. Registry-based data analysis might have introduced some biases in interpretations, though, including but not limited to variations in data entry, potential differences in approach to patients in different centers. The differences in spirometry applications and devices across centers could have led to measurement bias in the study. A number of patients were excluded from the analysis due to missing data of PFTs in consecutive years. This exclusion may lead to a "non-differential information bias" with an error toward the null in evaluating the effects of potential risk factors on disease severity, so the potential for bias needs to be kept in mind. Furthermore, we could not

calculate the sample size due to a registry-based study and we have included all the patients who had PFTs in three consecutive years which may cause type 2 error in this study. Lastly, variables of further concern, such as bronchiectasis, environmental effects, socio-economic status, and number of pulmonary exacerbations that may be confounders for the results could not be examined in the cohort, due to lack of data in the national registry. Further studies with data on such factors are needed for conclusive decisions.

In summary, our results recommend close follow-up of patients with normal initial ppFEV1 levels at baseline; advocate for early interventions for *P. aeruginosa* and underline the importance of nutritional interventions to slow down lung disease progression. The observational nature of the study based on registry data warrants further confirmation of our findings by prospective cohorts for conclusive evidence.

AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Nagehan Emiralioğlu, Banu Çakır, Ahmet Sertçelik, and Deniz Doğru. The first draft of the manuscript was written by Nagehan Emiralioğlu and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

AFFILIATIONS

[1]Department of Pediatric Pulmonology, Hacettepe University Faculty of Medicine, Ankara, Turkey

[2]Department of Public Health, Division of Epidemiology, Hacettepe University Faculty of Medicine, Ankara, Turkey

[3]Department of Pediatric Pulmonology, Dicle University Faculty of Medicine, Diyarbakır, Turkey

[4]Department of Pediatric Allergy and Immunology, Çukurova University Faculty of Medicine, Adana, Turkey

[5]Department of Pediatric Pulmonology, Cerrahpaşa Faculty of Medicine, İstanbul University-Cerrahpaşa, İstanbul, Turkey

[6]Department of Pediatric Pulmonology, Bezmi Alem University Faculty of Medicine, İstanbul, Turkey

[7]Department of Pediatric Pulmonology, Necmettin Erbakan University Faculty of Medicine, Konya, Turkey

[8]Department of Adult Pulmonology, Hacettepe University Faculty of Medicine, Ankara, Turkey

[9]Department of Pediatric Pulmonology, Ege University Faculty of Medicine, İzmir, Turkey

[10]Department of Pediatric Allergy, Immunology and Pulmonology, Akdeniz University Faculty of Medicine, Antalya, Turkey

[11]Department of Pediatric Allergy, Uludağ University Faculty of Medicine, Bursa, Turkey

[12]Department of Pediatric Pulmonology, Gazi University Faculty of Medicine, Ankara, Turkey

[13]Department of Pediatric Allergy, Osmangazi University Faculty of Medicine, Eskişehir, Turkey

[14]Department of Pediatric Pulmonology, Erciyes University Faculty of Medicine, Kayseri, Turkey

[15]Department of Pediatric Pulmonology, Mersin City Hospital, Mersin, Turkey

[16]Department of Pediatric Pulmonology, Ankara City Hospital, Ankara, Turkey

[17]Department of Pediatric Pulmonology, Ankara University Faculty of Medicine, Ankara, Turkey

[18]Department of Pediatric Infectious Disease, Karadeniz Technical University Faculty of Medicine, Trabzon, Turkey

[19]Department of Pediatric Allergy and Immunology, Gaziantep University Faculty of Medicine, Gaziantep, Turkey

[20]Department of Pediatric Allergy, Immunology and Pulmonology, Celal Bayar University Faculty of Medicine, Manisa, Turkey

[21]Department of Pediatric Pulmonology, Sarıyer Hamidiye Etfal Hospital, İstanbul, Turkey

[22]Department of Pediatric Allergy and Immunology, İnönü University Faculty of Medicine, Malatya, Turkey

[23]Department of Pediatric Gastroenterology, Ondokuz Mayıs University Faculty of Medicine, Samsun, Turkey

[24]Department of Pediatric Pulmonology, Balıkesir University Faculty of Medicine, Balıkesir, Turkey

[25]Department of Adult Pulmonology, Ege University Faculty of Medicine, İzmir, Turkey

[26]Department of Pediatric Allergy and Immunology, Fırat University Faculty of Medicine, Elazığ, Turkey

[27]Department of Pediatric Allergy and Immunology, İstanbul University İstanbul Faculty of Medicine, İstanbul, Turkey

[28]Department of Pediatric Pulmonology, İstinye University Faculty of Medicine, Istanbul, Turkey

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ETHICS STATEMENT

This study was performed in line with the principles of the Declaration of Helsinki and it was approved by the local institutional ethical committee (Hacettepe University Ethics Board, reference number: GO 2021/04-64, dated 23 February 2021).

ORCID

Ayşe Ayzıt Kılınç http://orcid.org/0000-0002-2879-8910
Hakan Yazan http://orcid.org/0000-0002-7680-4000
Tuğçe Çağlar http://orcid.org/0000-0003-1378-9250
Gökçen Öztürk http://orcid.org/0000-0002-0793-9710
Erdem Başaran http://orcid.org/0000-0002-9092-6936
Mehmet Köse http://orcid.org/0000-0002-3003-918X
Ali Özdemir http://orcid.org/0000-0001-7340-0409
Gökçen Tuğcu http://orcid.org/0000-0002-9804-1200
Sanem Eryılmaz Polat http://orcid.org/0000-0003-2309-7952
Gizem Özcan http://orcid.org/0000-0001-9063-4063
Şebnem Özdoğan http://orcid.org/0000-0002-1041-1124
Tuğba Şişmanlar Eyüboğlu http://orcid.org/0000-0001-7284-4999

Güzin Cinel http://orcid.org/0000-0002-6209-196X
Sevgi Pekcan http://orcid.org/0000-0002-8059-902X
Nazan Çobanoğlu http://orcid.org/0000-0002-3686-2927
Erkan Çakır http://orcid.org/0000-0002-1438-7854
Deniz Doğru http://orcid.org/0000-0001-9931-9473

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