The Turkish Journal of Pediatrics 2023; 65: 257-268
https://doi.org/10.24953/turkjped.2021.4930

Original Article

Clinical characteristics of patients requiring lung transplantation referral in national cystic fibrosis registry data

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Received 19th November 2021, revised 2nd January 2023, accepted 29th January 2023.

ABSTRACT

Background. We aimed to determine the number of cystic fibrosis (CF) patients recorded in the Cystic Fibrosis Registry of Türkiye (CFRT) who were in need of lung transplantation (LT) referral and examine clinical differences between patients who were LT candidates due to rapid forced expiratory volume in one second (FEV_1) decline and LT candidates without rapid FEV_1 decline in the last year to identify a preventable cause in patients with such rapid FEV_1 decline.

Methods. All CF patients recorded in the CFRT in 2018 were evaluated in terms of LT. Patients were divided into those with FEV_1 below 50% and in need of LT due to a decrease of 20% or more in the previous year (Group 1) and those who did not have FEV_1 decline of more than 20% in the previous year but had other indications for LT (Group 2). Demographic and clinical features were compared between the two groups.

Results. Of 1488 patients registered in CFRT, 58 had a need for LT. Twenty patients were included in Group 1 and others in Group 2. Our findings did not reveal any significant variations in treatment, chronic infection status, or complications between the two groups. The average weight z-score was significantly higher in Group 1. Positive correlations were detected between weight z-score and FEV_1 in 2017 in Group 1 and between FEV_1 values in 2017 and 2018 in Group 2.

Conclusions. There appears to be a relationship between the nutritional status and weight z-scores of CF patients and pulmonary function, which may indirectly affect the need for lung transplantation referral.

Key words: cystic fibrosis, lung transplantation, registry.

Cystic fibrosis (CF) is an autosomal recessive disease affecting approximately 1 in 2500 to 3500 newborns.[1,2] Lung disease remains the primary cause of morbidity, and end-stage lung disease remains the primary cause of mortality in CF patients. Lung transplantation (LT) has recently become the standard care[3,4], as it not only provides an additional management option but can also improve quality of life and survival.[5] However, finding a suitable transplant can take a long time. Moreover, LT is a major operation that may have serious complications and requires substantial amounts of medication postoperatively.[6] The most common indications for LT are interstitial lung diseases, advanced chronic obstructive pulmonary disease, cystic fibrosis, emphysema due to alpha-1-antityripsin deficiency, pulmonary arterial hypertension and re-transplantation in adults, while it is CF, idiopathic pulmonary arterial hypertension, and interstitial lung diseases among children.[7,8]

The pulmonary component of CF is characterized by progressive airway inflammation and recurrent lower respiratory infections that cause bronchiectasis and chronic respiratory failure, leading to significant morbidity and mortality in this population.[9] Nevertheless, a multidisciplinary approach and the introduction of modulators that directly target the basic defects in CF have improved patients' quality of life and life expectancy, which is now more than 40 years.[10]

A total of 2514 pediatric lung, 733 pediatric heart-lung, 69 200 adult lung, and 4128 adult heart-lung transplantations performed worldwide had been recorded in the International Thoracic Organ Transplant Registry by June 30, 2018.[7,11] While the annual pediatric LT number has remained stable, the number of heart-lung transplantations is decreasing.[7] CF is the most common indication for LT in children over the age of 11 years, accounting for 65%, compared to 48% in ages 6 to 10 years. In ages 1 to 5 years, the percentage of LT for CF is 3.4%.[6] In adults, it is the third most common indication in patients with advanced CF lung disease.[12] In the Thoracic Organ Transplant Registry, the total LT rate for adult patients with CF reported in 2019 was 15.2%, and most cases were bilateral (97.6%).[11]

In this study, we aimed to compare clinical features of patients with CF with an indication for LT referral with a rapid decrease in forced expiratory volume in the first second (FEV_1) in the last year and patients with other LT indications.

Material and Methods

Data of patients who were recorded in the Cystic Fibrosis Registry of Türkiye (CFRT) in 2018 and performed pulmonary function tests (PFT) were evaluated. CF patients who met the LT referral criteria according to the current guidelines[3] were included the study (Box 1). The patients were divided into those who had an FEV_1 % of under 50% and a decline of more than 20% in the previous year (Group 1) and those who did not have a rapid FEV_1 decline but had other indications for LT seen in Table 1 (Group 2). The flow chart of the study population is given in Fig. 1.

The patients' demographic and clinical characteristics were recorded, and comparisons between the two groups were performed. The analyzed characteristics included age, age at diagnosis, gender, first and second sweat chloride test results, weight and height z-scores, body mass index (BMI) in 2018, genetic mutations, FEV_1% values in 2017 and 2018, death, treatments, chronic infection status, complications, and history of meconium ileus. The z-scores were calculated as the ratio of the difference between the observed measurement and the sample mean to the standard deviation of the sample to describe how many standard deviations height and weight were above or below the sample mean. For patients under 18 years old, malnutrition was defined as having a BMI below the 5th percentile, and for patients 18 years or older, malnutrition was defined as having a BMI below 18.[3] Genetic mutations were classified as severe if two mutations were class I, II, or III and mild if one or more mutations were class IV or V.[13,14] Treatments included inhaled hypertonic saline, inhaled mannitol, inhaled antibiotics, bronchodilators, recombinant

Box 1. Lung transplantation criteria (adapted from Cystic Fibrosis Foundation Consensus Guideline[3]).

For individuals with CF who are under the age of 18 years old should be referred for LT when;

- FEV_1 is under 50% predicted and rapidly declining (>20% relative decline in FEV_1 within 12 months) or
- FEV_1 below 50% with markers of shortening survival;
  - room air hypoxemia (SpO_2 < 88% or PaO_2< 55mmHg at rest or with exercise, at sea level),
  - hypercarbia ($PaCO_2$ >50mmHg confirmed on arterial blood gas),
  - 6 minute-walking-test (6MWT) distance under 400 meters or
  - pulmonary hypertension findings (such as pulmonary arterial systolic pressure above 50 mmHg on echocardiogram or evidence of right ventricular dysfunction in the absence of a tricuspid regurgitant jet)

or

  - body mass index (BMI) under 5 percentile
- FEV_1 is below 40% predicted.

For individuals with CF who are 18 years and older, the CF Foundation recommends LT referral when;

- FEV_1 is under 50% predicted and rapidly decreasing (>20% relative reduction in FEV_1 in the last 12 months) or
- FEV_1 is below 40% predicted with markers of shortening survival;
  - BMI < 18 kg/m^2 or
  - scrambling to improve the nutritional status
  - more than two pulmonary exacerbation per year requiring intravenous antibiotics or 1 exacerbation requiring positive pressure ventilation (PPV) regardless of FEV_1 or
  - massive hemoptysis requiring intensive care unit (ICU) admission or
  - bronchial artery embolization or
  - pneumothorax or
  - regardless of FEV_1 when 6MWT distance under 400 meters or
  - hypoxemia or
  - hypercarbia or
  - pulmonary hypertension occurs) or
- FEV_1 is < 30% predicted.
- For females and individuals with short stature (height <162 cm) the CF Foundation also recommends special consideration for LT.

Table I. Clinical features of the entire study population.

Clinical feature	n	%
Gender (male/female)	29/29	50/50
Age <18 years	33	56.9
Age ≥18 years	25	43.1
History of meconium ileus	2	3.4
Treatment with		
Inhaled hypertonic saline	16	27.6
Inhaled mannitol	17	29.3
Inhaled antibiotic	40	68.9
Bronchodilator	30	51.7
rhDNase	58	100
Inhaled steroid	17	29.3
Oral steroid	4	6.9
Azithromycin prophylaxis	15	25.8
Ursodeoxycholic acid	15	25.8
PERT	55	94.8
PPI	16	27.6
Oxygen	15	25.8
NIPPV	11	18.9
Chronic infection status		
Pseudomonas aeruginosa	45	77.6
Staphylococcus aureus	25	43.1
Burkolderia cepacia	2	3.4
Haemophilus influenzae	7	12
Nontuberculous mycobacteria	1	1.7
Stenotrophomonas maltophilia	6	10.3
Achromobacter	4	6.9
MRSA	9	15.5
Complication related to CF		
Osteoporosis	13	22.4
Liver disease	9	15.5
ABPA	6	10.3
Hemoptysis	2	3.4
Clinical features	Mean ± SD	
Age (years)	18.8 ± 7.5	
Age at diagnosis (years)	5.2 ± 8.5	
Weight z-score	−1.8 ± 0.7	
Height z-score	−1.7 ± 1.3	
Body mass index	15.5 ± 3.0	
Body mass index z-score	−1.4 ± 0.7	
First sweat chloride test value (mmol/L)	96.9 ± 25.3	
Second sweat chloride test value (mmol/L)	96.1 ± 24.9	
FEV_1 value in 2017 (%)	48.4 ± 21.1	
FEV_1 value in 2018 (%)	32.9 ± 8.6	

ABPA: allergic bronchopulmonary aspergillosis, CF: cystic fibrosis, FEV1: forced expiratory volume in the first second, MRSA: methicillin-resistant *Staphylococcus aureus*, NIPPV: noninvasive positive pressure ventilation, rhDNase: recombinant human DNase, PERT: pancreatic enzyme replacement treatment, PPI: proton pump inhibitor, SD: standard deviation.

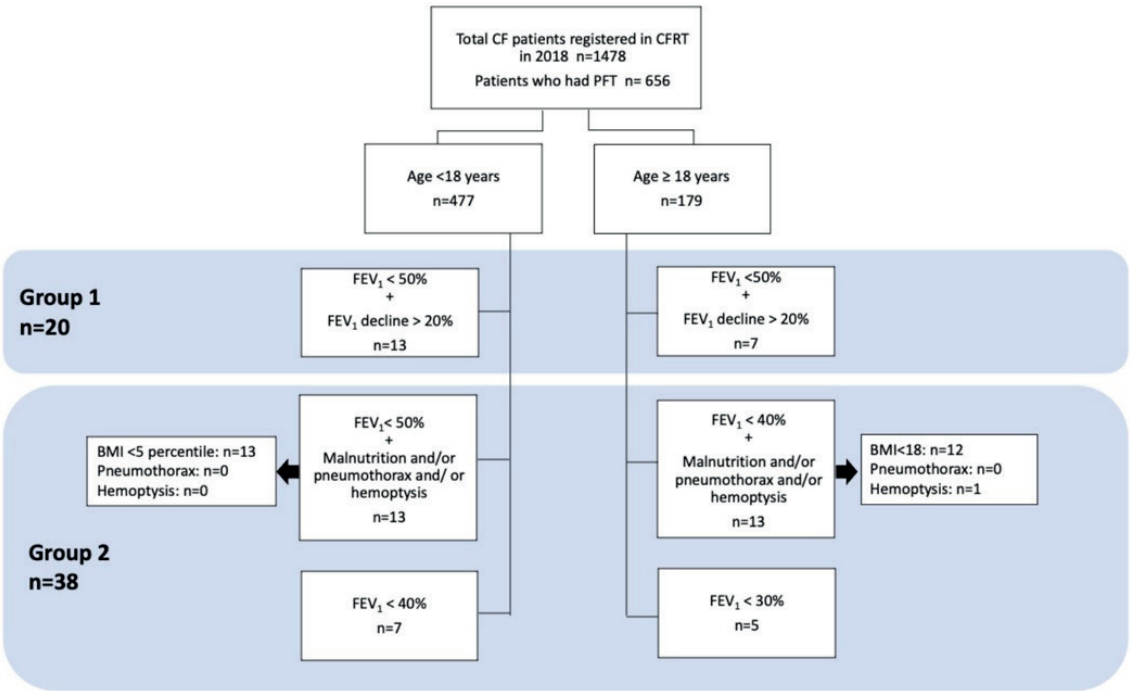

Fig. 1. The flow chart of the study.

human DNase (rhDNase), inhaled/oral steroids, azithromycin prophylaxis, ursodeoxycholic acid, pancreatic enzyme replacement treatment (PERT), proton pump inhibitors, and oxygen or noninvasive positive pressure ventilation (NIPPV). Chronic infection status was defined as three samples taken consecutively from the respiratory tract in the previous six months with at least one-month intervals[15] testing positive for *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Burkholderia cepacia*, *Haemophilus influenzae*, nontuberculous mycobacteria, *Stenotrophomonas maltophilia*, *Achromobacter*, or methicillin-resistant *Staphylococcus aureus* (MRSA). Complications included allergic bronchopulmonary aspergillosis (ABPA), distal intestinal obstruction syndrome (DIOS), hemoptysis, pneumothorax, osteoporosis, liver disease, CF-related diabetes mellitus, and pseudo-Bartter syndrome.

Statistical analysis

IBM SPSS Statistics 22.0 (IBM, Armonk, NY, USA) was used for the statistical analysis. For descriptive statistics, categorical variables were expressed as numbers and percentages, and continuous variables were expressed as means ± standard deviations or medians and ranges. To assess the statistical significance of numerical differences, independent sample t-test was used when the assumption of normal distribution was satisfied for the sample, and Mann-Whitney U test was used when the assumption was not satisfied. For comparisons between the two groups, Pearson chi-square test was used to assess the statistical significance of categorical differences. The relationship between data that did not conform to a normal distribution was evaluated by Spearman's correlation test, and the data that fit the normal distribution was evaluated by Pearson's correlation test. A p-value of less than 0.05 was considered statistically significant.

The study was conducted in accordance with the ethical standards of the institutional and/or national research committee (Hacettepe University Ethics Board, date: 12 April 2007, reference number: HEK 07/16-21 and date: 5 June 2018, reference number: GO 18/473-31) and with the 1964 declaration and its later

amendments or comparable ethical standards. Informed consent was obtained from all patients or their parents/ legal guardians.

Results

A total of 1488 CF patients were recorded in the CFRT in 2018, 656 of whom had PFT results. Of those, 58 (3.9%) met the LT criteria according to the current guidelines.[3] Twenty-nine patients (50%) were male. Thirty-three (56.9%) patients were under 18 years old. The median age of the patients was 17 years (range: 8.0–44.5 years), and the median age at diagnosis was 0.7 years (range: 0.1–41.0 years). The mean FEV_1 was 48.4% ± 21.1% in 2017 and 32.9% ± 8.6% in 2018. The average weight z-score was −1.8 ± 0.7, the average height z-score was −1.7 ± 1.3, and the average BMI z-score was −1.4 ± 0.7. All patients were receiving rhDNase, about one third of patients were receiving inhaled hypertonic saline, inhaled mannitol, and most of them were receiving PERT. Chronic infection with *P. aeruginosa* was the most common whereas nontuberculous mycobacteria was the least. The most common complication related to CF was osteoporosis. None of the patients included in the study had DIOS, pseudo-Bartter syndrome, pneumothorax, or CF-related diabetes or malignancy in 2018 and until 2018, 2 patients with CF who were registered in CFRT underwent LT. The clinical features of the entire study population are shown in Table I.

A total of 20 (34.5%) patients, 13 of whom were under 18 years of age and 7 were aged 18 and above, had FEV_1 under 50% and a decline of more than 20% in the previous year (Group 1). A total of 38 (65.5%) patients did not have a rapid FEV_1 decline in the previous year but had other indications for LT (Group 2). Thirteen of them were under 18 years old and had FEV_1 under 50% and a weight z-score below −2 and/ or pneumothorax and/or hemoptysis. Seven patients were aged under 18 and had FEV_1 under 40%. Thirteen patients were aged 18 and above and had FEV_1 under 40% and BMI below 18 and/or pneumothorax and/or hemoptysis. Five patients were aged 18 and above and had FEV_1 under 30%.

The median age of the patients was 16.6 years (range: 8–44.5 years) in Group 1 and 17.8 years (range: 10.1–41.9 years) in Group 2. The difference was not statistically significant (p = 0.659). The median age at diagnosis was 0.6 years (range: 0.1–41) years in Group 1 and 2 years (range: 0.1–37 years) in Group 2 (p = 0.302). More than half of the patients in Group 1 and about half of the patients in Group 2 were males (p = 0.581). Out of a total of 20 patients in Group 1, 13 (65%) were under the age of 18 years, compared to 20 out of 38 patients (52.6%) in Group 2 (p=0.126). There were no significant differences in the first and second sweat chloride test results between the two groups (p = 0.813 and p = 1.000, respectively). The average weight z-score was significantly higher in Group 1 than in Group 2 (−1.4 ± 0.8 and −2.0 ± 0.7, respectively; p = 0.011). Likewise, the mean BMI z-score was significantly higher in Group 1 than in Group 2 (−1.01 ± 0.86 and −1.57 ± 0.59, respectively; p = 0.015). The median height z-scores, on the other hand, did not differ significantly between Groups 1 and 2 (−1.7 [range: −3.4 to 1.4] and −2.1 [range: −4.2 to 1.8], respectively; p = 0.141). In Group 1, 35% (7 out of 20 patients) were found to be malnourished, while in Group 2, 73.6% (28 out of 38 patients) had malnutrition (p=0.001). Two (10%) patients in Group 1 and no patients in Group 2 had a history of meconium ileus. Because of the insufficient number of patients, a statistical analysis could not be performed.

Five (25%) patients in Group 1 and five (13.1%) in Group 2 had a heterozygous F508del mutation. Four (20%) patients in Group 1 and nine (23.6%) patients in Group 2 had a homozygous F508del mutation. The differences between the two groups were not statistically significant (p = 0.748 and p = 0.512, respectively). In total, 13 (65%) patients in Group 1 and 19 (50%) patients in Group 2 had severe genetic mutations, with no statistically significant difference between the two groups (p = 1.000). The FEV_1 values in 2017 and 2018 did not differ significantly between the two groups (p = 0.366 and

p = 0.255, respectively). No patients in Group 1 died during 2018, whereas five patients (13.2%) in Group 2 died during the same period. The demographic and clinical characteristics of the patients in Groups 1 and 2 are displayed in Table II.

In terms of treatments, one third of patients in Group 1 and one fourth of patients in Group 2 were receiving inhaled hypertonic saline (p = 0.392). About half of the patients in Group 1 and one fifth of patients in Group 2 were receiving inhaled mannitol (p = 0.057). More than half of the patients in Group 1 and more than three fourth of patients in Group 2 were receiving inhaled antibiotics (p = 0.095). One fifth of the patients in Group 1 and more than one fourth of patients in Group 2 were receiving oxygen (p = 0.460), while one fifth of patients in Group 1 and about one fifth of patients in Group 2 were receiving NIPPV (p = 1.000). The treatments in the two groups are shown in Table III.

Chronic infection with *P. aeruginosa* was the most prevalent, whereas infection with nontuberculous bacteria was the rarest. There were no statistically significant differences between the two groups in terms of chronic infections. The chronic infection status of the patients in the two groups is displayed in Table IV.

Osteoporosis was the most common complication, whereas DIOS, pseudo-Bartter syndrome, pneumothorax, and CF-related diabetes or malignancy were not noted.

In terms of FEV_1, a positive correlation was observed between FEV_1 in 2017 and the weight z-score in Group 1 (r = 0.521, p = 0.018). In Group 2, a positive correlation was found between the FEV_1 value in 2018 and that in 2017 (r = 0.768, p = 0.004) (Table V).

Table II. Comparison of demographic and clinical characteristics of patients with rapid FEV_1 decline and patients with other indications for lung transplantation.

Demographic and clinical characteristics	Group 1 n= 20	Group 2 n= 38	p
Age (years), median (range)	16.6 (8-44.5)	17.8 (10.1-41.9)	0.659[a]
Patients under the age 18, n (%)	13 (65)	20 (52.6)	0.126[b]
Age at diagnosis (years), median (range)	0.6 (0.1-41)	2 (0.1-37)	0.302[a]
Gender (male), n (%)	11 (55)	18 (47.4)	0.581[b]
FEV_1 in 2017 (%), mean ± SD	59.4 ± 18.6	30.2 ± 9.1	0.366[c]
FEV_1 in 2018 (%), mean ± SD	34.5 ± 10.2	32.5 ± 9.4	0.255[c]
First sweat chloride test value (mmol/L), mean ± SD	95.5 ± 28.2	92.3 ± 25.1	0.813[c]
Second sweat chloride test value (mmol/L), median (range)	96 (71-127)	96 (63-170)	1.000[a]
Weight z-score, mean ± SD	−1.4 ± 0.8	−2.0 ± 0.7	**0.011[c]**
Height z-score, median (range)	−1.7 (−3.4 to 1.4)	−2.1 (−4.2 to 1.8)	0.141[a]
Body mass index, mean ± SD	16.6 ± 3.3	14.9 ± 2.7	0.061[c]
Body mass index z-score, mean ± SD	−1.01 ± 0.86	−1.57 ± 0.59	**0.015[c]**
Presence of malnutrition, n (%)	7 (35)	28 (73.6)	**0.001[b]**
Genetic mutation, n (severe/mild)	13/1	19/3	1.000[b]
Heterozygous F508del mutation, n (%)	5 (25)	5 (13.1)	0.748[b]
Homozygous F508del mutation, n (%)	4 (20)	9 (23.6)	0.512[b]

FEV_1: forced expiratory volume in the first second, SD: standard deviation
[a] Mann-Whitney U test
[b] Chi-square test
[c] Independent sample t-test
P-values less than 0.05 were considered statistically significant and marked in bold.

Table III. Treatments in Groups 1 and 2.

Treatment	Group 1 n (%)	Group 2 n (%)	p
Inhaled hypertonic saline	7 (35)	9 (24.3)	0.392[a]
Inhaled mannitol	9 (45)	8 (21.1)	0.057[a]
Inhaled antibiotic	11 (55)	29 (76.3)	0.095[a]
Bronchodilator	9 (45)	21 (55.3)	0.457[a]
rhDNase	20 (100)	38 (100)	
Inhaled steroid	7 (35)	10 (26.3)	0.490[a]
Oral steroid	0 (0)	4 (10.5)	
Azithromycin prophylaxis	4 (20)	11 (28.9)	0.460[a]
Ursodeoxycholic acid	5 (25)	10 (26.3)	0.913[a]
PERT	19 (95)	36 (94.7)	1.000[a]
PPI	4 (20)	12 (31.6)	0.348[a]
Oxygen	4 (20)	11 (28.9)	0.460[a]
NIPPV	4 (20)	7 (18.4)	1.000[a]

NIPPV: noninvasive positive pressure ventilation, PERT: pancreatic enzyme replacement treatment, PPI: proton pump inhibitor, rhDNase: recombinant human DNase
[a] Chi-square test

Table IV. Chronic infection status of patients in Groups 1 and 2.

Chronic infection	Group 1 n (%)	Group 2 n (%)	p
Pseudomonas aeruginosa	14 (70)	31 (81.6)	0.339[a]
Staphylococcus aureus	8 (40)	17 (44.7)	0.729[a]
Burkholderia cepacia	0 (0)	2 (5.3)	
Haemophilus influenzae	5 (33.3)	2 (10)	0.112[a]
Nontuberculous mycobacteria	0 (0)	1 (2.6)	
Stenotrophomonas maltophilia	4 (20)	2 (5.3)	0.168[a]
Achromobacter	2 (13.3)	2 (10)	1.000[a]
MRSA	3 (20)	6 (31.6)	0.697[a]

MRSA: methicillin-resistant *Staphylococcus aureus*
[a] Chi-square test

Table V. Relationship between FEV_1 values and weight, height and BMI z-scores over two consecutive years.

			FEV_1 in 2017	FEV_1 in 2018	Weight z-score	Height z-score	BMI z-score
Group 1	FEV_1 in 2017	p	1	0.233	0.018	0.351	0.069
		r		0.279	0.521	-0.220	0.415
	FEV_1 in 2018	p	0.233	1	0.684	0.129	0.717
		r	0.279		-0.097	-0.351	-0.086
Group 2	FEV_1 in 2017	p	1	0.004	0.768	0.482	0.974
		r		0.768	0.095	-0.225	0.011
	FEV_1 in 2018	p	0.004	1	0.443	0.103	0.333
		r	0.768		-0.128	-0.269	-0.161

BMI: body mass index, FEV_1: forced expiratory volume in the first second

Discussion

This registry-based study aimed to compare the clinical characteristics of CF patients who needed LT referral due to a rapid decline in FEV_1 and who did not exhibit a rapid decline in FEV_1 but had other indications for LT referral by using the data of CFRT. We found that according to the latest guidelines, 3.9% of CF patients in Türkiye registered in CFRT were in need of LT referral. In our study, more than half of the patients in need for LT were in the pediatric age group. In total 20 patients had rapid decline on FEV_1 in the last year and became candidates for LT. When the demographic and clinical characteristics of the patients were compared, the weight z-score and BMI z-scores were found to be higher in patients with FEV_1 decline more than 20% in the last year than others. So, a rapid FEV_1 decline in the previous year was found to be associated with the patients' nutritional status and weight z-scores. There were no significant differences in chronic infection status, treatments, or complication status between patients with and without a rapid decline in FEV_1. This may be because both groups in the study had advanced lung disease and were candidates for lung transplantation, even though for different reasons.

Over the years, the rate of adult CF patients who have been followed-up has increased. Consequently, LT is seen more frequently in adults. An estimated 8% of CF patients undergoing LT in Canada from 1988 to 2016 were pediatric patients.[9] In the Italian CF registry, 8 (10.8%) of 76 CF patients undergoing LT in 2015 and 2016 were in the pediatric age group.[16] In the 2017 annual report of the European Cystic Fibrosis Society (ECFS), 32 (10.7%) of 299 patients undergoing LT were in the pediatric age group.[17] Since the number of LT in Türkiye is low, the patients who are candidates for LT were reviewed and 56.9% of the patients who were recorded in the CFRT and needed LT according to the latest guidelines were found to be in the pediatric age group.[3] This may be because the CFRT started recently, and more than half of registered patients are under 18 years of age. Moreover, adult patients' follow-up is not yet at the desired level. Over time, more adult CF patients are expected to be followed up closely.

Malnutrition and low BMI are associated with poorer pulmonary outcomes and are significant predictors of poor survival and earlier progression toward the need for LT in CF.[18,19] Because high basal metabolic rates with both exocrine and endocrine dysfunction predispose CF patients to undernutrition and low weight; their nutritional status should be closely monitored during long-term follow-ups.[19] On the other hand, it is also possible that severe lung disease itself may be associated with a poor nutritional state due to increased energy needs, decreased appetite, and gastrointestinal involvement, such as reflux and nausea.[20] Kerem et al.[20] found that a low BMI was the strongest potentially preventable factor for severe lung disease in patients recorded in the ECFS Patient Registry. Poor pulmonary function was six times higher in severely undernourished patients than in patients with normal BMI.[20] In our study, BMI average values and height z-scores were similar in patients with rapid FEV_1 decline and patients with other indications. Patients in Group 2 had a higher rate of malnutrition due to its inclusion criteria. Moreover, the weight and BMI z-scores were significantly lower in patients who had other indications for LT other than rapid FEV_1 decline. This may be because, apart from a rapid FEV_1 decline, patients can be candidates for LT due to poor nutritional status. It is also known that pancreatic insufficiency in CF patients doubles the risk of severe lung disease.[19] Monitoring and improving CF patients' nutritional status is a cornerstone of management to slow the progression to end-stage lung disease.[19] It is important to note that the presence of other conditions, such as pulmonary hypertension and right heart failure, in patients with advanced lung disease can negatively impact their nutritional status.[21] It is important to consider the potential adverse effects of poor nutritional status on the progression of lung

disease and the development of comorbidities, as these factors may further exacerbate the nutritional status and overall clinical condition of the patient. As our study highlights, it is important to remember that there are numerous factors, in addition to nutritional status, that can affect the candidacy of patients with advanced lung disease and CF for LT.

Because of CF patients' variable course of disease, the prediction of prognosis is often difficult. Milla and Warwick[22] found that the rate of yearly FEV_1 decline is a better predictor of early mortality than the FEV_1 percentage alone. As a result of our study, we would like to emphasize that the long-term follow-up of the nutritional status besides the lung functions of patients with CF is more important than the changes in the last 1 year. It should be kept in mind that CF patients should be followed up closely with a multidisciplinary approach, especially in terms of pathogen colonization, malnutrition, and complications that may affect lung function.

Although we included all CF patients recorded in the CFRT, our study has some limitations. One of them was the small sample size of the population included the study. This may undermine some differences between the two groups. Unfortunately, we were unable to include several important variables in the analysis, including hypercarbia, hypoxemia, six-minute walk-test results, pulmonary hypertension, number of hospitalizations, pulmonary exacerbations, and frequency of antibiotic use. Additionally, we were unable to include information about whether or not the patients were receiving adequate nutrition and dietary support or the timeframe in which this was provided because these data were not recorded in the CFRT. Also, the reason why there is a significant difference in the weight z-score and the BMI between the two groups is because low BMI could be a criterion for being included in Group 2 but not in Group 1. Additionally, it was also noteworthy that the mean FEV_1 values of the patients in Group 2 were higher in 2018 than in 2017. The fact that the expected decrease in FEV_1 was not seen in this group over the past year may be due to the intensive regulation of the treatment of the patient group who already have low FEV_1 values.

Patients with CF may develop end-stage lung disease in the long term for various reasons and become candidates for LT. As the number of patients recorded in the CFRT increases, the registry will provide clinicians with more information and assist in the identification of patients in need for LT. All CF patients' nutritional status should be carefully monitored. Weight gain is essential for CF patients to avoid the need for LT. Early identification of poor nutritional status could prevent lung function deterioration and delay the progression to end-stage lung disease. A yearly FEV_1 decline of 20% or more may not be associated with other clinical parameters. Overall, our findings highlight the importance of long-term monitoring of CF patients' clinical and nutritional status to protect lung functions and to identify patients in need of LT referral.

Acknowledgement

We thank the CFRT for providing access to the data and the center's representatives for permitting the use of the data.

Ethical approval

The study was conducted in accordance with the ethical standards of the institutional and/ or national research committee (Hacettepe University Ethics Board, date: 12 April 2007, reference number: HEK 07/16-21 and date: 5 June 2018, reference number: GO 18/473-31) and with the 1964 declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all patients or their parents/ legal guardians.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: ZRO, TŞE, ATA, TRG; data collection: EY, NK, NE, HSŞ, VŞ, GÜ, AİY, AAK, HÇ, AKB, HY, AÇ, SU, AŞŞ, DÖ, DUA, GKÖ, ED, AB, EB, ŞÇ, NS, İİ, ED, GDT, SEP, AÖ, KH, GK, MH, MK, ZT, HY, GÖ, ET, DC, PK, GC, MK, ŞÖ, EÇ, NÇ, SP, GC, UÖ, DD; analysis and interpretation of results: ZRO, TŞE, ATA, TRG; draft manuscript preparation: ZRO, TŞE, ATA, TRG, DD. All authors reviewed the results and approved the final version of the manuscript.

Source of funding

The authors declare the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

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