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ORIGINAL ARTICLE

Lung function outcomes of cystic fibrosis patients after early-life pulmonary exacerbations: National registry analysis

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Abstract

Background: Pulmonary exacerbations (PEs) are associated with a subsequent decline in lung function. We aim to evaluate lung function in cystic fibrosis (CF) patients with frequent PEs in their first 2 years of age using spirometry at age 6.

Methods: This retrospective cohort study included CF patients who were 6 years old from the CF registry of Turkey in 2019. According to the number of PEs, patients were classified: those who had two or fewer PEs in the first 2 years of age were defined as Group 1 and those who had more than two PEs were defined as Group 2. The patients' demographics and clinical characteristics were compared between Group 1 and Group 2.

Results: The study included 88 patients who had data on PE from their first 2 years and completed their sixth year by 2019. Fifty-nine patients were included in Group 1 and 29 in Group 2. The mean percent-predictive FEV1 (ppFEV1), percent-predictive FVC (ppFVC) values, and the mean age at first PE were lower in Group 2 than in Group 1 ($p=0.019$, $p=0.017$, $p<0.001$). The patients with chronic *Pseudomonas aeruginosa* (PA) colonization had lower mean ppFEV1 and ppFVC values than those without ($p=0.001$, $p=0.001$). Patients with PA in respiratory-sample culture during their first PE had lower ppFEV1 and ppFVC values than those with SA ($p=0.046$; 0.018).

For affiliations refer to page 7.

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Conclusions: This study showed that more frequent PEs in the first 2 years of age and chronic PA colonization were associated with poorer FEV1, FVC, and BMI values in CF patients.

KEYWORDS
chronic colonization, cystic fibrosis, pulmonary exacerbation, respiratory function

INTRODUCTION

Cystic fibrosis (CF) is a multisystemic genetic disease with high morbidity and mortality rates. The lung disease is the primary cause of morbidity and mortality.[1] CF lung disease has several distinctive features, including pulmonary exacerbation (PE) marked by increased respiratory symptoms, decreased lung function (LF), loss of energy, weight loss, and physical changes.[2] A decline in LF over time is seen in patients with CF, and attacks of PE exacerbate this decline.[3] An exacerbation results in an approximately 3% decline in FEV1, and 30% of CF patients fail to recover baseline FEV1 values.[4] Factors affecting poor LF recovery after PE treatment include gender, insurance type, baseline LF, time since previous PEs, relative PE-associated FEV1 drop, pancreatic function, nutritional status, ABPA, and exacerbation-causing bacteria.[5]

Thick mucus, impaired mucociliary function, and altered airway defenses in CF patients lead to infection, inflammation, and declining LF.[6] *Staphylococcus aureus* (*SA*), *Haemophilus influenzae* (*HI*), and *Pseudomonas aeruginosa* (*PA*) are the most common pathogens isolated from the sputum of patients with CF.[7] PA colonization is a factor in FEV1 decline in CF, increasing the risk of severe lung disease by 2.4 times and strongly impacting overall prognosis.[8,9]

We hypothesized that patients experiencing frequent PEs within the first 2 years of age would exhibit worse spirometry values at age 6 compared to their peers. Therefore, we aim to evaluate LF in CF patients with frequent PEs in their first 2 years of age using spirometry at age 6 and determine the factors that affect the FEV1 and FVC values.

METHODS

Study design and procedures

We conducted a retrospective cohort study using the 2019 data from the Cystic Fibrosis Registry of Turkey (CFRT), which contains information on CF patients from most CF centers in Turkey. Patients aged 6 in 2019 were included in the study, while those lacking PE data in the first 2 years were excluded.

The CFRT contains demographic and clinical data collected at accredited centers using a standardized entry form at each clinical encounter. A description of the database had been previously published.[10] The following information, in which the CFRT does not include, was also required from CF centers: the number of PEs and hospitalizations for PEs in the first 2 years of age, the age of the first PE, the microorganism isolated from sputum culture in the first PE, the SA or PA colonization age, and the BMI (body mass index) value when colonization is determined.

The amended Helsinki Declaration was used to conduct this study, and our local ethics committee approved all procedures involving human participants. Ethical approval was obtained from the clinical research ethics committee of Ankara Bilkent City Hospital (Reference number: E2-22-1877).

The diagnosis of CF was established upon typical clinical findings, with ≥2 positive sweat chloride tests and/or two CF-causing CFTR mutations.[11,12] In 2015, our country began screening newborns for CF using immune-reactive trypsinogen levels. The patient group in our study was born before 2015, so none were diagnosed through newborn screening tests (NBS). Instead, they were diagnosed with CF based on genetic testing for the CFTR gene and sweat tests performed because of their clinical symptoms.

The European Consensus Group defines PE as the need for additional antibiotic treatment as indicated by a recent change in at least two of the following: change in sputum volume or color, increased cough, increased dyspnea, increased malaise, fatigue or lethargy, anorexia or weight loss, decrease in pulmonary function by 10%, or radiographic changes.[13] Chronic colonization was defined as having more than 50% of sputum cultures positive for PA taken within 12 months.[14]

BMI was calculated as kg/m^2, and BMI *z*-scores were calculated using the Center for Disease Control reference values.[15] Spirometry indices were analyzed using the reference values of Quanjer et al.[16]

CFTR mutation, current BMI, BMI-z scores, percentage predicted FEV1 (ppFEV1), percentage predicted FVC (ppFVC), the use of oxygen, inhaled tobramycin/colistin/steroid/steroid+ long-acting beta-agonists (LABA), azithromycin prophylaxis, usage of oral feeding supplement, multivitamin, calcium support, insulin, proton pump inhibitor (PPI), ursodeoxycholic acid (UDCA), rhDNase, bronchodilator, chronic PA/SA colonization, allergic bronchopulmonary aspergillosis (ABPA), and gastroesophageal reflux disease (GERD) status were included for analyses. The CFRT database lacked data on expiratory flow indices like FEF25–75,

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sensitive indicators of early CF lung disease, so these could not be included in the analysis.

The mean number of PEs in 88 patients was 2.16 (SD: 2.38). According to the number of PEs, patients were classified: those who had two or fewer PEs in the first 2 years of age were defined as Group 1, and those who had more than two PEs were defined as Group 2. Then, the ppFEV1 and ppFVC values, the age of the first PE, number of hospitalizations for PEs, chronic colonization status with PA/SA, CFTR mutation, current BMI, BMI-z scores, the use of oxygen, noninvasive positive pressure ventilation (NIPPV), inhaled tobramycin/colistin/steroid/steroid+LABA, azithromycin prophylaxis, oral feeding supplement, multivitamin, calcium supplementation, insulin, PPI, UDCA, rhDNase, bronchodilator, and chronic PA/SA colonization status were used to compare Group 1 and Group 2.

Statistical analysis

The data were analyzed using SPSS for Windows version 20.0. Descriptive statistics were presented for categorical and numerical variables. Normal distribution of numerical data was tested using the Kolmogorov–Smirnov test. Parametric methods were applied to analyze normally distributed numerical variables, while non-parametric methods were used for non-normally distributed variables. The independent samples *t*-test and Mann–Whitney *U*-test were used to analyze differences between two independent groups. Correlation analysis was conducted using either the Pearson or Spearman test. Data were analyzed at a 95% confidence level, with a *p*-value of less than 0.05 considered statistically significant.

RESULTS

Cohort characteristics

Of 1637 patients in the CFRT-2019 database, 110 who turned 6 that year were included in the study. Information on PE during the first 2 years of age was available for 88 patients. Fifty-nine patients were in Group 1, and 29 in Group 2 (Figure 1).

In the study, 45 patients (51.1%) were female. All patients have pancreatic insufficiency. F508del (18.8%), N1303K (6.3%), and 2183AA->G (5.5%) were the three most frequently detected mutations among the study patients. F508del is present on at least one allele in 24 (27.3%) patients. The average ppFEV1 value was 85.77%, while the ppFVC value was 82.88%, and the mean BMI was 15.21. The mean number of PEs was 2.16 (SD: 2.38). The mean age at first PE was 1.57 years (SD: 1.85), and the mean number of hospitalizations was 2.59 (SD: 2.27). It was found that 8 (9.09%) were colonized by PA and SA, 8 (9.09%) by PA only, and 16 (18.18%) by SA only. Statistical evaluation was not possible due to the small sample size

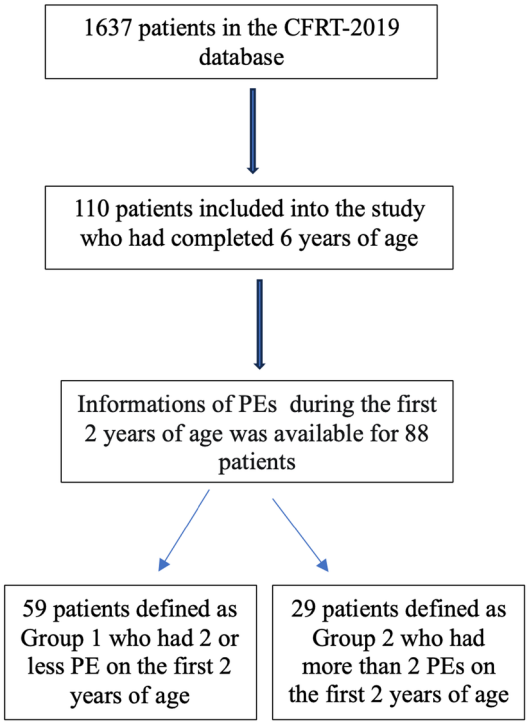


FIGURE 1 Identification of study group patients. From the UKKS 2019 database, 110 patients aged 6 were included from 1637 recorded. Data on pulmonary exacerbations, colonization status, and ages at colonization during the first 2 years were collected for 88 patients with available info by contacting monitoring centers. The average number of PEs during the first 2 years for these 88 patients was 2.16; patients with two or fewer PEs were assigned to Group 1, while those with more than two PEs were assigned to Group 2.

of 6-year-old CF patients, which precluded analysis of complications such as ABPA, osteopenia, and GERD.

The patients used the following treatments: 87 (98.9%) rhDNase, 79 (89.80%) multivitamins, 21 (23.90%) bronchodilators, 21 (23.90%) inhaled steroids, 18 (20.40%) inhaled tobramycin/colistin, 5 (5.70%) inhaled steroids and LABA, 4 (4.50%) azithromycin, 16 (18.20%) UDCA, 3 (3.40%) PPI, 1 (1.10%) calcium supplementation, and 2 (2.30%) insulin. Fifty-four patients (61.40%) used oral feeding supplements. Additionally, 2 (2.30%) were on oxygen support, and 1 (1.10%) was on NIPPV. None of the patients received modulatory therapies because they were not covered by insurance in our country.

There was no significant difference in the number of PEs between patients with at least one F508del allele and those without ($p=0.160$).

Comparison of clinical characteristics of the groups

The study population's clinical characteristics were compared between the groups when they were 6 years old. Group 2 had a lower mean ppFEV1(76.60%) and ppFVC (74.10%) than Group 1 (mean ppFEV1=90.20%; mean

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ppFVC=87.20%) (p=0.019; p=0.017, respectively). The mean age at first PE was lower in Group 2 than in Group 1 (p<0.001). The mean number of hospitalizations in Group 2 (4.52) was significantly higher than in Group 1 (1.64) (p<0.001). The frequency of F508del in at least one allele was higher in Group 1 than in Group 2 (p=0.012) (Table 1).

There were no significant differences between Group 1 and Group 2 according to the use of bronchodilators (p=0.120), inhaled tobramycin/colistin (p=0.999), oxygen (p=0.999), NIPPV (p=0.999), rhDNase (p=0.999), inhaled steroid (p=0.307), inhaled steroid and LABA (p=0.999), azithromycin (p=0.999), UDCA (p=0.873), PPI (p=0.548), oral feeding supplement (p=0.305), multivitamin (p=0.999), calcium supplementation (p=0.999), and insulin (p=0.999).

Comparison of clinical characteristics of the patients according to colonization status at 6th year of age

The patients with chronic PA colonization had lower mean ppFEV1 and ppFVC values than those without (p=0.001, p=0.001). The mean BMI of patients with chronic SA colonization was higher than those without (16.32 vs. 14.80, p=0.035). The mean BMI and mean ppFEV1 values of patients with chronic PA colonization were lower than those of patients with chronic SA (p=0.032, p=0.037) (Table 2).

The current BMI values of patients with chronic colonization of SA, PA, or both are significantly lower than their BMI values at the time of colonization detection (Corr. coeff=0.375, p=0.028). We compared the BMI-z scores of patients at the time of colonization with their current BMI-z scores. However, the comparison was hindered because 24 (27.20%) patients were under 2 years of age when chronic colonization was detected, and BMI assessment was inappropriate for children under 2 years of age.[15] No significant association was found between the number of PEs and current BMI values.

We found that individuals with PA in sputum culture during their first PE had lower ppFEV1 and ppFVC values than those with SA (p=0.046, 0.018).

TABLE 1 Comparison of clinical characteristics of the groups.

	Group 1 (n=59)	Group 2 (n=29)	p
Number of females, n (%)	34 (57.60)	11 (37.90)	0.082
The age at first PE, mean (SD)	2.12 (1.98)	0.56 (0.49)	**<0.001**
The number of hospitalizations, n (SD)	1.64 (1.65)	4.52 (2.16)	**<0.001**
Mean BMI, kg/m^2 (SD)	15.15 (2.10)	15.34 (3.32)	0.327
Mean ppFEV1, % (SD)	90.23 (22.42)	76.68 (29.16)	**0.019**
Mean FVC, % (SD)	87.20 (22.42)	74.10 (26.09)	**0.017**
F508del homozygote or compound heterozygotes with another known CF-causing mutation, n (%)	21 (35.60)	3 (10.34)	**0.012**
Inhaled antibiotic use, n (%)	11 (91.70)	5 (83.30)	0.999
Airway chronic bacterial colonization n (%)			
SA	15 (25.40)	9 (31.00)	0.579
PA	20 (33.90)	12 (41.40)	0.873

Note: The Mann–Whitney U-tests were performed to compare two groups concerning quantitative variables. The chi-squared tests were used to compare two groups in terms of proportions (relative frequencies). Bold indicates a p-value below 0.05 is regarded as statistically significant.

Abbreviations: BMI, body mass index; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; PA, *Pseudomonas aeruginosa*; pp, percent predicted; SA, *Staphylococcus aureus*.

TABLE 2 Comparison of clinical characteristics of the patients according to colonization status.

	Chronic PA colonization			Chronic SA colonization		
	Yes (n=16)	No (n=64)	p	Yes (n=24)	No (n=64)	p
The age at first PE, Mean (SD)	1.44 (1.58)	1.65 (1.85)	0.649	1.36 (1.52)	1.70 (1.89)	0.363
The number of hospitalizations, n (SD)	2.44 (1.86)	2.63 (2.37)	0.974	1.92 (1.79)	2.84 (2.39)	0.112
Mean BMI, kg/m^2 (SD)	14.85 (2.27)	15.29 (2.62)	0.399	16.32 (3.26)	14.80 (2.11)	**0.035**
Mean ppFEV1, % (SD)	65.81 (28.01)	90.20 (22.77)	**0.001**	85.83 (29.16)	85.75 (24.18)	0.948
Mean FVC, % (SD)	65.56 (27.44)	86.73 (22.01)	**0.001**	82.95 (24.56)	82.85 (24.45)	0.987

Note: For the comparison of two groups with respect to quantitative variables, the Mann–Whitney U-tests were performed. The chi-squared tests were used to compare two groups in terms of proportions (relative frequencies).

Abbreviations: BMI, body mass index; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; PE, pulmonary exacerbation; pp, percent predicted.

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DISCUSSION

PEs are a leading cause of morbidity and mortality in patients with CF. The study showed that having more than two PEs within the first two years of life leads to lower ppFEV1 and ppFVC at age 6, compared to having two or fewer PEs in the same period. An early age of PE attacks also led to frequent hospitalization.

Many PEs make LF worse. At 6 years of age and older, ppFEV1 is commonly used to monitor LF. Previous studies have assessed the impact of the frequency of PEs on FEV_1 decline.[5,17–20] The rate of exacerbations in the first 2 years was associated with reduced FEV1 *z*-score in a study[20] similar to our result, in which we showed that patients with more than two PEs had a lower mean ppFEV1 and ppFVC, respectively. In a study, the FEV1 decline was 5.3% lower for the group with two to four exacerbations and 7.9% lower for those with five or more exacerbations compared to the group with no exacerbations.[4] Sanders et al. analyzed US Cystic Fibrosis Foundation Patient Registry data and found that children with one or more exacerbations in 2003 had a significantly higher rate of FEV1 decline during 2004–2006 compared to those with no PEs.[17] They also showed that, after PEs, 25% failed to recover to baseline FEV1.[1] Another study revealed that the long-term decrease in FEV1 following a PE exacerbation happened regardless of whether antibiotics were given in hospitals or at home.[18] Wagener et al. published that only 27.7% of all PEs had complete ppFEV1 recovery.[5] In contrast, Anstead et al. found that, despite nearly half of the exacerbations in the CF population being linked to a sudden decrease in LF, these events did not have a significant effect on LF at the end of the 6-month trial.[19] In our study, we found that early-age frequent PEs significantly reduced ppFEV1, which is consistent with findings from many studies in the literature.

In cystic fibrosis patients, a key early indicator of airway damage is a reduction in FEF25–75%.[21] While some studies in the literature suggest that low FEF25–75% can be an early marker of airway damage in CF patients, others have found it not to be more effective than FEV1% during follow-up.[22,23] Because our national registry system lacks data on FEF25–75% assessments, we were unable to provide additional insights on this parameter.

Lung development in the first years of life is crucial for lifelong respiratory function, and studies have shown that, in people with CF, pulmonary inflammation starts early in infancy and is exaggerated in response to pulmonary infection.[24] Patients diagnosed with CF at an early age had better mean FEV1 values at follow-up.[25] The number of exacerbations and the specific pathogens colonizing the airways of CF patients are significant determinants of structural lung damage that can lead to further loss of LF,[26] and PEs in early age have a more negative impact on respiratory function in later age.[27] New treatment methods are reducing PEs and improving patients' respiratory functions with modulatory therapies.[28] For all these reasons, early diagnosis of CF, prevention of PEs, initiation of effective therapies at the right time, and use of modulatory therapies in appropriate patients are vital for the preservation of LF in CF patients.

F508del is the most common mutation in the Caucasian population.[11] Similarly, F508del was the most common mutation in our study population, while N1303K was the second most frequent one. Group 1 patients showed a higher frequency of the F508del mutation in at least one allele compared to Group 2. In a study by Leung et al., it was found that patients with N1303K mutations had worse LF than homozygous F508del.[29] In a study involving 2183AA->G, which is the third most common genetic alteration in our patient population, patients were found to have severe pancreatic involvement, failure to thrive, and variable lung involvement.[30] We found that, despite Group 1 patients having more severe CFTR mutations such as F508del, their LF was better compared to Group 2 patients, who experienced more frequent PEs during the first 2 years of age. This suggests that early-age PE frequency may impact LF more than the CFTR mutation type. The study's results may be affected by the wide distribution of the genetics of our patients and the lack of access to modulatory treatment.

The prognosis of patients depends on the extent of lung involvement because abnormal airway secretions lead to chronic inflammation and infections that progressively destroy the lungs.[31] Frequent PEs at an early age can lead to chronic colonization, resulting in progressive lung damage at an early age.[32] People with CF are often chronically infected with microorganisms such as PA and SA.[6] Early infection with PA is a major predictor of mortality and morbidity in young children with CF.[33] In our study, chronic PA colonization was associated with lower ppFEV1 and ppFVC. Additionally, individuals with PA in sputum culture during their first PE had lower ppFEV1 and ppFVC values than those with SA. Similarly, Sagel et al. found that patients with PA infection have greater airway inflammation and experience more airway damage over time than those with other bacterial infections.[34] Kerem et al. showed that chronic colonization increased the risk of severe lung disease by 2.4 times.[9] Similarly, Kampouras et al. found that patients with chronic PA colonization had lower ppFEV1 values.[8] Another study published that, at the age of 7, patients colonized with PA had a 10% lower ppFEV1 compared to non-colonized patients.[35] Pamukcu et al. found that patients colonized with PA had lower ppFEV1 values than the non-colonized group.[36] Nayir Büyükşahin et al. also highlighted that colonization with *Pseudomonas aeruginosa* in patients with CF is linked to worse lung function, a lower body mass index, and an increased frequency of pulmonary exacerbations.[37] In contrast, Pascoal et al. found no differences between groups regarding the predominant type of bacteria.[38] In light of this information,

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it is evident that early PE attacks, particularly colonization with PA, are associated with poor long-term LF.

We found that the mean number of hospitalizations in Group 2 was significantly higher than in Group 1. Wagener et al. found that untreated PE attacks resulted in a sudden decrease in FEV1, and LF did not recover to the baseline in the long-term follow-up of these patients.[39] They also found that patients treated with IV therapy had better long-term LF.[40] However, some studies have found no improvement in FEV1 even when patients were treated with IV therapy.[1] Byrnes et al. found that patients had an average of 3.66 PE episodes per year and that the exacerbation rate increased by 9% per year of age; hospital admission exacerbations were linked to a heightened risk of bronchiectasis.[20] To preserve LF and prevent lung structural damage in CF patients, it is necessary to avoid PE attacks, which are the leading cause of hospitalization in these patients.

It has been known for many years that chronic colonization is a risk factor for pulmonary function, both by itself and by impairing nutritional status.[41] Poor nutritional status is associated with decreased pulmonary function, impaired respiratory muscle function, and reduced exercise tolerance in CF patients.[41] We found that patients with chronic colonization had significantly lower BMI values than when colonization was first detected. Low BMI increases the risk of severe lung disease by six times.[9] Dhochak et al. followed CF patients for 3 years and found that the rate of PEs during the second and third years significantly negatively correlated with the weight-for-age *Z*-score at the beginning of the respective years.[42] Another study found that infection with SA was associated with a lower BMI.[43] Haack et al. found no correlation between nutritional status and colonization by PA.[44] Sunman et al. compared BMI values of children colonized with methicillin-susceptible SA and divided them into early-onset and late-onset. They found similar BMI values but lower ppFEV1, FVC and FEF25-75 in the early-onset group.[45] Our study did not find a significant correlation between the number of PEs and the current BMI values. However, we did observe that patients in Group 2, who experienced more frequent PEs in their first 2 years of age, tended to have higher BMI values, although this finding was not statistically significant. Therefore, we concluded that the number of PEs, rather than BMI, was a more substantial factor in the low mean ppFEV1 of Group 2 patients who had more PEs at an early age.

In our country, NBS started in 2015. Since all patients in our study were born before this year and were not diagnosed via NBS, we could not compare patient groups in this context. However, many studies over the years have shown that NBS programs allow for the diagnosis of CF before symptoms appear, preventing organ damage.[46,47] This results in less PE and colonization, leading to improved lung function and growth outcomes compared to patients diagnosed without NBS.[48,49] Another major breakthrough in CF treatment in the last decade has been the development of CFTR modulator therapies. However, since these therapies are not covered by insurance in our country, we could not assess their impact on the clinical and laboratory features of the patients in our study. Another local study has observed that CF patients without access to modulator therapy showed significant declines in FEV1 and BMI over time, along with increased colonization and oxygen needs.[50] Recent studies in the literature demonstrate that modulator treatments enhance pulmonary function and nutritional status, while also positively impacting structural lung disease.[51,52] For these reasons, early diagnosis of CF patients through NBS and prompt initiation of appropriate modulator therapy constitute the most critical management strategies for cystic fibrosis.

Our study has all the limitations of retrospective studies. The diagnosis of PE is not standardized and might have been affected by the clinician's opinion. The technical equipment in each center's microbiology laboratory varies, potentially impacting the growth of microorganisms in respiratory samples from CF patients. Our study data lacking FEF25–75%, a parameter indicating small airway function and early lung damage, might underestimate early peripheral airway involvement. Despite these limitations, this study was prepared using our national Cystic Fibrosis Registry database that provides detailed information from many tertiary centers where many CF patients' diagnosis and treatment processes are managed.

CONCLUSION

Our results showed that more frequent PEs in the first 2 years of age and chronic PA colonization were associated with poorer LFs and lower BMI values in children with CF. Further studies are needed to develop different modalities for preventing and treating frequent PEs at an early age to protect the lung health of CF patients.

AUTHOR CONTRIBUTIONS

All authors meet the requirements for authorship, having contributed significantly to the study. S. Özkan Tabakçı, G. Cinel, S. Uytun, S. Eryılmaz Polat: Conceptualization, methodology, formal analysis, investigation, writing—original draft. E. Yalçın, N. Kiper, M. Akgül Erdal, V. Şen, S. Savaş, Ö. Çelebi, D. Ufuk Altıntaş, M. Serbes, A. Ayzıt Kılınç, H. Çokuğraş, H. Arslan, H. Yazan, H. Molla Kafi, A. Çollak, G. Ünal, A. İ. Yılmaz, H. T. Çağlar, İ. Irmak, E. Damadoğlu, G. Kartal Öztürk, E. Demir, A.E. Başaran, A. Bingöl, Y. Canıtez, Ş. Çekiç, P. Asfuroğlu, A. Tana Aslan, K. Harmancı, G. Kılıç, M. Köse, A. Ersoy, M. Hangül, A. Özdemir, G. Özcan, N. Çobanoğlu, Z.G. Gayretli Aydın, Ö. Keskin, H. Yüksel, Ş. Özdoğan, E. Topal, G. Çaltepe, D. Can, P. Korkmaz Ekren, M. Kılıç, T. Şişmanlar Eyüboğlu, S. Pekcan, E.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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