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Examination of Cases Who Had Molecular Testing with the Presumptive Diagnosis of Cystic Fibrosis: Experience of a Single Center

Kistik Fibrozis Öntanısıyla Moleküler Test Yapılan Olguların İncelenmesi: Tek Merkez Deneyimi

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ABSTRACT

Objective: Cystic fibrosis (CF) is an autosomal recessive disorder caused by mutations in the Cystic Fibrosis Transmembrane Regulator (CFTR) gene, leading to multisystem involvement. Early diagnosis is crucial for managing complications and improving patient prognosis. This study aimed to evaluate the clinical and demographic characteristics and molecular analysis results of patients who underwent CFTR gene mutation analysis with a preliminary diagnosis of CF.

Materials and Methods: A total of 34 patients were included in the study. Clinical and demographic data, along with genetic analysis results, were retrospectively examined. The frequency of symptoms associated with CF was determined, and the relationship between genetic findings and clinical manifestations was analyzed.

Results: The most common reason for admission was respiratory symptoms, accounting for 64.7% of cases, followed by gastrointestinal complaints and malnutrition. Malnutrition was found to be significantly associated with a positive CFTR gene mutation (p=0.027). The risk of detecting a CFTR gene mutation was 5.667 times higher in patients with malnutrition.

Conclusions: This study highlights the necessity of considering CF in the differential diagnosis of children presenting with recurrent respiratory tract infections and malnutrition, even in the absence of a positive family history. While respiratory symptoms were the most common reason for admission, malnutrition was found to be significantly more prevalent among mutation-positive cases. These findings underscore the importance of supporting careful clinical evaluation with genetic analysis in the diagnostic process of CF. Further large-scale, multicenter studies are needed to confirm and expand upon these results.

Keywords: CFTR gene, cystic fibrosis, heterozygous mutation, malnutrition, recurrent lower respiratory tract infection

ÖZ

Giriş: Kistik fibrozis (KF), Cistic fibrosis Cystic Fibrosis Transmembrane Regulator (CFTR) genindeki mutasyonlar sonucu ortaya çıkan otozomal resesif geçişli bir hastalıktır ve multisistemik tutulum gösterir. Erken tanı, komplikasyonların yönetimi ve hasta prognozu açısından kritik öneme sahiptir. Bu çalışmada, KF ön tanısı ile CFTR gen mutasyon analizi yapılan hastaların klinik ve demografik özellikleri ile moleküler analiz sonuçlarının değerlendirilmesi amaçlandı.

Materyal ve Metot: Çalışmaya toplam 34 hasta dahil edilmiştir. Klinik, demografik veriler ve genetik analiz sonuçları retrospektif olarak incelenmiştir. KF ile ilişkili semptomların sıklığı belirlenmiş ve genetik bulgular ile klinik belirtiler arasındaki ilişki analiz edilmiştir.

Bulgular: Başvuru nedenleri arasında en yaygın olanı % 64,7 oranıyla solunum yolu semptomlarıydı; bunu gastrointestinal şikayetler ve malnütrisyon izledi. Malnütrisyon, CFTR gen mutasyonu pozitifliği ile anlamlı şekilde ilişkili bulundu (p=0,027). Malnütrisyonu olan hastalarda CFTR gen mutasyonu saptanma riski 5,667 kat daha yüksekti.

Sonuç: Bu çalışma, tekrarlayan solunum yolu enfeksiyonları ve malnütrisyon ile başvuran çocuklarda, aile öyküsü olmasa dahi, ayırıcı tanıda kistik fibrozisin mutlaka göz önünde bulundurulması gerektiğini vurgulamaktadır. Solunum semptomları en sık başvuru nedeni olmakla birlikte, malnütrisyonun mutasyon pozitif olgularda anlamlı derecede daha sık görüldüğü saptanmıştır. Bu bulgular, kistik fibrozis tanı sürecinde dikkatli klinik değerlendirmenin genetik analizle desteklenmesinin önemini ortaya koymaktadır. Bulguların doğrulanması ve genişletilmesi için daha geniş çaplı, çok merkezli çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: CFTR gen, heterozigot mutasyon, kistik fibrozis, malnutrisyon, tekrarlayan alt solunum yolu enfeksiyonu

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INTRODUCTION

Cystic fibrosis (CF) is an autosomal recessive disorder caused by mutations in the Cystic Fibrosis Transmembrane Regulator (CFTR) gene, which encodes a chloride channel protein in epithelial cells. It affects approximately 1 in 4.000 live births, with an estimated 89.00 cases worldwide. Over 2.000 CFTR mutations have been identified, with the ΔF508del mutation detected in 85.5% of CF patients.[1,2]

The CFTR protein belongs to the ATP-binding cassette transporter family and consists of 1.480 amino acids. It functions as a chloride channel in the cell membrane, regulated by cAMP-dependent protein kinases. ATP-dependent phosphorylation of CFTR triggers the channel to open, allowing chloride ion transport. Certain CFTR mutations produce defective proteins that fail to reach the cell membrane or remain nonfunctional. This disrupts chloride and water transport, leading to dehydrated mucus and secretions.[3]

CF patients frequently present with recurrent lower respiratory tract infections and malnutrition. *Staphylococcus aureus* and *Pseudomonas aeruginosa* contribute to chronic lung disease, bronchiectasis, progressive lung function decline, and respiratory failure, the primary cause of mortality. Treatment includes mucolytics, anti-inflammatory agents, and antibiotics.[4] Increased viscosity of pancreatic secretions leads to pancreatic duct obstruction, tissue damage, cyst formation, and fibrosis. Exocrine pancreatic insufficiency is present in 60–80% of patients at birth.[5] Other symptoms include excessive salt loss, male infertility, and pseudobartter syndrome.[4]

Diagnosis is based on CF-related symptoms, genetic testing, nasal potential difference measurement, or elevated chloride levels in sweat testing.[6] Newborn screening programs in many countries, including Türkiye, facilitate early detection. Advances in multidisciplinary care, including dietitians, respiratory physiotherapists, and social workers, have significantly improved the CF prognosis. The median survival age increased from 36.3 years in 2006 to 53.1 years in 2021.[2]

This study aimed to evaluate the demographic and clinical characteristics, as well as the molecular analysis findings, of patients who underwent CFTR gene mutation testing with a preliminary diagnosis of CF.

MATERIALS AND METHODS

Ethics Committee Approval: This research involving human subjects complied with all relevant national regulations and institutional policies and was conducted in accordance with the tenets of the Helsinki Declaration. The study was approved by the Duzce University Faculty of Medicine Ethics Committee (Date: 10.06.2024, decision no: 2024/126). Before inclusion, parents of all study participants were informed about the study's purpose, methodology, and implementation, and written consent was obtained.

Patient Selection: Clinical features such as recurrent lung infections, inadequate weight gain, malnutrition, chronic diarrhea, a history of nasal polyps, ileal obstruction, and a family history of cystic fibrosis are suggestive of cystic fibrosis.[7] This study included 34 cases who presented to the Duzce University Application and Research Hospital, Pediatrics clinics between 01.01.2015 and 01.01.2021.

Sample Collection and Genetic Analysis: Genomic DNA was isolated from peripheral blood samples of the patients, and whole-exome sequencing (WES) was performed using the Illumina SureSelect V6 Exome kit on an Illumina HiSeq4000 platform. The pathogenicity of detected variants was classified according to the guidelines established by the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG/AMP) for the interpretation of sequence variants (PMID: 25741868) and multiple databases and tools, including Illumina BaseSpace Variant Interpreter, InterVar, SIFT, Mutation Tester, PolyPhen-2, Franklin, VarSome, ClinVar, OMIM, and PubMed. Variants with a population frequency higher than 0.5% were excluded.

With the advancements in next-generation sequencing (NGS) technologies, more comprehensive information has been obtained regarding the diagnosis, prognosis, and etiopathogenesis of various diseases.[8-10] In our study, we evaluated the clinical symptoms and findings of patients who underwent genetic analysis via NGS with a preliminary diagnosis of cystic fibrosis.

Definition of Malnutrition: In our study, malnutrition was defined as a weight-for-age Z score below -2 SD, consistent with established pediatric growth assessment criteria.[11]

Clinical Data Collection: Demographic characteristics (age, sex, etc.) were recorded along with the presence of recurrent lung infections, inadequate weight gain, malnutrition, chronic diarrhea, history of nasal polyps, ileal obstruction, and family history of CF. Height and weight percentiles, respiratory system examination findings, and laboratory parameters [including plasma sodium, potassium, and chloride levels, as well as blood gas analysis (pH, HCO_3, and pCO_2 levels)] were evaluated alongside CFTR gene mutation analysis results.

Exclusion Criteria: Cases with bronchopulmonary dysplasia, asthma, and immunodeficiency syndromes that could lead to recurrent pulmonary infections, as well as those with celiac disease, other mal-

absorption syndromes, or existing malnutrition, were excluded from the study.

Statistical Analysis: Descriptive statistics were presented as frequency and percentage. Demographic data were presented as mean, standard deviation (SD), median, and Interquartile Range (IQR). For normality analysis, the bell curve was used when $n > 50$, whereas the Shapiro-Wilk test was applied when $n < 50$. The relationship between two independent categorical variables was analyzed using the Pearson Chi-square test or Fisher's Exact test. The Mann-Whitney U test was employed for non-normally distributed continuous variables between two independent groups, while the Student's *t*-test was used for normally distributed continuous variables. Statistical analyses were performed using SPSS software for Windows, version 25 (IBM, Chicago, IL, USA). A p -value < 0.05 was considered statistically significant.

RESULTS

A total of 34 cases were included in the study. The median age (IQR 25-75) was 6.50 (5-14.25) years, and 19 cases (55.9%) were male. The mean gestational age was 38.71 ± 1.21 weeks, and the mean birth weight was 3127.06 ± 430.84 g. A family history of CF was present in 11 cases (32.4%). The most common symptoms were respiratory-related, with 22 cases (64.7%) having a history of recurrent lower respiratory tract infections, bronchiectasis, or atelectasis. Malnutrition was observed in 10 cases (29.4%), while gastrointestinal symptoms such as vomiting, diarrhea, and feeding intolerance were seen in 11 cases (32.4%). Nasal polyps were detected in 5 cases (14.7%), and ileal atresia in 1 case. The median symptom duration (IQR 25-75) was 1 (1-3) years, and the median number of hospitalizations was 1.50 (1-4.25) (Table 1).

Some demographic data of the patients are presented in Table 1.

The laboratory findings of a cystic fibrosis patient who applied to the Pseudobartter syndrome clinic included plasma sodium of 142 mEq/L, potassium 2.9 mEq/L, chloride 66.4 mEq/L, blood gas pH 7.62, HCO_3^- 39.2 mEq/L, and pCO_2 37.2 mEq/L. Due to a history of recurrent respiratory infections, genetic analysis revealed a compound heterozygous mutation in exon 4 (c.328G>C p.Asp110His rs113993958) and exon 11 (c.1521_1523delCTT p.Phe508delPhe rs113993960). Median (IQR 25-75) plasma electrolyte values were: sodium 138 (135.75-140.25) mEq/L, potassium 4.55 (4.17-4.85) mEq/L, chloride 101.50 (99-104) mEq/L, blood gas pH 7.39 (7.36-7.42), pCO_2 38.40 (36.3-41) mmHg, and HCO_3^- 24 (22.95-24.65) mEq/L (Table 2).

Table 1. Descriptive data of patients diagnosed with CF.

Parameters		Data
Age, year [Median (IQR 25-75)]		6.50 (5-14.25)
Gender, n (%)	Boy	19 (55.9)
	Girl	15 (44.1)
Gestation age, week Mean ± SD		38.71 ± 1.21
Birth weight, grams Mean ± SD		3127.06 ± 430.84
Family history, n (%)		11 (32.4)
Hospitalization, Median (IQR 25-75)		1.50 (1-4.25)
Symptom time, Median (IQR 25-75)		1 (1-3)
Symptoms and findings, n (%)	Malnutrition	10 (29.4)
	GIS symptoms	11 (32.4)
	Respiratory system symptoms	22 (64.7)
	Nasal polyp	5 (14.7)
	Ileal atresia	1 (2.9)
	Gene Analysis, Positive	14 (41.1)

GIS: Gastrointestinal System; CF: Cystic fibrosis.

Table 2. Laboratory parameters of patients diagnosed with CF.

Laboratory Parameters	Median (IQR 25-75)
pH	7.39 (7.36-7.42)
pCO_2 (mmHg)	38.40 (36.3-41)
HCO_3^- (mEq/L)	24 (22.95-24.65)
Sodium (mEq/L)	138 (135.75-140.25)
Potassium (mEq/L)	4.55 (4.17-4.85)
Chloride (mEq/L)	101.50 (99-104)

CF: Cystic fibrosis.

CF results from autosomal recessive CFTR gene mutations. The mutations identified in our cases are presented in Table 3.

When comparing cases with and without detected mutations in genetic analysis, there were no significant differences in age, sex, gestational age, or birth weight (p=0.710, p=0.901, p=0.146, p=0.570). Although a family history of CF was more common in the mutation-positive group, it was not statistically significant (p=0.135). Hospitalization numbers and symptom durations were similar between the groups (p=0.580, p=0.500). Malnutrition was significantly more frequent in the mutation-positive group (p=0.027). No significant differences were found regarding gastrointestinal or respiratory symptoms (p=0.458, p=0.275). None of the five cases with nasal polyps had a detected mutation, and a significant difference was found between the groups (p=0.043) (Table 4).

Table 3. Genetic mutations detected variant in the patients.

Case No	Zygosity	Region (Exon/ Intron)	DNA Change	Protein Change	rs ID
1	Homozygous	Intron 9	c.1210-11T>G	-	rs73715573
2	Compound heterozygous	Exon 10 / Exon 14	c.1244A>G / c.2002C>T	p.N415S / p.R668C	rs1800100
3	Compound heterozygous	Exon 13 / Exon 14	c.1727G>C / c.2002C>T	p.Gly576Ala / p.Arg668Cys	rs1800098 / rs1800100
4	Compound heterozygous	Exon 4 / Exon 11	c.328G>C / c.1521_1523delCTT	p.Asp110His / p.Phe508delPhe	rs113993958 / rs113993960
5	Heterozygous	Exon 2	c.4332C>T	p.Ser1444Ser	-
6	Heterozygous	Exon 26	c.4231C>T	p.Q1411*	rs397508701
7	Heterozygous	Exon 6	c.650A>G	p.Glu217Gly	rs121909046
8	Heterozygous	Intron 9	c.1210-11T>G	-	rs73715573
9	Heterozygous	Exon 14	c.2052dupA	p.Gln685ThrfsTer4	rs746460279
10	Heterozygous	Exon 14	c.1897C>A	p.Leu633Ile	rs397508317
11	Heterozygous	Exon 6	c.650A>G	p.Glu217Gly	rs121909046
12	Heterozygous	Exon 20	c.3154T>G	p.Phe1052Val	-
13	Heterozygous	Exon 2	c.4332C>T	p.Ser1444Ser	-
14	Heterozygous	Intron 4	c.489+3A>G	-	rs377729736

Table 4. Comparison of parameters between patients with positive and negative genetic analysis results.

Parameters		Genetic Analysis		p-value
		Positive, n=14	Negative, n=20	
Age, year [Median (IQR 25-75)]		6 (5.75-15.50)	8 (5-14)	0.710*
Gender, n (%)	Boy	8 (57.1)	11 (55)	0.901**
	Girl	6 (42.9)	9 (45)	
Gestation age, week Mean ± SD		39.07 ± 1.07	38.45 ± 1.27	0.146***
Birth weight, grams Mean ± SD		3178.21 ± 486.80	3091.25 ± 396.19	0.570***
Family history, n (%)		7 (50)	4 (20)	0.135****
Hospitalization, Median (IQR 25-75)		2.50 (1-3.50)	1 (0.25-4.75)	0.580*
Symptom time, Median (IQR 25-75)		1 (1-3.50)	1 (1-2.75)	0.500*
Symptoms and findings, n (%)	Malnutrition	7 (50)	3 (15)	0.027****
	GIS Symptoms	6 (42.9)	5 (45.5)	0.458****
	Respiratory System Symptoms	11 (78.6)	11 (55)	0.275****
	Nasal Polyp	0 (0)	5 (25)	0.043****
	Ileal Atresia	0 (0)	1 (5)	0.588****
Laboratory Parameters, Median (IQR 25-75)	pH	7.42 (7.37-7.43)	7.38 (7.35-7.41)	0.094*
	pCO_2, mmHg	37. 2 (36.05-39.25)	39 (36.22-41.75)	0.361*
	HCO_3^-, mEq/L	24 (23.32-24.52)	24.05 (22.25-24.87)	0.861*
	Sodium, mEq/L	138.50 (135.50-141)	138 (135.25-140)	0.597*
	Potassium, mEq/L	4.65 (4-5.02)	4.5 (4.2-4.7)	0.752*
	Chloride, mEq/L	102.50 (101-104.50)	101 (98.25-102.75)	0.121*

*: p-value was obtained by Mann Whitney-U test; **: p-value was obtained by Pearson Chi-Square test; ***: p-value was obtained by Student's t-test; ****: p-value was obtained with Fisher-Exact test; GIS: Gastrointestinal system.

DISCUSSION AND CONCLUSION

This study retrospectively analyzed the demographic characteristics, clinical findings, and laboratory results of patients with suspected CF at Duzce University Application and Research Hospital. The most frequently recurring respiratory system symptoms, followed by gastrointestinal symptoms and malnutrition, were detected in the patients included in the study. Malnutrition was more frequently observed in cases with detected mutations in genetic analysis.

Priel et al.[12] found that CFTR heterozygous mutations were linked to higher rates of asthma and recurrent neutrophilic bronchitis due to CFTR hypofunction. They also reported that patients with recurrent bronchitis and severe asthma were four times more likely to have a CFTR heterozygous mutation. Studies have shown that individuals carrying heterozygous CFTR gene mutations exhibit a significantly higher prevalence of 57 out of 59 clinical conditions associated with cystic fibrosis, including respiratory diseases such as asthma, chronic rhinosinusitis, and respiratory tract infections, as well as gastrointestinal disorders like gastroesophageal reflux and chronic pancreatitis, compared to control groups.[13] In our study, malnutrition was found to be significantly more frequent in mutation-positive cases. Additionally, patients with malnutrition were 5.667 times more likely to have CF compared to those without malnutrition [OR: 5.667; (CI: 1.129; 28.454)]. This challenges the belief that individuals with CFTR heterozygous mutations are asymptomatic.

Lung disease and malnutrition are significant challenges in CF. Studies show a positive link between good nutritional status and better lung function.[14] Hyperviscous mucus accumulation in the pancreas impairs enzyme secretion, leading to acinar tissue damage and exocrine pancreatic insufficiency, which results in malabsorption and malnutrition.[15] Malnutrition in CF is caused by various factors, including dietary deficiencies, malabsorption, CF-related liver disease, CF-related diabetes, and stress. Malnourished CF patients tend to have a worse prognosis and lower life expectancy.[14] Collectively, these findings reinforce the perspective put forward by Priel et al.[12] that heterozygous CFTR mutations can be clinically relevant and should not be considered entirely benign.

CF pulmonary symptoms involve abnormal chloride and sodium ion movement across airway epithelial cells, leading to poor airway secretion clearance and chronic bronchial infections. The immune response causes intense neutrophilic inflammation, and neutrophil death thickens sputum, further obstructing clearance. This cycle leads to recurrent infections, bronchiectasis, and respiratory failure.[3] In our study, CFTR gene analysis was requested for cases with frequent recurrent respiratory pathologies, and 64.7% had respiratory symptoms. Recurrent lower respiratory tract infections are a leading cause of death in CF patients in early adulthood, making CF a consideration in such cases.[4]

The number of hospitalizations is typically higher in patients with positive CFTR gene mutations.[12] In our study, while the number of hospitalizations was higher in mutation-positive patients, no significant difference was found between the two groups. This may be due to the majority of mutation-positive cases being heterozygous. Schlüter et al.[16] reported that children with CF are more likely to be born prematurely and with low birth weight. In our study, however, no significant difference was found in birth weight or gestational age between the mutation-positive and mutation-negative groups.

Ninety percent of CF cases are diagnosed before the age of 10. The most common symptoms include progressive lung disease or exocrine pancreatic insufficiency, or laboratory findings related to abnormalities in the CFTR gene or protein. In cases where the diagnosis is made later in life, symptoms tend to begin later and are milder, due to partial CFTR gene mutation or protein function. Since the sweat chloride test sensitivity and specificity are low in these cases, genetic testing becomes more prominent for diagnosis.[17] In our study, the median (IQR 25-75) age of diagnosis for mutation-positive cases was 6 (5.75-15.50) years, and all 5 cases with a genetic mutation detected after the age of 10 had heterozygous mutations. This is likely due to the later onset and milder course of symptoms in heterozygous mutation cases.

Studies have reported that boys are more commonly diagnosed with CF than girls, but that the mortality and morbidity in female patients are higher.[18] In our study, 57.1% of the cases were male. When we compared mutation-positive male and female cases, no significant differences were found in terms of symptoms and laboratory findings ($p>0.05$). Although clinical presentations in female patients are reported to be more severe in some studies, since CFTR gene mutations are autosomal recessive, it is not expected that clinical outcomes to vary by sex. Our study also did not find a significant difference.

Studies have reported that 5-15% of children with CF develop nasal polyps, and the likelihood of developing nasal polyps increases with age. The etiology of nasal polyps involves many factors, and although rare, CF should be considered as a possible cause.[19] In our study, genetic analysis was performed on the cases with nasal polyps, but no mutations were detected.

The pulmonary and pancreatic morbidities of CF are well known, but rare complications, such as pseudobartter syndrome, may go unnoticed. Bartter syndrome is a hereditary tubulopathy that affects the

thick ascending limb of the loop of Henle, and is characterized by hypokalemia, hyponatremia, hypochloremia, and metabolic alkalosis. In CF, a similar metabolic disturbance is observed, and this condition is referred to as pseudobartter syndrome.[20] In one of the cases included in our study, pseudobartter syndrome was detected, and genetic analysis revealed compound heterozygous mutations at exon 4 (c.328G>C, p.Asp110His, rs113993958) and exon 11 (c.1521_1523delCTT, p.Phe508delPhe, rs113993960).

In a study by Steinraths et al.[21] on CF cases, the mean age of diagnosis was reported to be 3.6 years, and the average duration between symptom onset and diagnosis was 2.1 years. In our study, the median (IQR 25-75) age of diagnosis in the mutation-positive group was 6 (5.75-15.50) years, and the duration between symptom onset and diagnosis was 1 (1-3.50) year. No significant differences were found between the mutation-positive and mutation-negative groups in terms of age at onset and symptom duration. This is likely due to the fact that the majority of our cases had heterozygous mutations, which are associated with later symptom onset. It is also possible that as the age of the cases increases, earlier genetic testing is requested to address concerns about diagnostic delays, which is why the symptom duration in our study was relatively shorter.

Since CFTR gene mutations are inherited in an autosomal recessive manner, mutation-positive cases are expected to have a higher frequency of CF diagnosis in their family history. However, in our study, although mutation-positive cases were more likely to have a family history of CF, no significant difference was found between the two groups. This may be attributed to the small sample size in our study.

The number of hospitalizations is expected to be higher in cases with positive CFTR gene mutations compared to those with negative mutations. In our study, no significant difference was found between the two groups in terms of hospitalization frequency. It is believed that the majority of mutation-positive cases having heterozygous mutations likely contributed to this result.

In this study, the clinical and demographic characteristics of patients who presented to Duzce University Application and Research Hospital with a prediagnosis of CF and underwent CFTR gene mutation analysis were retrospectively analyzed.

In conclusion, among the cases included in the study, the majority of those with a positive genetic analysis were identified as carriers of CFTR gene mutations. CFTR gene analysis was most frequently requested for patients presenting with recurrent lower respiratory tract symptoms, followed by gastrointestinal symptoms and malnutrition. It was observed that CFTR gene mutations were significantly more prevalent in cases with malnutrition. These findings underscore the critical importance of thorough clinical evaluation of symptoms and the indispensable role of genetic analyses in the diagnosis of cystic fibrosis. It should also be considered that patients carrying heterozygous CFTR mutations may exhibit certain clinical symptoms, necessitating a careful evaluation during the diagnostic process. This study has some limitations. Firstly, since the study was designed retrospectively, patient data were reviewed from the past, and some clinical information may be incomplete or inadequate. Secondly, since the study was conducted at a single center, the findings may not fully reflect the broader population. Additionally, the lack of statistically significant findings in some parts may be due to the small sample size. Finally, only specific mutations were analyzed in the CFTR gene mutation analysis, and rare or new mutations may have been excluded from the evaluation. Therefore, further studies with larger patient groups and multicenter designs are needed.

Ethics Committee Approval: This research involving human subjects complied with all relevant national regulations and institutional policies and was conducted in accordance with the tenets of the Helsinki Declaration. The study was approved by the Duzce University Faculty of Medicine Ethics Committee (Date: 10.06.2024, decision no: 2024/126). Before inclusion, parents of all study participants were informed about the study's purpose, methodology, and implementation, and written consent was obtained.

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

Author Contributions: Concept – FK, RE; Supervision – FK, RE; Materials – FK, RE; Data Collection and/or Processing – FK, RE; Analysis and/or Interpretation – RE; Writing –FK.

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