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ORIGINAL ARTICLE

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Comparison of clinical features of cystic fibrosis patients eligible but not on CFTR modulators to ineligible for CFTR modulators

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Abstract

Introduction: Cystic fibrosis transmembrane conductance regulator (CFTR) modulator drugs target the underlying defect and improve CFTR function. They are a part of standard care in many countries, but not all patients are eligible for these drugs due to age and genotype. Here, we aimed to determine the characteristics of non-eligible patients for CFTR modulators in the CF registry of Turkey (CFRT) to highlight their clinical needs.

Methods: This retrospective cohort study included CF patient data from the CFRT in 2021. The decision of eligibility for the CFTR modulator was determined according to the 'Vertex treatment-Finder' on the Vertex® website. Demographic and clinical

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characteristics of patients were compared between eligible (group 1) and ineligible (group 2) groups for CFTR modulators.

Results: Among the study population ($N = 1527$), 873 (57.2%) were in group 1 and 654 (42.8%) were in group 2. There was no statistical difference between groups regarding sex, meconium ileus history, diagnoses via newborn screening, FEV1 z-score, CF-associated complications, organ transplant history, and death. Patients in group 2 had a higher incidence of pancreatic insufficiency (87.7% vs. 83.2%, $p = .010$), lower median height z-scores (−0.87 vs. −0.55, $p < .001$), lower median body mass index z-scores (−0.65 vs. −0.50, $p < .001$), longer days receiving antibiotics due to pulmonary exacerbation (0 [interquartile range, IQR: 0–2] vs. 0 [IQR: 0–7], $p = 0.001$), and more non-invasive ventilation support (2.6% vs. 0.9%, $p = 0.008$) than patients in group 1.

Conclusion: The ineligible group had worse clinical outcomes than the eligible group. This highlights their need for life-changing drugs to improve clinical outcomes.

KEYWORDS

CFTR modulators, clinical features, cystic fibrosis, eligibility, registry

1 | INTRODUCTION

Cystic fibrosis (CF) is an autosomal recessive genetic disease caused by CF transmembrane conductance regulator (CFTR) gene variants. CFTR mutations are classified according to the degree of decrease in CFTR protein synthesis, function, or stability. CFTR modulators target the underlying defect and improve CFTR function.[1] Drugs acting as a potentiator (ivacaftor) improve the CFTR channel opening, and drugs acting as correctors (lumacaftor, tezacaftor, elexacaftor) improve CFTR protein folding and trafficking. Although some side effects (such as cataracts, liver disease, and high blood pressure) may occur, CFTR modulators are part of standard care in many countries because their clinical benefits are demonstrated in real-world experiences.[2–4] On the other hand, CFTR modulators exposed the true-life disparities for patients with CF because access to them worldwide remains an issue due to their higher cost.[5] These therapies are not reimbursed in Turkey; patients can only access these drugs by court decision.

Besides the cost of CFTR modulators, another problem is that they are not eligible for all patients with CF due to age and genotype. Thanks to the continuous and rapid developments in this area, the suitability of younger ages is increasing, but it still does not cover all genotypes. Desai et al.[6] reported that 10% of patients in the UK CF Registry in 2019 were non-eligible for CFTR modulators. This number is much higher in countries such as Turkey, where the diversity of mutations is great.[7]

In the present study, we aimed to determine the characteristics of patients who were non-eligible for CFTR modulators in the CF registry of Turkey (CFRT), compare their clinical findings with eligible patients for this treatment, and highlight their clinical needs.

2 | MATERIALS AND METHODS

2.1 | Study design and ethics

This retrospective cohort study included data from patients in the CFRT in 2021. In the registry, each center recorded patients' data annually in a software program specially developed for the CFRT. The CFRT consisted of 15 recorded demographic data and 79 annual data variables.[7] The data included variables such as sex, current age, age at diagnosis, weight, height, spirometry results, medications, presence of microorganisms, complications, transplants, and death. Pulmonary function test values in the CFRT database showed the best value of the year obtained during the patients' healthy period. Weight and height z-scores, which were the best values of the year, were calculated using the World Health Organization anthropometric calculator.

The local ethics committee approved the establishment of the national registry and data input (Hacettepe University Ethics Board, reference numbers: HEK 07/16-21 and GO 18/473-31). Informed consent was obtained from all patients/parents before being included in the registration system.

2.2 | Patients and procedures

Patients were divided into two groups: those eligible for any CFTR modulator (group 1) and those ineligible for CFTR modulatory (group 2) treatment. Patients receiving CFTR modulator therapy and patients without extended genotyping analysis were excluded from the study.

Each percent-predicted z-score of FEV1 was calculated using Global Lung Initiative (GLI) reference equations.[8] The severity of lung function was assessed using FEV1 z-scores: z-score > −1.645 as normal, z-score between −1.65 and −2.5 as mild, z-score between −2.51 and −4 as moderate, and z-scores < −4.1 as severe.[9]

2.3 | Assays of the CFTR modulator eligibility

The decision of eligibility for modulator drugs was determined according to the "Vertex treatment-Finder" on the Vertex® website.[10] Those over 2 years and carrying at least one copy of F508del were considered eligible for triple therapy because it is well known that it is a highly effective treatment option for these patients.[4,11] Patients older than 1 month and with the gating mutation were considered eligible for ivacaftor as a potentiator. Patients aged between 1 and 2 years with two copies of the F508del mutation in their CFTR gene were considered eligible for lumacaftor/ivacaftor treatment.

2.4 | Statistical analysis

Statistical analyzes were performed using the SPSS 22 software package (IBM Corp.). The variables suitable for normal distribution were assessed using Shapiro–Wilk tests. Non-normally distributed continuous variables were analyzed using the Mann–Whitney *U* test and expressed as median (1st–3rd quartile). Categorical variables are presented as numbers and percentages (%) and analyzed using Pearson's Chi-square test or Fisher's exact test. All *p*-values of <.05 were considered statistically significant.

3 | RESULTS

3.1 | Demographic features

There were 1948 registered patients from 34 centers in 2021. Among the study population ($n = 1527$), 873 (57.2%) were in group 1 and 654 (42.8%) were in group 2. Patients included in the study are shown in Figure 1.

The CFTR variants of the patients in group 1 were as follows: 184 (21.0%) were F508 homozygous, 249 (28.5%) were F508 heterozygous, the rest had other mutations, while in group 2, 6 (0.9%) were F508 homozygous, 21 (21%) were F508 heterozygous, and the rest had other mutations. Among group 1, 580 (66.4%) patients were eligible for elexacaftor/tezacaftor/ivacaftor (ETI), 283 (32.4%) patients were eligible for ivacaftor, and 10 (1.1%) patients were eligible for lumacaftor/ivacaftor. Twenty-seven patients who carried at least one copy of F508del were in group 2 because they were aged under 2 years.

There was no statistical difference between the two groups regarding sex and meconium ileus history. Patients in group 2 had a statistically younger median age (7.33 vs. 8.91 years, $p < .001$), higher incidence of pancreatic insufficiency (87.7% vs. 83.2%, $p = .010$), lower median height z-scores (−0.87 vs. −0.55, $p < .001$), and among patients over 2 years of age lower median body mass index (BMI) z-scores (−0.67 vs. −0.50, $p < .001$) than patients in group 1.

Newborn screening for CF was implemented in Turkey on January 1st, 2015.[12] NBS was performed in 285 of 873 patients in the first group and 253 (88.7%) of them were positive, and in 266 of 654 patients in the second group and 241 (90.6%) of them were positive. Among the patients who underwent NBS (n: 551), CF diagnosis via NBS was not different between the two groups ($p = .481$).

3.2 | The reasons why eligible patients were not receiving modulator therapy

Only 3.8% of known eligible patients 35/(35 + 873) living with CF in 2021 were receiving modulator therapy. All patients in group 2 were not receiving CFTR modulator therapy due to the high cost of treatment, as these drugs are not reimbursed in Turkey. Thirty-five patients, excluded from the study to ensure that clinical improvement status does not bias the results, could use the drug for 3 months only by court decisions, and in between the court decisions, most of the patients could not receive the treatment.

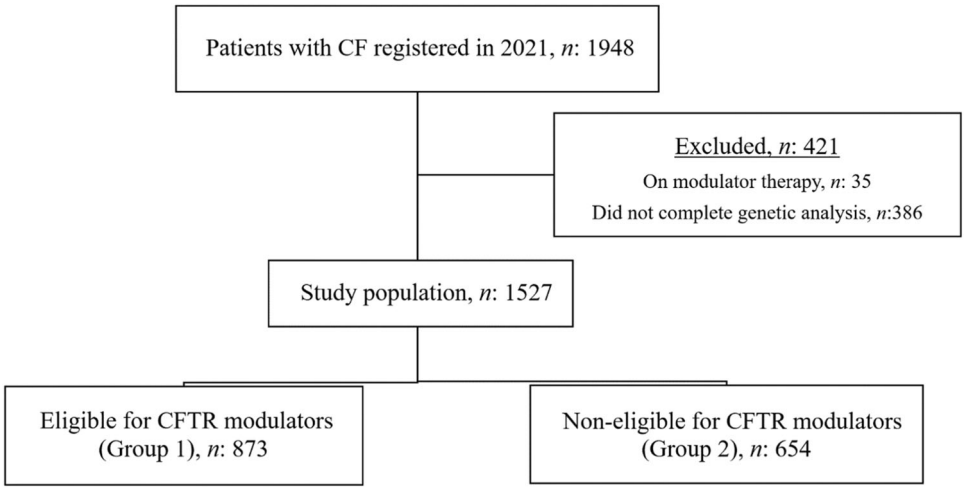

FIGURE 1 Flow chart for including patients in the study.

3.3 | Treatments

Patients in group 2 had statistically longer duration of antibiotic therapy for pulmonary exacerbations (0 [interquartile range, IQR: 0–2] vs. 0 [IQR: 0–7], $p = .001$), and had more non-invasive ventilation support (2.6% vs. 0.9%, $p = .008$) than patients in group 1. A comparison of the clinical features of the groups is given in Table 1.

3.4 | Complications

There was no statistical difference between the two groups regarding CF-related diabetes mellitus, liver disease, allergic bronchopulmonary aspergillosis, haemoptysis, pneumothorax, distal intestinal obstruction syndrome, pseudo bartter syndrome, organ transplant history, and death. There were no patients with malignancy in either group.

3.5 | Sensitivity analysis to determine the effect of including patients who are F508del carriers ineligible for CFTR modulator therapy due to age only

Due to including the carreing F508del patients under 2 years of age may have introduced selection bias and could explain some of the apparent differences between the groups we re-compare statistically clinically significant differences between two groups by excluding F508 carriers (*n*: 27) who are ineligible due to age. But, we found that it did not affect the results. Re-comparison of statistically significant clinical differences between two groups by excluding F508 carriers who are ineligible due to age is given in Table 2.

4 | DISCUSSION

The results of this study showed that according to current eligibility criteria, 42.8% of the patients in the CFRT in 2021 were not eligible for any modulator therapies. Patients who were not eligible for CFTR modulators had worse nutritional parameters and more non-invasive ventilation requirements, than patients who were eligible for CFTR modulators, and had similar CF-associated conditions and mortality. And, only 3.8% of known eligible patients living with CF in 2021 were receiving modulator therapy.

In this study, the frequency of patients who were not eligible for CFTR modulators was much higher than that reported in the literature. According to the 2021 US CF registry data, about 10% of patients were ineligible for CFTR modulator therapies.[13] The UK Registry reported that based on the presence of at least one copy of the F508del mutation, 8.6% of patients were ineligible and also in terms of ethnicity, African-American, Asian, and minority ethnic backgrounds were less likely to be eligible.[6] McGarry et al.[14] analyzed eligibility for CFTR modulator therapy by race and ethnicity using the 2018 US CF registry data, and they showed that for each CFTR modulator, African-American patients were least likely to have eligible mutations. Colombo et al.[15] evaluated the ineligibility of the triple combination of CFTR modulator treatment in patients with severe CF-liver disease (CFLD) among an international cohort which included 1591 patients of whom 171 with severe CFLD, and they showed that 11% of the study population ($n = 19/171$) were ineligible for CFTR modulator therapy.

The high rate of ineligibility for CFTR modulators in our study is due to the diversity of mutations in our country. Across the world, 82% of people with CF have at least one copy of F508del.[16] In Turkey, this ratio was reported as 21.7% in the first data from the national registry.[7] Nevertheless, according to the CFRT data, the number of patients eligible for modulators was reported as 23% in 2018 by Çobanoğlu et al.,[17] whereas, in our study, this ratio reached 57.2% using the current extended eligibility criteria. Unfortunately, these patients cannot access the drugs since the drugs are not reimbursed, and we know their clinical symptoms worsened during follow-up from the registry-based study done by Uytun et al.[18] They reported worsening clinical outcomes over 1 year, from 2018 to 2019, in patients who were eligible for CFTR modulator treatments but were unable to obtain them, including deterioration in nutritional and infection status and pulmonary support requirements.

It is well known that CFTR modulators have significant benefits in respiratory function, number of acute lung exacerbations, nutritional status, sweat chloride level, and quality of life in the respiratory symptom score domain.[19,20] Unfortunately, global inequalities in accessing expensive life-saving CFTR drugs are expected to result in differences in CF care and outcomes between high-income and low-middle-income countries.[21] Besides, current drugs correct the CFTR protein dysfunction, and it is known that protein synthesis is defective in Class 1 mutations (such as G542X and W1282X). Even if there is no problem with access to these drugs and the mutations they address are expanded, there will be a group not targeted by those drugs, as protein is not synthesized. Therefore, development of novel therapeutics for cover all individuals with CF is necessary.

Our study's major limitation is the exclusion of one-fifth of the registered patients due to missing genetic analysis. The underlying reason for this is that genetic tests are expensive and some centers in the registry do not have access to advanced genotyping tests such as sequence analysis and multiplex ligation-based probe amplification. It is mandatory that genetic analysis should be available and accessible for all patients to accurately determine the need for CFTR modulator therapy in Turkey. Nevertheless, presentation of the clinical features of the ineligible group for CFTR modulators with a large cohort from our country with a large mutational diversity is the strength of this study.

In conclusion, our results showed that the ineligible group had worse clinical status in terms of nutritional parameters and non-invasive ventilation. This highlights their need for life-changing drugs to improve their clinical outcomes. In addition, to prevent inequality of care in patients with CF worldwide, all patients eligible for CFTR modulators should have access to the drugs as soon as possible.

TABLE 1 Comparison of clinical features of patients eligible but not on modulators to ineligible for modulators (*n*: 1527).

	Eligible for CFTR modulators (Group 1) (*n*: 873, 57.2%)		Ineligible for CFTR modulators (Group 2) (*n*: 654, 42.8%)	*p*-value
Age (years)	8.91 (4.91–15.25)		7.0 (3.17–12.17)	**<.001**
Male	451 (51.6)		351 (53.6)	.43
Median age at CF diagnosis (years)	0.33 (0.17–1.0)		0.33 (0.17–0.75)	**.001**
Meconium ileus	49 (5.6)		49 (7.4)	.13
Height for age z-score	−0.55 (−1.38 to 0.32)		−0.87 (−1.81 to −0.01)	**<.001**
Weight for age z-score (≤2 years of age, *n*: 175)	−2.03 (−3.16 to −0.65)		−1.86 (−3.13 to −0.65)	.77
Body mass index z-score (>2 years of age, *n*:1352)	−0.50 (−1.06 to 0.34)		−0,67 (−1.24 to 0.03)	**<.001**
Pancreatic insufficiency, *n* (%)	727 (83.2)		580 (88.6)	**.003**
FEV1 z-score, *n*: 526	−1.45 (−2.68 to −0.23)		−1.58 (−2.80 to −0.21)	.50
FEV1 z-score severity, *n* (%)	*n*: 325		*n*: 201	.83
• Normal	174 (53.5)		105 (52.2)	
• Mild	62 (19.0)		35 (17.4)	
• Moderate	49 (15.0)		31 (4.7)	
• Severe	40 (12.3)		30 (4.5)	
Chronic colonization, *n* (%)				
• *Pseudomonas aeruginosa*	145 (16.6)	145 (16.6)	92 (14.0)	.17
• Methicillin-susceptible *Staphylococcus aureus*	171 (19.5)	171 (19.5)	113 (17.2)	.25
	51 (5.8)	51 (5.8)	37 (5.6)	.87
• Methicillin-resistant *Staphylococcus aureus*	10 (1.1)	10 (1.1)	8 (1.2)	.88
	2 (0.2)	2 (0.2)	2 (0.3)	.77
• *Hemophilus influenzae*	3 (0.3)	3 (0.3)	3 (0.4)	.72
• *Stenotrophomonas maltophilia*				
• *Achromobacter*				
Lung protective treatments, *n* (%)				
• Recombinant human DNase	760 (87.0)		577 (88.8)	.49
	163 (18.6)		109 (16.6)	.31
• Hypertonic saline	32 (3.6)		23 (3.5)	.87
• Mannitol	159 (18.2)		97 (14.8)	.14
• Inhaled antibiotics	112 (12.8)		104 (15.9)	.08
• Inhaled corticosteroids	49 (5.6)		44 (6.7)	.36
• Azithromycin	8 (0.9)		18 (2.7)	**.006**
• Non-invasive ventilation	20 (2.2)		23 (3.5)	.15
• Oxygen				
Anual IV antibiotics days due to PEx	0 (0–2)		0 (0–7)	**.001**
Cystic fibrosis-associated conditions, *n* (%)				
• CF-related diabetes mellitus	36 (4.1)		36 (5.5)	.20
	88 (10.0)		83 (12.6)	.10
• Liver disease	27 (3.0)		12 (1.8)	.12
• Allergic bronchopulmonary aspergillosis	1 (0.1)		3 (0.4)	.19
	4 (0.4)		1 (0.1)	.30
	5 (0.5)		7 (1.0)	.27
• Haemoptysis	40 (4.5)		42 (6.4)	.11
• Pneumothorax				
• Distal intestinal obstruction syndrome				

(Continues)

TABLE 1 (Continued)

	Eligible for CFTR modulators (Group 1) (*n*: 873, 57.2%)	Ineligible for CFTR modulators (Group 2) (*n*: 654, 42.8%)	*p*-value
• Pseudo Bartter syndrome			
History of transplantation, *n* (%)			
• Lung	7 (0.8)	2 (0.3)	.21
• Liver	2 (0.2)	0 (0)	NA
• Kidney	0 (0)	1 (0)	NA
Died, *n* (%)	8 (0.9)	4 (0.6)	.50

Note: Non-normally distributed continuous variables expressed as median (1st–3rd quartile). Categorical variables were presented as number and percentages (%). Bold values indicates statistical significances.

Abbreviations: CFTR, cystic fibrosis transmembrane conductance regulator; IV, intravenoz; NA, not available; PEx, pulmonary exacerbations.

TABLE 2 Sensitivity analysis to determine the effect of including patients who are F508del carriers ineligible for CFTR modulator therapy due to age only (*n*: 1500).

	Group 1 (*n*: 873, 58.2%)	Group 2 (*n*: 627, 41.8%)	*p*-value
Age (years)	8.91 (4.91–15.25)	7.25 (3.83–12.41)	**<.001**
Median age at CF diagnosis (years)	0.33 (0.17–1.0)	0.33 (0.17–0.75)	**.004**
Height for age z-score	−0.55 (−1.38 to 0.32)	−0.88 (−1.81 to −0.06)	**<.001**
Pancreatic insufficiency, *n* (%)	727 (83.2)	559 (89.1)	**.001**
Lung protective treatments, *n* (%)	8 (0.9)	18 (2.8)	**.004**
• Non-invasive ventilation			
Anual IV antibiotics days due to PEx	0 (0–2)	0 (0–7)	**.002**

Note: Group 1: Eligible for CFTR modulators. Group 2: Ineligible for CFTR modulators without patients carring F508 mutation. Non-normally distributed continuous variables expressed as median (1st–3rd quartile). Categorical variables were presented as number and percentages (%). Bold values indicates statistical significances.

Abbreviations: CFTR, cystic fibrosis transmembrane conductance regulator; IV, intravenoz; NA, not available; PEx, pulmonary exacerbations.

AUTHOR CONTRIBUTIONS

Halime Nayır Büyükşahin: Conceptualization; methodology. **Nagehan Emiralioğlu**: Data curation; writing—review & editing. **Ebru Yalçın**: Data curation; writing—review & editing. **Velat Şen**: Writing—review & editing; data curation. **Hadice Selimoğlu Şen**: Data curation; writing—review & editing. **Hüseyin Arslan**: writing—review & editing. **Azer Kılıç Başkan**: Data curation; writing—review & editing. **Fatma Betül Çakır**: Data curation; writing—review & editing. **Cem Fırat Koray**: Data curation; writing—review & editing. **Aslı İmran Yılmaz**: Data curation; writing—review & editing. **Fatih Ercan**: Data curation; writing—review & editing. **Derya Ufuk Altıntaş**: Writing—review & editing; data curation. **Mahir Serbes**: Data curation; writing—review & editing. **Özlem Keskin**: Data curation; writing—review & editing. **Elif Arık**: Data curation; Writing—review & editing. **Figen Gülen**: Data curation; writing—review & editing. **Meral Barlık**: Data curation; writing—review & editing. **Oğuz Karcıoğlu**: Data curation; writing—review & editing. **Ebru Damadoğlu**: Data curation; writing—review & editing. **Mehmet Köse**: Data curation; writing—review & editing. **Ali Ersoy**: Data curation; writing—review & editing. **Ayşen Bingöl**: Data curation; writing—review & editing. **Erdem Başaran**: Data curation; writing—review & editing. **Eylül Pınar Çakır**: Data curation; writing—review & editing. **Ayşe Tana Aslan**: Writing—review & editing; data curation. **Yakup Canıtez**: Data curation; writing—review & editing. **Merve Korkmaz**: Data curation; writing—review & editing. **Ali Özdemir**: Data curation; writing—review & editing. **Koray Harmancı**: Data curation; writing—review & editing. **Şule Selin Soydaş**: Writing—review & editing; data curation. **Melih Hangül**: Data curation; writing—review & editing. **Hasan Yüksel**: Data curation; writing—review & editing. **Gizem Özcan**: Writing—review & editing; data curation. **Pervin Korkmaz**: Data curation; writing—review & editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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