Pediatric Pulmonology

WILEY

ORIGINAL ARTICLE OPEN ACCESS

Elexacaftor/Tezacaftor/Ivacaftor Treatment Accessibility and Mental Health: Reducing Anxiety in People With Cystic Fibrosis

Burcu Uzunoglu[1] | Merve Selcuk Balci[2] | Mine Kalyoncu[2] | Seyda Karabulut[2] | Neval Metin Cakar[2] | Ceren Ayca Yildiz[2] | Gamze Tastan[1] | Damla Kocaman[3] | Almala Pinar Ergenekon[2] | Yasemin Gökdemir[2] | Ela Erdem Eralp[2] | Fazilet Karakoc[2] | Bülent Karadag[2]

[1]Selim Cöremen Cystic Fibrosis Center, Pendik Education and Training Hospital, Marmara University, Istanbul, Turkey | [2]Division of Pediatric Pulmonology, School of Medicine, Marmara University, Istanbul, Turkey | [3]Nutrition and Dietetics, Pendik Education and Training Hospital, Marmara University, Istanbul, Turkey

Correspondence: Merve Selcuk Balci (dr.merveselcuk@gmail.com)

Received: 4 September 2024 | **Revised:** 26 February 2025 | **Accepted:** 1 March 2025

Funding: The authors received no specific funding for this work.

Keywords: anxiety | CFTR modulator | cystic fibrosis | depression | ineligible

ABSTRACT

Background: Although modulator therapies have proven effective in cystic fibrosis (CF) access is limited due to reimbursement issues in Turkey. We aimed to examine anxiety and depression levels of people with CF (pwCF) and their caregivers according to their access to modulator treatment.

Methods: Participants genetically eligible for elexacaftor/tezacaftor/ivacaftor (ETI) were divided into Group 1 (access via court decision, not yet on treatment) and Group 2 (unable to access due to reimbursement issues). Genetically ineligible participants formed Group 3. All pwCF and parents of those under 18 were screened for depression by the Patient Health Questionnaire-9 (PHQ-9) and for anxiety by the Generalized Anxiety Disorder-7 (GAD-7). Surveys for Group 1 patients were conducted just before starting ETI. Binary logistic regression analysis was performed to evaluate the effects of independent variables on anxiety and depression in pwCF and their primary caregivers.

Results: A total of 389 pwCF and 285 caregivers were included. Group 3 (ineligible) had the highest depression rate (72.9%, $n = 35$), while Group 1 (pre-ETI) had the lowest (50.0%, $n = 35$). Median PHQ-9 scores were significantly lower in Group 1 ($p < 0.006$). Anxiety rates were higher in Groups 2 and 3 compared to Group 1 ($p = 0.011$ and $p = 0.003$, respectively). Access to ETI reduced the odds of anxiety by 67.7% ($p = 0.029$). Caregiver GAD-7 scores showed a weak negative correlation with pwCF age ($r = -0.117$).

Conclusion: Limited access to modulator therapies is associated with higher depression and anxiety symptoms among pwCF. Addressing these barriers is critical to improving their well-being.

Burcu Uzunoglu and Merve Selcuk Balci contributed equally to this work.

1 | Introduction

Cystic fibrosis is an autosomal recessive genetic disorder caused by mutations in the Cystic Fibrosis transmembrane regulator (CFTR) gene, affecting approximately 100,000 people globally [1].

Over the past decade, there has been a significant shift in the treatment landscape of people with cystic fibrosis (pwCF). Unlike the approaches in previous decades, which have focused on managing the signs and symptoms of CF, there are currently four approved oral modulator therapies that address the fundamental defects in CF. CFTR modulators enhance CFTR protein transport and function; these medications significantly improve lung function, weight, and overall quality of life and can be used by pwCF of appropriate age and with certain genetic mutations [2]. Although the initially approved CFTR modulator therapy was limited to approximately 4% of pwCF cases, it currently accounts for approximately 90% of the pwCF population in the United States of America (USA) and Western/Northern Europe [3, 4].

In most of European countries and the USA, these drugs are provided by social security institutions (SSI). However, in Turkey, modulatory therapies are not covered by SSI reimbursements; therefore, access to medication by pwCF is limited. Only a small group of pwCF has been able to use CFTR modulators through court approval [5]. Additionally, almost 30% of pwCF at our center have mutations that are ineligible for modulator therapy [6]. People with CF with eligible genetic variants must initiate legal action through specialized attorneys to obtain access to modulator therapy. These legal proceedings are lengthy, and no patient has yet achieved final judicial approval for continuous treatment. Additionally, patients who proceed with the legal process are at financial risk if their cases are unsuccessful, as they may face significant debt due to the high cost of therapy. This creates a challenging scenario where pwCF and their caregivers must choose between initiating legal action to access therapy or forgoing treatment entirely. Even when legal action is taken, access to the medication is not immediate and may not be guaranteed in the long term. These uncertainties, combined with the existing burden of CF, are thought to significantly affect the mental health of both pwCF and their caregivers.

Various studies have found that, similar to other chronic diseases, individuals with CF experience symptoms of depression and anxiety more frequently than the general population [7, 8]. The International Depression Epidemiological Study (TIDES), the most extensive psychological screening study on CF, revealed that the prevalence of depression is twice as high among pwCF and 2–3 times higher among parents of children with CF than among the general population [9]. In a study conducted at our center in 2021, Mursaloglu et al. found that 51% of adolescents had anxiety disorders and 74% had symptoms of depression [10].

CFTR modulator therapy may also change the trajectory of the disease and mortality rates in the long-term. Projection studies indicate that delayed access to elexacaftor/tezacaftor/ivacaftor (ETI) will lead to preventable healthcare utilization and increased mortality [11]. Despite having a mutation eligible for modulator therapy, lack of access to this treatment may increase pre-existing anxiety and depression in these patients.

According to a study by Jonathan Guo et all. in 2022, an estimated 162,428 individuals are living with CF across 94 countries, with approximately 105,400 (65%) diagnosed and 19,500 (12%) receiving triple combination therapy [12]. Although majority of the pwCF can't access to modulator treatment, only a few studies have evaluated the mental health status of these patients and revealed that pwCF who are ineligible, intolerant, or lack access to modulators have a high burden of disease impacting their physical and mental health [13]. Furthermore, despite the fact that most pwCF who are eligible for modulator therapy do not have access to it, and 30%–40% are not eligible for modulator therapy, no study has evaluated the effects of this situation on mental health in our region [14].

This study aimed to comprehensively evaluate the mental health burden associated with access to ETI therapy or lack thereof on anxiety and depression levels in pwCF and their caregivers. Participants were categorized into three distinct groups [15]: Patients who are genetically eligible and have gained access to ETI therapy through legal action but have not yet started treatment [15], patients who are genetically eligible but have chosen not to pursue legal action due to the associated challenges and risks, and (3) patients who are genetically ineligible for ETI. The primary focus is on the mental health burden associated with ETI eligibility and the ability or inability to access it, as experienced by pwCF and their caregivers. The secondary aim of the study is to evaluate whether clinical factors, such as disease severity and other health-related variables, contribute to anxiety and depression in pwCF and their caregivers, beyond the effects of ETI eligibility and accessibility.

2 | Methods

2.1 | Study Population

This cross-sectional single-center study was conducted between August and December 2023 at the Marmara University (MU) Faculty of Medicine, Division of Pediatric Pulmonology, Selim Çöremen Cystic Fibrosis Center (CFC). The Marmara University CF Center follows all pwCF, both pediatric (0–18 years) and adult (> 18 years), and all patients have been registered in the European Cystic Fibrosis Society Patient Registry since 2015 [8]. For this study, all pwCF and their primary caregivers for children under 18 years, as well as adult pwCF, were invited to participate. Individuals who did not consent to participate, primary caregivers reporting a pre-existing mental health diagnosis unrelated to CF caregiving, parents of pwCF who passed away during the study period, and pwCF receiving CFTR modulators other than elexacaftor/tezacaftor/ivacaftor (ETI) were excluded from the study. Participants were divided into three groups based on their eligibility for and use of ETI. The eligibility of patients with ETI was determined through the utilization of the online database provided by Vertex Pharmaceuticals. Group 1 (Eligible/pre- ETI) included pwCF who were eligible for ETI therapy and could access it through a court decision. Group 2 (Eligible/not on ETI) included pwCF who were genetically eligible for ETI therapy but were not receiving

treatment. Seven children who were genetically eligible for ETI but were under the age of 2 and therefore did not have access to the medication were also included in this group. Group 3 (Ineligible) included pwCF who were genetically ineligible for CFTR modulator therapy.

2.2 | Clinical Data Collection

The collected data included the latest body mass index (BMI) scores for growth assessment, the best value of maximum forced expiratory volume in the first second (FEV1) (as percentage) in the past year, and the presence of CF-related diabetes (CFRD), allergic bronchopulmonary aspergillosis (ABPA), CF-related liver disease (CFLD), and colonization by *Methicillin-Sensitive Staphylococcus Aureus* (MSSA), *Methicillin-Resistant Staphylococcus Aureus* (MRSA), *Pseudomonas Aeruginosa* (PsA), *Burkholderia cepacia*. Additionally, the need for noninvasive positive pressure ventilation (NIPPV) or nasal oxygen support in the last year was noted.

The definitions of ABPA were based on the Cystic Fibrosis Foundation (CFF) consensus recommendations [16]. For the definitions of CFRD and CFLD [17], the guidelines from the ECFS were utilized [18, 19]. Chronic microbial colonization was defined as having 50% or more positive samples over the previous 12 months [20]. FEV1 values were assessed according to the GLI 2022 standards [21].

2.3 | Screening for Depression and Anxiety in People With CF and Their Caregivers

In accordance with the guidelines from the ECFS and the CFF, to screen for depression and anxiety, participants were required to complete the validated Turkish versions of the Patient Health Questionnaire-9 (PHQ-9) and the Generalized Anxiety Disorder-7 (GAD-7) [22, 23]. The screening tests were completed by the primary caregivers of pwCF aged 0–11, and both the children and their parents completed them for those aged 12–17 [21]. Individuals with CF aged 18 years and older completed the questionnaires on their own. Screening tests for Group 1 participants were performed face-to-face at the outpatient clinic immediately before starting ETI therapy. For Groups 2 and 3, who were not receiving ETI treatment, the screenings were conducted face-to-face during outpatient clinic visits (Figure 1).

The PHQ-9 assesses depressive symptoms based on the Diagnostic and Statistical Manual of Mental Disorders-4th edition (DSM-IV) criteria and includes nine items. Turkish version of this questionnaire was found to be quite reliable (Cronbach's alpha 0.842) [24]. Participants rated the frequency of these symptoms over the past 2 weeks on a 4-point Likert scale, resulting in a severity score ranging from 0 to 27 [25].

The GAD-7, used to assess generalized anxiety disorder, comprises seven items reflecting DSM-IV criteria for GAD-7 (e.g.,

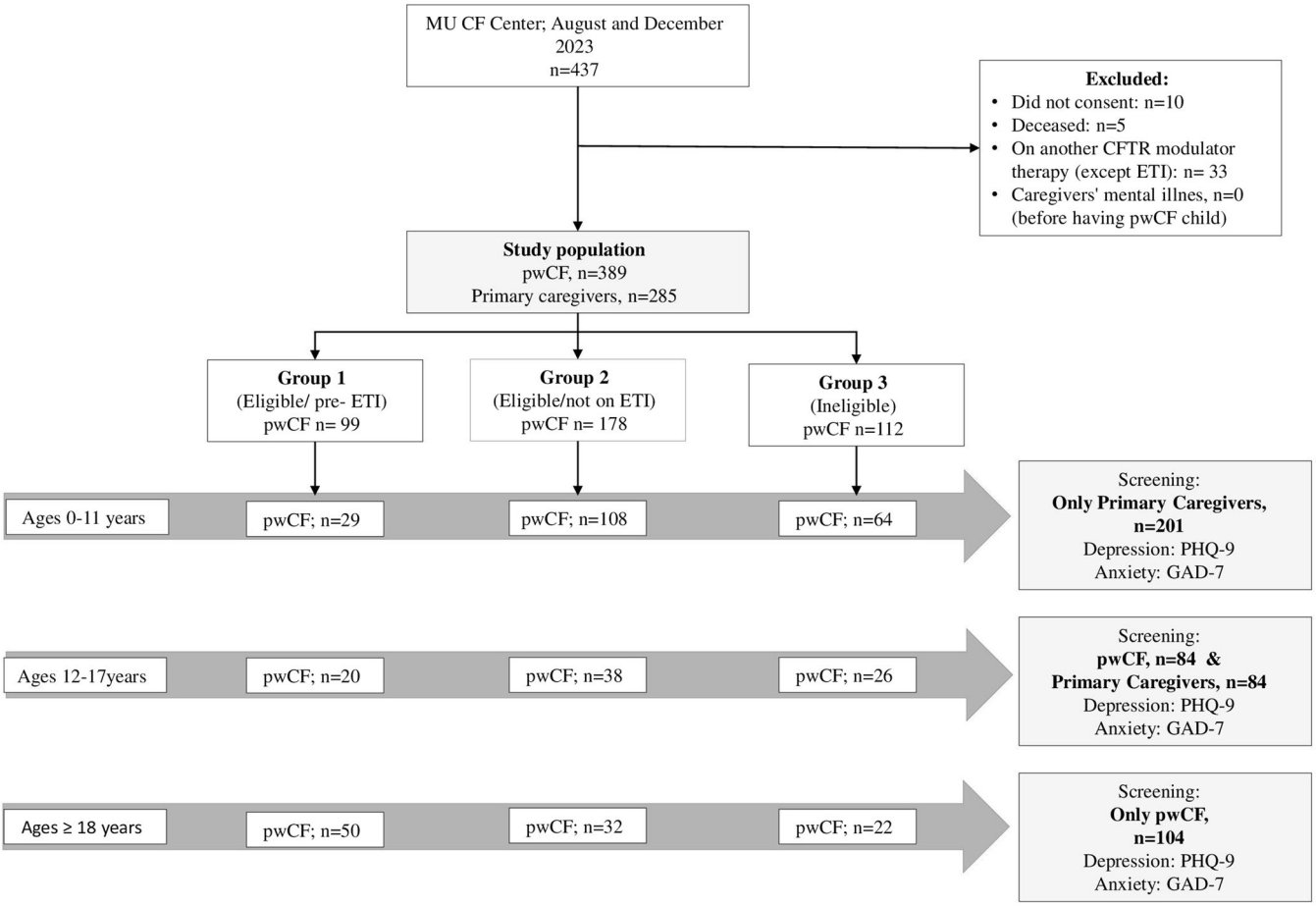

FIGURE 1 | Study population and methodological workflow.

"Feeling nervous, anxious or on edge"). Participants indicated how often they experienced each symptom in the past 2 weeks, again using a 4-point Likert scale, with scores ranging from 0 to 21 [26]. The Turkish version of the GAD-7 has demonstrated good internal consistency (Cronbach's $\alpha = 0.85$) and test-retest reliability (intraclass correlation = 0.83) [27].

Severity scores for both PHQ-9 and GAD-7 were categorized as follows: no symptoms (1–4), mild (5–9), moderate (10–15), and severe (above 15).

2.4 | Ethical Considerations

This study was reviewed and approved by the Research Ethics Committee of the Marmara University Medical Faculty (protocol number 09.2023.1785). According to the Research Ethics Committee of the Marmara University Medical Faculty, information about testing was provided and written patient/parent informed content for data collection was obtained from the patients.

Although it was not the focus of the study, parents and pwCF who required intervention based on the screening test results were referred to psychiatric clinics for depression and anxiety, according to CFF/ECFS guidelines [22]. The outcomes of these interventions were not included in the study.

2.5 | Statistical Analysis

The analysis of data was conducted using the Statistical Program for Social Sciences (SPSS, version 23.0). Descriptive statistics were used to provide numerical summaries, including counts, means, standard deviations (SDs), and interquartile ranges (IQR), depending on the distribution of continuous variables. For continuous variables across more than two groups, the Kruskal-Wallis test was performed for nonparametric tests. For continuous variables in nonparametric distributions between two groups, the Mann-Whitney U test was used. Significance was determined using the Bonferroni correction, with a p-value < 0.017 (0.05/3) considered significant for comparisons among the three groups. The Chi-square or Fisher's exact test was used for categorical variables. For nonparametric tests between two groups, a p-value < 0.05 was considered significant.

To demonstrate the effect of independent variables on the dependent variable, presence of anxiety and depression, binary logistic regression analysis was separately conducted for pwCF and their primary caregivers. The independent variables included in the model were age, sex, PsA colonization, BMI, % predicted FEV1, CFRD, CFLD, NIPPV and oxygen usage, eligibility for CFTR modulator therapies, and access to ETI treatment. The model was constructed using the Enter method, where all selected independent variables were entered into the regression equation simultaneously. The Enter method was used, and for a dependent variable with a p-value < 0.05, the Hosmer-Lemeshow goodness-of-fit test with $p > 0.05$ was considered to indicate good fit. Additionally, the effect of independent variables on the dependent variable was tested using the Wald test.

Spearman's ρ correlation coefficient was used to assess the relationship between PHQ-9/GAD-7 scores and age, age at diagnosis, BMI, and FEV1% predicted. A p-value of < 0.05 was used for statistical significance.

3 | Results

3.1 | Study Design, Demographic and Clinical Features

The study included 389 pwCF and their primary caregivers for those under 18 years of age ($n = 285$). PwCF were divided into three groups according to their eligibility for CFTR modulators and access to ETI. Group 1 included 99 pwCF treated with ETI. Group 2 included 178 pwCF who were eligible but not treated with ETI. Group 3 included 112 pwCF who were ineligible for modulator therapy.

The median age of the participants was 11.5 years (IQR: 6.2–18.4) and 46.7% were female ($n = 182$). Group 1 (eligible/pre- ETI) had a significantly higher median age of 18.7 years (IQR: 11.6–26.9), compared to 13.7 years (IQR: 9.2–18.0) in Group 2 (eligible but not on ETI) ($p < 0.001$). The comparison of baseline characteristics between pwCF in Group 1(eligible/pre-ETI) and Group 3 (ineligible) revealed significant differences. Group 3 had lower BMI values ($p = 0.039$) and higher prevalence of CFLD ($p < 0.001$) compared to Group 1. Additionally, pwCF in Group 2 had higher predicted FEV1% ($p < 0.001$), lower prevalence of CFRD ($p = 0.004$) and PsA colonization ($p < 0.001$), and required less oxygen ($p < 0.001$) and NIPPV support ($p = 0.014$) compared to those in Group 1 (Table 1).

3.2 | PHQ-9 Questionnaire Scores and Depression Rates in pwCF

Among pwCF, Group 3 (ineligible) had the highest rate of depression symptoms, with 35 patients (72.9%) scoring at least in the mild range on the PHQ-9, indicating signs of depression. This was followed by Group 2 (eligible/not on ETI) with 49 patients (70%) and Group 1 (eligible/pre- ETI) with 35 patients (50.0%) (Table 2). There was no significant difference in depression rates between Groups 2 and 3 ($p = 0.732$). However, significant differences were observed between Group 1 and Group 2, and between Group 1 and Group 3 ($p = 0.016$ and $p = 0.013$, respectively).

The median PHQ-9 score of pwCF in Group 1 (eligible/pre- ETI) was statistically significantly lower, with a median (IQR) value of 5.0 (3.0–8.0), compared to pwCF not on ETI, both Group 2 and 3 ($p < 0.006$). When comparing the groups not receiving modulators, no significant difference was observed between Group 2 (eligible/not on ETI) and Group 3 (ineligible) ($p = 0.313$).

3.3 | GAD-7 Questionnaire Scores and Anxiety Rates in pwCF

Among the pwCF surveyed (total $n = 188$), Group 3 (ineligible) had the highest rate of anxiety symptoms, with 30 patients (62.5%)

TABLE 1 | Demographic and characteristic features of the study population.

	Group 1 (Eligible/pre-ETI) $N = 99$ (25.4%)	Group 2 (Eligible/not on ETI) $N = 178$ (45.8%)	Group 3 (Ineligible) $N = 112$ (28.8%)
Sex, Female, n (%)	51 (51.5%)	76 (42.7%)	55 (49.1)
Age (year), median (IQR)	18.7 (11.6–26.9)	13.7 (9.2–18.0)	12.5 (8.3–17.9)
Age at diagnosis (year), median (IQR)	0.30 (0.2–5.7)	0.6 (0.3–5.5)	0.4 (0.2–0.7)
Gene mutation, n (%)			
ΔF508del homozygous	39 (39.4%)	31 (17.4%)	0 (0%)
ΔF508del heterozygous	36 (36.3%)	58 (32.6%)	0 (0%)
Other mutations	24 (24.2%)	89 (50.0%)	112 (100.0%)
% FEV pred, median (IQR), $n = 304$	69.5 (44.1–97.0)	92.1 (82.1–100.4)	85.9 (71.1–97.6)
BMI, median (IQR)	19.4 (15.8–22.2)	17.7 (15.5–21.4)	17.1 (14.9–19.9)
Colonization, n (%)			
MSSA	18 (18.2%)	22 (12.4%)	21 (18.8%)
PsA	46 (46.9%)	12 (6.7%)	17 (15.2%)
MRSA	2 (2.0%)	1 (0.6%)	2 (1.8%)
Burkholderia cepacia	0 (0)	1 (0.6%)	0 (0)
ABPA, n (%)	2 (2.0%)	1 (0.6%)	2 (1.8%)
CFLD, n (%)	10 (10.1%)	17 (9.6%)	32 (28.6%)
CFRD, n (%)	11 (11.1%)	4 (2.2%)	9 (8.0%)
NIPPV, n (%)	5 (5.1%)	1 (0.6%)	4 (3.6%)
Oxygen support, n (%)	12 (12.1%)	1 (0.6%)	6 (5.4%)

Abbreviations: ABPA, Allergic Bronchopulmonary Aspergillosis; BMI, Body Mass Index; CF, Cystic Fibrosis; CFRD, CF-related diabetes; CFLD, CF-related liver disease; FEV1%, Forced Expiratory Volume in 1 s; IQR, Interquartile Range; MSSA, Methicillin-Sensitive *Staphylococcus aureus*; MRSA, Methicillin-Resistant *Staphylococcus aureus*; NIPPV, noninvasive positive pressure ventilation; Pred, Predicted; PsA, Pseudomonas Aeruginosa.

TABLE 2 | PHQ-9 and GAD-7 scores and percentages of depression and anxiety symptoms by severity in pwCF.

	Group 1 (Eligible/pre-ETI) $N = 70$	Group 2 (Eligible/not on ETI) $N = 70$	Group 3 (Ineligible) $N = 48$
PHQ-9 scores, median (IQR)	5.0 (3.0–8.0)	7.0 (4.0–9.0)	7.0 (4.0–11.7)
No symptoms, n (%)	35 (50.0%)	21 (30.0%)	13 (27.1%)
Mild, n (%)	24 (34.2%)	34 (48.6%)	18 (37.5%)
Moderate, n (%)	10 (14.2%)	12 (17.1%)	13 (27.0%)
Severe, n (%)	1 (1.4%)	3 (4.2%)	4 (8.3%)
GAD-7 scores, median (IQR)	4.0 (2.0–7.75)	5.0 (3.0–8.2)	6.5 (4.0–7.0)
No symptoms, n (%)	46 (65.7%)	30 (42.9%)	18 (37.5%)
Mild, n (%)	14 (20.0%)	26 (37.1%)	15 (31.3%)
Moderate, n (%)	7 (10.0%)	12 (17.1%)	10 (20.8%)
Severe, n (%)	3 (4.2%)	2 (2.8%)	5 (10.4%)

Note: PHQ-9 and GAD-7 Scoring: 1–4: No symptoms; 5–9: Mild symptoms; 10–14: Moderate symptoms; 15 or greater: Severe symptoms.
Abbreviations: GAD-7, Generalized Anxiety Disorder Questionnaire; PHQ-9, Patient Health Questionnaire.

scoring at least in the mild range on the GAD-7, indicating signs of anxiety. This was followed by Group 2 (eligible/not on ETI) with 40 patients (57.1%), and Group 1 (eligible/pre-ETI) with 24 patients (34.3%) showing mild to severe anxiety symptoms (Table 2). Participants in Group 2 had significantly higher rates of anxiety compared to Group 1 ($p = 0.011$), and similarly, Group 3 had higher anxiety rates compared to Group 1 ($p = 0.003$). Anxiety rates were similar between the groups not receiving modulator therapy (Groups 2 and 3) ($p = 0.696$).

The median GAD-7 score of pwCF in Group 1 (eligible/pre- ETI) was statistically significantly lower, with a median (IQR) value of 4.0 (2.0–7.75), compared to pwCF not on ETI ($p < 0.001$). When comparing the groups not receiving modulators, no significant

difference was observed between Group 2 (eligible/not on ETI) and Group 3 (ineligible) ($p = 0.053$).

3.4 | PHQ-9 Questionnaire Scores and Depression Rates in Primary Caregivers

In Group 3 (ineligible), 73 primary caregivers (81.1%) of pwCF under the age of 18 showed mild to severe depression symptoms. This rate was 71.4% ($n = 35$) in Group 1 (eligible/pre- ETI) and 65.8% ($n = 96$) in Group 2 (eligible/not on ETI). When comparing the depression rates between the groups, a significant difference was found only between Group 2 and Group 3 ($p = 0.016$). The p-values were 0.465 between Group 1 and Group 2, and 0.190 between Group 1 and Group 3. The median PHQ-9 scores of the groups were similar ($p = 0.066$) (Table 3).

3.5 | GAD-7 Questionnaire Scores and Depression Rates in Primary Caregivers

When assessing the anxiety rates of primary caregivers of pwCF under the age of 18, Group 3 (ineligible) had the highest anxiety rate at 67.8% ($n = 61$), followed by Group 2 (eligible/not on ETI) with 92 parents (63.0%), and Group 1 (eligible/pre- ETI) with 28 parents (57.1%) (Table 3). However, no statistically significant difference was observed between the groups (p-values were 0.465 between Group 1 and Group 2, 0.212 between Group 1 and Group 3, and 0.457 between Group 2 and Group 3). The median GAD-7 scores of the groups were similar ($p = 0.738$).

3.6 | Influence of Independent Variables on Depression and Anxiety

The effects of age, sex, PsA colonization, BMI, % predicted FEV1, CFRD, CFLD, NIPPV and oxygen use, eligibility for CFTR modulator therapies, and access to ETI on the likelihood of anxiety and depression were analyzed using binary logistic regression. However, the logistic regression model did not show a good fit for predicting the presence of depression in pwCF and the presence of anxiety and depression in parents when using the Enter method ($p > 0.05$) and the Hosmer-Lemeshow goodness-of-fit test ($p < 0.05$).

Conversely, the model for predicting the presence of anxiety in pwCF showed significant results. Access to ETI significantly reduced the likelihood of anxiety ($p = 0.029$, 95% CI [0.117, 0.890]) in pwCF. People with CF who can access ETI had approximately 67.7% lower odds of experiencing anxiety compared to those not using the therapy (Table 4).

A correlation analysis was performed to examine the relationship between age, age at diagnosis, BMI, and FEV1% predicted with PHQ-9 and GAD-7 scores in pwCF and their primary caregivers. Among these factors, the age of pwCF showed a weak negative correlation with the GAD-7 scores of the caregivers ($r = -0.117$). Despite being weak, this correlation was found to be statistically significant ($p = 0.049$) (Table 5).

4 | Discussion

This study sheds light on the intricate relationship between access to CFTR modulator therapy and psychological well-being in pwCF. The results also indicate substantial barriers to treatment, which manifest in the mental health of affected individuals. Our research revealed high rates of depression and anxiety among pwCF, with significant differences observed based on their access to modulator therapy. In the context of this study, "access" specifically refers to the opportunity to obtain ETI therapy through a legal process, as none of the patients in this study had yet started ETI therapy. Rather than focusing on the effects of ETI therapy itself on mental health, "access" emphasizes the ability of pwCF to pursue legal action to secure SSI reimbursement and ultimately gain access to the modulator therapy. Ineligibility and lack of access to modulator therapy were associated with even higher rates of depression and anxiety. The rates of depression and anxiety in pwCF who could access ETI treatment were significantly lower. PHQ-9 and GAD-7 scores were also significantly lower in pwCF with access

TABLE 3 | PHQ-9 and GAD-7 scores and percentages of depression and anxiety symptoms by severity in primary caregivers.

	Group 1 (Eligible/pre-ETI) $N = 49$	Group 2 (Eligible/not on ETI) $N = 146$	Group 3 (Noneligible) $N = 90$
PHQ-9 scores, median (IQR)	6.0 (4.0–10.0)	6.0 (3.0–9.0)	7.0 (5.0–10.0)
No symptoms, n (%)	14 (28.6%)	50 (34.2%)	17 (18.9%)
Mild, n (%)	22 (44.8%)	63 (43.2%)	49 (54.4%)
Moderate, n (%)	7 (14.3%)	25 (17.1%)	21 (23.3%)
Severe, n (%)	6 (12.2%)	8 (5.4%)	3 (3.3%)
GAD-7 scores, median (IQR)	6.0 (3.0–11.0)	6.0 (3.0–10.0)	6.5 (4.0–10.0)
No symptoms, n (%)	21 (42.9%)	54 (37.0%)	29 (32.2%)
Mild, n (%)	14 (28.6%)	52 (35.6%)	37 (41.1%)
Moderate, n (%)	8 (16.3%)	33 (22.6%)	18 (20.0%)
Severe, n (%)	6 (12.2%)	7 (4.8%)	6 (6.6%)

Note: PHQ-9 and GAD-7 Scoring: 1–4: No symptoms; 5–9: Mild symptoms; 10–14: Moderate symptoms; 15 or greater: Severe symptoms.
Abbreviations: GAD-7, Generalized Anxiety Disorder Questionnaire; PHQ-9, Patient Health Questionnaire.

TABLE 4 | Logistic regression analysis for independent factors affecting anxiety in PwCF.

Independent Variables	B	Exp(B)	95% C.I. for Exp(B)	*p* value
Age	0.043	1.044	0.968–1.125	0.266
Sex	−0.256	0.774	0.349–1.715	0.528
BMI	0.103	1.109	0.977–1.259	0.110
FEV1% predicted	−0.005	0.995	0.972–1.018	0.652
PsA colonization	0.047	1.048	0.353–3.116	0.932
Oxygen usage	0.555	1.741	0.373–8.133	0.481
NIPPV usage	−0.923	0.397	0.033–4.788	0.467
CFRD	−0.427	0.652	0.184–2.311	0.508
CFLD	0.417	1.518	0.414–5.560	0.529
CFTR modulator theraphy eligibility	−0.831	0.436	0.140–1.357	0.152
ETI accessibility	−1.130	0.323	0.117–0.890	***0.029***

Abbreviations: BMI, Body Mass Index; CFLD, CF-related liver disease; CFRD, CF-related diabetes; CFTR, Cystic Fibrosis transmembrane regulator (CFTR); ETI, Elexacaftor/Tezacaftor/Ivacaftor; FEV1%, Forced Expiratory Volume in 1 s; IQR, Interquartile Range; NIPPV, noninvasive positive pressure ventilation; Pred, Predicted; PsA, *Pseudomonas Aeruginosa*; Exp(B), Exponentiated Beta or Odss Ratio; 95% C.I. For Exp(B), 95% Confidence Interval for the Exponentiated Beta Coefficient.

TABLE 5 | Spearman's ρ correlation results of relationship between PHQ-9/GAD-7 and continuous demographic and clinical variables.

	pwCF		Primary Caregivers	
	PHQ-9	GAD-7	PHQ-9	GAD-7
Age	−0.006	0.088	−0.045	−0.017*
Age at diagnosis	0.054	0.008	−0.041	−0.075
BMI	0.107	0.118	0.047	0.068
FEV1% predicted	−0.081	−0.30	−0.120	−0.27

Note: Correlation coefficients are presented in the table. * This correlation is statistically significant with p value 0.049. All other correlations are not statistically significant ($p > 0.05$).
Abbreviations: BMI, body mass index; FEV1, forced expiratory volume in 1 s; GAD-7, Generalized Anxiety Disorder Questionnaire; PHQ-9, Patient Health Questionnaire.

to ETI. Furthermore, our study found that access to ETI significantly reduced the likelihood of anxiety. Additionally, it was observed that parents' anxiety scores decreased as their children's lifespan increased.

Our study found that access to ETI significantly reduced the likelihood of anxiety in pwCF but was not predictive of depression, despite the high prevalence of depression in the sample and similar group differences in both anxiety and depression rates. This discrepancy may stem from the distinct mechanisms underlying anxiety and depression. Anxiety is often more closely linked to acute external stressors, such as uncertainty or financial burdens, which may be alleviated by gaining access to ETI [28, 29]. Conversely, depression may be more influenced by long-term psychosocial factors, including the chronic burden of living with CF, pre-existing mental health conditions, and limited social support. Additionally, the logistic regression model for depression did not show a good fit, suggesting that other unmeasured factors may have a stronger impact on depressive symptoms.

The prevalence of depression is high among pwCF and their parents compared to that in the general population. The largest international screening study (TIDES) reported a prevalence of depression among adolescents ranging from 5% to 19% [9]. Although data from Turkey were excluded from this study because of the limited sample size and inability to access standard medication during the study period, the findings from the Turkish sample in the TIDES study ($n = 50$) revealed higher depressive symptoms by 29% on the Hospital Anxiety and Depression Scale (HADS) and 52% on the Center for Epidemiologic Studies-Depression Scale (CES-D) [9].

Several studies have also revealed high levels of depression and anxiety in pw CF patients in Turkey [7, 10, 30]. A recent cross-sectional study conducted by Senses-Dinc et al. evaluated differences in depression and anxiety levels between a group of 35 pwCF and a control group of 40 healthy individuals using the Children's Depression Inventory (CDI) and State-Trait Anxiety Inventory for Children (STAI-C) [30]. In this study pwCF exhibited higher prevalence of depression and anxiety symptoms and had lower scores in terms of quality of life than healthy controls. Moreover, among the children in the CF group, 54.3% were diagnosed with anxiety disorders and 20% with depressive disorders [30].

In a previous study conducted at our CF center, Musaloğlu et al. evaluated depression and anxiety in pwCF using the PHQ-9 and GAD-7 [10]. This study found that 74% of adolescents with CF showed symptoms of depression and 51% of participants showed symptoms of anxiety [10]. In our study 75% of pwCF did not have access to CFTR modulator therapy because of reimbursement issues or inappropriate genetic mutations. A high rate of depressive symptoms, ranging from 70% to 73%, was observed in both groups.

These findings are consistent with those of a survey by Kramer-Golinkoff of 431 participants from five continents, which highlighted the challenges faced by pwCF that do not benefit from CFTR modulators [13]. The majority of these individuals had moderate lung disease, were ineligible for modulators due to their CFTR mutations, and experienced significant impacts on their mental and physical health. Despite supporting those who benefit from modulators, many feel neglected and forgotten in the current therapeutic environment, underscoring the need for more inclusive treatment approaches [13].

In our study, the baseline median FEV1 scores for pwCF who were eligible and currently can access for ETI therapy were significantly lower than those who were eligible but not using ETI. This finding aligns with the CFF 2022 Annual Report, which observed that in the group without a CFTR modulator prescription from 2018 to 2022, the annual average lung function was better than that in the population prescribed CFTR modulators [31]. Additionally, in our study, the baseline characteristics of the ETI therapy group included higher PSA colonization rates, a greater prevalence of diabetes, more frequent need for respiratory support, and an older median age. Among these variables, we found that the most significant factor affecting patients' mental health was the usage of ETI. People with CF on ETI had approximately 67.7% lower odds of experiencing anxiety compared to those not using the therapy.

There was no significant difference in depression and anxiety rates among the groups for primary caregivers; even among those who had access to the medication, anxiety and depression rates exceeded 50%. This suggests that the legal process undertaken by primary caregivers to access modulator therapies through SSI, which often continues even after the medication is received, may be creating challenges that negatively impact their mental health.

A major limitation of this study is the small number of patients receiving modulator therapy, particularly ETI. Additionally, there is a lack of information on how anxiety and depression levels change over time in patients under ETI therapy. Due to the limited number of patients who reached a 1-year follow-up period on ETI therapy, follow-up results were not included in the study. Furthermore, the heterogeneity of anxiety and depression levels between these groups in earlier periods was not evaluated in this study. Future studies conducted in Turkey are crucial to understand the impact of modulator therapy on mental health.

In conclusion, a lack of access to ETI is a major factor in increasing anxiety and depression in pwCF. This rate was even higher in pwCF who were not eligible for modulator treatment. Our study demonstrated that the accessibility of ETI significantly reduces the likelihood of anxiety and observed that parents' anxiety scores decreased as the lifespan of their children increased. Reimbursement for modulatory treatment in our country may improve the mental status of pwCF who are eligible for treatment but are not currently receiving it. During this process, we plan to provide psychological counseling to all patients to improve their mental health.

Author Contributions

Burcu Uzunoglu: conceptualization, investigation, writing – original draft, writing – review and editing, visualization, validation, methodology, software, formal analysis, project administration, resources, data curation. **Merve Selcuk Balci:** conceptualization, investigation, funding acquisition, writing – original draft, writing – review and editing, visualization, validation, methodology, software, formal analysis, project administration, data curation, resources. **Mine Kalyoncu:** visualization, data curation. **Seyda Karabulut:** resources, data curation, visualization, validation, methodology. **Neval Metin Cakar:** validation, visualization, resources, data curation. **Ceren Ayca Yildiz:** visualization, data curation, resources, methodology. **Gamze Tastan:** visualization, resources, data curation. **Damla Kocaman:** data curation, resources, visualization. **Almala Pinar Ergenekon:** writing – review and editing, validation, methodology, supervision. **Yasemin Gokdemir:** resources, supervision, data curation, project administration, formal analysis, software, methodology, validation, visualization, writing – review and editing. **Ela Erdem Eralp:** project administration, writing – review and editing, visualization, methodology, validation, software, formal analysis, data curation, supervision, resources. **Fazilet Karakoc:** writing – review and editing, visualization, validation, methodology, software, project administration, supervision, resources. **Bülent Karadag:** supervision, resources, data curation, project administration, software, writing – review and editing, methodology, validation, visualization.

Acknowledgments

The authors would like to thank all patients who participated.

Conflicts of Interest

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.

References

1. L. Allen, L. Allen, S. B. Carr, et al., "Future Therapies for Cystic Fibrosis," *Nature Communications* 14, no. 1 (2023): 693.

2. J. L. Taylor-Cousar, M. A. Mall, B. W. Ramsey, et al., "Clinical Development of Triple-Combination CFTR Modulators for Cystic Fibrosis Patients With One or Two F508del Alleles," *ERJ Open Research* 5, no. 2 (2019): 00082-2019.

3. M. E. McGarry, E. R. Gibb, G. R. Oates, and M. S. Schechter, "Left Behind: The Potential Impact of CFTR Modulators on Racial and Ethnic Disparities in Cystic Fibrosis," *Paediatric Respiratory Reviews* 42 (2022): 35–42.

4. M. E. McGarry and S. A. McColley, "Cystic Fibrosis Patients of Minority Race and Ethnicity Less Likely Eligible for CFTR Modulators Based on CFTR Genotype," *Pediatric Pulmonology* 56, no. 6 (2021): 1496–1503.

5. European Cystic Fibrosis Society Patient Registry. 2021 Annual Report From the European Cystic Fibrosis Society Patient Registry (ECFSPR). March 2024.

6. A. Ergenekon, M. C. Yanaz, A. Guliyeva, et al. 422 Outcomes of Patients With Intermittent Versus Continuous Access to CFTR Modulator Therapy in Turkey. 2023;22:S221.

7. U. Gundogdu, N. P. Fis, E. E. Eralp, and B. T. Karadag, "Major Depression and Psychiatric Comorbidity in Turkish Children and Adolescents With Cystic Fibrosis," *Pediatric Pulmonology* 54, no. 12 (2019): 1927–1935.

8. J. Abbott, T. Havermans, S. Jarvholm, et al., "Mental Health Screening in Cystic Fibrosis Centres Across Europe," *Journal of Cystic Fibrosis* 18, no. 2 (2019): 299–303.

9. A. L. Quittner, L. Goldbeck, J. Abbott, et al., "Prevalence of Depression and Anxiety in Patients With Cystic Fibrosis and Parent Caregivers: Results of the International Depression Epidemiological Study Across Nine Countries," *Thorax* 69, no. 12 (2014): 1090–1097.

10. H. H. Mursaloğlu, C. Yılmaz Yeğit, A. P. Ergenekon, et al., "Screening of Depression and Anxiety in Adolescents With Cystic Fibrosis and Caregivers in Turkey by PHQ-9 and GAD-7 Questionnaires," *Pediatric Pulmonology* 56, no. 6 (2021): 1514–1520.

11. S. Stanojevic, K. Vukovojac, J. Sykes, F. Ratjen, E. Tullis, and A. L. Stephenson, "Projecting the Impact of Delayed Access to Elexacaftor/Tezacaftor/Ivacaftor for People With Cystic Fibrosis," *Journal of Cystic Fibrosis* 20, no. 2 (2021): 243–249.

12. J. Guo, A. Garratt, and A. Hill, "Worldwide Rates of Diagnosis and Effective Treatment for Cystic Fibrosis," *Journal of Cystic Fibrosis* 21, no. 3 (2022): 456–462.

13. E. Kramer-Golinkoff, A. Camacho, L. Kramer, and J. L. Taylor-Cousar, "A Survey: Understanding the Health and Perspectives of People With CF not Benefiting From CFTR Modulators," *Pediatric Pulmonology* 57, no. 5 (2022): 1253–1261, https://doi.org/10.1002/ppul.25859.

14. N. Çobanoğlu, U. Özçelik, E. Çakır, et al., "Patients Eligible for Modulator Drugs: Data From Cystic Fibrosis Registry of Turkey," *Pediatric Pulmonology* 55, no. 9 (2020): 2302–2306.

15. S. Dick, A. Friend, K. Dynes, et al., "A Systematic Review of Associations Between Environmental Exposures and Development of Asthma in Children Aged up to 9 Years," *BMJ Open* 4, no. 11 (2014): e006554.

16. D. A. Stevens, R. B. Moss, V. P. Kurup, et al., "Allergic Bronchopulmonary Aspergillosis in Cystic Fibrosis—State of the Art: Cystic Fibrosis Foundation Consensus Conference," *Clinical Infectious Diseases* 37, no. Suppl_3 (2003): S225–S264.

17. D. Debray, D. Kelly, R. Houwen, B. Strandvik, and C. Colombo, "Best Practice Guidance for the Diagnosis and Management of Cystic Fibrosis-Associated Liver Disease," *Journal of Cystic Fibrosis* 10 (2011): S29–S36.

18. C. E. Milla, W. J. Warwick, and A. Moran, "Trends in Pulmonary Function in Patients With Cystic Fibrosis Correlate With the Degree of Glucose Intolerance at Baseline," *American Journal of Respiratory and Critical Care Medicine* 162, no. 3 (2000): 891–895.

19. E. Kerem, S. Conway, S. Elborn, and H. Heijerman, "Standards of Care for Patients With Cystic Fibrosis: A European Consensus," *Journal of Cystic Fibrosis* 4, no. 1 (2005): 7–26.

20. T. Pressler, C. Bohmova, S. Conway, et al., "Chronic Pseudomonas Aeruginosa Infection Definition: EuroCareCF Working Group Report," *Journal of Cystic Fibrosis* 10 (2011): S75–S78.

21. C. Bowerman, N. R. Bhakta, D. Brazzale, et al., "A Race-Neutral Approach to the Interpretation of Lung Function Measurements," *American Journal of Respiratory and Critical Care Medicine* 207, no. 6 (2023): 768–774.

22. A. L. Quittner, J. Abbott, A. M. Georgiopoulos, et al., "International Committee on Mental Health in Cystic Fibrosis: Cystic Fibrosis Foundation and European Cystic Fibrosis Society Consensus Statements for Screening and Treating Depression and Anxiety," *Thorax* 71, no. 1 (2016): 26–34.

23. A. Corapcioglu and G. U. Ozer, "Adaptation of Revised Brief PHQ (Brief-PHQ-r) for Diagnosis of Depression, Panic Disorder and Somatoform Disorder in Primary Healthcare Settings," *International Journal of Psychiatry in Clinical Practice* 8, no. 1 (2004): 11–18.

24. Y. E. Sari, B. Kokoglu, H. Balcioglu, U. Bilge, E. Colak, and I. Unluoglu, "Turkish Reliability of the Patient Health Questionnaire-9," *Biomedical Research-India* 27 (2016): S460–S462.

25. K. Kroenke, R. L. Spitzer, and J. B. W. Williams, "The PHQ-9: Validity of a Brief Depression Severity Measure," *Journal of General Internal Medicine* 16, no. 9 (2001): 606–613.

26. R. L. Spitzer, K. Kroenke, J. B. W. Williams, and B. Löwe, "A Brief Measure for Assessing Generalized Anxiety Disorder: The GAD-7," *Archives of Internal Medicine* 166, no. 10 (2006): 1092–1097.

27. R. Konkan, Ö. Şenormanci, O. Güçlü, E. Aydin, and M. Z. Sungur, "Yaygın Anksiyete Bozukluğu-7 (YAB-7) Testi Türkçe Uyarlaması, Geçerlik ve Güvenirliği," *Nöro Psikiyatri Arşivi* 50, no. 1 (2013): 53–58.

28. C. Grillon, R. Duncko, M. F. Covington, L. Kopperman, and M. A. Kling, "Acute Stress Potentiates Anxiety in Humans," *Biological Psychiatry* 62, no. 10 (2007): 1183–1186.

29. M. W. Eysenck and M. Fajkowska, *Anxiety and Depression: Toward Overlapping and Distinctive Features* (Taylor & Francis, 2018), 1391–1400.

30. G. Şenses-Dinç, N. Kiper, S. Pekcan, et al., "Psychiatric Morbidity and Quality of Life in Children and Adolescents With Cystic Fibrosis," *Turkish Journal of Pediatrics* 60, no. 1 (2018): 32–40.

31. A. S. Özbek, S. Kavuncuoğlu, S. Ugan Atik, E. Y. Aldemir, M. Payaslı, and S. Sander, "2004-2008 Yılları arasında yenidoğan yoğun bakım ünitesinde pnömotoraks tanısıyla izlenen olguların incelenmesi," *JOPP Derg* 3 (2011): 79–85.