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Patient Perspectives on Chronic Rhinosinusitis in cystic fibrosis: Symptom prioritization in the era of highly effective modulator therapy

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ORIGINAL ARTICLE

Patient perspectives on chronic rhinosinusitis in cystic fibrosis: Symptom prioritization in the era of highly effective modulator therapy

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Abstract

Background: Chronic rhinosinusitis (CRS) is common in people with cystic fibrosis (PwCF). Rhinologic symptom prioritization and areas that influence CRS

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treatment choices, including pursuing endoscopic sinus surgery (ESS), remain understudied.

Methods: Adult PwCF + CRS were enrolled at eight centers into a prospective, observational study (2019–2023). Participants were administered the 22-SinoNasal Outcome Test (SNOT-22) survey and a modified SNOT-22 instrument examining symptom importance. We determined importance rankings for individual symptoms and SNOT-22 symptom importance subdomains in two sets of subgroups—those pursuing ESS versus continuing medical management (CMT), and those on elexacaftor/tezacaftor/ivacaftor (ETI) versus not on ETI.

Results: Among 69 participants, the highest priorities were nasal congestion (n = 48, 69.6% important), post-nasal discharge (32, 46.4%), facial pain (29, 43.3%), waking up tired (27, 39.1%), and fatigue (26, 37.7%). Those electing surgery (n = 23) prioritized sleep and psychological dysfunction symptoms compared to those pursuing CMT (n = 49) (sleep median score = 19.0 [interquartile range: 12.0, 25.0] vs. 4.5 [0.0, 12.8]; $p < 0.0001$; psychological = 17.0 [7.0, 26.0] vs. 7.0 [0.0, 15.8]; $p = 0.002$). ETI users had comparable SNOT-22 total symptom importance scores to non-ETI users ($p = 0.14$). Non-ETI users (n = 34) showed a trend toward prioritizing sleep symptoms compared to ETI users (n = 35) (13.0 [2.8, 22.3] vs. 6.0 [2.0, 17.0]; $p = 0.055$).

Conclusions: Nasal congestion and post-nasal discharge were top priorities reported by PwCF + CRS. Those electing surgery prioritized sleep and psychological symptoms, highlighting their importance in pre-operative discussions. Non-ETI users' prioritization of sleep improvement may highlight their unique disease impact and therapeutic needs; however, additional investigation is required.

KEYWORDS
chronic rhinosinusitis, cystic fibrosis, endoscopic sinus surgery, highly effective modulator therapy, patient priorities, patient symptoms, symptom importance

1 | INTRODUCTION

Cystic fibrosis (CF) is caused by non-functioning or abnormally functioning cystic fibrosis transmembrane conductance regulator (CFTR) protein. Dysregulated chloride ion transport results in reduced epithelial water transport into mucosal secretions and causes the production of thick, inspissated mucus that affects the sinopulmonary, gastrointestinal, pancreatic, and biliary systems. Persistent mucosal inflammation in the upper airways and paranasal sinuses manifests as chronic rhinosinusitis (CRS).[1] In the unified airway model, the paranasal sinuses can serve as bacterial reservoirs, triggering sinopulmonary exacerbations that compromise lung health.[2] Thus, management of CRS is an important aspect of CF treatment.[3]

The CF treatment landscape has transformed with the availability of highly effective CFTR modulator therapies (HEMT) since 2019.[4] The highly effective modulator therapy elexacaftor/tezacaftor/ivacaftor (ETI) is available for ~90% of CF patients.[4] ETI decreases the severity of CRS in some patients but does not fully resolve CRS symptoms.[5,6] Despite HEMT, a subset of people with CF with recalcitrant CRS (PwCF + CRS) are faced with the need to consider endoscopic sinus surgery (ESS), and some PwCF are not eligible for or cannot tolerate HEMT.[7] Understanding what symptoms are a priority for treatment in the current era remains critical for CF-related CRS management.

Mattos et al. examined symptom importance in non-CF CRS patients and found that participants considered nasal-related, smell-related, and sleep-related symptoms to be among the most important reasons to undergo ESS.[8] The priorities driving PwCF + CRS to seek care are understudied. To provide personalized care, it is vital to understand PwCF's areas of importance for optimal counseling, clinical decision making, and patient satisfaction. Recognizing

these priorities enables clinicians to tailor CRS treatment approaches.

The objectives of this study are to (1) identify the most important symptoms that drive PwCF to seek treatment for CRS, and (2) assess potential differences in symptom area priorities among PwCF who opted for ESS versus continued medical therapy (CMT) for CRS, and among those who were taking HEMT versus not on HEMT.

2 | PATIENTS AND METHODS

2.1 | Study design

Study participants were prospectively enrolled in a multi-institutional, observational study between 2019 and 2023 from the University of California (Los Angeles, CA), the Medical University of South Carolina (Charleston, SC), the National Jewish Health (Denver, CO), the Oregon Health and Science University (Portland, OR), the University of Colorado (Aurora, CO), the University of Utah (Salt Lake City, UT), the University of North Carolina at Chapel Hill (Chapel Hill, NC), and the Stanford University (Palo Alto, CA). All participating sites are CF Foundation-Accredited Care Centers and received local Institutional Review Board (IRB) approval. IRB approval for the primary coordinating site was granted by UCLA approval number 20-002079. All study participants provided written informed consent.

2.2 | Study population and inclusion criteria

As previously described,[9] participants included adults (≥18 years) with a diagnosis of CF and comorbid CRS, with or without nasal polyposis. Those who had undergone ESS within the past 12 months, or initiated or changed CFTR modulator therapies within the past 3 months were excluded to avoid potential confounding effects. Treatment for CF-related CRS was driven by guidelines and consensus statements.[7,10] Enrolled participants provided sociodemographic and comprehensive medical history information. Treatment, either ESS or continued appropriate medical therapy, followed clinical practice guidelines and consensus statements.[10,11]

2.3 | Patient-reported and clinical measures of disease severity

Participants completed the 22-question SinoNasal Outcome Test (SNOT-22) at enrollment. The SNOT-22 is a validated, 22-item survey developed to quantify symptom severity associated with chronic sinonasal conditions (2006, Washington University, St. Louis, MO). Each of the 22 symptoms is given a score using ordinal scale responses (0 = no problem, 1 = very mild problem, 2 = mild/slight problem, 3 = moderate problem, 4 = severe problem, and 5 = problem as bad as it can be). Total scores range from 0 to 110, with higher total scores reflecting worse overall sinonasal symptom severity and/or patient function.[12] Subsequent factor analyses of SNOT-22 survey have previously identified five distinct symptom subdomains including rhinologic symptoms (range: 0–30), extra-nasal rhinologic symptoms (range: 0–15), ear/facial symptoms (range: 0–25), psychological dysfunction (range: 0–35), and sleep dysfunction (range: 0–25), which were also summarized across individual response scores.[13]

Nasal endoscopy was scored according to the Lund–Kennedy (LK) staging system (range: 0–20), and sinus computed tomography (CT) scans were scored according to Lund–Mackay (LM) staging (range: 0–24) by the treating rhinologist. Higher nasal endoscopy and sinus CT scores indicate worse observed disease. Pulmonary function test results were obtained from clinical records.

2.4 | Patient reported symptom importance measurements

The SNOT-22 symptom importance survey was utilized to determine relative CRS-related symptom importance. As previously reported,[8] the SNOT-22 symptom importance survey enumerated each symptom described in the SNOT-22 instrument, and patients were asked to rank "How important it is for you to have improvement in the items below following treatment for your sinusitis" on an ordinal scale (0 = not relevant, 1 = relevant, 2 = less important, 3 = somewhat important, 4 = important, 5 = very important). Total importance scores were summed across all symptoms (range 0–110) as well as importance scores of the five SNOT-22 symptom subdomains (same ranges as SNOT-22 subdomains). For example, for each patient, we added the individual importance score for sneezing, ear fullness, dizziness, ear pain, and facial pain/pressure to calculate the SNOT-22 ear/facial symptom subdomain importance score.

Importance rankings were determined in two sets of subgroups: those who pursued ESS versus CMT for CRS, and those taking HEMT versus not taking HEMT. ETI was the only HEMT in this study.

2.5 | Statistical analysis

Descriptive statistics for baseline and demographic factors were performed using commercially available software

(SPSS v.29.0; IBM Corp.). The percentage (%) of patients who indicated improvement in a particular symptom was important to them in their CRS treatment was categorized to include those who indicated 4 = important and 5 = very important. For this analysis, % importance indicates that patients selected either the "important" or "very important" ranking. Rankings were initially ranked in descending % importance, and if these values were the same across multiple symptoms, then ranking was determined by descending mean. Descriptive statistics and % importance were conducted for each symptom in the two symptom importance surveys and for SNOT-22 subdomain groupings. Mann–Whitney *U*-test compared distributions between two subgroups (ESS vs. CMT and PwCF on ETI vs. not on ETI) for individual symptoms and comparing SNOT-22 symptom subdomains. Fisher's exact test compared the proportions of % importance between different subgroups. To analyze the association between SNOT-22 total score and SNOT-22 symptom importance total score, Pearson's correlation coefficient (R) was also estimated. Internal consistency of both the SNOT-22 and Symptom Improvement Survey was evaluated for both the final cohort and both ESS and CMT treatment subgroups using Cronbach's alpha (α). Type-I error probability (p-values) are reported for all associations as well as 95% confidence intervals (CIs) for mean comparisons of subgroups, with predetermined threshold of 0.05 for statistical significance per convention.

3 | RESULTS

3.1 | Baseline characteristics

A total of 69 PwCF + CRS were included in this study. All participants completed a SNOT-22 survey and SNOT-22 symptom importance instrument. Aligned with a prior report,[9] the mean [±standard deviation] patient age was 34.6 [±10.9], and the majority (n = 45, 65.2%) were female. The majority (45, 65.2%) of patients were actively on CFTR modulator therapy, and of those on a modulator, most (35, 77.8%) were managed with ETI. Overall, 46 (66.7%) of study participants elected to pursue CMT, contrasted with 23 (33.3%) participants who elected to pursue ESS. A total of 52 (75.4%) had a prior history of ESS. Mean SNOT-22 scores were 34.78 [±19.18] for the entire cohort. PwCF + CRS demonstrated high rates of self-reported depression (32, 47.8%) and anxiety (42, 62.7%). Demographics, clinical characteristics, and SNOT-22 subdomain breakdowns are reported in Table 1.

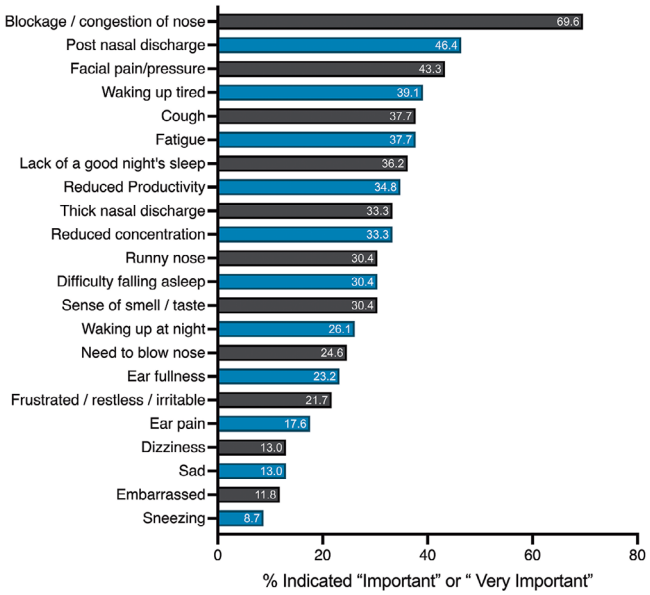

FIGURE 1 Importance ratings of items that comprise the 22-question SinoNasal Outcome Test in people with cystic fibrosis with medical refractory chronic rhinosinusitis (n = 69).

3.2 | Overall cohort importance ratings and correlation between total SNOT-22 score and total SNOT-22 symptom importance score

In PwCF + CRS, the most important SNOT-22 symptoms (n, % important) were blockage/congestion of nose (48, 69.57%), post-nasal discharge (32, 46.28%), facial pain/pressure (29, 43.28%), waking up tired (27, 39.13%), fatigue (26, 37.68%), and cough (26, 37.68%) (Figure 1). Total SNOT-22 symptom importance scores and SNOT-22 symptom importance subdomains scores are shown in Table 2.

SNOT-22 total scores, indicating greater CRS severity, were strongly associated with SNOT-22 total symptom importance scores (n = 69, R = 0.73, $p < 0.001$).

3.3 | Comparison of SNOT-22 symptom importance ratings between medical and surgical groups

The percentage of patients rating each symptom at least as "important" (n, % important) was compared between participants who pursued ESS (n = 23) and those who CMT (n = 46). Symptoms that significantly differed and were prioritized by PwCF + CRS pursuing ESS compared

TABLE 1 Patient demographics and baseline characteristics ($n = 69$).

Characteristics	*N* (%)	Mean [±SD]	Range: LL, UL	Median (*Q1*, *Q3*)
Age (years)	69 (100%)	34.6 [±10.9]	20.0, 63.0	33.0 (26.0, 39.0)
Male	24 (34.8%)	–	–	–
Female	45 (65.2%)	–	–	–
Race/ethnicity				
White/Caucasian	65 (94.2%)	–	–	–
Black	1 (1.4%)	–	–	–
More than one race	3 (4.3%)	–	–	–
Hispanic/Latino	2 (2.9%)	–	–	–
BMI	69 (100%)	24.4 [±4.55]	16.1, 40.6	24.1 (20.6, 26.4)
Treatment modality				
ESS	23 (33.3%)	–	–	–
CMT	46 (66.7%)	–	–	–
Nasal polyposis	36 (52.2%)	–	–	–
Septal deviation	22 (31.9%)	–	–	–
Prior ESS	52 (75.4%)	–	–	–
F508del mutation	57 (82.6%)	–	–	–
F508del homozygous	25 (36.2%)	–	–	–
Prior lung transplant	8 (11.8%)	–	–	–
Headache	46 (68.7%)	–	–	–
Depression	32 (47.8%)	–	–	–
Anxiety	42 (62.7%)	–	–	–
Current smoking/tobacco use	1 (1.5%)	–	–	–
Former smoking/tobacco use	1 (1.5%)	–	–	–
History of				
Pseudomonas positivity	52 (76.5%)	–	–	–
Pancreatic insufficiency	59 (85.5%)	–	–	–
CF-related DM	28 (40.6%)	–	–	–
Active CFTR modulator therapy	45 (65.2%)			
Elexacaftor/tezacaftor/ivacaftor	35 (77.8%)	–	–	–
Ivacaftor	3 (6.7%)	–	–	–
Tezacaftor/ivacaftor	7 (15.6%)	–	–	–
Lund–Kennedy endoscopy score	56 (81.2%)	6.93 [±4.48]	0.00, 18.0	6.00 (4.00, 10.0)
Lund–Mackay CT score	45 (65.2%)	12.0 [±7.10]	0.00, 24.0	12.0 (6.50, 18.0)
FEV1 % predicted	63 (91.3%)	74.7 [±26.2]	−4.37, 118	76.0 (51.8, 94.0)
SIT total score	56 (81.2%)	27.36 [±9.32]	8.00, 39.00	30.50 (19.00, 35.00)
Anosmia	12 (21.4%)	12.42 [±3.94]	8.00, 18.00	11.00 (9.00, 16.75)
Hyposmia/microsmia	27 (48.2%)	28.44 [±4.38]	19.00, 33.00	30.00 (26.00, 32.00)
Normosmia	16 (28.6%)	36.63 [±1.15]	35.00, 39.00	37.00 (36.00, 37.00)
Total SNOT-22 score	69 (100%)	34.78 [±19.18]	5.00, 80.0	33.0 (19.0, 50.5)
Rhinologic symptom domain	69 (100%)	10.96 [±6.18]	0.00, 26.0	11.0 (7.00, 14.0)
Extra-nasal rhinologic symptom domain	69 (100%)	5.70 [±3.65]	0.00, 15.0	5.00 (3.00, 8.00)
Ear/facial symptom domain	69 (100%)	6.52 [±4.31]	0.00, 18.0	5.00 (4.00, 9.00)
Psychological dysfunction domain	69 (100%)	10.32 [±7.75]	0.00, 27.0	10.0 (3.50, 15.0)
Sleep dysfunction domain	69 (100%)	8.72 [±6.51]	0.00, 23.0	8.00 (3.00, 13.5)

Abbreviations: BMI, body mass index; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; CMT, continuing medical management; CT, computed tomography; DM, diabetes mellitus; ESS, endoscopic sinus surgery; FEV, forced expiratory volume; LL, lower limit; *N*, sample size; SD, standard deviation; SIT, Smell Identification Test (UPSIT, Sensonics International, Inc.), SNOT-22, 22-item SinoNasal Outcome Test survey; *Q1*, first quartile; *Q3*, third quartile; UL, upper limit.

TABLE 2 Symptom importance rankings stratified by 22-question SinoNasal Outcome Test (SNOT-22) symptom subdomains of entire cohort of people with cystic fibrosis and comorbid chronic rhinosinusitis ($n = 69$).

SNOT-22 domain	Mean [±SD]	Median (*Q1*, *Q3*)	Score range
Total importance score	44.7 [± 26.4]	43.0 (25.0, 64.0)	0–110
Rhinologic	13.91 [± 7.57]	14.0 (8.0, 19.0)	0–30
Extra-nasal	7.55 [± 4.60]	6.0 (4.0, 12.0)	0–15
Ear/facial	8.46 [± 5.78]	7.0 (4.0, 13.0)	0–25
Psychological	12.52 [± 11.12]	10.0 (2.0, 21.0)	0–35
Sleep dysfunction	10.75 [± 9.03]	10.0 (2.0, 20.0)	0–25

Abbreviations: *Q1*, first quartile; *Q3*, third quartile; SD, standard deviation.

to those who chose CMT were blockage/congestion of nose (ESS: 20, 86.96%; CMT: 28, 60.87%; $p = 0.03$), lack of a good night's sleep (ESS: 14, 60.87%; CMT: 11, 23.91%; $p = 0.004$), waking up tired (ESS: 14, 60.87%; CMT: 13, 28.26%; $p = 0.017$), difficulty falling asleep (ESS: 14, 60.87%; CMT: 7, 15.22%; $p < 0.001$), waking up at night (ESS: 13, 56.52%; CMT: 5, 10.87%; $p < 0.001$), fatigue (ESS: 13, 56.52%; CMT: 13, 28.26%; $p = 0.035$), reduced concentration (ESS: 12, 52.17%; CMT: 11, 23.91%; $p = 0.030$), and reduced productivity (ESS: 12, 52.17%; CMT: 12, 26.09%; $p = 0.059$). No symptoms were ranked as significantly more important to the CMT group compared to the ESS group. Only two symptoms, blockage/congestion of the nose and post-nasal discharge, were among the top five important symptoms in both groups. Symptom importance ratings are detailed in Table 3.

Patients who chose ESS had a significantly higher (median difference [95% CI] = 23.0 [9.0, 35.0]; $p = 0.001$) total symptom importance scores (median [first quartile *Q1*, third quartile *Q3*]: 56.0 [43.0, 80.0]) compared to the CMT group (33.0 [17.3, 51.0]). Those who chose to pursue ESS indicated greater importance (median [*Q1*, *Q3*]) in improvement of extra-nasal (ESS: 10.0 [5.0, 13.0]; CMT: 6.0 [3.0, 11.0]; $p = 0.027$), psychological (ESS: 17.0 [7.0, 26.0]; CMT: 7.0 [0.0, 15.8]; $p = 0.002$), and sleep dysfunction (ESS: 19.0 [12.0, 25.0]; CMT: 4.5 [0.0, 12.8]; $p < 0.0001$) symptom domains. Comparison of total SNOT-22 symptom importance score and symptom importance subdomain scores are described in Figure 2 and Table S1.

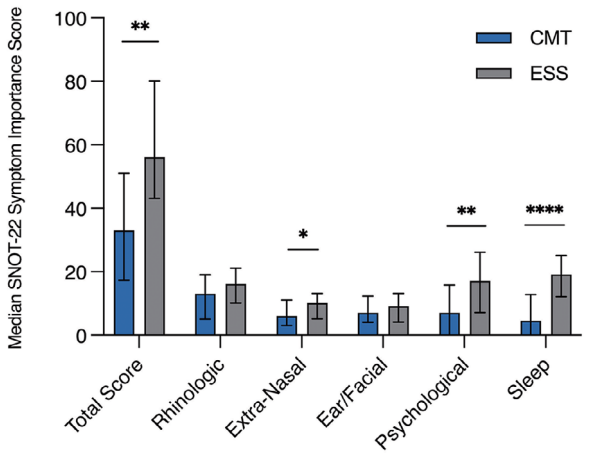

FIGURE 2 Differences in 22-question SinoNasal Outcome Test (SNOT-22) symptom subdomain importance ratings between surgical (endoscopic sinus surgery [ESS], $n = 23$) and medical (continued medical therapy [CMT], $n = 46$) management patients with cystic fibrosis-related chronic rhinosinusitis. Data presented as median scores with interquartile ranges. *p-value < 0.05, **p-value < 0.01, ***p-value < 0.001, ****p-value < 0.0001. Total score, total SNOT-22 symptom importance score.

3.4 | Comparison of SNOT-22 symptom importance ratings between participants on HEMT and not on HEMT

Thirty-five patients in this cohort were on ETI. Of those on ETI, 30 (85.7%) chose CMT, and five (14.3%) chose ESS. For the 34 patients not on ETI, 10 (29.4%) were on other moderately (not highly) effective CFTR modulators. The three PwCF on ivacaftor lacked the G551D mutation, so ivacaftor was not considered highly effective.

No individual symptom in the ETI group was ranked as significantly more important when compared to the non-ETI group. In contrast, the non-ETI group (n, % important) differed from the ETI group in highly rating blockage/congestion of nose (non-ETI: 28, 82.35%; ETI: 20, 57.14%; $p = 0.036$), waking up tired (non-ETI: 18, 52.94% important; ETI: 9, 25.71%; $p = 0.027$), lack of a good night's sleep (non-ETI: 17, 50.00%; ETI: 8, 22.86%; $p = 0.025$), and waking up at night (non-ETI: 13, 38.24%; ETI: 5, 14.29%; $p = 0.03$). Both the non-ETI and ETI groups shared blockage/congestion of the nose (percentages listed above), post-nasal discharge (non-ETI: 17, 50.00%; ETI: 15, 42.86%; $p = 0.63$), and facial pain/pressure (non-ETI: 16, 50.00%; ETI: 13, 37.14%; $p = 0.33$) as top five symptom priorities. The results of ratings are detailed in Table 4.

Consistent with the individual symptom results, sleep dysfunction subdomain showed a trend toward prioritization (median [*Q1*, *Q3*]) in participants not on ETI compared

TABLE 3 People with cystic fibrosis differed in priorities of 22-SinoNasal Outcome Test (SNOT-22) survey symptoms based on electing surgical versus medical management for chronic rhinosinusitis.

	ESS ($n = 23$)			CMT ($n = 46$)				
SNOT-22 symptom	*N* (% important)	Mean [±SD]	Median (*Q*1, *Q*3)	*N* (%)	Mean [±SD]	Median (*Q*1, *Q*3)	Mann–Whitney *U*-test, *p*-values	Fisher's exact test, *p*-value
Blockage/congestion of nose	[1] 20 (86.96%)	4.17 [±1.15]	4.00 (4.00, 5.00)	[1] 28 (60.87%)	3.37 [±1.65]	4.00 (2.25, 5.00)	**0.041**	**0.030**
Lack of a good night's sleep	[2] 14 (60.87%)	3.52 [±1.68]	4.00 (2.00, 5.00)	11 (23.91%)	1.57 [±1.92]	1.00 (0.00, 2.75)	**<0.0001**	**0.004**
Waking up tired	[3] 14 (60.87%)	3.48 [±1.65]	4.00 (2.00, 5.00)	13 (28.26%)	1.93 [±1.95]	1.00 (0.00, 4.00)	**0.002**	**0.017**
Difficulty falling asleep	[4] 14 (60.87%)	3.39 [±1.75]	4.00 (2.50, 5.00)	7 (15.22%)	1.11 [±1.68]	0.00 (0.00, 2.00)	**<0.0001**	**0.0002**
Post-nasal discharge	[5] 13 (56.52%)	3.48 [±1.62]	4.00 (2.50, 5.00)	[2] 19 (41.30%)	2.61 [±1.67]	3.00 (1.00, 4.00)	**0.033**	0.307
Waking up at night	13 (56.52%)	3.30 [±1.77]	4.00 (2.00, 5.00)	5 (10.87%)	1.13 [±1.57]	0.00 (0.00, 2.00)	**<0.0001**	**<0.0001**
Fatigue	13 (56.52%)	3.26 [±1.89]	4.00 (1.50, 5.00)	13 (28.26%)	1.91 [±1.86]	1.50 (0.00, 4.00)	**0.007**	**0.035**
Facial pain/pressure	11 (52.38%)	3.33 [±1.62]	4.00 (2.00, 5.00)	[3] 18 (39.13%)	2.74 [±1.83]	3.00 (1.00, 4.00)	0.210	0.426
Reduced concentration	12 (52.17%)	3.09 [±1.73]	4.00 (2.00, 4.50)	11 (23.91%)	1.59 [±1.90]	1.00 (0.00, 3.00)	**0.002**	**0.03**
Reduced productivity	12 (52.17%)	3.04 [±1.82]	4.00 (2.00, 4.50)	12 (26.09%)	1.65 [±2.00]	1.00 (0.00, 3.75)	**0.010**	0.059
Cough	11 (47.83%)	2.83 [±2.01]	3.00 (1.00, 5.00)	[4] 15 (32.61%)	1.91 [±1.94]	1.00 (0.00, 4.00)	0.075	0.293
Thick nasal discharge	9 (39.13%)	2.91 [±1.68]	3.00 (2.00, 4.50)	[5] 14 (30.43%)	2.20 [±1.87]	2.00 (0.00, 4.00)	0.118	0.589
Sense of smell/taste	9 (39.13%)	2.35 [±2.04]	2.00 (0.00, 4.00)	12 (26.09%)	1.83 [±1.87]	1.50 (0.00, 3.75)	0.280	0.282
Runny nose	8 (34.78%)	2.52 [±1.75]	2.00 (1.00, 4.00)	13 (28.26%)	2.07 [±1.78]	2.00 (0.00, 4.00)	0.302	0.591
Frustrated/restless/irritable	8 (34.78%)	2.52 [±1.90]	3.00 (0.50, 4.00)	7 (15.22%)	1.28 [±1.73]	0.00 (0.00, 2.00)	**0.008**	0.119
Ear fullness	7 (30.43%)	2.17 [±1.83]	1.00 (1.00, 4.00)	9 (19.57%)	1.70 [±1.67]	1.50 (0.00, 3.00)	0.230	0.370
Ear pain	6 (27.27%)	1.77 [±1.93]	1.00 (0.00, 3.75)	6 (13.04%)	1.24 [±1.65]	0.00 (0.00, 3.00)	0.219	0.182
Dizziness	5 (21.74%)	1.26 [±1.86]	0.00 (0.00, 2.50)	4 (8.70%)	1.00 [±1.48]	0.00 (0.00, 2.00)	0.751	0.148
Need to blow nose	4 (17.39%)	2.30 [±1.52]	2.00 (1.00, 3.00)	13 (28.26%)	2.35 [±1.72]	3.00 (1.00, 4.00)	0.884	0.387
Sad	4 (17.39%)	1.52 [±1.86]	1.00 (0.00, 2.50)	5 (10.87%)	0.85 [±1.53]	0.00 (0.00, 1.00)	**0.026**	0.468
Embarrassed	4 (17.39%)	1.09 [±1.73]	0.00 (0.00, 1.50)	4 (8.89%)	0.58 [±1.39]	0.00 (0.00, 0.00)	0.075	0.429
Sneezing	1 (4.35%)	1.17 [±1.40]	1.00 (0.00, 2.00)	5 (10.87%)	1.35 [±1.48]	1.00 (0.00, 2.75)	0.679	0.656

Note: [#] indicates top 5 rankings by % important. % Important includes those who indicated "important" or "very important" on Likert scale. *t*-Test *p*-values compare means. Fisher's exact *p*-values compare % important. Bold values indicate *p*-values less than or equal to 0.05.

Abbreviations: CMT, continued appropriate medical therapy; ESS, endoscopy sinus surgery; *Q*1, first quartile; *Q*3, third quartile; SD, standard deviation; SNOT-22, 22-item SinoNasal Outcome Test survey.

TABLE 4 22-SinoNasal Outcome Test survey symptom importance prioritization in people with cystic fibrosis and chronic rhinosinusitis actively taking highly effective modulator triple combination elexacaftor/tezacaftor/ivacaftor (ETI) versus not taking ETI.

	ETI ($n = 35$)			Non-ETI ($n = 34$)			Mann–Whitney *U*-test, *p*-values	Fisher's exact test, *p*-value
Symptom	***N* (% important)**	**Mean [±SD]**	**Median (*Q*1, *Q*3)**	***N* (% "important" and "very important")**	**Mean [±SD]**	**Median (*Q*1, *Q*3)**		
Blockage/congestion of nose	[1] 20 (57.14%)	3.14 [±1.80]	4.00 (1.00, 5.00)	[1] 28 (82.35%)	4.15 [±1.02]	4.00 (4.00, 5.00)	**0.022**	**0.036**
Post-nasal discharge	[2] 15 (42.86%)	2.74 [±1.63]	3.00 (1.50, 4.00)	[3] 17 (50.00%)	3.06 [±1.76]	3.50 (1.25, 5.00)	0.350	0.632
Cough	[3] 15 (42.86%)	2.34 [±1.95]	3.00 (0.00, 4.00)	11 (32.35%)	2.09 [±2.07]	1.00 (0.00, 4.00)	0.683	0.458
Facial pain/pressure	[4] 13 (37.14%)	2.60 [±1.82]	3.00 (1.00, 4.00)	[4] 16 (50.00%)	3.28 [±1.69]	3.50 (2.00, 5.00)	0.115	0.331
Need to blow nose	[5] 10 (28.57%)	2.29 [±1.86]	2.00 (0.00, 4.00)	7 (20.59%)	2.38 [±1.41]	3.00 (1.00, 3.00)	0.746	0.578
Thick nasal discharge	10 (28.57%)	2.20 [±1.83]	3.00 (0.00, 4.00)	13 (38.24%)	2.68 [±1.82]	2.00 (1.00, 4.75)	0.268	0.450
Runny nose	10 (28.57%)	2.11 [±1.84]	2.00 (0.00, 4.00)	11 (32.35%)	2.32 [±1.72]	2.00 (1.00, 4.00)	0.583	0.797
Fatigue	10 (28.57%)	2.06 [±1.86]	2.00 (0.00, 4.00)	16 (47.06%)	2.68 [±2.04]	3.00 (1.00, 5.00)	0.188	0.140
Sense of smell/taste	10 (28.57%)	1.94 [±1.88]	2.00 (0.00, 4.00)	11 (32.35%)	2.06 [±2.00]	2.00 (0.00, 4.00)	0.831	0.797
Waking up tired	9 (25.71%)	1.94 [±1.80]	2.00 (0.00, 3.50)	[2] 18 (52.94%)	2.97 [±2.05]	4.00 (1.00, 5.00)	**0.017**	**0.027**
Reduced productivity	9 (25.71%)	1.66 [±1.97]	1.00 (0.00, 3.50)	15 (44.12%)	2.59 [±2.03]	3.00 (0.25, 4.75)	0.064	0.134
Reduced concentration	9 (25.71%)	1.66 [±1.95]	1.00 (0.00, 3.50)	14 (41.18%)	2.53 [±1.91]	2.50 (1.00, 4.00)	0.055	0.208
Lack of a good night's sleep	8 (22.86%)	1.69 [±1.81]	1.00 (0.00, 3.00)	[5] 17 (50.00%)	2.76 [±2.16]	3.50 (0.25, 5.00)	**0.034**	**0.025**
Difficulty falling asleep	8 (22.86%)	1.54 [±1.87]	1.00 (0.00, 3.00)	13 (38.24%)	2.21 [±2.11]	2.00 (0.00, 4.00)	0.199	0.198
Ear fullness	7 (20.00%)	1.74 [±1.75]	1.00 (0.00, 3.00)	9 (26.47%)	1.97 [±1.71]	2.00 (0.25, 3.75)	0.511	0.578
Ear pain	7 (20.00%)	1.51 [±1.82]	0.00 (0.00, 3.00)	5 (15.15%)	1.30 [±1.69]	0.00 (0.00, 3.00)	0.749	0.753
Frustrated/restless/irritable	7 (20.00%)	1.46 [±1.87]	0.00 (0.00, 3.00)	8 (23.53%)	1.94 [±1.87]	2.00 (0.00, 3.00)	0.241	0.777
Waking up at night	5 (14.29%)	1.31 [±1.66]	0.00 (0.00, 2.00)	13 (38.24%)	2.41 [±2.05]	2.00 (0.00, 4.75)	**0.017**	**0.030**
Sneezing	4 (11.43%)	1.57 [±1.50]	2.00 (0.00, 3.00)	2 (5.88%)	1.00 [±1.35]	0.00 (0.00, 2.00)	0.087	0.673
Sad	4 (11.43%)	1.00 [±1.59]	0.00 (0.00, 1.50)	5 (14.71%)	1.15 [±1.76]	0.00 (0.00, 1.75)	0.726	0.734
Embarrassed	3 (8.82%)	0.68 [±1.36]	0.00 (0.00, 0.75)	5 (14.71%)	0.82 [±1.68]	0.00 (0.00, 0.00)	0.693	0.709
Dizziness	3 (8.57%)	1.26 [±1.54]	0.00 (0.00, 3.00)	6 (17.65%)	0.91 [±1.68]	0.00 (0.00, 1.00)	0.199	0.306

Note: [#] indicates top 5 rankings by % important. % Important includes those who indicated "important" or "very important" on Likert scale. *t*-Test *p*-values compare means. Fisher's exact *p*-values compare % important. Bold values indicate *p*-values less than or equal to 0.05.

Abbreviations: CMT, continued appropriate medical therapy; non-ETI, not taking ETI; *Q*1, first quartile; *Q*3, third quartile; SD, standard deviation; SNOT-22, 22-item SinoNasal Outcome Test survey.

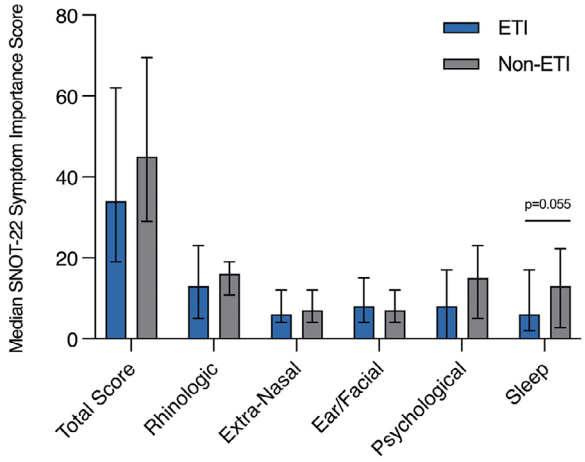

FIGURE 3 Differences in 22-question SinoNasal Outcome Test (SNOT-22) symptom subdomain importance ratings between patients actively taking elexacaftor/tezacaftor/ivacaftor (ETI) ($n = 35$) and those not on ETI ($n = 34$). Data presented as median scores with interquartile ranges. non-ETI, not currently taking ETI; total score, total SNOT-22 symptom importance score.

to those on ETI (non-ETI: 13.0 [2.75, 22.3]; ETI: 6.00 [2.0, 17.0]; $p = 0.055$). Participants on ETI had comparable SNOT-22 total symptom importance scores (median [$Q1$, $Q3$]) to those not on ETI (ETI: 34.00 [19.0, 62.0]; non-ETI: 45.00 [29.0, 69.5]; $p = 0.140$). With the notable exception of the sleep subdomain, all other SNOT-22 symptom subdomains had comparable importance ratings between the two groups (p-values ≥ 0.05). Comparison of total SNOT-22 symptom importance score and subdomain scores are described in Figure 3 and Table S2.

3.5 | Reliability statistics

Internal consistency of the SNOT-22 survey instrument itself has been historically well established[12] and the scale was also found to be highly reliable both within the total cohort ($n = 69$; Cronbach's $\alpha = 0.92$) and for both CMT and ESS treatment modality subgroups (Cronbach's $\alpha = 0.93$ and 0.80, respectively).

4 | DISCUSSION

Bearing in mind patient preferences and personal values as it relates to their clinical treatment can improve patient satisfaction,[14,15] compliance with prescribed therapies,[16] and health outcomes.[17] In patients with complex chronic diseases, incorporation of patients' relative values and areas of importance may help direct therapy, provide better counseling and satisfaction, and inform meaningful selection of clinical trial endpoints.[18]

In this multi-institutional, prospective, observational study, we evaluated relative importance of health status and symptoms in PwCF + CRS. Our cohort prioritized nasal blockage/congestion, post-nasal discharge, and facial pain/pressure; with nasal congestion/blockage and post-nasal discharge consistently ranking as the most important symptoms for treatment improvement across all subgroups. Nasal blockage/congestion is the only symptom that was selected by the majority of participants and subgroups, which not only indicates the severe impact of nasal congestion on quality of life, but also its importance despite the different groups. Sleep dysfunction symptoms such as waking up tired and lack of a good night's sleep were also ranked as high priority for multiple groups: the entire cohort, patients who pursued surgical management, and PwCF not actively taking ETI.

Both CF and non-CF patients with CRS prioritize rhinologic symptom improvement. In non-CF patients undergoing ESS, blockage/congestion of nose, sense of smell/taste, thick nasal discharge, need to blow nose, and post-nasal discharge were the top five symptom priorities.[8] However, PwCF + CRS more highly valued quality of life symptoms that caused psychological dysfunction (e.g., waking up tired and reduced productivity) and sleep dysfunction. Reduced quality of sleep is multifactorial, with CF, CRS, female sex, and depression as individual risk factors all associated with sleep dysfunction.[19–21] The majority of this cohort exhibit one or multiple of these risk factors, which could have influenced their symptom rankings. The 2022 CF Foundation patient registry report indicated anxiety and depression in 29.4% and 29.6% of adult PwCF, respectively, compared to higher rates of 62.7% for self-reported anxiety and 47.8% for self-reported depression in our cohort.[22] The higher rates in this study may be attributed to greater disease burden or the subjective nature of self-reporting as opposed to standardized psychological assessments used in the patient registry report. This study additionally found that SNOT-22 scores were highly correlated to total importance scores, suggesting that greater symptom severity is related to greater patient prioritization for improvement.

Surprisingly, olfactory loss was not identified as a high priority symptom despite a large portion of this cohort having objective olfactory dysfunction. This is substantially different from previous studies evaluating non-CF CRS patients, who considered sense of smell and taste as the second most important symptoms related to their CRS.[8] OD is prevalent in PwCF,[23,24] but understanding why smell is not a top priority in PwCF + CRS requires further investigation.

All PwCF + CRS prioritized rhinologic symptom improvement, but PwCF pursuing ESS valued quality of life symptoms that caused psychological and sleep dysfunction, which were assessed by SNOT-22 importance subdomains. Though differences in prioritization were modest, these findings are supported by our previous work using dedicated outcome measures,[9] which showed that sleep quality (Pittsburgh Sleep Quality Index) and depression (Patient Health Questionnaire 9—Revised) were factors associated with electing ESS. For addressing CRS patients' sleep concerns, surgical treatment significantly improves sleep quality compared to medically managed CRS patients in the non-CF population[25–27]; therefore, evaluating post-surgical outcomes in PwCF + CRS is an area of future work. If sleep and psychological dysfunction-related symptoms are primary motivators for patients electing to pursue surgical intervention, the ability to target these specific domains via other interventions may alleviate the need for surgical intervention.

Our findings are consistent with our previous work, noting that HEMT reduced sinonasal symptom burden and minimized the need for surgical intervention in PwCF + CRS.[9] We aimed to identify what persistent symptoms existed in those on HEMT and to compare these priorities to those not taking HEMT. In our study, participants taking HEMT identified persistent symptoms of nasal congestion, post-nasal discharge, cough, and facial pain/pressure as highest priority for improvement with subsequent treatment. What was absent from the top priorities in PwCF + CRS taking HEMT was prominent sleep dysfunction symptoms, a priority symptom reported among PwCF + CRS not taking HEMT. Differences in priority levels between HEMT versus non-HEMT groups were modest, therefore, additional investigation is required. Preliminary studies have shown that triple combination ETI improves sleep-disordered breathing,[28,29] a common complication in chronic lung disease in PwCF, and improves respiratory muscle strength.[28] There is evidence that ETI may improve sleep in young adults (18–25 years of age) with CF.[30] However, prior studies do not specifically assess ETI's impact on sleep-related quality of life in the context of CF-related CRS. Ivacaftor, the earliest approved CFTR modulator which functions as a chloride channel potentiator, is considered a highly effective therapy in PwCF with G551D variants.[31] Ivacaftor has demonstrated improvement in sleep-related quality of life (difficulty falling asleep, waking up at night, and lack of a good night's sleep) in PwCF + CRS >6 years of age with low symptom burden (75% of cohort with SNOT-20 scores <1).[32] Building on our earlier findings that taking ETI is associated with less need to pursue sinus surgery,[9] this study supports further investigation into HEMT's potential to address sleep concerns and circumvent surgical intervention in CF-related CRS treatment.

Approximately 10% of PwCF are ineligible for HEMT[4] and must rely on other treatment modalities.[22] PwCF who cannot use, lack access to, or cannot tolerate CFTR modulators experience high burden of disease and pronounced impacts on physical, mental, and social well-being.[33] In a survey assessing the perspectives of PwCF not benefiting from CFTR modulators, the current treatment environment has left them feeling scared, neglected, and forgotten.[33] Identifying the persistent symptoms and treatment priorities for non-HEMT individuals not only provides insight into HEMT's disease impact that extends beyond direct medical benefits, but also helps inform clinicians of the unique treatment needs of this subgroup.

The strengths of our study include its multi-center design, permitting a greater sample size, and its prospective design with a comparator group (CMT) for those who underwent ESS. Limitations of our study include the possibility for type 2 error in subgroup comparisons. Some observed between-group differences may not be clinically meaningful and additional work should be considered toward defining clinically important between-group differences for both treatment modalities and ETI/non-ETI users. This can better define potential effect size difference reflective of patient discernment. Referral bias may be present which may limit generalizability.

5 | CONCLUSIONS

This study investigated participant-identified areas of rhinologic symptom importance among PwCF. Nasal congestion, post-nasal discharge, facial pain, awaking tired, and fatigue are critical symptoms. PwCF pursuing surgical management for CRS were more likely to prioritize psychological dysfunction symptoms compared to the medically managed group. PwCF + CRS electing surgery and those not on highly effective modulator therapy had a greater likelihood of reporting sleep-related symptoms as a priority influencing CRS treatment choices.

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CONFLICT OF INTEREST STATEMENT

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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