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RESEARCH NOTE

Objective and patient-based measures of chronic rhinosinusitis in people with cystic fibrosis treated with highly effective modulator therapy

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1 | INTRODUCTION

The highly effective cystic fibrosis transmembrane conductance regulator modulator therapy (HEMT) with elexacaftor/tezacaftor/ivacaftor (ETI) improves pulmonary disease and chronic rhinosinusitis (CRS) in people with cystic fibrosis (PwCF).[1,2] Adequately managing the sinonasal manifestations of CF is critical for maximizing quality of

life (QOL) and optimizing pulmonary status.[3] CRS severity can be quantified by patient-reported, radiographic, and endoscopic methods, with patient-reported and objective measures thought to represent different constructs of disease. Previous evaluations of potential associations between these two assessment categories have been performed primarily in individuals with CRS without CF. Most studies have failed to demonstrate a correlation between symptoms and extent of disease on sinus computed tomography (CT) scan, which can make screening for an accurate diagnosis challenging, although incorporation of additional radiologic details may increase the ability of CT scores to predict symptoms.[4–6]

Correlations between patient-reported outcomes and objective measures of sinonasal disease severity have not been adequately studied in PwCF. Further, studies investigating correlations incorporating radiologic and patient-reported data both before treatment and after intervention are lacking. The aim of this analysis was to investigate potential correlations in changes in measures of sinonasal disease severity measure after treatment with HEMT in PwCF.

2 | PATIENTS AND METHODS

Adults with CRS + CF who were homozgyous for F508del or heterozgyous for F508del/minimal function mutations were prospectively enrolled at a single center in an observational study conducted from August 2019 to October 2020.[2] Subjects provided written informed consent for this institutional review board–approved study. This analysis was conducted using data from a study with the primary aim of assessing the impact of ETI on CRS.[2]

At baseline and after 6 months of ETI treatment, study participants completed outcome measures, including spirometry, sinus CT scans, the 22-item Sino-Nasal Outcome Test (SNOT-22), and the 5-dimenional Euro-Qol Questionnaire (EQ-5D), from which health utility value (HUV) was calculated using pre-existing algorithms.[7] Sinus CT scans were analyzed by a convolutional neural network (CNN) approach, which calculated the percent of total opacification of the sinuses,[8] and were scored using the Lund-Mackay (LM) system by a study-blind rhinologist (D.M.B.). Questionnaires were scored according to published protocols. Statistical analysis, including Pearson testing, was performed to evaluate correlations between outcome measures before and after ETI initiation. $p < 0.05$ was considered statistically significant.

3 | RESULTS

Twenty-five adults with CF completed the study. The cohort had moderate pulmonary disease and substantial CRS and QOL deficit at baseline, and participants had statistically and clinically meaningful improvements across outcomes after ETI initiation ($p < 0.01$) (see Table S1 in the Supporting Information for previously reported detailed data).[2] At baseline, a strong correlation existed between SNOT-22 scores and HUV and between sinus CT opacification via CNN analysis and LM score, and a moderate correlation was present between SNOT-22 scores and the percent of predicted forced expiratory volume in 1 second ($ppFEV_1$) (Fig. 1, left panel). After treatment, a strong correlation remained between SNOT-22 score and HUV and between sinus CT opacification via CNN analysis and LM score (Fig. 1, middle panel). When investigating changes in outcomes with ETI, both correlations remained, yet were modestly weaker (Fig. 1, right panel). There were no correlations between SNOT-22 scores and sinus CT scores using either LM staging or opacification calculated via CNN analysis. When SNOT-22 scores were categorized by subdomain, LM score correlated with the ear/facial pain domain (Table 1).

4 | DISCUSSION

HEMT improves CRS in PwCF across both patient-reported and objective measures of disease.[2,9] Despite improvement in multiple outcomes, no correlations were observed between improvements in sinonasal symptoms and radiologic findings. This finding was unanticipated given the robust improvements seen with ETI in this cohort.[2] However, this result is consistent with previous studies in other populations that primarily demonstrated a lack of correlation between patient-reported and objective measures of CRS severity.[4,5]

In PwCF, upper airway disease worsens lower airway status. The lack of correlation between sinonasal symptoms and radiologic disease in this population, even after treatment with HEMT, suggests that an absence of sinonasal symptoms may not be indicative of a near-normal sinus CT scan. The lack of a correlation between sinonasal symptoms and lung function ($ppFEV_1$) after treatment with ETI further supports this idea.

Findings from this study show consistent correlations between SNOT-22 score and HUV for PwCF treated with ETI over time. DiMango et al demonstrated that CF

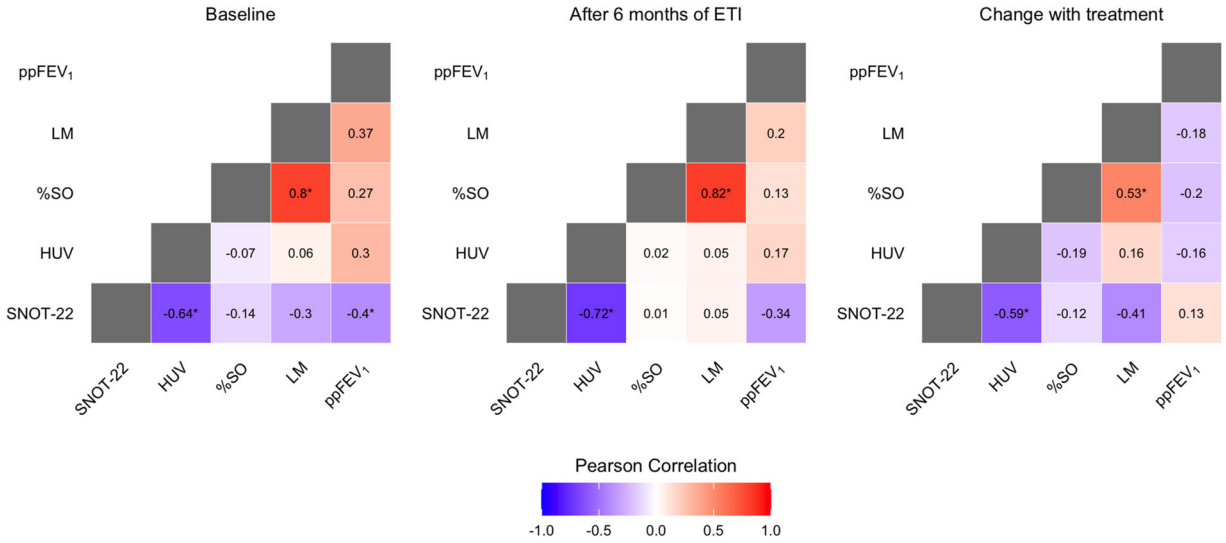

FIGURE 1 Pearson correlation values for outcome measures at baseline (left), at follow-up after 6 months of treatment with ETI (middle), and for the change seen with treatment with ETI (right). The bottom panel demonstrates the color correlation scale. A value in this figure was previously published and was included here to provide a global view of correlations.[2] $^{*}p < 0.05$. Abbreviations: ETI = elexacaftor/tezacaftor/ivacaftor; HUV = health utility value; LM = Lund-Mackay; $ppFEV_1$ = percent of predicted forced expiratory volume in 1 second; SNOT-22 = 22-item Sino-Nasal Outcome Test; %SO = sinus computed tomography opacification assessed via convolutional neural network analysis

TABLE 1 Correlation between change in SNOT-22 domain scores and change in sinus CT scores using two imaging assessment methods after initiation of elexacaftor/tezacaftor/ivacaftor

	Lund-Mackay score		CNN analysis	
SNOT-22 domain	**Pearson coefficient**	***p* value**	**Pearson coefficient**	***p* value**
Rhinologic	−0.07	0.76	−0.03	0.90
Extranasal rhinologic	−0.05	0.81	−0.08	0.69
Ear/facial pain	−0.43	0.03	−0.21	0.31
Psychological dysfunction	−0.35	0.09	0.08	0.69
Sleep dysfunction	−0.39	0.06	−0.11	0.61

Abbreviations: CNN = convolutional neural network; CT = computed tomography; SNOT-22 = 22-item Sino-Nasal Outcome Test.

Questionnaire-Revised Respiratory Domain scores did not correlate with total SNOT-22 scores.[10] Taken together, this suggests that variable correlations exist between sinonasal and general QOL for PwCF.

Earlier work in a non-CF cohort showed that a stronger association between radiologic and patient-reported CRS severity was evident when density-weighted LM scoring, based on Hounsfield units, was incorporated.[6] In this study, there were no correlations between SNOT-22 scores and sinus CT opacification that was precisely calculated via CNN analysis, based on a Hounsfield unit threshold.[8] There was no correlation between SNOT-22 scores and classic LM staging. Although change in the SNOT-22 extranasal rhinologic subdomain was correlated with change in LM score, this should be viewed cautiously, given the possibility of type 1 error and lack of correlations with other total or domain scores.

Overall, these findings highlight the complex relationship in PwCF that exists between sinonasal symptoms, general QOL, and upper and lower airway inflammation. A thorough understanding of these relationships is needed to guide management. Despite robust improvements in CRS with ETI, there were limited correlations between patient-based and objective measures of disease severity at baseline and after treatment. In PwCF, management of both sinonasal symptoms and objective sinus inflammation is critical to optimize QOL and minimize lower airway effects that stem from upper airway disease.

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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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