Sex-based differences in cystic fibrosis pulmonary exacerbations: Subanalysis of the Standardized Treatment of Pulmonary Exacerbations-2 cohort

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Background: Data have shown that women and girls with cystic fibrosis (CF) have higher morbidity and mortality than men and boys, yet evaluations of differences in clinical trials outcomes according to sex in CF are limited. Using the Standardized Treatment of Pulmonary Exacerbations-2 (STOP2) cohort, we examined sex-based differences in pulmonary exacerbation (PEX) outcomes in people with CF treated with intravenous (IV) antibiotics.

Methods: STOP2 was a multi-center, randomized, controlled, clinical trial of treatment duration in adults with CF who received IV antibiotics for a PEx conducted from July 2016 through January 2020. Participants were randomized to 10 vs 14 days of antimicrobials (early robust responder) if they demonstrated predefined lung function and symptom improvements after 7 to 10 days of treatment or were randomized to 14 vs 21 days (non-early robust responders). Aligning with STOP2, our primary outcome was the difference in the sexes in absolute change in percentage predicted forced expiratory volume in 1 second (FEV1pp) from treatment initiation (Visit 1) to 2 weeks after IV antibiotics (Visit 3) using multivariable linear regression models adjusted for trial stratification variables and a priori demographic and clinical characteristics. Secondary endpoints included Chronic Respiratory Infection Symptom Score (CRISS), weight, time to next PEx, and adverse events.

Results: Nine hundred eighty-two participants (496 (50.5%) female) were randomized and constitute the intention to treat population. Overall, women and girls were more likely to have had an IV-treated PEx in the prior year, have higher maximum and average baseline FEV1pp in the prior year, and more likely to be prescribed steroids during STOP2 than men and boys. We found no sex differences in mean FEV1pp decline from 6 months before the study baseline to Visit 1 (difference 1.16; 95% CI, −0.07–2.40). Women and girls had a significantly higher mean FEV1pp than men and boys (52.7% vs 47.0%; p < 0.001) at Visit 1, but there was no difference in FEV1pp change from Visit 1 to Visit 3 between (difference −0.73; 95% CI, −1.78–0.33). Similarly, CRISS was significantly higher (worse) for women and girls than for men and boys at study enrollment (52.3 vs 49.2; p < 0.001), but there was no statistically significant difference in CRISS change from Visit 1 to Visit 3 between the sexes (difference −0.27; 95% CI, −1.94–1.41). Women and girls gained less weight from Visit 1 to Visit 3 (difference between groups −0.73 kg; 95% CI, −1.04, −0.42) and were at greater risk of a subsequent IV-treated PEx (HR 1.26; 95% CI, 1.07–1.47) than men and boys. We found no difference in adverse events (any or serious) according to sex. Results were generally consistent within the early robust responder and non-early robust responders study arms.

Conclusions: Our results suggest that there are sex-related differences in PEx presentation. Women and girls started with a better lung function at treatment initiation yet reported worse respiratory symptoms than men and boys. Although we found no sex difference in lung function or respiratory symptoms after IV antibiotic treatment, female sex was associated with greater risk for future IV-treated PEx. Understanding sex disparities in CF is a priority for the CF community and needs to be further explored in relation to highly effective modulator therapy.

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Patent foramen ovale and oxygenation in patients with cystic fibrosis

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Background: The prevalence of patent foramen ovale (PFO) in the general population is estimated to be around 24% [1]. The prevalence of PFO in people with cystic fibrosis (PwCF) is unknown, but potentially high pulmonary artery pressure in CF could increase shunting through an existing PFO. This study assessed the prevalence of PFO in PwCF and evaluated potential associations with hypoxemia, pulmonary function, and mortality.

Methods: We conducted a retrospective study of PwCF who attended the adult CF center at the University of Utah and had an echocardiogram with bubble study performed. For each PwCF with an echocardiogram with bubble study, we identified 1 or 2 non-CF control patients who were matched in age and sex and had a similar study performed within six months. We used logistic regression and proportional hazards modeling to understand the impact of a PFO in CF.

Results: Of 64 people with CF who had a previous echocardiography with bubble study performed, 35 (55%) had a PFO. Of 93 non-CF age- and sex-matched controls who had echocardiograms with bubble studies performed at a similar time, 32 (34%) had a PFO. In age- and sex-adjusted logistic regression, PwCF were more likely to have a PFO (OR 2.4, p = 0.01). PwCF with PFO were more likely to have hypoxemia (OR 5.1, p = 0.01). With a linear regression model, we did not find an association between PFO and lower percentage predicted forced expiratory volume in 1 second (FEV1pp). Twenty-one PwCF with PFO died between 1998 and 2021. During the same period, 10 PwCF without a PFO died, and four underwent lung transplantation. A proportional hazards regression model did not show that PFO was associated with greater CF mortality or a combined endpoint of death or lung transplantation.

Conclusions: Our study showed that PFO is more common in PwCF than in those without (Figure 1). PwCF with a PFO are more likely to need supplemental oxygen but do not have a lower FEV1pp, suggesting that PFOs are independently associated with hypoxemia and need for supplemental oxygen. We recommend echocardiogram with bubble study at least once in PwCF who require supplemental oxygen. Further study is needed to
understand underlying mechanisms. PFOs had no significant association with survival, although this should be evaluated in a larger study.

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130 Machine-learning approach to estimating percentage predicted forced expiratory volume in 1 second in cystic fibrosis using computed tomography-derived lung parenchymal biomarkers

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Background: Computed tomography (CT) attenuation patterns in the lung become more complex with disease progression in people with cystic fibrosis (PwCF) because of chronic inflammation of lung parenchyma [1]. Although pulmonary function tests (PFTs) are the gold standard for monitoring lung disease in CF, some studies have demonstrated that CT-based radiology scores can detect changes earlier than PFT, suggesting CT sensitivity in CF [2], but obtaining radiology scores is time consuming and subjective. Lung parenchymal biomarkers derived from CT image processing are quick and reproducible and have been demonstrated to quantify parenchymal abnormalities [3]. Our central hypothesis was that imaging biomarkers would have translational applications in CF. To test this hypothesis, we developed a machine learning (ML) model to estimate percentage predicted forced expiratory volume in 1 second (FEV1,pp) in PwCF using CT-derived lung parenchymal measures alone.

Methods: Lung parenchymal biomarkers describing different components of CT attenuation distribution were derived using an in-house-developed automated program and pyradiomics [4]. Individuals with CT and PFTs within 3 months from our CF center were included. We trained ML regression models using decision trees, random forest, and extreme gradient boosting (XGBoost) to estimate FEV1,pp measured using PFT using CT-derived parenchymal measures. The dataset was split 70:30 between training and testing tasks of ML using stratified sampling. Ten-fold cross-validation was used to find the best hyperparameters for each model. Root mean squared error (RMSE) was used to assess ML model performance.

Results: We included 153 PwCF (age 14.3 ± 3.6; 59 male/94 female; FEV1,pp as measured by PFT: 82.8 ± 22.8%). ML regression models were trained on 23 of 121 lung parenchymal measures derived from CT scans, after feature selection. The XGBoost regression model performed best in estimating FEV1,pp (RMSE 6.4%). The ML model error in FEV1,pp is on the same order of repeatability errors in FEV1,pp in spirometry reported in the 2012 NIOSH Spirometry Quality Assurance Study.

Conclusions: This study demonstrates that ML models have translational applications in predicting FEV1,pp in CF. Future studies will further refine this ML model by including clinical data and demographic characteristics and will eventually deploy the model to inform clinical practice.

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References


131 Feasibility of telehealth spirometry for people with cystic fibrosis

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Background: Telemedicine has flourished during the COVID-19 pandemic. There is increasing interest in performing spirometry at home as part of a telehealth program, especially in cystic fibrosis (CF), to follow the course of the disease, but it is unclear whether the quality and accuracy of home spirometry are comparable with those of in-clinic spirometry [1–3]. This study aimed to evaluate the feasibility and measurement quality of telehealth spirometry assessments for people with CF.

Methods: Patients with acceptable hardware at home were provided with a flow sensor portable spirometer (Spirobank Smart) compatible with ATS/ERS 2019 standards for volume accuracy. They performed spirometry during “home admissions” or ongoing home monitoring for 1 year during the COVID–19 pandemic (January 2021 to January 2022). At the end of each session, the family forwarded the data to the CF center.

Results: Twenty-nine people were evaluated (median age 17.4, range 6.7–34; 58% female; mean baseline percentage predicted forced expiratory volume in 1 second 79.8 ± 21.4%). According to American Thoracic Society/European Respiratory Society criteria, spirometry was performed successfully in 320 of 430 (74.5%) attempted sessions. The median distance between the subject’s home and the hospital was 124 km (range 49–418 km)—a median travel time saving of 1.5 hours per hospital visit.

Conclusions: Home-based telehealth spirometry is feasible in people with CF and can support the CF team in ongoing outpatient monitoring.

References


132 Respiratory symptom changes during menstrual cycles in women with cystic fibrosis

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Background: Women with cystic fibrosis (WwCF) have worse outcomes than their male counterparts. After puberty, WwCF have higher rates of pulmonary exacerbations, faster decline in lung function, and poorer nutrition [1]. The etiology of this gender gap is unclear and probably multifactorial; given the estrogen and progesterone receptors in lung tissue, sex hormones and their changes play a role. Inflammatory lung biomarkers and lung function fluctuate during the menstrual cycle of WwCF [2]. With this study, we aimed to determine changes in respiratory symptoms in WwCF throughout their menstrual cycle.

Methods: We included WwCF with regular menstrual cycles who were not taking any hormonal contraceptives. Participants notified the investigator during

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References

