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Poor recovery from a pulmonary exacerbation does not lead to accelerated FEV_1 decline

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Abstract

Background—Patients with CF treated for pulmonary exacerbations (PEx) may experience faster subsequent declines in FEV_1. Additionally, incomplete recovery to baseline FEV_1 occurs frequently following PEx treatment. Whether accelerated declines in FEV_1 are preceded by poor PEx recovery has not been studied.

Methods—From 2004–2011 CF Foundation Patient Registry data, we randomly selected one PEx among patients ≥6 years of age with no organ transplantations, ≥12 months of data before and after the PEx, and ≥1 FEV_1 recorded within the 6 months before and 3 months after the PEx. We defined poor PEx recovery as the best FEV_1 in the 3 months after the PEx <90% of the best FEV_1 in the 6 months before the PEx. We calculated mean (95% CI) hazard ratios (HR) of having >5% predicted/year FEV_1 decline and poor PEx recovery using multi-state Markov models.

Results—From 13,954 PEx, FEV_1 declines of >5% predicted/year were more likely to precede poor spirometric recovery, HR 1.17 (1.08, 1.26), in Markov models adjusted for age and sex. Non-Responders were less likely to have a subsequent fast FEV_1 decline, HR 0.41 (0.37, 0.46), than patients who recovered to >90% of baseline FEV_1 following PEx treatment.

Conclusions—Accelerated declines in FEV_1 are more likely to precede a PEx with poor recovery than to occur in the following year. Preventing or halting declines in FEV_1 may also have the benefit of preventing PEx episodes.

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1. Introduction

Pulmonary exacerbations (PEx) treated with intravenous (IV) antibiotics in patients with cystic fibrosis (CF) are associated with increased mortality, worsening forced expiratory volume in one second (FEV_1), poorer quality of life, and increased healthcare costs (1–4). Epidemiologic studies have shown that patients with CF may have a faster subsequent decline in FEV_1 after PEx treatment (5, 6). Studies have also shown that patients frequently do not recover to near their previous spirometry baseline following a PEx (7–10). The timing of these events is important in order to target prevention and treatment strategies: if PEx contribute to accelerating FEV_1 decline, then preventing or improving outcomes after PExs should be a focus. On the other hand, if larger FEV_1 declines typically precede PEx treatments, then anticipating a PEx by preventing declines in FEV_1 should be a focus. We hypothesized that patients who experienced poor recovery of FEV_1 following treatment with IV antibiotics for a PEx would be more likely to have an accelerated subsequent decline in FEV_1.

2. Methods

Data were obtained from the CF Foundation Patient Registry (CFFPR) between 2004 and 2011. Written informed consent and assent was obtained for data to be included in the CFFPR and the Institutional Review Board of the University of Wisconsin approved the study. For this analysis, we included one PEx randomly selected for each patient ≥6 years of age if the patient had not had an organ transplantation, there was at least 12 months of data available before and after the selected PEx, and there was at least one measurement of FEV_1 recorded within the 6 months before and 3 months after the PEx. Patients were defined as Non-Responders if their best FEV_1 in the 3 months after the PEx was <90% of the best FEV_1 in the 6 months before the PEx. We excluded PEx episodes where another PEx occurred before the best FEV_1 in the 3 months following the PEx. We used linear regression to determine the annual change in FEV_1 for each individual patient in the 12 months before and 12 months after the PEx using all measurements of FEV_1 excluding measurements that occurred during the PEx. An accelerated decline of FEV_1 referred to hereafter as “fast FEV_1 decline” was defined as >5% predicted in the year before or after the PEx; this value represents more than double estimates of the average annual decline in FEV_1 (2, 11).

PEx recovery and FEV_1 declines were modeled using multi-state Markov models (12, 13). Multistate Markov models can be used to describe how an individual moves through a series of disease states over time. CF lung disease is only observed at arbitrary times (i.e., clinic visits, hospitalizations), so that the exact times when the disease state changes are unobserved. In Markov models, the next disease state to which the individual moves, or “transitions,” and the timing of the change, are governed by a set of transition intensities, or probabilities, for each pair of states. These transition intensities represent the instantaneous risks of moving from one state to another, and may depend on the time of the process, and on individual characteristics such as patient age and sex. Once the Markov model is fitted, the ratio of the transition intensities can be used to determine whether one state transition is more likely than another. The Markov model assumes all patients begin in the same disease state. Once patients progress into a new disease state, they do not transition back.

For our study, we compared the likelihood of transitioning from a slow to fast FEV_1 decline and to being a Non-Responder after PEx treatment (Figure 1). Since, if monitored continuously, a transition to a fast FEV_1 decline and to being a Non-Responder would not happen simultaneously, our Markov model did not allow direct transitions from disease state 1 (neither a fast FEV_1 decline nor a Non-Responder) to disease state 4 (fast FEV_1 decline and Non-Responder). Once patients were classified as having a fast decline in FEV_1 or being a Non-Responder, they could not transition back to their previous categorization. The likelihoods of moving from one disease state to another were modeled using log-linear models adjusted for age and sex. Differences in the intercepts of these models represent the effects of FEV_1 decline on PEx recovery and vice versa. Estimates from the models are exponentiated and interpreted as hazard ratios (HR). Analyses were conducted with SAS (Version 9.4, SAS Institute Inc, Cary, NC, USA, 2013) and R (version 3.2.1, the R Foundation for Statistical Computing, Vienna, Austria, 2015).

3. Results

There were 35,516 patients with 197,085 hospitalizations and/or home courses of IV antibiotics recorded in the CFFPR in 2004–2011. Of these, Responder status could be determined for 13,954 PExs (1 per patient) that met inclusion/exclusion criteria were randomly chosen (Figure E1 online supplement). Cohort characteristics are included in Table 1. Comparing the best values of FEV_1 before and after the analyzed PEx, 19.8% of patients were classified as Non-Responders. Non-Responders were more likely to be adult patients, undernourished, on Medicaid/state insurance, have persistent infections with *Pseudomonas aeruginosa* and mucoid *P. aeruginosa*, have baseline FEV_1 <80% predicted, and have CF-related diabetes (Table 1).

The mean (SD) best FEV_1 recorded in the 6 months prior to the PEx was 70 (26)% predicted. Annual declines in FEV_1 could be determined for 13,774 patients prior to the PEx and 13,953 patients following the PEx, using a mean of 5.3 and 6.0 FEV_1 measurements, respectively. The median annual decline in FEV_1 was −4.3% predicted in the year prior to the PEx and −2.6% predicted in the year after the PEx. Forty-eight percent of patients had >5% predicted annual decline in FEV_1 before the PEx and 40% of patients had >5% predicted decline in FEV_1 after the PEx. Patients with declines >5% predicted in the year prior to the PEx were generally similar to patients with declines ≤5% predicted (see online supplement Table E1). At the completion of the study, only 23% of patients were neither Non-Responders nor had a fast decline in FEV_1.

To determine if being a Non-Responder was more likely to precede or follow a fast FEV_1 decline, we compared the probability of moving from State 3 (fast FEV_1 decline only) to State 4 (fast FEV_1 decline and Non-Responder) to the probability of moving from State 1 (neither) to State 2 (Non-Responder only) (Figure 1). Patients who were Non-Responders at the time of the analyzed PEx were at lower risk of having a subsequent fast decline of FEV_1 than patients who were Responders, HR 0.41 (95% CI 0.37, 0.46).

To determine if having a fast decline in FEV_1 was more likely to precede being a Non-Responder, we compared the probability of moving from State 2 (Non-Responder only) to

State 4 (fast FEV_1 decline and Non-Responder) to the probability of moving from State 1 (neither) to State 3 (fast FEV_1 decline only). Patients with a fast decline in FEV_1 in the year prior to the analyzed PEx were at increased risk of being Non-Responders than patients without a fast FEV_1 decline, HR 1.17 (95% CI 1.08, 1.26).

Results were similar for pediatric and adult patients, and if we used a cut-off of >3% predicted/year to define fast FEV_1 decline (data not shown). In the year prior to the analyzed PEx, 8,069 patients had 0–1 PEx and 5,885 had ≥2 PEx episodes. Patients with 0–1 and ≥2 PEx episodes in the prior year had similar rates of annual FEV_1 decline prior to the analyzed PEx. Hazard ratios were similar to the overall cohort, indicating that, regardless of the number of PEx in the prior-year, patients who had a fast decline prior to the analyzed PEx were at increased risk of being Non-Responders and patients who were Non-Responders at the analyzed PEx were at low risk of having a subsequent fast decline in FEV_1.

4. Discussion

Epidemiologic studies have demonstrated that pulmonary exacerbations treated with IV antibiotics are associated with both acute declines in FEV_1 and accelerated subsequent FEV_1 declines (5, 6, 14). Physiologic changes that may occur following a PEx, e.g., changes in the inflammatory milieu (15), changes in the microbiota (16), and incomplete spirometric recovery, suggest that PEx episodes may lead to further poor outcomes. For example, the number of prior PEx is the greatest risk factor for having another PEx treated with IV antibiotics (17). In this report, we have attempted to identify whether an accelerated decline in FEV_1 or poor spirometric recovery following a PEx is more likely to occur first. We found that having a fast decline in FEV_1 is more likely to precede a PEx. This would suggest that efforts to avoid or halt declines in FEV_1 will have the added benefit of preventing PEx and the many adverse effects associated with PEx. Acute declines in FEV_1 are common and often do not lead to treatment with IV antibiotics (14). By monitoring and treating these acute declines in FEV_1clinicians have a significant opportunity to avoid acute PEx and long-term progression of CF lung disease.

There are limitations to our study. The Markov model assumes that patients are neither Non-Responders, nor are experiencing fast declines in FEV_1 at the start of the study period. However, we are not able to verify that that is the case. In part to avoid indication bias, we used an annual decline of FEV_1 and excluded measurements of FEV_1 that occurred during the PEx. However, it is possible that acute or subacute decreases in FEV_1 that preceded the PEx are still captured with our definition of FEV_1 decline. Moreover, compartmentalizing changes in FEV_1 to before, during, and after PExs is an artificial construct necessary for this type of analysis. Others have estimated the degree of overall loss of FEV_1 that is attributable to PEx (5). The mean annual declines in FEV_1 (−4.3% predicted prior to the PEx and −2.6% predicted after the PEx) are higher than typically reported. This is because in order to use the Markov model, it was necessary to calculate the annual FEV_1 decline for each individual separately. The corresponding mean annual declines in FEV_1 for the study cohort were −1.1% predicted before and after the PEx, similar to other recent reports that have used data from the CFFPR (2, 18, 19). In addition, this is an observational study, so we cannot make conclusions about causation. FEV_1 measurements are entered into the CFFPR at irregular

intervals and may not represent a patient's best possible values. We excluded PEx if another PEx occurred before the best FEV_1 in the 3 months following the analyzed PEx was recorded, so our results may not apply to patients with short intervals between PEx, who may be at higher risk of accelerated FEV_1 decline (5).

In conclusion, an accelerated decline of FEV_1 is more likely to precede poor spirometric recovery from a PEx than to occur in the year following the PEx. Interventional studies designed to prevent PEx should consider strategies to prevent or halt declines in FEV_1. Insights from our observations also support current efforts to monitor FEV_1 regularly and closely once CF lung disease develops.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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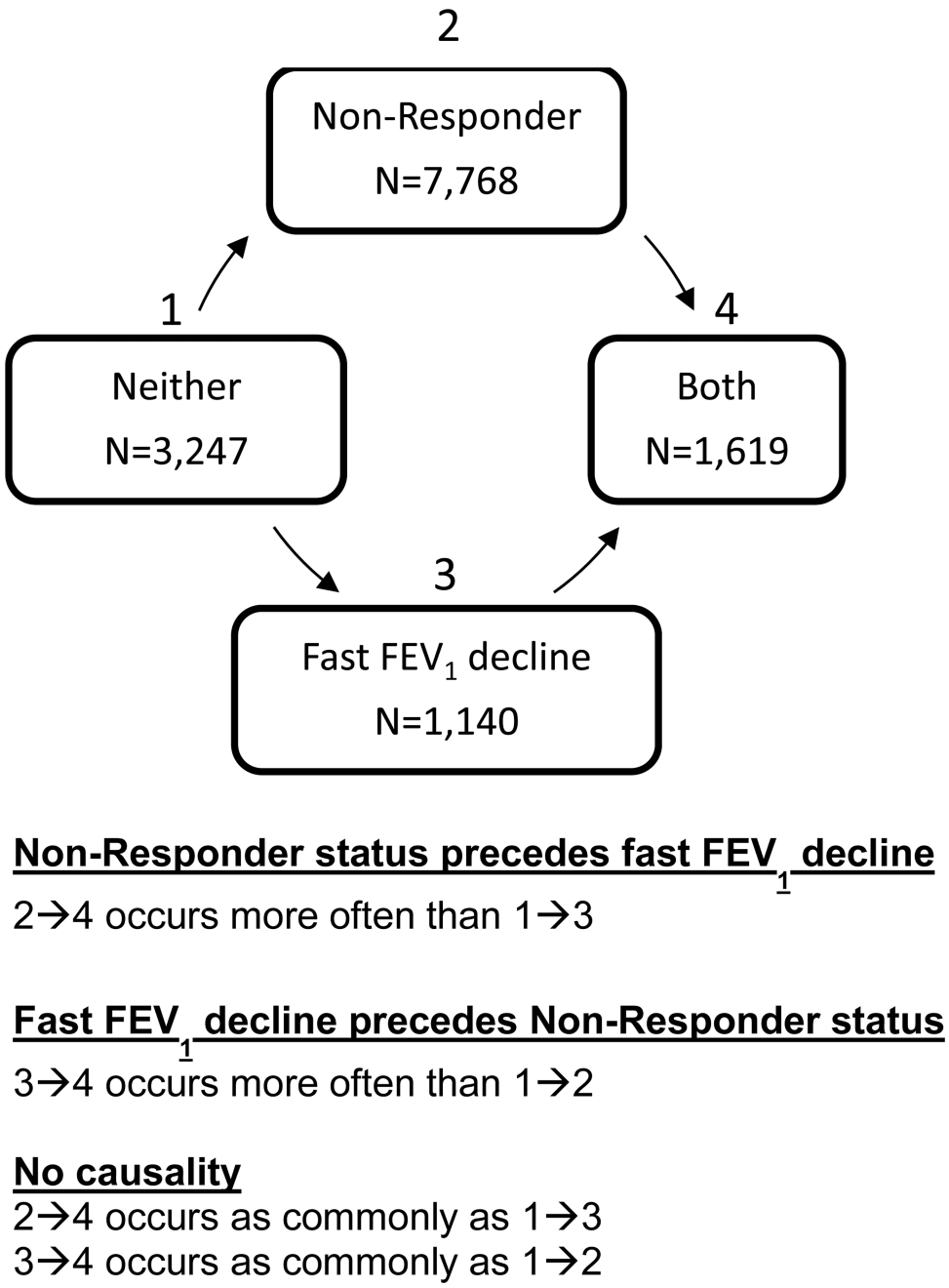

Figure 1.

Four-state longitudinal model assessing temporal relationships between PEx response and FEV_1 decline. Patients were assessed before and after a randomly selected PEx and classified into one of these four disease states. The relative probability of moving from one state to another suggests the temporal relationship between these events. N represents the number of patients in each disease state at the end of the study.

Table 1

Cohort characteristics according to Responder status

Characteristic	Responders (n=11,192) N (%) or mean (SD)	Non-Responders (n=2,762) N(%) or mean (SD)	Total (n=13,954) N (%) or mean (SD)
Female sex	5,654 (50.5)	1,441 (52.2)	7,095 (50.9)
Age (all patients)	20.8 (11.3)	23.1 (11.0)	21.2 (11.2)
Age (pediatric patients)	12.2 (3.5)	12.7 (3.6)	12.3 (3.5)
Adult patients (≥18 years old)	5,674 (50.7)	1,803 (65.3)	7,477 (53.6)
Age (adult patients)	29.1 (9.9)	28.7 (9.4)	29.0 (9.8)
Undernourished[a]	1,506 (13.5)	633 (22.9)	2,139 (15.3)
BMI percentile (pediatric patients)	43.3 (26.7)	36.7 (27.6)	42.3 (26.9)
BMI (adult patients)	21.7 (3.6)	20.9 (5.0)	21.5 (4.0)
Pancreatic enzyme replacement therapy	10,471 (93.6)	2,608 (94.4)	13,079 (93.7)
Homozygous F508del	5,478 (48.9)	1,330 (48.1)	6,808 (48.8)
Heterozygous F508del	3,977 (35.5)	983 (35.6)	4,960 (35.6)
Other/Unknown mutations	1,737 (15.5)	449 (16.3)	2,186 (15.7)
Medicaid/state insurance	5,169 (46.2)	1,478 (53.5)	6,647 (47.6)
Persistent *P. aeruginosa* infection[a]	5,540 (49.5)	1,642 (59.6)	7,182 (51.5)
Persistent *B. cepacia* complex infection[a]	296 (2.6)	114 (4.1)	410 (2.9)
Persistent mucoid *P. aerginosa* infection[a]	3,921 (35.0)	1,221 (44.2)	5,142 (36.9)
Persistent MRSA infection[a]	2,275 (20.3)	659 (23.9)	2,934 (21.0)
Nontuberculous *Mycobacteria*	264 (2.4)	73 (2.6)	337 (2.4)
Allergic bronchopulmonary aspergillosis (ABPA)	815 (7.3)	238 (8.6)	1,053 (7.5)
Baseline FEV_1			
<40% predicted	1,629 (14.6)	618 (22.4)	2,247 (16.1)
40–59% predicted	2,092 (18.7)	713 (25.8)	2,805 (20.1)
60–79% predicted	2,775 (24.8)	617 (22.3)	3,392 (24.3)
≥80% predicted	4,691 (41.9)	814 (29.5)	5,505 (39.5)
CF-related diabetes mellitus	2,314 (20.7)	803 (29.1)	3,117 (22.3)
Time between baseline and start of IV antibiotics (weeks)	11.9 (8.3)	14.6 (7.7)	12.4 (8.2)
Change in FEV_1 % predicted from baseline to start of IV antibiotics[b]	−13.1 (14.3)	−23.9 (16.4)	−15.1 (15.3)
PExs treated with IV antibiotics in the previous 12 months	1.6 (1.1)	2.3 (1.5)	1.8 (1.2)
Duration of PEx treatment (days)	15.5 (15.3)	18.2 (22.3)	16.0 (16.9)

[a]Persistent infection defined as ≥2 positive culture in the 12 months before the PEx

[b]Baseline defined as the best FEV_1 % predicted in the 6 months before the PEx among 7,678 patients with FEV_1 measured within 3 days of the start of IV antibiotics