BRIEF REPORT

Rate of Lung Function Decline in People with Cystic Fibrosis Having a Residual Function Gene Mutation

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ABSTRACT

Introduction: Cystic fibrosis (CF) is an autosomal recessive disease caused by mutations in the CF transmembrane conductance regulator (*CFTR*) gene. Approximately 5% of people with CF have residual function (RF) *CFTR* mutations that result in partially retained CFTR activity.

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Published literature on disease trajectory among those with RF mutations is limited. In this retrospective study, we characterized lung function decline across different age groups in CFTR modulator-untreated people with CF heterozygous for *F508del* and an RF mutation (*F*/RF).

Methods: Rate of decline in percent predicted forced expiratory volume in 1 s (ppFEV$_1$) was analyzed using data from the US CF Foundation Patient Registry (2006–2014) in *F*/RF (all), *F*/RF (excluding *R117H*), and *F508del* homozygous (*F/F*) cohorts. Annual rates of ppFEV$_1$ decline were estimated over 2-year periods based on

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calendar year. Subgroup analyses by age [6–12 (children), 13–17 (adolescents), 18–24 (young adults), and ≥ 25 years (adults)] were performed.

Results: The estimated annualized rate of ppFEV$_1$ decline was − 0.70 percentage points per year (95% CI −1.09, −0.30) in the *F/RF* (all) cohort (N = 1242) versus −1.91 percentage points per year (95% CI −2.01, −1.80) in the *F/F* cohort (N = 11,916) [difference, 1.29 percentage points per year (95% CI 0.88, 1.70); *P* < 0.001]. In the *F/RF* (all) cohort, all age groups demonstrated lung function decline ranging from −0.30 to −1.38. In the *F/RF* (excluding *R117H*) cohort, the rate of decline was −1.05 percentage points per year (95% CI −1.51, −0.60) [difference versus *F/F* cohort, 0.95 percentage points per year (95% CI 0.48, 1.41; *P* < 0.001); not statistically significant in children and young adults].

Conclusion: Progressive lung function decline was observed in people with *F/RF* genotypes across all assessed age groups, reinforcing the importance of early intervention and clinical monitoring to preserve lung function in all people with CF.

PLAIN LANGUAGE SUMMARY

In people with cystic fibrosis, lung function typically decreases over time and is linked to the severity of the disease. How fast lung function decreases (referred to as the rate of lung function decline) in cystic fibrosis depends on the specific mutations (changes) in the *CFTR* gene (which causes the disease). Lung function decline has been well studied in some mutation groups, but not many previous studies have looked at lung function decline in people with one copy of the *F508del-CFTR* mutation (which is the most common *CFTR* mutation and results in little to no functional CFTR protein) and another *CFTR* mutation called a residual function mutation (referred to as people with *F/RF* genotypes). We used data from the US Cystic Fibrosis Foundation Patient Registry (which collects information on the health of people in the USA who have cystic fibrosis), to look at the rate of lung function decline in people with *F/RF* genotypes. We found that people with cystic fibrosis who have *F/RF* genotypes experience lung function loss over time. We also found that this lung function loss occurred in people of all ages with *F/RF* genotypes. This finding supports the importance of early treatment to help prevent lung function loss in all people with cystic fibrosis, including people with *F/RF* genotypes.

Key Summary Points

Although approximately 5% of people with cystic fibrosis (CF) have residual function (RF) *CFTR* mutations, published data on disease trajectory in this population is limited

This retrospective study characterized lung function decline in CFTR modulator-untreated patients who were heterozygous for *F508del-CFTR* and an RF mutation (*F/RF* genotypes) compared with patients who were homozygous for *F508del-CFTR* (*F/F* genotype)

Lung function decline was observed in all age groups of patients with *F/RF* genotypes

Findings reinforce the importance of early intervention to preserve lung function in all people with CF, including those with *F/RF* genotypes

INTRODUCTION

Cystic fibrosis (CF) is a progressive, life-shortening, multisystem, autosomal recessive disease affecting > 80,000 people worldwide [1]. CF is caused by mutations in the CF transmembrane

conductance regulator (*CFTR*) gene that result in reduced quantity and/or function of CFTR protein [1, 2]. Loss of chloride transport activity can lead to various clinical manifestations, including mucus accumulation in the airways, pulmonary exacerbations, reduced lung function, exocrine pancreatic insufficiency, intestinal malabsorption, reproductive dysfunction, and elevated sweat chloride concentration [1]. Disease severity and rate of progression vary in people with CF and may be determined in part by the extent of chloride transport loss associated with each mutation [3–6]. Lung function and its rate of decline are important clinical outcomes in CF [5, 7].

Approximately 5% of people with CF have residual function (RF) *CFTR* mutations that exhibit residual CFTR-mediated ion transport due to partially retained CFTR activity [6, 8]. Those with RF mutations are most frequently heterozygous with an *F508del-CFTR* mutation (*F*/RF genotypes) [9], although RF mutations may be found in combination with other mutations. *F*/RF genotypes can result in a range of molecular defects, including reduced or variable synthesis of CFTR channels, moderate defects in CFTR processing and trafficking, impaired channel gating, and altered channel conductance [10–12]. These defects result in a reduced quantity of normal CFTR channels at the cell surface or a normal quantity of CFTR channels at the cell surface that exhibit reduced chloride ion transport ability [8, 13–15]. Compared with people with CF who are homozygous for *F508del-CFTR* (*F/F* genotype), those with *F*/RF genotypes—including those with the most common RF mutation, *R117H*—may have slower disease progression and are more likely to be pancreatic sufficient and have lower sweat chloride concentrations, indicative of partially maintained CFTR activity [10, 16, 17]. Nevertheless, people with CF who have *F*/RF genotypes have been shown to develop progressive lung disease with age and die prematurely [6].

As published literature on the disease trajectory in people with CF with RF mutations is limited, we sought to characterize lung function decline in a CFTR modulator-untreated cohort of people with CF with *F*/RF genotypes compared with that in people with the *F/F* genotype. Here, we report the findings from a retrospective study of longitudinal registry data evaluating the rate of percent predicted forced expiratory volume in 1 s (ppFEV$_1$) decline in people with CF with *F*/RF genotypes.

METHODS

Analysis Population

Data from participants in the US Cystic Fibrosis Foundation Patient Registry (CFFPR) [18] from 2006 to 2014 were used to assess lung function in people with CF with *F*/RF and *F/F* genotypes, none of whom were receiving CFTR modulator therapy during this study period. RF mutations were identified based on clinical or in vitro evidence of residual ion transport. RF mutations are listed in the Supplementary Material (Table S1). Individuals were excluded if they had presumed CF-related metabolic syndrome, in which an *R117H* mutation was detected by newborn screening and sweat chloride level was < 60 mmol/L or no sweat test result was recorded. Clinic encounters recorded in the 2006–2014 period were censored at death, lung transplant, ivacaftor treatment initiation, or last encounter, whichever occurred first. The study included individuals who had a qualifying genotype, were aged 6–45 years, and had ≥ 3 ppFEV$_1$ measurements spanning ≥ 0.5 years in a randomly chosen two-calendar year period beginning at the first ppFEV$_1$ measurement in the calendar year.

Analysis was performed in three subpopulations: (1) *F/F*; (2) *F*/RF (all), comprising participants with *F508del* on one allele and any RF mutation on the second allele; and (3) *F*/RF (excluding *R117H*), comprising participants with *F508del* on one allele and any RF mutation except *R117H* on the second allele. In each subpopulation, the following age groups were analyzed: 6–12 (children), 13–17 (adolescents), 18–24 (young adults), and ≥ 25 years (adults). Inclusion age in the study was between 6 and 45 years to ensure balanced proportions of participants with *F*/RF and *F/F* genotypes in each age group.

Data Analysis

Initially, the 2006–2014 period was divided into overlapping two-calendar year periods (i.e., 2006–2007, 2007–2008 ... 2013–2014). We identified analyzable periods in which individuals had ≥ 3 ppFEV$_1$ measurements spanning ≥ 0.5 years in a randomly chosen 2-year period beginning at the first ppFEV$_1$ measurement in the calendar year. Age was defined as age at the first encounter (i.e., baseline) in each of these randomly chosen 2-year periods.

Demographic and baseline clinical characteristics were descriptively summarized for each subpopulation. The *F/F* subpopulation was compared with the other two subpopulations using the *t*-test for continuous measurements and chi-square test for discrete measurements.

The intercept and slope (rate of change) of ppFEV$_1$, based on 2012 Global Lung Initiative equations [19], were estimated over 2-year periods using all available measurements. Two repeated-measures models were developed: one comparing *F/F* with *F*/RF (all) and one comparing *F/F* with *F*/RF (excluding *R117H*). The dependent variable was ppFEV$_1$, with mutation group, age group, calendar year, and time (years since baseline) as fixed effects. All interaction terms, except those with both age group and calendar year, were included. Compound symmetry was specified as the covariance structure to account for correlated data within each individual. The intercept and slope estimates were calculated overall and by each age group from these models. The proportion of participants in each age group was used to calculate the overall values.

Sensitivity analyses using Wang–Hankinson equations [20, 21] for ppFEV$_1$ were also performed.

All statistical tests were two sided. *P*-values ≤ 0.05 were considered statistically significant. The analysis was performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).

Compliance with Ethical Guidelines

This study was conducted in accordance with the current Good Clinical Practice Guidelines as described by the International Council for Harmonisation, the Declaration of Helsinki, and all applicable local regulations. People with CF provided informed consent to participate in the US Cystic Fibrosis Foundation Patient Registry and to have their data included in the registry. The study did not involve primary data collection and used only de-identified data; thus, institutional review board approval was not required.

RESULTS

Participants and Baseline Characteristics

A total of 1242 participants with *F*/RF genotypes and 11,916 with the *F/F* genotype were included in the analysis. The most common RF mutations were *R117H* [$n = 353$ (28.4%)], $3849 + 10KBC \rightarrow T$ [$n = 228$ (18.4%)], and $2789 + 5G \rightarrow A$ [$n = 206$ (16.6%)] (Supplementary Material, Table S1). The mean (SD) baseline ppFEV$_1$ was 80.4 (24.8), 78.6 (25.3), and 73.4 (26.5) percentage points (Table 1), respectively, in the *F*/RF (all), *F*/RF (excluding *R117H*), and *F/F* cohorts. *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Aspergillus*, *Stenotrophomonas maltophilia*, and *Burkholderia cepacia* were detected in all genotype groups at baseline (Table 1). The *F*/RF (all) cohort had significantly lower rates of *P. aeruginosa* ($P < 0.001$), *Aspergillus* ($P < 0.001$), *B. cepacia* ($P < 0.001$), *S. maltophilia* ($P < 0.01$), and *S. aureus* ($P < 0.05$) than the *F/F* cohort, whereas rates were more similar between the *F*/RF (excluding *R117H*) and *F/F* cohorts (Table 1).

Lung Function

The *F*/RF (all) cohort exhibited progressive lung function loss, with an estimated annualized ppFEV$_1$ rate of decline of -0.70 percentage points per year (95% CI -1.09, -0.30). When

Table 1 Demographic and Clinical Characteristics, by Mutation

Characteristic	F/F ($n = 11{,}916$)	F/RF (all) ($n = 1242$)	P-value[a]	F/RF (excluding $R117H$) ($n = 889$)	P-value[b]
Age, years, mean (SD)	18.0 (9.6)	23.0 (12.1)	< 0.001	23.6 (11.8)	< 0.001
Female, n (%)	5698 (47.8)	645 (51.9)	0.006	473 (53.2)	0.002
Height-for-age z-score, mean (SD)	−0.49 (1.03)	0.04 (1.03)	< 0.001	−0.01 (1.02)	< 0.001
Weight-for-age z-score, mean (SD)	−0.48 (1.11)	0.36 (1.14)	< 0.001	0.29 (1.15)	< 0.001
BMI-for-age z-score, mean (SD)	−0.29 (1.08)	0.36 (1.09)	< 0.001	0.29 (1.10)	< 0.001
$ppFEV_1$ at baseline visit, %, mean (SD)	73.4 (26.5)	80.4 (24.8)	< 0.001	78.6 (25.3)	< 0.001
Patients with positive microbiology n (%)[c]					
Staphylococcus aureus	5386 (45.2)	524 (42.2)	0.042	402 (45.2)	0.99
Pseudomonas aeruginosa	4131 (34.7)	277 (22.3)	< 0.001	234 (26.3)	< 0.001
Haemophilus influenzae	662 (5.6)	69 (5.6)	1.00	49 (5.5)	0.96
Aspergillus species	688 (5.8)	42 (3.4)	< 0.001	32 (3.6)	0.007
Stenotrophomonas maltophilia	677 (5.7)	48 (3.9)	0.008	38 (4.3)	0.078
Burkholderia cepacia	237 (2.0)	7 (0.6)	< 0.001	7 (0.8)	0.012

BMI body mass index, *F* F508del, *ppFEV₁* percent predicted forced expiratory volume in 1 s, *RF* residual function
[a]*F*/F versus *F*/RF (all)
[b]*F*/F versus *F*/RF (excluding *R117H*)
[c]At first visit in the 2-year period

participants with an *R117H* mutation were excluded, the rate of decline was −1.05 percentage points per year (95% CI −1.51, −0.60). The rate of decline in the *F*/F cohort was −1.91 percentage points per year (95% CI −2.01, −1.80). The difference in the annual rate of decline between the *F*/RF (all) cohort and the *F*/F cohort was 1.29 percentage points per year (95% CI 0.88, 1.70; *P* < 0.001; Fig. 1), and the difference between the *F*/RF (excluding *R117H*) cohort and the *F*/F cohort was 0.95 percentage points per year (95% CI 0.48, 1.41; *P* < 0.001).

The *F*/RF genotype cohorts [*F*/RF (all) and *F*/RF (excluding *R117H*)] demonstrated lung function decline in all age groups (Fig. 2). The rates of decline in children with *F*/RF (all) and *F*/RF (excluding *R117H*) genotypes were −0.30 (95% CI −0.93, 0.34) and −0.80 (95% CI

−1.58, −0.02) percentage points per year, respectively (Fig. 2). These were similar to the rates of lung function decline in adolescents [*F*/RF (all), −0.30 (95% CI −1.05, 0.45) percentage points per year; *F*/RF (excluding *R117H*), −0.57 (95% CI −1.41, 0.28) percentage points per year] (Fig. 2). In young adults and adults, the rates of lung function decline were greater in magnitude, with rates of −1.38 (95% CI −2.14, −0.61) and −0.94 (95% CI −1.45, −0.44) percentage points per year in the *F*/RF (all) cohort and −1.85 (95% CI −2.69, −1.01) and −1.06 (95% CI −1.64, −0.48) percentage points per year in the *F*/RF (excluding *R117H*) cohort, respectively. Although the rates of decline were slower for all age groups in the *F*/RF (all) cohort than in the *F*/F cohort, rates between the *F*/RF (excluding
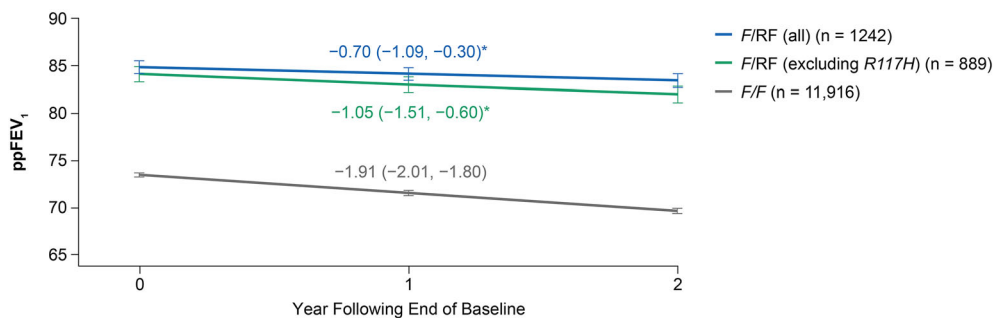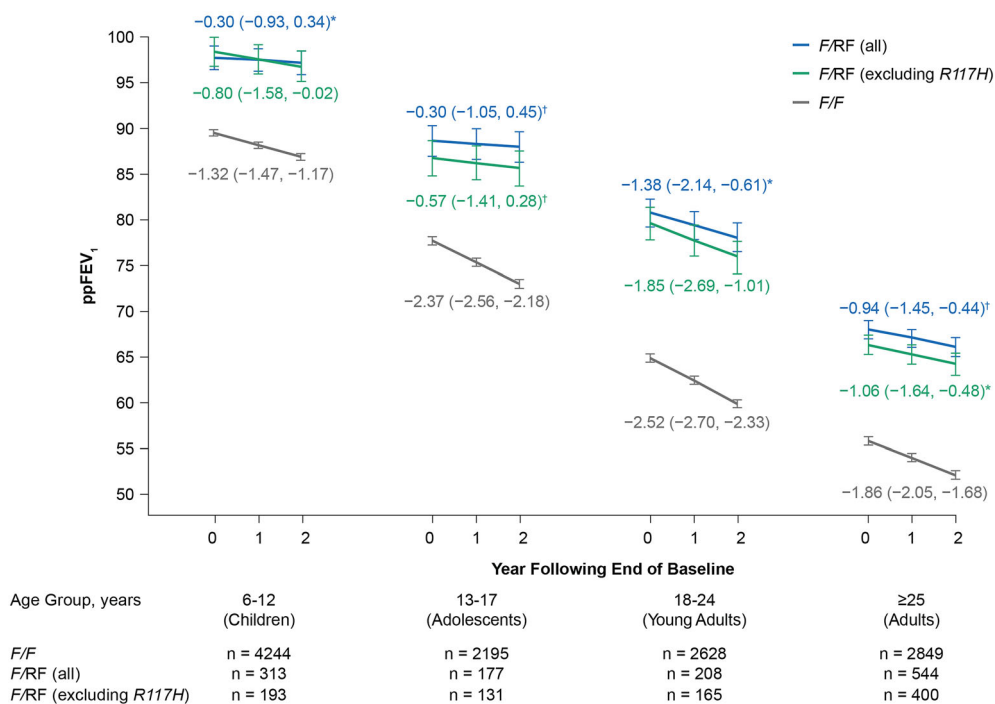
Fig. 1 Estimated slope of ppFEV$_1$, by mutation. *F* *F508del*, *ppFEV$_1$* percent predicted forced expiratory volume in 1 s, *RF* residual function. Annual rates of ppFEV$_1$ decline were based on 2012 Global Lung Initiative equations [19]. Error bars represent SE; values in parentheses are the 95% CI of the slope. *$P < 0.001$ versus *F/F*

R117H) versus *F/F* cohorts were not statistically significantly different in children [difference, 0.52 percentage points per year (95% CI −0.27, 1.31)] or young adults [difference, 0.67 percentage points per year (95% CI −0.19, 1.53)] (Fig. 2). The estimated intercepts and rates of decline in the overall population and by age group were similar in sensitivity analyses using the Wang–Hankinson equations (Table 2).

DISCUSSION

We sought to better understand the rate of lung function decline in people with CF who have an RF *CFTR* mutation. We used data from 2006 to 2014 to ensure an adequate sample size for CFTR modulator-untreated cohorts. Our data showed a decline in ppFEV$_1$ in those with *F/RF* genotypes across all age groups, although the rate of decline varied by age. Overall, the rate of ppFEV$_1$ decline observed in participants with *F/RF* genotypes was slower than that in participants with *F/F* genotypes, consistent with the findings reported by Leung et al. [22]. When participants with an *R117H* mutation were excluded from the analyses, rates of lung function decline in children and young adults were not statistically significantly different compared with rates in the same age groups in the *F/F* cohort. This finding indicates that, despite having better preserved lung function compared with the *F/F* cohort at baseline, the *F/RF* (excluding *R117H*) cohort also experienced a progressive decline in lung function. The findings of this study demonstrate the progressive nature of CF in people with the *F/RF* genotype, highlighting the importance of beginning treatment to preserve lung function as early as possible. Since the analysis, several CFTR modulators have become available for this patient population, including ivacaftor (Kalydeco), tezacaftor/ivacaftor and ivacaftor (Symdeko), and, most recently, elexacaftor/tezacaftor/ivacaftor and ivacaftor (Trikafta) [23–25].

This retrospective study had several limitations. The severity of disease in individuals with *F/RF* genotypes was highly variable and influenced by several factors, including environment and the presence of modifier genes [10]. It is possible that in the current era of widespread newborn CF screening, children with *F/RF* genotypes with mild symptoms are being diagnosed with CF more frequently, while the adult *F/RF* population in this study may have been diagnosed due to being symptomatic (instead of via newborn screening) and therefore may exhibit greater lung function decline than younger *F/RF* populations. Phenotypic variability in people with CF who have an *R117H* mutation has also been shown to be influenced by polymorphisms in the polythymidine tract of intron 8 of the *CFTR* gene [26]; this could not be examined in these analyses due to lack of data availability in the registry.

Table 2 Estimated intercept and annualized slope for ppFEV$_1$ using Wang–Hankinson equations (sensitivity analysis)

Characteristic	F/F^a (n = 11,916)	F/RF (all) (n = 1242)	F/RF (excluding R117H) (n = 889)
Intercept (95% CI)			
Overall	74.88 (74.49, 75.28)	86.25 (84.92, 87.58)	85.49 (83.89, 87.10)
6–12 years of age	91.88 (91.21, 92.55)	99.85 (97.34, 102.36)	100.52 (97.32, 103.71)
13–17 years of age	81.18 (80.26, 82.10)	92.02 (88.76, 95.28)	90.12 (86.32, 93.92)
18–24 years of age	64.86 (64.02, 65.70)	80.98 (77.97, 83.99)	79.78 (76.39, 83.17)
≥ 25 years of age	56.02 (55.21, 56.83)	68.34 (66.48, 70.21)	66.58 (64.40, 68.76)
Slope (95% CI)			
Overall	−1.93 (−2.03, −1.82)	−0.74 (−1.14, −0.34)	−1.09 (−1.56, −0.63)
6–12 years of age	−0.75 (−0.90, −0.59)	0.13 (−0.52, 0.78)	−0.43 (−1.23, 0.36)
13–17 years of age	−3.56 (−3.75, −3.37)	−1.26 (−2.03, −0.49)	−1.43 (−2.30, −0.57)
18–24 years of age	−2.51 (−2.70, −2.33)	−1.39 (−2.17, −0.61)	−1.84 (−2.70, −0.98)
≥ 25 years of age	−1.88 (−2.07, −1.69)	−1.01 (−1.52, −0.49)	−1.11 (−1.71, −0.52)

F F508del, ppFEV$_1$ percent predicted forced expiratory volume in 1 s, RF residual function

^{a}Intercepts and slopes were calculated by weighting each age group category pooled across the F/F and F/RF (all) cohorts

Fig. 2 Estimated slope of ppFEV$_1$, by mutation and age group. F F508del, ppFEV$_1$ percent predicted forced expiratory volume in 1 s, RF residual function. Annual rates of ppFEV$_1$ decline were based on 2012 Global Lung Initiative equations [19]. Error bars represent SE; values in parentheses are the 95% CI of the slope. *P < 0.05 versus F/F; †P < 0.001 versus F/F

CONCLUSION

These results demonstrate substantial disease burden characterized by progressive lung function decline in people with CF across all age groups evaluated, regardless of genotype. The decline across all age groups reinforces the importance of early treatment intervention and clinical monitoring to preserve lung function in people with CF, including people with *F*/RF genotypes.

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Compliance with Ethics Guidelines. This study was conducted in accordance with the current Good Clinical Practice Guidelines as described by the International Council for Harmonisation, the Declaration of Helsinki, and all applicable local regulations. People with CF provided informed consent to participate in the US Cystic Fibrosis Foundation Patient Registry and to have their data included in the registry. The study did not involve primary data collection and used only de-identified data; thus, institutional review board approval was not required.

Data Availability. The data sets generated during and/or analyzed during the current study are available from the US Cystic Fibrosis Foundation Patient Registry, https://www.cff.org/researchers/patient-registry-data-requests. The US Cystic Fibrosis Foundation Patient Registry collects and manages its own data and maintains processes for researchers to request summarized data.

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