Received: 27 August 2019 | Revised: 31 January 2022 | Accepted: 8 March 2022

DOI: 10.1002/bimj.201900255

Biometrical Journal

RESEARCH ARTICLE

Application of gap time analysis with flexible hazards to pulmonary exacerbations in the EPIC observational study

John D. Rice[1,2] | **Rachel L. Johnson**[1] | **Elizabeth Juarez-Colunga**[1] | **Edith T. Zemanick**[3] | **Margaret Rosenfeld**[4] | **Brandie D. Wagner**[1]

[1]Department of Biostatistics and Informatics, Colorado School of Public Health, University of Colorado Anschutz Medical Campus, Aurora, CO, USA

[2]Adult and Child Consortium for Health Outcomes Research and Delivery Science, University of Colorado Anschutz Medical Campus, Aurora, CO, USA

[3]Department of Pediatrics, University of Colorado School of Medicine and Children's Health Colorado, Aurora, CO, USA

[4]Division of Pulmonology, Seattle Children's Hospital, OC.7.720 - Pulmonary,, Seattle, WA, USA

Correspondence
John D. Rice, Department of Biostatistics and Informatics, Colorado School of Public Health, University of Colorado Anschutz Medical Campus, Aurora, CO 80045, USA.
Email: john.rice@cuanschutz.edu

Funding information
Cystic Fibrosis Foundation Therapeutics, Grant/Award Numbers: OBSERV13K0, WAGNER15A0

This article has earned an open data badge "**Reproducible Research**" for making publicly available the code necessary to reproduce the reported results. The results reported in this article are partially reproducible as the data are not publicly available.

Abstract

Cystic fibrosis and other chronic lung disease clinical trials often use time to first pulmonary exacerbation (PEx) or total PEx count as endpoints. The use of these outcomes may fail to capture patterns or timing of multiple exacerbations and how covariates influence the risk of future exacerbations. Analysis of gap times between PEx provides a useful framework to understand risks of subsequent events, particularly to assess if there is a temporary increase in a hazard of a subsequent PEx following the occurrence of a PEx. This may be useful for estimating the amount of time needed to follow patients after a PEx and predicting which patients are more likely to have multiple PEx. We propose a smoothed hazard for gap times to account for elevated hazards after exacerbations. A simulation study was conducted to explore model performance and was able to appropriately estimate parameters in all situations with an underlying change point with independent or correlated recurrent events. Models with different change-point structures and trends are compared using Early Pseudomonas Infection Control (EPIC) observational study data, using a quasi-likelihood modification of the Akaike information criterion; a model with a change-point provided a better fit than a model without one. The analysis suggests that the change point may be 1.8 years (SE 0.09) after the end of a PEx. Models including covariates in the hazard function revealed that having one or two copies of the ΔF508 mutation, female sex, and higher numbers of previous PEx were significantly associated with increased risk of another PEx.

KEYWORDS
change-point hazard model, gap time model, pulmonary exacerbations

1 | INTRODUCTION

Cystic fibrosis (CF) is a genetic disorder affecting approximately 30,000 individuals in the United States and 70,000 worldwide (Treggiari et al., 2009), making it the most common life-shortening inherited disorder in Caucasians (Yan & Fine,

2008), though it affects all races and ethnicities. One of the hallmarks of CF is pulmonary exacerbations (PEx), which are periods of increased sputum production, chest congestion, coughing, fatigue, and decreased lung function (Rosenfeld et al., 2001). In addition to being associated with significant medical costs, PEx causes significant lung and respiratory damage, reduced quality of life, and, over time, increased mortality (Parkins et al., 2012; Rosenfeld et al., 2001; VanDevanter et al., 2016). It has also been suggested that the occurrence of PEx is associated with greater subsequent declines in lung function (Waters et al., 2012). Thus, PEx are important clinical outcomes in CF that warrant further evaluation.

Given the importance of PEx in CF, obtaining a better understanding of the risk for recurrent exacerbations over time may be useful for preventing future events. A carryover effect after each PEx, in which the occurrence of one event produces a temporary increase in hazard or risk of a future event, has been previously studied (Çiğşar & Lawless, 2012) and is the focus of our work. The study that motivates this work is the Early Pseudomonas Infection Control (EPIC) observational study, a multicenter study that enrolled and followed over 1700 patients diagnosed with cystic fibrosis (Rosenfeld et al., 2012; Treggiari et al., 2009). Data are available from the earliest registry entry or PEx.

Existing approaches to modeling PEx as a study endpoint include analysis of time to first exacerbation, one randomly selected exacerbation, or number or rate of exacerbations (Ferkol et al., 2006; Ramsey et al., 1999; Saiman et al., 2003; Sanders et al., 2010, VanDevanter and Konstan, 2010). These approaches exclude exacerbation data if only considering the first exacerbation or a randomly selected exacerbation, and they fail to address timing of exacerbations or dependence between events when only considering the total number or rate. With few exceptions (Espel et al., 2017; Mayer-Hamblett et al., 2018), most previous studies that have considered recurrent PEx in the analysis only included a subset of all exacerbations, such as the number of PEx in a baseline period (Sequeiros and Jarad, 2012, Smith et al., 1999; VanDevanter et al., 2016). All such approaches fail to incorporate some aspect of the PEx disease process.

Our particular interest with these data is in testing whether there is a temporary increase in the hazard of a subsequent PEx following the occurrence of a PEx. Understanding how the hazard of having a PEx changes over time could be useful for (i) better estimating the amount of time needed to follow patients after a PEx, (ii) predicting which patients are more likely to have multiple PEx, and (iii) in future work, identifying predictors observable at the end of a PEx that suggest whether the patient will have another in a short time, and if so, that treatment may be needed. The lengthy follow-up period of the EPIC study allows for studying and testing this important problem.

Models that explicitly incorporate a change in the hazard of an event have been proposed in the literature, including the classical change-point model allowing for a sudden change in the hazard of an event. However, this model is most appropriate when there is expected to be a sharp change in the level of the hazard, which is not necessarily the case in many biological processes. Müller and Wang (1994) proposed a smoothed approximation change-point model in which the "point of most rapid change" is defined as the maximum of the first derivative of the hazard. We propose a parametric function for the hazard that still estimates the point of most rapid decline but converges to the classical change point in the limit when one of the parameters approaches zero (Zelterman et al., 1994); we therefore refer to this model as a *smoothed change-point model*.

In this paper, we propose a recurrent-events model with a smooth, flexible hazard to address the question of whether there is an increased risk of having a future PEx after the conclusion of a prior PEx. To our knowledge, this is the first application of a gap time analysis to address this important clinical question and therefore represents a significant contribution to the literature. Our approach incorporates two important characteristics. First, it allows for the estimation of the "point of most rapid change" (Müller & Wang, 1994, p. 226) with a flexible hazard. For brevity, we refer to this as a smooth change-point model, although our model only coincides with the classical change-point hazard model in a limiting sense. The smoothness of our adaptation of the classical model is achieved through the use of a logistic cumulative distribution function (CDF) to approximate the indicator function implicit in the classical change-point hazard model: when the scale parameter of this CDF approaches zero, the model converges to the classical change-point model (Zelterman et al., 1994). Second, our approach allows for the hazard to depend on event history, thereby allowing individuals' hazards to increase over time in association with the number of previous PEx. This relaxes the usual independent and identically distributed assumptions of renewal processes (Cook & Lawless, 2007; Heggland & Lindqvist, 2007) through the use of robust covariance estimation. Analyzing exacerbations within our proposed framework uses all exacerbation data, rather than restricting to only one exacerbation, a subset, or a total count (Cook & Lawless, 2007; Heltshe et al., 2016; Twisk et al., 2005; Waters et al., 2015).

The remainder of the paper is structured as follows. The motivating example from the EPIC observational study is detailed in Section 2. Section 3 describes the smoothed change-point model (Section 3.1) and the likelihood construction

TABLE 1 Demographic and clinical information about the $N = 1017$ individuals with at least one pulmonary exacerbation (PEx) recorded in the EPIC observational study, presented with frequencies (percent) or medians (interquartile range)

Variable	*N* (%)
Sex	
female	518 (50.9%)
male	499 (49.1%)
Number of copies of F508del	
0	86 (8.5%)
1	369 (36.3%)
2	562 (55.3%)
PEx recorded	
1	325 (32.0%)
2	178 (17.5%)
3	123 (12.1%)
4	76 (7.5%)
5+	315 (31.0%)
Variable	Median (interquartile range)
Age at first PEx (years)	0.28 (1.5)
Age at final visit (years)	15.45 (4.4)
Follow-up time (years)	14.37 (5.1)
Total number of PEx	3.00 (4.0)
Length of gap time (years)	
After the first PEx	1.94 (3.9)
After the second PEx	1.15 (2.1)
After the third PEx	0.90 (1.4)
After the fourth PEx	0.73 (1.1)
After the 5+th PEx	0.38 (0.6)

(Section 3.2). Simulation studies investigating model misspecification and the effect of correlated versus independent events are described in Section 4. The data analysis is summarized in Section 5, including model results (Section 5.1), covariate effects (Section 5.2), and goodness of fit (Section 5.3). The paper concludes with the discussion of these results and other applications of this model in Section 6.

2 | EARLY PSEUDOMONAS INFECTION CONTROL (EPIC) OBSERVATIONAL STUDY

Data on the gap times between PEx were drawn from the EPIC observational study, where data were collected through the Cystic Fibrosis Foundation Patient Registry (CFFPR). This study enrolled CF patients who had either no prior isolation of *Pseudomonas aeruginosa*, or at least a 2-year period with no isolation of *P. aeruginosa* (Treggiari et al., 2009). Data collected in the EPIC observational study are longitudinal and include demographic and risk factor data, respiratory cultures, clinical encounter information, and clinical outcomes, such as bacterial infections or PEx (see Table 1). PEx are in an important clinical outcome defined by the requirement of IV antibiotics or hospitalization for respiratory symptoms (Cystic Fibrosis Foundation, 2016). If an individual started a PEx within 1 week of the end of their last exacerbation, those events were treated as a single exacerbation (VanDevanter et al., 2016). The exacerbation data are recorded in age to the nearest hundredth of a year, meaning that PEx that begin and end within 0.02 years of one another are treated as a single exacerbation. It is more conservative to combine PEx that start and end within one week of one another into a single exacerbation rather than combining PEx within a larger time window because this provides us with greater capabilities to model the risk directly after PEx, particularly when PEx are closely spaced in time. PEx duration was not included in the model, since our interest lies in hazards directly after a PEx concluded.

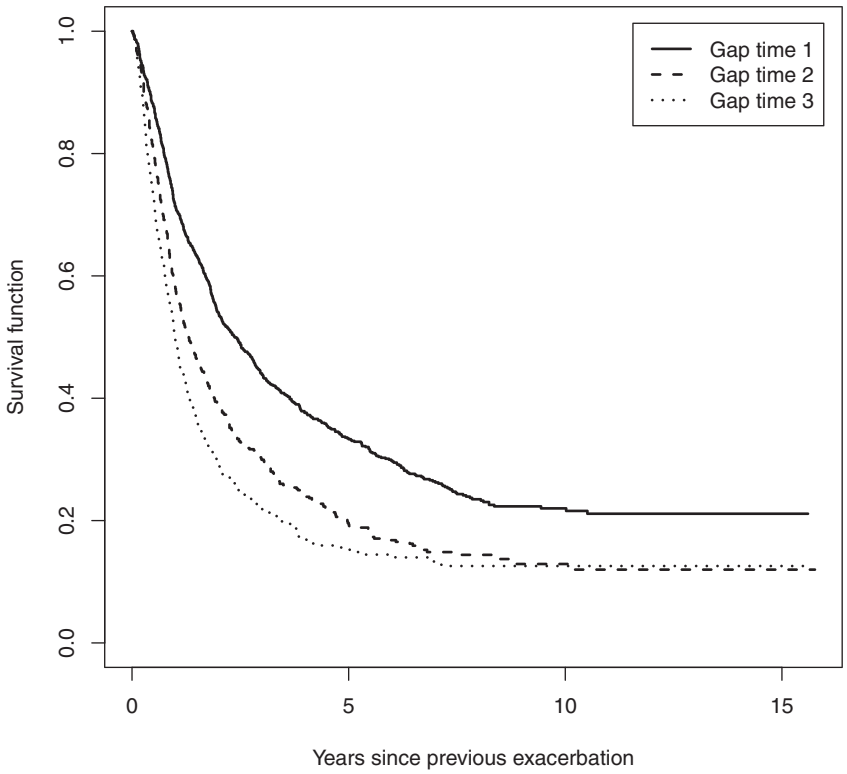

FIGURE 1 Kaplan–Meier estimates of the survival curves for the first gap time (between the first and second exacerbations; $N = 692$ individuals with PEx, 325 individuals censored), the second gap time (between the second and third exacerbations; $N = 514$ PEx, 168 censored), and the third gap time (between the third and fourth exacerbations; $N = 391$ PEx, 118 censored).

The beginning of follow-up was defined as an individual's earliest registry entry or PEx; a registry entry could have occurred before their enrollment in the EPIC observational study. The end of follow-up in the study was defined as a patient's latest CF registry encounter or PEx. These data include observations through 2014.

Predictors of clinical interest considered in our analyses were determined a priori and included genotype and sex. Our genotype of interest was defined by the number of confirmed ΔF508 (F508del) mutations (0, 1, or 2), where 0 included both those with 0 known copies and those with unknown status with respect to this mutation. Homozygosity of ΔF508 (ΔF508/ΔF508), the most common CF-causing mutation (Cystic Fibrosis Foundation, 2016), is associated with an increased risk of infection and lower lung function in CF (Rosenfeld et al., 2012; Sanders et al., 2010).

Gap times between PEx were defined as years between the end of one PEx and the start of the next PEx. Durations of PEx are excluded from gap times since an individual is not at risk for another exacerbation before their current exacerbation has ended. Kaplan–Meier curves (Figure 1) suggest that gap times may have different distributions depending on the number of previous exacerbations.

3 | GAP TIME ANALYSIS MODEL WITH SMOOTHED CHANGE POINT

3.1 | Model of recurrent exacerbations with smoothed change-point hazard

The classical change-point hazard (Matthews & Farewell, 1985; Müller & Wang, 1994) can be written as $h(t) = \lambda_0(t)\mathbf{I}(t > \omega) + \lambda_1(t)\mathbf{I}(t \leq \omega)$ for some change-point $\omega \geq 0$, where the indicator function $\mathbf{I}$ is equal to 1 when true and 0 otherwise. The hazard is equal to $\lambda_0(t)$ when the gap time is greater than some change-point ω, and the hazard is equal to $\lambda_1(t)$ when the gap time is less than ω. In this context, $\lambda_1(t)$ represents the hazard of having a future PEx immediately after a PEx ends, and $\lambda_0(t)$ represents the baseline hazard of having a PEx that all individuals are assumed to return to.

However, the change point is unlikely to be this "sharp" in a biological process, so a hazard rate that allows for more flexibility in shape is required to test our specific hypotheses of interest related to the EPIC observational data. We therefore replace this change-point hazard formulation with a smooth function, $G(t; \omega, \sigma) = \{1 + \exp[-(t - \omega)/\sigma]\}^{-1}$, where σ is the smoothing parameter associated with the change point. The logistic CDF is a natural choice for G since it has closed-form integrals and is a symmetric location-scale family CDF. Therefore, it can smoothly approximate our function of

interest if the location parameter is set equal to ω, while the scale parameter approaches 0 (Zelterman et al., 1994). Indeed, any such CDF could equally serve this purpose, including the normal distribution function; however, the specific choice of CDF used to smoothly approximate the indicator is not expected to impact results substantially. Thus, we write the change-point hazard

$$h(t) = \frac{\lambda_0}{1 + \exp\left(-\frac{t-\omega}{\sigma}\right)} + \frac{\lambda_1}{1 + \exp\left(\frac{t-\omega}{\sigma}\right)}. \tag{1}$$

3.2 | Likelihood construction

If times between exacerbations have the distribution defined by the smoothed change-point hazard in (1), then each subject has a renewal process $N_i(t)$, which assumes independence between event times within a subject, $i = 1, \dots, M$. We take the approach of constructing the likelihood based on this assumed "working" independence correlation structure, and then adjust the standard errors of the resulting estimates using a robust estimator for the covariance matrix (Croux et al., 2003). Since the likelihood construction assumes independence between events, after maximizing the working-independence likelihood, robust standard errors from sandwich estimators may be obtained to account for within-subject correlation.

For each subject, let n_i be the number of exacerbations observed. Let z_i be the time from the end of the last exacerbation to their last recorded event, and let $t_{i,1}, t_{i,2}, \dots, t_{i,k_i}$ denote the k_i gap times between exacerbations for individual i. Each subject's likelihood contribution will depend on whether $n_i = 1$ or $n_i \geq 2$. Note that subjects with no events would not contribute to the likelihood since they have no information on times between exacerbations and are considered to be waiting for their first exacerbation. For an individual with exactly one exacerbation recorded during follow-up time, their only contribution to the likelihood would come from the gap time after the end of their first exacerbation z_i, which would contribute to the survival function. Thus, the likelihood contribution for this subject would be $L_i = S(z_i) = \exp(-H(z_i))$.

Otherwise, for an individual with more than one exacerbation recorded over the course of their follow-up time, the gap time(s) between exacerbations for individual i, $t_{i,1}, t_{i,2}, \dots, t_{i,k_i}$, would contribute to the likelihood as observed event times. Then, the gap time from the end of their last exacerbation to their last recorded event, z_i, would contribute to the survival function. Thus, a subject with more than one exacerbation would contribute the following:

$$L_i = S(z_i) \prod_{j=1}^{k_i} f(t_{i,j}) = \exp\left(-H(z_i)\right) \prod_{j=1}^{k_i} h(t_{i,j}) \exp(-H(t_{i,j})). \tag{2}$$

The model may be generalized to allow inclusion of covariates in a proportional hazards framework and nonindependent or nonidentically distributed gap times; note that the assumptions of independent and identically distributed observations have been violated, so this cannot be classified as a renewal process. Since we have clinical rationale to believe that individuals' hazards of having another exacerbation differ based on their sex, number of copies of ΔF508, and number of previous exacerbations, we propose modifying (1) to allow for greater flexibility in hazards at each gap time j and to allow for covariates to affect the hazards as well.

Let $\mathbf{x}_i$ be a vector of fixed covariates for individual i. The hazard function for the jth gap time, $j = 1, \dots, J$, and the ith subject will be equal to

$$h_{ij}(t) = \left[\frac{\lambda_{0j}}{1 + \exp\left(-\frac{t-\omega}{\sigma}\right)} + \frac{\lambda_{1j}}{1 + \exp\left(\frac{t-\omega}{\sigma}\right)} \right] \exp(\mathbf{x}_i' \boldsymbol{\beta}), \tag{3}$$

where the baseline (λ_{0j}) and postevent (λ_{1j}) hazards may depend on previous exacerbations and include fixed covariates, for example, gender, that act multiplicatively in both hazards. Further generalizations of this work could extend to time-dependent covariates. When no covariates are included, $\boldsymbol{\beta}$ is restricted to $\mathbf{0}$.

4 | SIMULATION STUDIES

First, a simulation study was conducted under eight scenarios to determine that (i) the model is estimating the correct change point when one exists, (ii) that when there is no change point the model provides evidence of that, and (iii) to assess the effect of censoring on estimating parameters of the change-point model. For each of the scenarios, 1000 datasets with 1000 subjects in each were simulated with one gap time per subject. Each of these datasets was then analyzed with the simplest model that included a smoothed change-point hazard (1). When applicable in the scenarios, the two hazards, λ_1 and λ_0, were set equal to 0.7 and 0.2, respectively, to reflect the relatively low event rate observed in our dataset and to be similar to the hazard rates in the model without trend parameters or covariates. The change-point ω was set equal to 2.0, which was similar to the change-point estimated from our data.

The five scenarios with no censoring were specified as follows:

(i) Simulation U1: a "sharp" change point ($\sigma = 0$),
(ii) Simulation U2: a smoothed change point where $\sigma = 0.2$,
(iii) Simulation U3: a smoothed change point where $\sigma = 0.35$,
(iv) Simulation U4: a smoothed change point where $\sigma = 0.5$, and
(v) Simulation U5: no change point (an exponential distribution with a hazard rate of 0.7).

The results of these simulations are shown in Table 2, and the comparison of the true parameter values and the parameters estimated from the simulated data are presented for these five simulations in the supplement in Figure S1. Note that in scenarios U1 and U5, numerical issues prevented estimation of standard errors using the information matrix, so we recommend bootstrapping for inference when standard error estimates seem unreasonable or when a sharp change point is suspected.

In simulation scenario U1, we aimed to test whether the model would be able to estimate the change point well when there was a "sharp" change point. The change point was well estimated, with model estimates of the smoothing parameter tending towards zero.

In simulation scenarios U2–U4, in which the model was correctly specified, the results were largely unbiased with small empirical standard errors.

The results under simulation scenario U5 suggest that the model performs as expected when fitting a model containing parameters that have no meaning in the data-generating mechanism. Specifically, under an exponential model, several possible configurations of parameters in the change-point hazard model could produce an equivalent fit to the data. For example, setting the change point equal to 0, the smoothing parameter and one of the hazard rate parameters could take any value; the remaining hazard rate parameter would then correspond to the exponential rate parameter. This results in a situation where the model is not identifiable. The estimates under this simulation scenario, particularly for the change point, consequently were observed to have very large standard errors. Bias in estimating λ_1 was slightly higher in this scenario than in others, but it was still relatively small.

Next, to determine the effect of censoring on parameter estimation, three simulations were run under different rates of censoring. The two hazards, λ_1 and λ_0, were set equal to 0.7 and 0.2, the change-point ω was set equal to 2.0, and the smoothing parameter σ was set equal to 0.5 (1):

(i) Simulation C1: censoring rate of 10%,
(ii) Simulation C2: censoring rate of 25%, and
(iii) Simulation C3: censoring rate of 40%.

Each of these datasets was then analyzed with the smoothed change-point hazard model. The results of these simulations are also shown in Table 2, and the comparison of the true parameters and estimated parameters are presented for these three simulations in Figure S1.

The results of simulations C1–C3 suggest that censoring does not prevent accurate estimation of the hazards, change point, or smoothing parameter, although standard errors increased incrementally as censoring rates increased. There are slight biases in estimation of the change-point and smoothing parameter as censoring rates increase, but likely not large enough to change clinical interpretation.

TABLE 2 This table displays the results of the eight simulation scenarios for non-recurrent events

Simulation	Parameter		Mean	Median	Empirical SE	Avg. estimated SE*	Bias
U1	λ_0	0.2	0.200	0.199	0.013	*	0.000
	λ_1	0.7	0.705	0.705	0.026	*	0.005
	ω	2	1.989	1.991	0.039	*	−0.011
	σ	0	0.051	0.043	0.033	*	0.051
U2	λ_0	0.2	0.200	0.200	0.014	0.014	0.000
	λ_1	0.7	0.703	0.703	0.031	0.031	0.003
	ω	2	1.994	1.995	0.103	0.103	−0.006
	σ	0.2	0.206	0.196	0.089	0.083	0.006
U3	λ_0	0.2	0.201	0.200	0.015	0.015	0.001
	λ_1	0.7	0.706	0.703	0.044	0.041	0.006
	ω	2	1.987	1.991	0.157	0.155	−0.013
	σ	0.35	0.353	0.336	0.132	0.123	0.003
U4	λ_0	0.2	0.201	0.200	0.015	0.016	0.001
	λ_1	0.7	0.713	0.702	0.070	0.061	0.013
	ω	2	1.962	1.980	0.254	0.238	−0.038
	σ	0.5	0.508	0.487	0.187	0.174	0.008
U5	λ_0	-	8.856	0.706	163.37	*	*
	λ_1	0.7	0.642	0.694	0.263	*	−0.058
	ω	-	3.542	1.239	9.535	*	*
	σ	-	4.730	1.402	7.773	*	*
C1	λ_0	0.2	0.200	0.200	0.020	0.019	0.000
	λ_1	0.7	0.716	0.702	0.073	0.065	0.016
	ω	2	1.954	1.982	0.269	0.251	−0.046
	σ	0.5	0.504	0.478	0.198	0.187	0.004
C2	λ_0	0.2	0.199	0.198	0.034	0.033	−0.001
	λ_1	0.7	0.727	0.702	0.108	0.077	0.027
	ω	2	1.928	1.974	0.361	0.302	−0.072
	σ	0.5	0.521	0.467	0.276	0.235	0.021
C3	λ_0	0.2	0.193	0.195	0.057	0.051	−0.007
	λ_1	0.7	0.740	0.703	0.138	0.098	0.040
	ω	2	1.909	1.975	0.454	0.384	−0.091
	σ	0.5	0.555	0.464	0.385	0.300	0.055

Note: Data were simulated from a sharp change point ($\sigma = 0$) in simulation U1, a smoothed change point with $\sigma = 0.2$ in simulation U2, a smoothed change point with $\sigma = 0.35$ in simulation U3, a smoothed change point with $\sigma = 0.5$ in simulation U4, and no change point (an exponential distribution) in simulation U5. Simulations C1, C2, and C3 were all simulated from the same parameters ($\lambda_0 = 0.2, \lambda_1 = 0.7, \omega = 2.0$, and $\sigma = 0.5$), but with different levels of censoring. Simulation C1 had a censoring rate of 10%, simulation C2 had a censoring rate of 25%, and simulation C3 had a censoring rate of 40%. Each of these simulated datasets was analyzed with a model that included a smoothed change-point hazard. *Average estimated standard errors that could not be estimated due to numerical issues are marked with asterisks.

Finally, a separate simulation study was conducted in which recurrent events were simulated from a smoothed-change-point hazard model with parameters $\lambda_0 = 0.2$, $\lambda_1 = 0.7$, $\omega = 2.0$, and $\sigma = 0.5$. These data were simulated under nine scenarios with three follow-up times and three frailty variances. The follow-up times considered were 7.6 years (50th percentile) and 9.7 years (75th percentile) to allow for different event rates across scenarios. Three variance structures were considered for the frailty from which the data were simulated: independent recurrent events, a low frailty variance (0.10), and a higher frailty variance (0.45).

The results of these simulations are summarized in Table 3. Bias is not shown since we are fitting a marginal model while simulating data from a conditional model: we would only expect unbiased parameter estimation in the zero frailty variance case, which we do see from these results. Variance estimation was good in all scenarios, with robust standard

TABLE 3 This table displays the results of the nine simulation scenarios with two follow-up times (7.6 years, or the 50th percentile; 9.7 years, or the 75th percentile) and three frailty variances (no variance, low variance, and high variance)

Follow-up time	Frailty variance	Parameter	Mean	Median	ESD	ANSE	ARSE	Fails
7.6	0	λ_0	0.200	0.199	0.014	0.014	0.014	0
		λ_1	0.702	0.699	0.025	0.025	0.025	
		ω	2.000	2.004	0.104	0.102	0.103	
		σ	0.502	0.497	0.095	0.091	0.093	
7.6	0.1	λ_0	0.171	0.171	0.014	0.014	0.014	0.2
		λ_1	0.786	0.781	0.042	0.038	0.039	
		ω	1.818	1.830	0.123	0.118	0.120	
		σ	0.598	0.587	0.102	0.097	0.100	
7.6	0.45	λ_0	0.112	0.113	0.012	0.012	0.012	0.7
		λ_1	1.217	1.181	0.174	0.148	0.158	
		ω	1.086	1.137	0.272	0.246	0.261	
		σ	0.819	0.808	0.116	0.111	0.117	
9.7	0	λ_0	0.200	0.200	0.011	0.011	0.011	0.4
		λ_1	0.702	0.701	0.023	0.022	0.022	
		ω	1.999	2.000	0.090	0.091	0.092	
		σ	0.502	0.498	0.080	0.079	0.080	
9.7	0.1	λ_0	0.174	0.174	0.010	0.010	0.011	0
		λ_1	0.788	0.782	0.037	0.033	0.034	
		ω	1.831	1.842	0.111	0.105	0.107	
		σ	0.592	0.584	0.087	0.083	0.086	
9.7	0.45	λ_0	0.116	0.116	0.009	0.009	0.009	0
		λ_1	1.252	1.216	0.167	0.135	0.143	
		ω	1.077	1.123	0.264	0.227	0.239	
		σ	0.836	0.822	0.112	0.099	0.105	

Note: One thousand trials of recurrent event data with 1000 individuals in each dataset were simulated from a smoothed change-point in all scenarios with parameters ($\lambda_0 = 0.2, \lambda_1 = 0.7, \omega = 2.0$, and $\sigma = 0.5$). Empirical standard deviations (ESD), asymptotic normal standard error (ANSE), asymptotic robust standard error (ARSE), and the percentage of trials that had numerical issues due to a negative hessian are reported (Fails).

errors improving slightly over model based. Results shown in the supplement also consider a shorter follow-up time and smaller sample size to examine the impact of fewer observed events. Here we found that the rate of numerical failures was low (<1%) for the larger of the two follow-up times considered, suggesting that performance of the proposed methods may be impacted when too few events are observed.

5 | APPLICATION TO EPIC STUDY

A total of 1772 subjects with CF were included in the dataset, nine of whom were excluded from the analysis because they received a lung transplant during the course of the study. Ideally, we would treat these patients as censored at the time of lung transplant, but lung transplant data were not specific enough to determine when transplants occurred with respect to PEx. Individuals with at least one exacerbation recorded as longer than 60 days were also removed ($n = 16$), since these durations were considered to be clinically unlikely and possibly due to data entry errors. Others were removed because of missing start or end times for exacerbations or follow-up ($n = 15$). Of the remaining study population, 1017 individuals with at least one exacerbation and at least one nonzero gap time during follow-up comprised the analysis cohort. Summary demographic information on the individuals comprising the analytic dataset is given in Table 1. Approximately half of the included individuals were male. The median follow-up time was 14.37 years, and individuals experienced a median of three PEx.

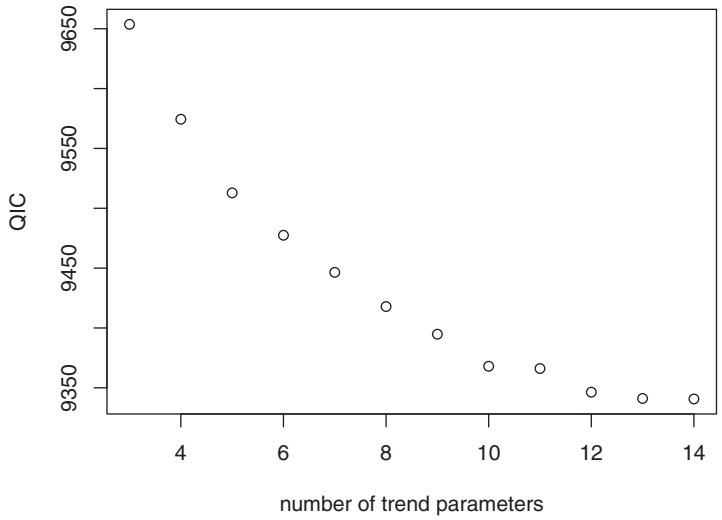

FIGURE 2 Model fit comparisons on the basis of QIC. The x-axis shows the number of trend parameters included while the y-axis shows the associated quasi-information criterion values for each model. The optimal model was chosen at the "elbow" around 10 trend parameters.

5.1 | Model development

While the model in (3) could be made more flexible by allowing the "baseline" hazard λ_{0j} to depend on the number of previous events, we were concerned about overparameterizing the model, so this parameter is assumed constant for the purposes of the EPIC data analysis, $\lambda_{0j} = \lambda_0$. Future work may investigate this or other possibilities for increased flexibility. On the other hand, since we hypothesized that the hazard for time to next PEx would increase as an individual's cumulative number of exacerbations increased, this parameter λ_{1j} depends on previous PEx. Thus trend parameters that multiply the hazard directly after an exacerbation are included in the intensity function (3) as follows:

$$\lambda_{1j} = \begin{cases} \lambda_1, & j = 1 \\ \lambda_1 \exp(\gamma_j), & 1 < j < J \\ \lambda_1 \exp(\gamma_J), & j \geq J, \end{cases} \tag{4}$$

where the factors of $\exp(\gamma_j)$ multiplying the hazard of a recurrent PEx prior to return to baseline risk level allow for either an increase ($\gamma_j > 0$) or decrease ($\gamma_j < 0$) relative to the hazard for the first gap time. We vary J in order to balance model complexity and goodness of fit: increasing J allows more flexibility, but there will be less data to estimate the γ_j values as j increases since fewer participants will have experienced j PEx for larger values of j.

The EPIC analysis is conducted in two stages: the first focuses on evaluating the change point and trend parameters of the model and the second one assesses covariates. To compare models and assess fit in the EPIC data, we used the quasi-likelihood under the independence model criterion (QIC), a modification of Akaike's information criterion (AIC) that is commonly utilized in generalized estimating equations (GEE) framework in which response data are correlated (Pan, 2001). It can be employed in a straightforward manner in cases such as this, where working independence is assumed. QIC is calculated similarly to AIC; the likelihood used in AIC is replaced by a quasi-likelihood, and an adjustment is made to the penalty term to account for the fact that the GEE estimator has different asymptotic properties than the maximum likelihood estimator (MLE) used for AIC.

These models were each fit to the EPIC study data by maximizing the working-independence likelihood with model-based standard errors and robust standard errors from sandwich estimators. Bootstrapped standard errors were also estimated, but were very similar to robust standard errors and are therefore omitted. Based on model fit statistics (Figure 2), a model with 10 trend parameters was selected as the optimal model. We chose a candidate set of models with up to 14 trend parameters on the basis of acceptable model parsimony. We observed that 10 trend parameters were approximately at the "elbow" of the QIC criterion, as beyond this point there was relatively little distinction in fit between models.

Results for all models are presented in the supplement in Table S2, and hazards are plotted over time in the supplement in Figure S2. Note that we also considered generalizations of the model in which we allowed the change-point or smoothing parameter to vary by gap time, but the results did not differ appreciably from the results presented here.

TABLE 4 This table displays the parameter estimates from our final model

	Estimate	SE (robust)	95% robust LCL	95% robust UCL
λ_0	0.092	0.011	0.073	0.117
λ_1	0.286	0.026	0.239	0.342
ω	1.862	0.093	1.688	2.053
σ	0.479	0.062	0.371	0.618
$\exp(\gamma_1)$	1.591	0.109	1.392	1.819
$\exp(\gamma_2)$	2.076	0.149	1.803	2.389
$\exp(\gamma_3)$	2.549	0.185	2.210	2.939
$\exp(\gamma_4)$	2.902	0.224	2.495	3.376
$\exp(\gamma_5)$	3.436	0.295	2.904	4.067
$\exp(\gamma_6)$	3.668	0.343	3.055	4.405
$\exp(\gamma_7)$	3.884	0.394	3.184	4.738
$\exp(\gamma_8)$	4.301	0.456	3.494	5.295
$\exp(\gamma_9)$	4.302	0.540	3.364	5.503
$\exp(\gamma_{10})$	7.655	0.561	6.631	8.837
$\exp(\beta_{G1})$	1.154	0.093	0.985	1.351
$\exp(\beta_{G2})$	1.174	0.092	1.007	1.369
$\exp(\beta_F)$	1.117	0.040	1.041	1.198

Note: This model was a smoothed change-point model with 10 trend parameters and covariates for genotype and sex. Abbreviations: LCL, lower confidence limit; SE, standard error; UCL, upper confidence limit.

To determine the significance of the change-point itself while avoiding the pitfalls associated with nonidentifiability of parameters under the null, we performed a separate bootstrap likelihood ratio test. This compared our final model (alternative hypothesis H_1) to a model without a change point (null hypothesis H_0). We fit each to the observed data, obtaining estimates $\hat{M}_0$ and $\hat{M}_1$, respectively, and calculating the likelihood ratio test statistic based on the difference between these models. We repeated this B times and generated data $y_{1b}, y_{2b}, \ldots, y_{nb}$ using observed covariate values but estimates $\hat{M}_0$. Finally, we compared the value $-2 * (\ell_0 - \ell_1)$ with the simulated null distribution based on $-2 * (\ell_{01} - \ell_{11}), -2 * (\ell_{02} - \ell_{12}), \ldots, -2 * (\ell_{0B} - \ell_{1B})$. Thus, the bootstrap p-value will be the proportion of times the simulated null value of the test statistic is less than the observed value. Using $B = 1000$ bootstrap samples, we observed $p < 0.001$, suggesting that our model fits the data significantly better than a model with no smoothed change point and flexible hazard. This same p-value was observed when we accounted for correlation within patients by incorporating a cluster-resampling step (Cheng et al., 2013) into the parametric bootstrap procedure described above.

5.2 | Effect of covariates

Table 4 presents the results of fitting the best-fitting model to the EPIC data with both genotype and sex included as covariates affecting hazard rate parameters. The addition of covariates had no strong effect on the estimation of the change point, which was estimated at 1.862 years.

There was a borderline significant difference in hazard multipliers between having one copy of ΔF508 and no copies of ΔF508 ($p = 0.076$) and for having two copies of ΔF508 compared to no copies ($p = 0.040$). Each increase in the number of ΔF508 copies increased the hazard multiplier, suggesting higher risks of having a future PEx for those with the greater number of mutation copies. There was also a significant difference in the post-PEx hazards for males and females ($p = 0.002$), with females having a hazard that was 1.117 (95% CI: [1.041, 1.198]) times that of males' hazards of a future PEx.

5.3 | Goodness of fit

To assess model fit, a parametric bootstrap was performed (Pewsey, 2018) based on the results of the final selected model, which included a smoothed change-point hazard, 10 trend parameters, and genotype and sex as covariates. Parameters

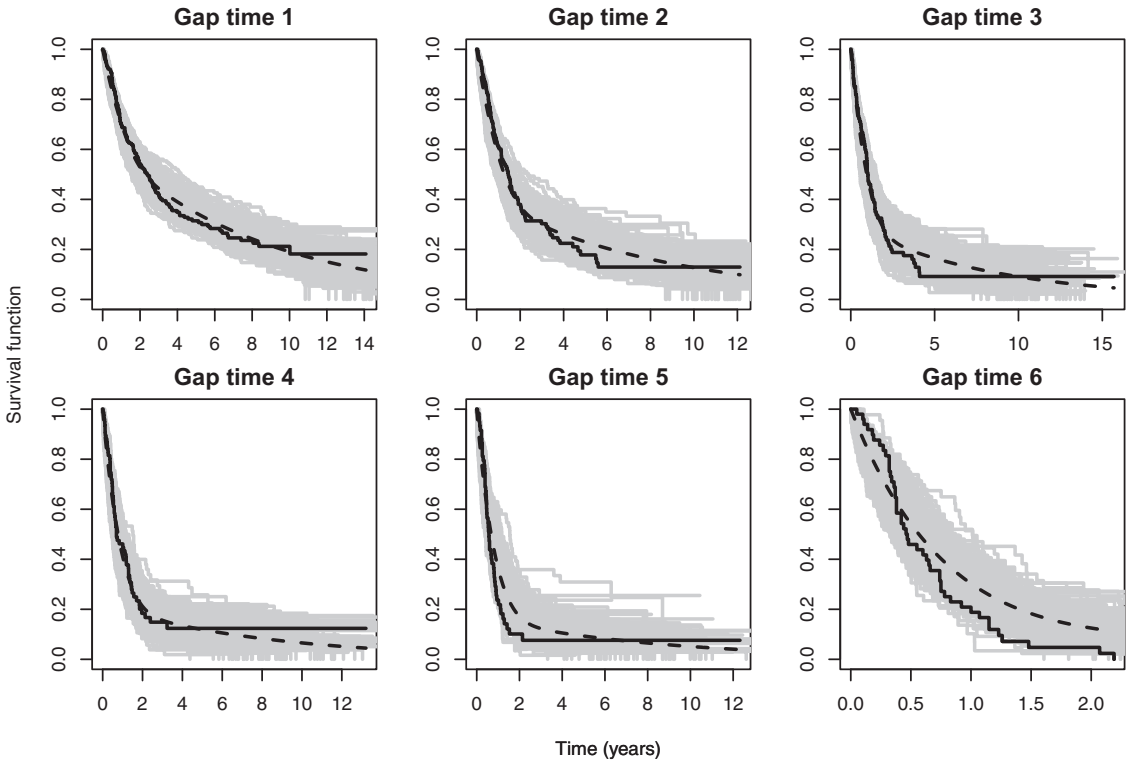

FIGURE 3 Kaplan–Meier estimates of survival curves of the parametric bootstrap results for females with one copy of ΔF508. Note that the *x*-axis differs in each panel. Kaplan–Meier curves for the simulated results in the parametric bootstrap (gray) are compared to the survival curve of the data (black) and the model fit (dashed).

were simulated from the multivariate normal distribution using the parameter estimates and their estimated variance–covariance matrix. Each of the 1017 individuals' follow-up times and covariates were treated as fixed. Then, gap times between exacerbations were simulated until the cumulative sum of the gap times surpassed the follow-up time; the last gap time simulated was considered to be censored. Kaplan–Meier curves for the simulated gap times 1–6 were plotted alongside the Kaplan–Meier curves for the full data and model fit for direct comparison.

This process was repeated 200 times, and the Kaplan–Meier curves for one randomly selected covariate combination—females with one copy of ΔF508—are shown in Figure 3 alongside the Kaplan–Meier curves for the EPIC data and model fit. Kaplan–Meier curves for the other five covariate combinations are shown in the supplement in Figures S3–S7. These figures can then be examined to compare the simulated parametric bootstrap curves to the EPIC data and model fit. There is some deviation among the EPIC data, model fit, and parametric bootstrap curves, but when it occurs it is usually much further into the tails of the distributions in question, where we have less data available on which to judge model fit. The simulated curves completely cover the data and model fit curves in many of the figures, suggesting that the model fits the data well (Figure 3).

6 | DISCUSSION

In this paper, we have proposed a smoothed flexible hazard for modeling gap times between exacerbations in order to address the clinical question of whether there is a period of elevated risk of further exacerbations following the current exacerbation's conclusion. Our parametric approach takes full advantage of the recurrent event structure of the data in the sense that the times of all PEx for a subject are included in the analysis, rather than only using information on time to the first PEx or the total number of events as in previous studies. Applying our proposed approach to data from the EPIC observational study, we were able to determine how hazards of having a future PEx in children with cystic fibrosis change over time and how these flexible hazard rates are associated with genotype, sex, and number of previous PEx. We were able to conclude that while the proposed model fits the data significantly better than a model without a change point, the clinical relevance of this finding is unclear due to the lengthy change-point time estimated: it was anticipated based

on clinical considerations that any elevation in hazard following a PEx would last weeks or months rather than almost 2 years as estimated using our model. These results may be useful in informing clinical practice related to estimating the amount of time needed to follow patients after a PEx, and predicting which patients are more likely to have multiple PEx.

In simulation studies, the proposed model estimated the hazard rates, change point, and smoothing parameter well in all situations when data were simulated from a model with a change point. When there was no change point, as expected, standard errors were much larger suggesting that a change point could take on a wide range of values. In a real data analysis, this would indicate that most likely there is no change point. There were slight biases when the smoothing parameter was large, but the medians of the parameter estimates were largely unbiased in these situations. The larger the smoothing parameter, the less sharply the hazard decreases at the change point, so estimation of a change point may have less relevance in such situations. Numerical issues prevented estimation of standard errors using the information matrix in simulation scenarios U1 and U5, so we recommend bootstrapping for inference when estimates seem unreasonable or when a sharp change point is suspected. In further simulation scenarios in which recurrent events were simulated from a smoothed-change-point hazard with varying follow-up times and frailty variances, variance estimation remained accurate, particularly when using cluster-robust standard errors. These simulations also suggested that the method's performance may be negatively impacted by reduced follow-up time (i.e., high censoring rates), which is a common concern in any time-to-event modeling.

The EPIC observational study represents an important data source for the exploration of these changing hazards in CF patients since the study had a median follow-up time of 14.4 years per patient, allowing for sufficient data to investigate the existence of a change point. Based on QIC, model M5 provided the best fit for the data. The results of the model showed a clear period of increased risk of a future PEx of approximately 1.86 (SE = 0.09) years. Increasing numbers of copies of ΔF508 mutation and female sex were significantly associated with increased hazard rates. Therefore, there is evidence of a change point in these data, but since the estimated change point is approximately 2 years after an exacerbation ends, its clinical relevance may be questionable; had the change point been much smaller, it could have affected which patients clinicians should closely monitor post-PEx and for how long. However, the hazards are flexible in that they may increase or decrease over time, so the fact that they decrease after an exacerbation suggests clustering of exacerbations (Winkelmann, 1995) and provides an adaptable framework for modeling recurrent events.

The question of model selection was raised during peer review, as in the EPIC data analysis QIC did not reveal a clear minimizing candidate model. Further investigation (results not shown) revealed very little dependence of the estimates of $\lambda_0, \lambda_1, \omega, \sigma$ on the number of trend parameters. This means that we would obtain very similar conclusions as to the existence and length of a window of increased risk following PEx regardless of how many trend parameters were included. While this may not be true generally, it is reassuring in the analysis of the EPIC dataset given the lack of a clear minimizing QIC value.

Two sensitivity analyses were conducted using the best-fitting model with covariates included. First, to determine whether the definition of a PEx affected the results, the analysis was repeated with multiple PEx within 14 days (0.04 years) of completing treatment defined as a single exacerbation (in contrast to the period of 7 days [0.02 years] used in the primary analysis). Minimal differences were observed relative to the model based on the 7-day definition. A second sensitivity analysis was conducted to determine whether the sample was biased towards sicker patients since patients with more exacerbations contribute more observations to the likelihood than patients with no or few exacerbations. This analysis was restricted to the 315 individuals who had at least five exacerbations (30.9% of analysis cohort). The results of the model fitted to this subpopulation were similar to those based on the full sample; the only exception was the change point, which was estimated at 1.456 years compared to the estimate of 1.86 years from the full sample. Therefore, while sicker patients may have contributed more to the likelihood compared to patients with fewer PEx, clinical interpretations of the model do not change.

There are a few limitations of the analysis and results in this paper. First, these results cannot necessarily be generalized to the entire CF population; this was a fairly young cohort with relatively mild disease and a low PEx rate. Next, this model does not account for the duration of exacerbation, which includes the length of treatment. A 14-day treatment is considered fairly standard, but there is some variation around this standard that was not accounted for. If treatment duration were of particular interest, it could be accounted for by extending the modeling framework of an alternating renewal process (Alvarez, 2006), with adaptations of the generalized Cox model (Hu et al., 2011), or with a nonparametric approach (Bhattacharya, 2018). Additionally, due to the enrollment mechanism for the CF registry, we cannot include accurate information about time to first PEx in our model since we were not able to evaluate what a true time zero would be for the patients. This is because we do not know exactly how people are entered into the database and why; however, as this was not related to our research questions, this was not of concern for this analysis. Our covariates were limited

to only include the number of copies of ΔF508 and sex due to their importance in previous CF research and treatment; future work will explore other factors that could affect risk of PEx, including time-varying covariates, such as *P. aeruginosa* infection. Future work could also allow covariates to affect other parameters in the model including the change point or the smoothing parameter. Finally, as an alternative to our GEE-like approach that treats gap times as independent and uses robust standard errors, future work could include the frailty in the model to account for within-subject correlation (Hougaard, 1995; Wienke, 2010), although this could introduce numerical difficulties in computing and maximizing the marginal likelihood.

A gap time model with a smoothed change-point hazard such as we have proposed in this paper has potential applications in understanding a variety of diseases or disorders characterized by a progressive nature. Examples include recurrent opportunistic infections in people living with HIV, recurrent ischemic attacks in individuals with cerebrovascular disease, repeated pyogenic infections in chronic granulomatous disease, recurrent asthma attacks in children (Eshaghi et al., 2016), persistent epileptic seizures (Kwan & Brodie, 2000), periods of acute respiratory worsening in idiopathic pulmonary fibrosis (Raghu et al., 2011), and exacerbations of chronic obstructive pulmonary disease (COPD) (Garcia-Aymerich et al., 2003). These models could also accommodate disease processes that improve over time or with treatment since they allow flexibility in the direction of trends.

7 | AVAILABILITY OF DATA AND MATERIALS

While we are unable to share the data used in this study, code used to fit the model will be publicly available in the Supporting Information.

ACKNOWLEDGMENTS

This research was jointly supervised by Elizabeth Juarez-Colunga and John Rice as part of Rachel Johnson's master's thesis. This work was funded by Cystic Fibrosis Foundation Therapeutics (OBSERV13K0 - Rosenfeld; WAGNER15A0 - Wagner and Juarez-Colunga).

CONFLICT OF INTEREST

The authors have declared no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the Cystic Fibrosis registry. Restrictions apply to the availability of these data, which were used under license for this study.

OPEN RESEARCH BADGES

This article has earned an Open Data badge for making publicly available the digitally-shareable data necessary to reproduce the reported results. The data is available in the Supporting Information section.

This article has earned an open data badge "**Reproducible Research**" for making publicly available the code necessary to reproduce the reported results. The results reported in this article are partially reproducible as the data are not publicly available.

ORCID

John D. Rice https://orcid.org/0000-0003-4338-481X
Rachel L. Johnson https://orcid.org/0000-0003-3002-5412

REFERENCES

Alvarez, E. E. (2006). Maximum likelihood estimation in alternating renewal processes under window censoring. *Stochastic Models*, *22*(1), 55–76.

Bhattacharya, S. (2018). A novel approach for analyzing data on recurrent events with duration to estimate the combined cumulative rate of both variables over time. *Contemporary Clinical Trials Communications*, *10*, 50–56.

Cheng, G., Yu, Z., Huang, J. Z. (2013). The cluster bootstrap consistency in generalized estimating equations. *Journal of Multivariate Analysis*, *115*, 33–47.

Çiğşar & Lawless. (2012). Assessing transient carryover effects in recurrent event processes, with application to chronic health conditions. *The Annals of Applied Statistics*, *6*(4), 1641–1663.

Cook, R. J., & Lawless, J. (2007) *The statistical analysis of recurrent events*. Springer Science & Business Media.

Croux, C., Dhaene, G., & Hoorelbeke, D. (2003). *Robust standard errors for robust estimators*. Faculty of Economics and Applied Economics, Katholieke Universiteit, Leuven.

Eshaghi, E., Baghishani, H., & Shahsavani, D. (2016). Time-varying coefficients models for recurrent event data when different varying coefficients admit different degrees of smoothness: Application to heart disease modeling. *Statistics in Medicine*, *35*(23), 4166–4182.

Espel, J. C., Palac, H. L., Cullina, J. F., Clarke, A. P., McColley, S. A., Prickett, M. H., & Jain, M. (2017). Antibiotic duration and changes in FEV 1 are not associated with time until next exacerbation in adult cystic fibrosis: a single center study. *BMC Pulmonary Medicine*, *17*(1), 160.

Ferkol, T., Rosenfeld, M., & Milla, C. E. (2006). Cystic fibrosis pulmonary exacerbations. *The Journal of Pediatrics*, *148*(2), 259–264.

Garcia-Aymerich, J., Farrero, E., Felez, M. A., Izquierdo, J., Marrades, R. M., & Anto, J. M. (2003). Risk factors of readmission to hospital for a COPD exacerbation: a prospective study. *Thorax*, *58*(2), 100–105.

Heggland, K., & Lindqvist, B. H. (2007). A non-parametric monotone maximum likelihood estimator of time trend for repairable system data. *Reliability Engineering & System Safety*, *92*(5), 575–584.

Heltshe, S. L., Goss, C. H., Thompson, V., Sagel, S. D., Sanders, D. B., Marshall, B. C., & Flume, P. A. (2016). Short-term and long-term response to pulmonary exacerbation treatment in cystic fibrosis. *Thorax*, *71*(3), 223–229.

Hougaard, P. (1995). Frailty models for survival data. *Lifetime Data Analysis*, *1*(3), 255–273.

Hu, X. J., Lorenzi, M., Spinelli, J. J., Ying, S. C., & McBride, M. L. (2011). Analysis of recurrent events with non-negligible event duration, with application to assessing hospital utilization. *Lifetime Data Analysis*, *17*(2), 215–233.

Kwan, P., & Brodie, M. J. (2000). Early identification of refractory epilepsy. *New England Journal of Medicine*, *342*(5), 314–319.

Matthews, D. E., & Farewell, V. T. (1985). On a singularity in the likelihood for a change-point hazard rate model. *Biometrika*, *72*(3), 703–704.

Mayer-Hamblett, N., Retsch-Bogart, G., Kloster, M., Accurso, F., Rosenfeld, M., Albers, G., Black, P., Brown, P., Cairns, A., Davis, S. D., & Graff, G. R. (2018). Azithromycin for early *Pseudomonas* infection in cystic fibrosis. The OPTIMIZE randomized trial. *American Journal of Respiratory and Critical Care Medicine*, *198*(9), 1177–1187.

Müller, H. G., & Wang, J. L. (1994). Change-point models for hazard functions. *Lecture Notes-Monograph Series*, *23*, 224–241.

Pan, W. (2001). Akaike's information criterion in generalized estimating equations. *Biometrics*, *57*(1), 120–125.

Parkins, M. D., Rendall, J. C., & Elborn, J. S. (2012). Incidence and risk factors for pulmonary exacerbation treatment failures in patients with cystic fibrosis chronically infected with *Pseudomonas aeruginosa*. *Chest*, *141*(2), 485–493.

Pewsey, A. (2018). Parametric bootstrap EDF-based goodness-of-fit testing for sinh-arcsinh distributions. *Test*, *27*(1), 147–172.

Raghu, G., Collard, H. R., Egan, J. J., Martinez, F. J., Behr, J., Brown, K. K., Colby, T. V., Cordier, J. F., Flaherty, K. R., Lasky, J. A., & Lynch, D. A. (2011). An official ATS/ERS/JRS/ALAT statement. Idiopathic pulmonary fibrosis: Evidence-based guidelines for diagnosis and management. *American Journal of Respiratory and Critical Care Medicine*, *183*(6), 788–824.

Ramsey, B. W., Pepe, M. S., Quan, J. M., Otto, K. L., Montgomery, A. B., Williams-Warren, J., Vasiljev-k, M., Borowitz, D., Bowman, C. M., Marshall, B. C., & Marshall, S. (1999). Intermittent administration of inhaled tobramycin in patients with cystic fibrosis. *New England Journal of Medicine*, *340*(1), 23–30.

Rosenfeld, M., Emerson, J., McNamara, S., Thompson, V., Ramsey, B. W., Morgan, W., Gibson, R. L., & EPIC Study Group., (2012). Risk factors for age at initial *Pseudomonas* acquisition in the cystic fibrosis EPIC observational cohort. *Journal of Cystic Fibrosis*, *11*(5), 446–453.

Rosenfeld, M., Emerson, J., Williams-Warren, J., Pepe, M., Smith, A., Montgomery, A. B., & Ramsey, B. (2001). Defining a pulmonary exacerbation in cystic fibrosis. *The Journal of Pediatrics*, *139*(3), 359–365.

Saiman, L., Marshall, B. C., Mayer-Hamblett, N., Burns, J. L., Quittner, A. L., Cibene, D. A., Coquillette, S., Fieberg, A. Y., Accurso, F. J., Campbell, P. W., III, & Macrolide Study Group. (2003). Azithromycin in patients with cystic fibrosis chronically infected with *Pseudomonas aeruginosa*: A randomized controlled trial. *JAMA*, *290*(13), 1749–1756.

Sanders, D. B., Bittner, R. C., Rosenfeld, M., Hoffman, L. R., Redding, G. J., & Goss, C. H. (2010). Failure to recover to baseline pulmonary function after cystic fibrosis pulmonary exacerbation. *American Journal of Respiratory and Critical Care Medicine*, *182*(5), 627–632.

Sequeiros, I. M., & Jarad, N. (2012). Factors associated with a shorter time until the next pulmonary exacerbation in adult patients with cystic fibrosis. *Chronic Respiratory Disease*, *9*(1), 9–16.

Smith, A. L., Doershuk, C., Goldmann, D., Gore, E., Hilman, B., Marks, M., Moss, R., Ramsey, B., Redding, G., Rubio, T., & Williams-Warren, J. (1999). Comparison of a beta-lactam alone versus beta-lactam and an aminoglycoside for pulmonary exacerbation in cystic fibrosis. *The Journal of Pediatrics*, *134*(4), 413–421.

Treggiari, M. M., Rosenfeld, M., Mayer-Hamblett, N., Retsch-Bogart, G., Gibson, R. L., Williams, J., Emerson, J., Kronmal, R. A., Ramsey, B. W., & EPIC Study Group. (2009). Early anti-pseudomonal acquisition in young patients with cystic fibrosis: Rationale and design of the EPIC clinical trial and observational study. *Contemporary Clinical Trials*, *30*(3), 256–268.

Twisk, J. W., Smidt, N., & de Vente, W. (2005). Applied analysis of recurrent events: A practical overview. *Journal of Epidemiology & Community Health*, *59*(8), 706–710.

VanDevanter, D. R., Flume, P. A., Morris, N., & Konstan, M. W. (2016). Probability of IV antibiotic retreatment within thirty days is associated with duration and location of IV antibiotic treatment for pulmonary exacerbation in cystic fibrosis. *Journal of Cystic Fibrosis*, *15*(6), 783–790.

Waters, V., Stanojevic, S., Atenafu, E. G., Lu, A., Yau, Y., Tullis, E., & Ratjen, F. (2012). Effect of pulmonary exacerbations on long-term lung function decline in cystic fibrosis. *European Respiratory Journal*, *40*(1), 61–66.

Waters, V. J., Stanojevic, S., Sonneveld, N., Klingel, M., Grasemann, H., Yau, Y. C., Tullis, E., Wilcox, P., Freitag, A., Chilvers, M., & Ratjen, F. A. (2015). Factors associated with response to treatment of pulmonary exacerbations in cystic fibrosis patients. *Journal of Cystic Fibrosis*, *14*(6), 755–762.

Wienke, A. (2010). *Frailty models in survival analysis*. Chapman and Hall/CRC.

Winkelmann, R. (1995). Duration dependence and dispersion in count-data models. *Journal of Business & Economic Statistics*, *13*(4), 467–474.

Yan, J., & Fine, J. P. (2008). Analysis of episodic data with application to recurrent pulmonary exacerbations in cystic fibrosis patients. *Journal of the American Statistical Association*, *103*(482), 498–510.

Zelterman, D., Grambsch, P. M., Le, C. T., Ma, J. Z., & Curtsinger, J. W. (1994). Piecewise exponential survival curves with smooth transitions. *Mathematical Biosciences*, *120*(2), 233–250.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Rice J. D., Johnson R. L., Juarez-Colunga E., Zemanick E. T., Rosenfeld M., Wagner B. D. (2022). Application of gap time analysis with flexible hazards to pulmonary exacerbations in the EPIC observational study. *Biometrical Journal*, 1–15. https://doi.org/10.1002/bimj.201900255