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Dynamics of Disease Progression and Gastrostomy Tube Placement in Children and Adolescents with Cystic Fibrosis: Application of Joint Models for Longitudinal and Time-to-Event Data

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Abstract

Background—Previous small-sample studies have examined the effect of gastrostomy (g-) tube placement on weight, height, and lung function in adolescent patients with cystic fibrosis (CF), but there are no RCTs to date reporting efficacy. The goal of this study was to implement a dynamic prediction model to 1) understand the role of rapid lung function decline in g-tube placement in real-world clinical settings; 2) provide a prognostic tool with the potential to aid clinicians in optimizing the timing of g-tube placement, in relation to rate of lung function decline and current nutrition status.

Methods—A dynamic prediction model was developed, utilizing data on patients 6–21 years of age from the Cystic Fibrosis Foundation Patient Registry (1997–2013). A joint model was implemented, which coupled a semiparametric mixed model to characterize rapid lung function decline with a time-to-event model to identify risk factors for g-tube initiation.

Results—The 4,034 individuals (21.3%) who underwent g-tube placement during adolescence or young adulthood had poorer nutrition and lung function at baseline and initially had increased rates of pancreatic enzyme use, infection and gastroesophageal reflux disease, compared to those who did not receive g-tubes; these associations changed over follow up. Rapid lung function decline was associated with increased risk of g-tube supplementation.

Conclusions—By jointly modeling longitudinal patterns of lung function decline with g-tube delivery, it is possible to construct prognostic aids to evaluate treatment delivery in relation to the onset of rapid lung function decline and other important clinical markers. These algorithms have the potential to enable more effective monitoring of disease progression and promote more timely treatment delivery.

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Keywords

cystic fibrosis patient registry; functional data analysis; individualized prediction; longitudinal analysis; nutrition; pulmonary function

1. INTRODUCTION

The natural history of cystic fibrosis (CF) disease progression has been studied over the past several decades, consistently providing insights into the importance of maintaining lung function and nutrition over the lifespan(1–3). Many CF patients experience attenuated decreases in their lung function (expressed as forced expiratory volume in 1 second of % predicted, or FEV₁) during adolescence and young adulthood. These precipitous drops in FEV₁ are referred to as periods of rapid lung function decline and can be observed in profiles of individual patients (Figure 1, left panel). Poor nutrition and other indicators of severity have been identified as predictors of rapid FEV₁ decline(4). The US Cystic Fibrosis Foundation Guidelines recommend gastrostomy (g-) tube placement if an individual's BMI is below the 50th percentile(5); however, BMI percentile is not as accurate for children of short stature(6). In 2013, 11.2% of patients treated at accredited US CF centers were reported as using g-tubes, but median BMI percentile among these patients 2–19 years of age was 53.3(7). Only a handful of studies have reported g-tube effectiveness for patients and there are no randomized controlled trials(8).

Despite sparse findings on g-tube initiation and clinical outcomes like FEV₁, the immense amount of data from CF patient registries continues to grow; meanwhile, there have been several statistical developments to aid in modeling complex associations between clinical markers measured repeatedly over time and events of interest, as well as prediction of clinical outcomes. Joint models are gaining favor in the statistical literature for these purposes(9). In a recent example, a joint model was developed to provide a prognostic calculator for risk of prostate cancer recurrence(10). The overarching joint model is a combination—typically of a longitudinal submodel and a time-to-event submodel. The goal of the current study was to harness the power of joint modeling and intensive data on longitudinal FEV₁ decline and other important markers in CF to develop an epidemiologic model with potential prognostic utility in assessing the need for g-tube initiation.

2. METHODS

2.1 Study design and data

A retrospective longitudinal cohort study was performed using the US Cystic Fibrosis Foundation Patient Registry (CFFPR), examining the association between patterns of age-related lung function decline and g-tube initiation. Observed FEV₁ was expressed as percentage of predicted using established reference equations(11, 12). The study was approved by the local IRB. Data acquired after lung transplant were excluded.

Patients with encounter-level FEV₁ data recorded during childhood and adolescence (ages: 6–21 years) in the CFFPR between January 1, 1997, and December 31, 2013, were eligible. G-tube initiation (yes or no) was defined using the encounter-level CFFPR variable

supplemental feeding (route: g tube/button). Patients younger than 6 years of age were excluded due to potentially unreliable pulmonary function testing. Because the majority of relevant explanatory variables associated with FEV₁ decline and/or g-tube initiation were consistently documented in the CFFPR beginning in 1997, available data from 1997 onward was considered. Baseline for each patient was defined as the time that the first measurement was available during the eligibility period. Time since baseline (in years) is referred to as follow up during this period.

2.2 Model development

Prior to model development, descriptive statistics, including mean (SD) or median (range) as appropriate for continuous variables and n (%) for categorical variables, were used to summarize cohort characteristics, overall and according to g-tube initiation. The two outcomes of interest were longitudinal FEV₁ and g-tube initiation; a submodel was specified for each of these outcomes. Covariates for each of the two submodels were selected based on literature review of nutrition and lung function decline in CF. The structure of the joint model follows the shared parameter framework that has been described previously in the literature(13). Briefly, the overarching model consists of two components or submodels; in this study, the longitudinal submodel for FEV₁ is a semiparametric mixed effects model, and the event submodel for g-tube placement is a parametric Weibull model.

Longitudinal submodel—Prior to implementing the joint model, longitudinal FEV₁ was fit using a semiparametric mixed effects model that has been previously used to estimate rapid lung function decline(14). The evolution of FEV₁ was modeled as a function of time since baseline using cubic b-splines to characterize its nonlinearity (Figure 1, right panel). Allowing for nonlinearity in the FEV₁ trajectories is important, because incorrect assumptions about the curvature can lead to biased estimates of the trends over time, particularly for joint models(15). Baseline covariates included age, FEV₁ and gender. Time-varying covariates, collected at each clinical encounter, included cystic fibrosis related diabetes (CFRD), gastroesophageal reflux disease (GERD), methicillin-resistant *Staphylococcus aureus* (MRSA), *pseudomonas aeruginosa* (*Pa*), and socioeconomic status (SES, defined as having state insurance). Annual number of pulmonary exacerbations (PEs) was also included as a time-varying covariate; this variable was categorized as 0, 1, 2, 3 or more for a given year. To characterize variation in FEV₁, both between patients and within an individual patient over time, subject-specific random intercepts and slopes were included. The remaining variation was expressed as measurement error. Estimates from the separate longitudinal analysis were used as initial values for the joint model estimation. The complete longitudinal submodel is presented in Appendix A2.1.

Event submodel—A Kaplan-Meier curve was first used to estimate timing of g-tube initiation (the event of interest) over follow up (Figure A1 in Appendix). A Weibull time-to-event model was used to examine associations between g-tube initiation and relevant covariates. The baseline hazard for the Weibull model was estimated using cubic b-splines (see Appendix A2.2). Due to software package constraints, only covariates that are constant (i.e., non-time-varying) could be incorporated into the joint model. Baseline covariates included age, gender, and age at CF diagnosis. To overcome the software limitation, the last

observed value of each of the following variables as covariates was used: CFRD, GERD, pancreatic enzyme use, number of PEs within the year, and BMI percentile; for individuals who received g-tubes, their covariate values were the observations at the time of first recorded g-tube use. Data subsequent to the g-tube initiation event were not included in the modeling. Random intercepts and slopes were also included in this model.

Shared parameters—The joint model was implemented with the parameters specified above for the longitudinal and event submodels, and additionally included shared parameters. Parameters that were shared between the models were 1) the mean evolution of FEV₁ over time for each subject, which is meant to estimate the true longitudinal process of FEV₁ for each patient; 2) the corresponding derivative of this longitudinal process, which provides subject-specific estimates of rate of lung function decline. These processes were shared by including them in the event submodel, which is fully specified in Appendix A2.2. Having these shared parameters or common functions between the two submodels enabled dynamic prediction of g-tube initiation while accounting for degree of rapid lung function decline in the individual patient.

Implementation—All analyses were performed using R (R Foundation for Statistical Computing, Vienna, Austria); the joint model was implemented using the Markov Chain Monte Carlo (MCMC) algorithms available in the JMBayes package(16). Coefficient estimates were obtained through Bayesian analysis. A total of 30,000 MCMC iterations were performed with 20,000 iterations removed for burn-in (Appendix A3). Results are expressed as the posterior mean and 95% credible interval (CI). In the longitudinal submodel, estimates in which the 95% CI do not contain zero are considered statistically significant. In the event submodel, hazard ratio estimates in which the 95% CI does not include the value 1 are considered statistically significant. Model diagnostics and implementation code are available in the Appendix (Sections A3 and A4, respectively).

3. RESULTS

3.1 Study cohort

The analysis cohort included 18,911 patients with 282,201 observations. Patients had a median (IQR) follow-up time of 4.4 (1.5–8.1) years with 12.0 (5.0–23.0) encounters. Patients with recorded g-tube use tended to be younger and had more severe clinical characteristics, compared to their counterparts who were not prescribed g-tubes (Table 1). As expected, pancreatic enzyme use was higher among g-tube patients at baseline, although most patients who did not receive g-tubes were eventually prescribed pancreatic enzymes. Similarly, the percentage of GERD cases was substantially higher in the g-tube group at baseline, but both groups had similar GERD occurrence over follow up. Baseline FEV₁ was higher in the g-tube group.

3.2 Model findings

Longitudinal submodel—Spline coefficient estimates and overall results indicated that FEV₁ progression was not linear with respect to patient age or follow-up time, and rate of decline was variable among patients (Figure 2). Male patients with higher baseline FEV₁,

pancreatic enzyme use and higher SES and BMI percentile tended to have better FEV₁ over time (Table 2). Higher PE frequency was associated with worse FEV₁. Having GERD was not associated with change in FEV₁. Infection with MRSA or *Pa* contributed to worse FEV₁.

Event submodel—Younger patients who were diagnosed early with CF and had GERD, CFRD or used pancreatic enzymes were less likely to undergo g-tube placement (Table 1). Although BMI percentile was a statistically significant predictor of increased risk of g-tube initiation, the hazard ratio was 0.99, indicating a lack of clinical significance. Patients who experienced no PEs had a 28% reduction in risk for g-tube initiation.

Shared parameters—The longitudinal evolution of FEV₁ was associated with g-tube initiation (Table 2, next-to-last row), implying that having higher lung function over time corresponded to a 3.2% decreased risk of g-tube initiation. A given patient would be less likely to undergo g-tube placement, provided her lung function levels remain high (Figure 3). Similarly, having a higher rate of FEV₁ over time (i.e. an increasing FEV₁ trajectory) was associated with a 5.6% decreased risk of g-tube initiation (Table 2, last row). Based on this result, a patient is less likely to undergo g-tube placement if she maintains lung function over time (Figure 4).

Although the risk reductions for g-tube initiation were slight, particularly for the evolution of lung function, the joint model enabled dynamic predictions of individual patients over follow-up times. For illustration of the clinical relevance, a female CF patient who entered the CFFPR at 6.63 years of age is displayed. Dynamic prediction was performed for this patient over a range of follow up times after her first encounter: 2.7, 3.7, 4.7 and 5.8 years. It is of interest to determine her risk of needing a g-tube based on her current status (clinical covariates and FEV₁ trajectory) at a given clinical visit. At the first visit, it appears highly likely that she will not need g-tube placement over the next few years (Figure 3, upper-left panel). After additional FEV₁ data are acquired one year later, her probability of remaining g-tube free slightly increases (Figure 3, upper-right panel). Based on the joint model, this result would be expected if the patient has maintained or improved her lung function over time. After another year has passed, her risk has elevated (Figure 3, lower-left panel). By the time of her next follow up, about 5.8 years from baseline, decline in FEV₁ is more apparent and the probability that she will remain g-tube free in the coming years has decreased. Additional patients taken from the CFFPR are displayed in the Appendix (Figures A6–A9).

As shown in the model, the patient's ability to maintain or improve lung function will impact the likelihood of g-tube placement. For the female CF patient, her estimated rate of lung function decline at the first follow-up visit is about 3% predicted/year (Figure 4, upper-left panel). As expected based on CF disease progression, her rate of decline worsens over follow-up visits. There is a slight worsening from 2.7 to 3.7 years of follow up (Figure 4, upper-right panel), then from 3.7 to 4.7 years of follow up (Figure 4, lower-left panel). By the last follow-up visit, her rate of decline is about 4% predicted/year, and it is noticeable that her probability of remaining g-tube free in subsequent years is as low as 65% (Figure 4, lower-right panel).

4. DISCUSSION

This is the first study, to the authors' knowledge, investigating the association between g-tube initiation and patterns of CF lung function decline using a patient registry and providing individual dynamic predictions that could be used in real-world clinical settings. Although an increasing number of studies have reported nonlinearity in CF lung function trajectories, there have been limited applications that provide dynamic prediction through joint modeling(17, 18). This study illustrates how application of state-of-art methodology can provide insights into CF disease progression and treatment delivery that were previously unknowable with conventional analytic techniques, such as the separate linear mixed effects model or time-to-event analyses that are typically employed. Using either of these approaches alone would not have allowed inferential testing of the associations between lung function patterns and G-tube placement or individualized dynamic prediction.

Many of the associations found in the study were expected, such as more severe clinical characteristics being indicative of worsening lung function. The lack of associations, particularly in the G-tube event submodel, was surprising. Most noteworthy is the hazard ratio for BMI percentile and G-tube initiation. It was also striking that pancreatic enzyme use and being diagnosed with GERD or CFRD corresponded to a reduced risk of receiving a g-tube. Although these associations could be related to the covariate construction in the event submodel, it is also possible that other considerations are made when deciding whether to prescribe g-tubes. Given the quality improvement initiatives of the CF Foundation and its many accredited centers, considerations could be provider or center dependent and may not be recorded as variables in the database. This scenario lends itself to confounding-by-indication bias, which plagues analyses of CF and other registry data(19).

This study corroborates findings on rapid lung function decline in CF that have been published previously, which have found that lung function decline is nonlinear during adolescence and young adulthood. One of these studies has shown that individuals experienced most rapid decline at a median (IQR) of 16.3 (13.5–21.0) years; average degree of maximal FEV₁ loss was 2.0% predicted/year(14). Another recent retrospective single-center analysis (20) fit FEV₁ trajectories of CF patients 6–25 years of age with a random change point model to allow the timing of rapid decline to differ by individual. The study revealed two subgroups of adolescents; at roughly 14.6 years of age, about 30% experienced steady FEV₁ decline (0.5% predicted/year), while the remaining 70% experienced more progressive FEV₁ decline (4.4% predicted/year). In addition to this variable decline, each individual FEV₁ trajectory exhibits strong within-patient correlation. This model captures this correlation through random effects in the longitudinal submodel. There are also random effects included in the event submodel.

There are the usual pitfalls with observational data sources such as the CFFPR(21). The data used for this study do not have adherence metrics available, which could provide insight into g-tube tolerability. Although age at CF diagnosis is adjusted for in the model, it is possible that estimates are sensitive to left truncation, which is a pervasive issue in registry analyses. There are several extensions that could be made using this approach to further investigate g-tube initiation and clinical outcomes in CF. For example, it may be useful to extend the g-

tube event submodel to accommodate recurrent events (i.e., individuals who undergo g-tube placement more than once). This approach could give some indication of g-tube tolerability in the absence of adherence data. Future statistical work should focus on extending the implementation used here to time-varying covariates for the event submodel. To combat the treatment selection bias inherent in g-tube placement, instrumental variables analysis could be considered(22). It would be of particular clinical interest to apply a high-dimensional joint model to understand the evolution of associations among the many clinical markers important in CF, particularly the associations among FEV₁, BMI and g-tube use. The current work and any of these extensions could further understanding of g-tube initiation and clinical outcomes in real-world settings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflicts of Interest and Sources of Funding

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Figure 1. Observed lung function trajectories of cystic fibrosis patients

For 100 randomly selected cystic fibrosis patients. The blue lines represent 50 patients who received g-tubes; the points without lines represent 50 patients who did not receive g-tubes; graphs are displayed with respect to disease progression over age (left panel) and over follow up time (right panel).

Figure 2. Fitted lung function trajectories of cystic fibrosis patients

For the 100 randomly selected cystic fibrosis patients from Figure 1. FEV_1 trajectories were fitted using the joint model (see Methods). The red lines represent 50 patients who received g-tubes; the black lines represent 50 patients who did not receive g-tubes; graphs are displayed with respect to disease progression over age (left panel) and over follow up time (right panel).

Figure 3. Dynamic prediction for G-tube probability of a given cystic fibrosis patient according to evolution of lung function during follow up

Plots are for a female cystic fibrosis patient who entered the registry at 6.63 years of age and is followed up at four different times (2.7, 3.7, 4.7 and 5.8 years). The left side of each plot shows her FEV₁ data (marked as “*”) that have been observed up to a particular follow-up time; the red line is the fitted FEV₁ trajectory up to the follow up time. The dashed vertical line indicates the time of prediction (e.g. clinical visit). The right side of each plot shows her probability of remaining g-tube free (denoted by the smooth red line) with 95% confidence bands (shaded gray) for prediction uncertainty.

Figure 4. Dynamic prediction for G-tube probability of a given cystic fibrosis patient according to rate of lung function decline during follow up
Plots are a continuation from Figure 3. The left side of each plot shows her estimated rate of FEV₁ decline (black line) up to a particular follow-up time based on observed FEV₁. On the right side of each plot, her probability of future g-tube initiation is shown.

Table 1

Baseline characteristics of cystic fibrosis patients, overall and by g-tube initiation

Patient Characteristics	G-Tube	Non G-tube	Overall
N(%)	4,034 (21.3)	14,877 (78.7)	18,911
Baseline age, in years	9.42 (9.31, 9.53)	11.35 (11.29, 11.41)	10.94 (10.89, 11.00)
Baseline FEV ₁ %	86.16 (85.60, 86.72)	78.52 (78.20, 78.85)	80.15 (79.87, 80.44)
BMI percentile	32.59 (32.18, 33.01)	30.19 (29.96, 30.42)	30.70 (30.50, 30.90)
CFRD			
At baseline, %	1.8	0.8	1.0
Ever during follow-up, %	6.5	11.1	10.1
GERD			
At baseline, %	8.2	1.0	2.5
Ever during follow-up, %	8.6	12.0	11.3
Male, %	49.8	52.5	51.9
MRSA			
At baseline, %	9.7	3.2	4.6
Ever during follow-up, %	20.1	26.2	24.9
<i>Pa</i>			
At baseline, %	20.9	31.2	29.0
Ever during follow-up, %	67.2	72.7	71.5
PE, annual number [^]			
0	74.4	66.3	68.0
1	16.7	13.4	14.1
2	5.4	9.7	8.8
3 or more	3.5	10.7	9.1
Pancreatic enzymes			
At baseline, %	50.7	6.3	15.7
Ever during follow-up, %	36.8	59.7	54.8
Lower SES ^{^^}			
At baseline, %	39.6	35.6	36.5
Ever during follow-up, %	54.3	51.2	51.8

BMI = body mass index; CFRD = cystic fibrosis related diabetes; GERD = gastroesophageal reflux disease; MRSA = methicillin-resistant *Staphylococcus aureus*; *Pa* = *pseudomonas aeruginosa*; PE = pulmonary exacerbation; SES = socioeconomic status;

[^] number of occurrences during the baseline year;

^{^^} indicated by state insurance

Table 2

Coefficients and standard error of coefficients for the joint model predicting G-tube initiation and evolution of cystic fibrosis lung function decline

	Parameter	95% CI*	
	Estimate	Lower	Upper
Semiparametric longitudinal submodel for FEV₁ decline^a			
Curve			
Intercept	17.01	16.27	17.72
Spline coefficients			
b_1	-1.66	-1.87	-1.43
b_2	-4.80	-5.07	-4.52
b_3	-13.25	-13.74	-12.76
b_4	-25.63	-26.46	-24.99
b_5	-34.10	-35.13	-33.26
Baseline age	-0.40	-0.43	-0.37
Male	0.38	0.10	0.62
Baseline FEV ₁	0.77	0.76	0.78
GERD	0.24	-0.05	0.49
CFRD	-0.01	-0.29	0.27
MRSA	-0.35	-0.52	-0.18
Pa	-0.35	-0.43	-0.26
Lower SES	-0.35	-0.49	-0.22
Pancreatic Enzymes	0.56	0.45	0.68
PE, annual number (Ref: 1) ^			
2	-0.71	-0.88	-0.56
3 or more	-2.11	-2.31	-1.93
0	1.33	1.21	1.46
BMI percentile	0.17	0.17	0.17
Variation			
Measurement error (σ)	9.09	9.07	9.12
Intercept (σ_0)	7.78	---	---
Slope (σ_1)	2.49	---	---
Weibull event submodel for g-tube initiation^b			
Male	0.980	0.920	1.048
Baseline age	0.836	0.828	0.846
Age at Diagnosis	0.949	0.936	0.963
GERD	0.788	0.702	0.892
CFRD	0.348	0.308	0.398
PancEnzymes	0.549	0.512	0.586
PE, annual number (Ref: 1) ^			

	Parameter	95% CI [*]	
	Estimate	Lower	Upper
2	1.187	1.078	1.308
3	1.368	1.247	1.516
0	0.722	0.665	0.788
BMI percentile	0.994	0.992	0.996
Shared parameters			
Longitudinal evolution of FEV ₁ ($\gamma_1, \eta_i(t)$)	0.968	0.966	0.970
Rate of decline in FEV ₁ ($\gamma_2, \eta'_i(t)$)	0.944	0.922	0.967

BMI = body mass index; CFRD = cystic fibrosis related diabetes; GERD = gastroesophageal reflux disease; MRSA = methicillin-resistant *Staphylococcus aureus*; *Pa* = *Pseudomonas aeruginosa*; PE = pulmonary exacerbation; SES = socioeconomic status;

^a Each effect is expressed as linear mixed model;

^b Each effect is expressed as the estimated hazard ratio (HR), where HR > 1 indicates increased risk of g-tube initiation;

^{*} Results in which zero is not contained in the CI are considered statistically significant;

[^] number of occurrences during the baseline year where 1 PE in the year is the reference category;

^{^^} indicated by state insurance; the coefficients $b = (b_1, \dots, b_5)$ are for natural cubic spline (see Methods); $(\sigma, \sigma_0, \sigma_1)$ are the square root of variance of e_{ij} , b_{0i} and b_{1i} , respectively (see Appendix A2); (γ_1, γ_2) are for shared parameters $\eta_i(t)$ and $\eta'_i(t)$ (see Methods and Appendix A2).