ARTICLE

Parametric Time-to-Event Model for Acute Exacerbations in Idiopathic Pulmonary Fibrosis

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We describe a parametric time-to-event model for idiopathic pulmonary fibrosis (IPF) exacerbations and identify predictors of exacerbation risk using data obtained for the tyrosine-kinase inhibitor nintedanib in two phase III studies (INPULSIS-1/2). Parametric survival analysis was performed on time to first exacerbation (censoring on day 372), with univariate analysis to select statistically significant covariates ($P = 0.05$). Multivariate covariate models were developed using stepwise covariate modeling with forward inclusion ($P = 0.05$) and backward elimination ($P = 0.01$). Sixty-three first exacerbation events were reported across 1,061 subjects in the INPULSIS studies. Baseline and decline of forced vital capacity (FVC)/percent-predicted FVC (%pFVC), supplemental oxygen use, baseline CO diffusing capacity and age were statistically significant in the univariate analysis. The final covariate model included decline in FVC to week 52, baseline %pFVC, supplemental oxygen use, and age. The developed model may be used to identify patients at high risk of IPF exacerbations and accelerate development of novel treatments.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Acute exacerbations are clinically significant in idiopathic pulmonary fibrosis (IPF) and are associated with high mortality rates. Risk factors, including decreased pulmonary function, have been identified.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ A parametric survival analysis on acute exacerbations has never been conducted. This study aimed to characterize the time-dependent profile of exacerbation risk and quantify the effect of potential predictors.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ A parametric time-to-event model was developed to quantify the risk of acute exacerbations in IPF within 52 weeks. Decline in forced vital capacity, baseline percent-predicted forced vital capacity, supplemental oxygen, and age were selected in the final covariate model incorporating both baseline variables and longitudinal change in pulmonary function.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ Better understanding of predictors of acute exacerbations can contribute to more efficient trial design and patient selection in clinical studies aiming to reduce acute exacerbations in IPF. Identification of patients at high risk may aid appropriate patient management and timely initiation of prevention strategies in clinical practice in this vulnerable patient population.

Idiopathic pulmonary fibrosis (IPF) is a chronic disease of unknown etiology involving progressive fibrosis of the lungs, affecting 10–60 people per 100,000 in the United States.[1] IPF is of particular clinical interest due to current incomplete understanding of its pathobiology, its susceptibility to misdiagnosis and inappropriate management, and its poor prognosis with a median survival of ~ 3 years.[1–4] Two approved antifibrotic treatments for IPF—nintedanib and pirfenidone—have been shown to slow the annual rate of decline in forced vital capacity (FVC) consistent with slowing disease progression,[5–8] and nintedanib has also been shown to reduce the risk of an acute exacerbation in a pooled analysis of phase II and III studies.[9]

In the INPULSIS trials, on which nintedanib approval was based, an acute exacerbation of IPF was defined as an event meeting all of the following criteria: unexplained worsening or development of dyspnea within the previous 30 days; new diffuse pulmonary infiltrates visualized on chest radiography, high-resolution computed tomography, or both, or the development of parenchymal abnormalities with no pneumothorax or pleural effusion (new ground-glass opacities) since the preceding visit.[5] The reported annual incidence of acute exacerbations in patients with IPF ranges between 1% and 20%.[3,10,11] It is currently unknown whether unexplained acute exacerbations occur as a response to external insults leading to sudden respiratory decline, or due to an intrinsic acceleration of the underlying pathobiological progression.[10,11] Multiple studies have demonstrated a significant association between acute

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Received: September 12, 2019; accepted: November 11, 2019. doi:10.1002/psp4.12485

exacerbations and mortality, with short-term mortality of ~ 50% reported in patients with acute exacerbations.[12–14] In IPF, the definition of acute exacerbation may vary between studies, and may be expanded to include events for which a trigger, such as infection, can be identified.[11] Given the difficulties in defining exacerbations and risk, incorporation of acute exacerbation risk and management into treatment guidelines and regulatory thresholds remains suboptimal. In the INPULSIS trials, the incidence of acute exacerbations (using the definition above, excluding events with a known trigger) was a key secondary endpoint.[5] With the high variability in the clinical course of IPF and the unpredictability of the occurrence of acute exacerbations,[14–16] there is need for further understanding of the underlying risk factors, with the goal of identifying patients most likely to benefit from prevention or treatment of acute exacerbations. A number of studies have reported various risk factors for acute exacerbation of IPF. The most consistently reported risk factor is low FVC,[11] whereas other proposed predictors include pulmonary hypertension, dyspnea (Medical Research Council dyspnea scale), alveolar to arterial oxygen pressure difference (A_aDO_2), emphysema, and recent decline in FVC. Conflicting evidence has been presented on diffusing capacity of the lung for carbon monoxide (DL_{CO}), emphysema, smoking, and body mass index as predictors for acute exacerbations.[12,13,17–19] Other candidate predictors include the bronchoalveolar lavage cell cytokine profile and pepsin level as well as baseline KL-6 level.[20–22] Additionally, there are data suggesting the presence of identifiable triggers for some cases of acute exacerbations, such as cold weather, immunosuppression, infection, aspiration, pollution, and certain surgical procedures.[3] Age and sex have not been shown to be predictors of acute exacerbations.[12,15,18,20–22]

Although numerous studies have investigated risk factors for acute exacerbations, conflicting evidence exists with many different proposed factors. Furthermore, many analyses were limited by their small sample sizes. To our knowledge, parametric time-to-event (TTE) survival analysis has never been performed to quantify the hazard for development of acute exacerbations with consideration of potential risk factors. The phase III INPULSIS-1 and 2 studies demonstrated efficacy of nintedanib in slowing progression in patients with IPF.[5] In addition, nintedanib numerically reduced the risk of a first acute exacerbation by 36% vs. placebo (hazard ratio (HR) 0.64; 95% confidence interval (CI) 0.39, 1.05) in a prespecified pooled analysis.[5] [Correction added on 4th February, 2020, after first online publication: In the preceding sentence, punctuation was missing in between the values 0.39 1.05, it should be 0.39, 1.05]. The aim of this study was to develop a parametric TTE model to quantitatively characterize the hazard for acute exacerbations and assess the effect of potential predictors using pooled data from the INPULSIS-1 and 2 studies, and to investigate the association between longitudinal changes in pulmonary function and exacerbation risk within the framework of TTE analysis.

METHODS

Subjects

This analysis included all patients who received at least one dose of nintedanib or placebo in either of two randomized, double-blind, placebo-controlled phase III trials—INPULSIS-1 and 2 (NCT01335464 and NCT01335477).[5] Patients in these two trials were randomized in a 3:2 ratio to receive nintedanib 150 mg twice daily or placebo for 52 weeks. The dose of nintedanib could be interrupted or reduced to 100 mg twice daily to manage adverse events. Spirometric tests were performed at baseline, at 2, 4, 6, 12, 24, 36, and 52 weeks, and at the follow-up visit 4 weeks after the treatment period ended. Patients who discontinued treatment prior to the end of 52 weeks were asked to attend all visits as planned except for the follow-up visit. The protocol for the INPULSIS trials was approved by an ethics committee or institutional review board at every participating center, and informed consent was obtained from all participants.

Base model development

All investigator-reported acute exacerbations up to 372 days were used for the parametric TTE analysis, and patients who did not experience an acute exacerbation were censored at day 372. Data set processing, exploratory analysis, and graphical analysis were conducted in R (version 3.4.3; The R Foundation for Statistical Computing, Vienna, Austria). Models were developed using the Laplace estimation method in NONMEM (version 7.4.3; ICON Development Solutions, San Antonio, TX).

Exponential, Weibull, Gompertz, and log-logistic distributions, among the most commonly used parametric hazard distributions, were tested for the base hazard model. Parameterization for each of the distributions is shown in Eqs. 1–4, respectively:

$$h_0(t) = \lambda \tag{1}$$

$$h_0(t) = \lambda e^{\gamma \ln(t)} \text{ or } h_0(t) = \lambda t^{\gamma} \tag{2}$$

$$h_0(t) = \lambda e^{\gamma t} \tag{3}$$

$$h_0(t) = \frac{\lambda \gamma t^{\gamma - 1}}{(1 + \lambda t^{\gamma})} \tag{4}$$

where $h_0(t)$ represents the base hazard at time t, while λ and γ represent estimated parameters. The base model was selected based on the objective function value (OFV) between nested models, where a decrease in OFV of > 3.84 (corresponding to a P value < 0.05) was needed to select a more complex model. Akaike information criterion (AIC) was used to compare non-nested models. In addition, a base model was accepted only if adequate precision of the parameter estimates could be achieved. Predictive performance of the selected base model was evaluated with the visual predictive check (VPC) plot produced by PsN (version 4.8.1; Uppsala University, Uppsala, Sweden), which consists of the Kaplan–Meier curve of the observed data overlaid with the 95% prediction interval derived from 100 simulations, with censoring applied at 372 days.

Univariate analysis

The following variables were evaluated as predictors in covariate model building: (i) demographic factors (age, sex, height,

body mass index, body surface area, race, smoking status, and alcohol consumption), (ii) treatment-related factors (study arm, comedication of systemic corticosteroids, bronchodilators, supplemental oxygen, proton pump inhibitor, or histamine receptor-2 (H_2) inhibitor), and (iii) disease-related factors (baseline FVC, baseline percent-predicted FVC (%pFVC), baseline percent-predicted DL_{CO} (%pDL_{CO}), emphysema, and predicted changes in FVC or %pFVC from baseline to 4, 6, 12, 24, 36, and 52 weeks).

All variables were available at baseline except for predicted changes in FVC and %pFVC values from baseline to 4, 6, 12, 24, 36, and 52 weeks. These predicted variables were obtained from two linear disease progression models (simplified from Schmid *et al.*[23]), which were previously developed from spirometry data from a nintedanib phase II study (TOMORROW)[6] and INPULSIS[5] (**Table S1**).

Initial screening of potential predictors was performed using stratified VPC plots of the selected base model. In the univariate analysis, predictors identified as influential in this graphical evaluation were incorporated in the hazard model assuming proportional hazards following Eqs. 5 and 6 for categorical and continuous variables, respectively:

$$h_i(t) = h_0(t) \times e^{\theta \times \mathrm{cov}_i} \quad (5)$$

$$h_i(t) = h_0(t) \times e^{\theta \times (\mathrm{cov}_i - \mathrm{cov}_{\mathrm{median}})} \quad (6)$$

where $h_0(t)$ is the baseline hazard as a function of t, $h_i(t)$ represents the hazard at time t for the i^{th} individual, cov_i is the value of a covariate for the i^{th} individual, θ represents the effect of the covariate on the hazard of developing acute exacerbation, and $\mathrm{cov}_{\mathrm{median}}$ represents the median value of a continuous covariate. All categorical variables were coded as dichotomous variables with values of 0 or 1. Missing continuous variables were imputed with the median value, and missing categorical variables were imputed with the value of the most common category. A decrease in OFV > 3.84, corresponding to a P value < 0.05, was used as the cutoff for determining statistical significance of a covariate. HRs and their CIs were computed based on the point estimate and standard error of the coefficient θ produced by NONMEM. Variables that were statistically significant in the univariate analysis were subsequently tested in a multivariate analysis.

Covariate model development

Two multivariate covariate models were developed using the stepwise covariate modeling (SCM) procedure in PsN: one with baseline variables available at time $t = 0$, and the other with baseline variables and variable(s) representing longitudinal change in pulmonary function. A value of 0.05 was used as the P value for the forward selection, and 0.01 as the P value for the backward elimination. Predictive performance of the covariate TTE models was evaluated with VPC plots produced by PsN, as described above. One thousand bootstraps conducted in PsN were used to estimate uncertainty in the parameter estimates and the associated HRs in the covariate models.

RESULTS

Base hazard model

All 1,061 patients from the treated set of the INPULSIS studies were included in the parametric TTE analysis. The baseline demographics summarized in **Table 1** were comparable between the placebo and active treatment group. Overall, 63 first acute exacerbations were reported until

Table 1 Baseline demographics in the INPULSIS studies

	Placebo (*N* = 423)	Nintedanib (*N* = 638)	Total (*N* = 1061)
Age, years	67.00 ± 7.88	66.6 ± 8.13	66.80 ± 8.03
Male	334 (78.96%)	507 (79.47%)	841 (79.26%)
Race			
Asian	128 (30.26%)	194 (30.41%)	322 (30.35%)
Others (white/black/missing)	295 (69.74%)	444 (69.59%)	739 (69.65%)
Height, cm	168.00 ± 9.11	167.00 ± 9.31	168.00 ± 9.24
BMI, kg/m^2	27.60 ± 4.58	28.10 ± 4.56	27.90 ± 4.57
BSA, m^2	1.88 ± 0.22	1.88 ± 0.22	1.88 ± 0.22
Ex-smoker or current smoker	301 (71.16%)	464 (72.73%)	765 (72.10%)
Alcohol use	238 (56. 26%)	379 (59.40%)	617 (58.15%)
FVC, L	2.73 ± 0.81	2.71 ± 0.76	2.72 ± 0.78
FVC (% predicted)	79.30 ± 18.20	79.70 ± 17.60	79.60 ± 17.80
DL_{CO} (% predicted)	47.00 ± 13.40	47.40 ± 13.50	47.20 ± 13.50
Emphysema	166 (39.24%)	254 (39.81%)	420 (39.59%)
Supplemental oxygen	35 (8.27%)	57 (8.93%)	92 (8.67%)
Bronchodilators	72 (17.02%)	129 (20.22%)	201 (18.94%)
Systemic corticosteroids	89 (21.04%)	136 (21.32%)	225 (21.21%)
PPI/H_2 inhibitor	162 (38.29%)	244 (38.24%)	406 (38.27%)

BMI, body mass index; BSA, body surface area; DL_{CO}, diffusing capacity of the lung for carbon monoxide; FVC, forced vital capacity; H_2, histamine receptor-2; PPI, proton pump inhibitor.
Continuous variables are presented as mean ± SD, and categorical variables are presented as numbers (percentage).

the censoring time point of 372 days, and the observed Kaplan–Meier plot with CI is shown in **Figure 1a**.

Table 2 summarizes the parameter estimates for four base hazard models evaluated with their OFV and AIC values. Differences in OFV values for the Weibull and Gompertz models compared with the nested exponential model were not statistically significant, and the parameter γ was poorly estimated for both the Weibull and Gompertz models. When comparing the non-nested exponential and log-logistic models, the AIC value favored the selection of the exponential model as the base hazard model, and, therefore, *t* the exponential model was selected. The overall VPC plot of the base exponential hazard model presented in **Figure 1b** shows an adequate prediction of the observed data. Visual screening of VPC plots stratified by potential predictors of exacerbations (**Figure S1**) found apparent discrepancies among observed data and 95% prediction intervals for supplemental oxygen use, baseline FVC/%pFVC, and absolute decline in %pFVC (the largest decline from baseline recorded at any visit during 52 weeks).

Univariate analysis

HRs for key variables in the univariate analysis are summarized in **Figure 2**. Significant baseline variables

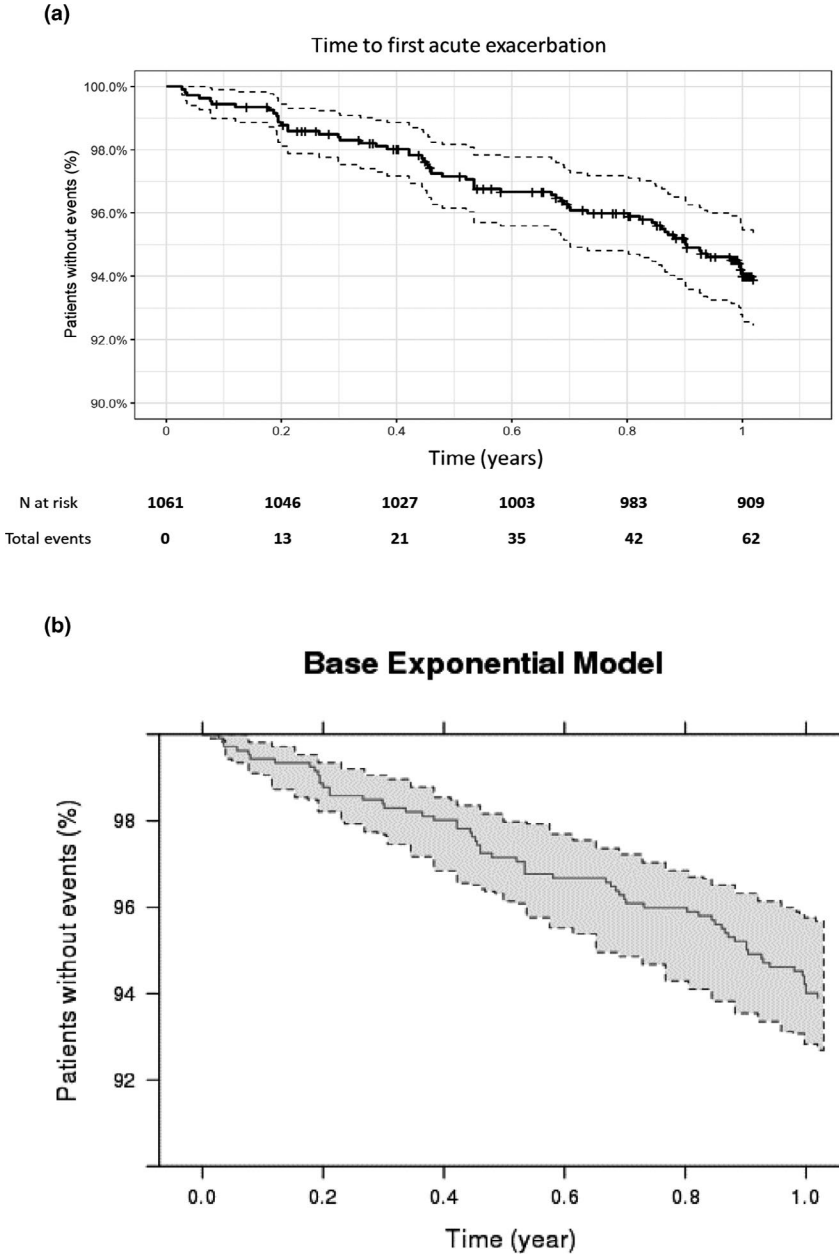

Figure 1 Observed data and base model prediction. (**a**) Kaplan–Meier plot with 95% confidence interval (dashed lines) for the observed time to first acute exacerbation data in INPULSIS. (**b**) Visual predictive check of the base exponential hazard model. The solid line represents the Kaplan-Meier curve of the observed data and the shaded area represents the 95% prediction interval.

Table 2 Parameter estimates of the four tested base hazard models

Parameter	Estimate	RSE (%)	OFV	AIC
Exponential model				
λ (year^{-1})	0.0612	12.6	477.966	479.966
Weibull model				
λ (year^{-1})	0.0708	18.0	476.693	480.693
γ	0.155	95.6		
Gompertz model				
λ (year^{-1})	0.0441	28.6	475.859	479.859
γ	0.625	74.3		
Log-logistic model				
λ (year^{-1})	0.0632	13.0	476.851	480.851
γ	1.17	12.8		

AIC, Akaike information criterion; OFV, objective function value; RSE, relative standard error.

included baseline %pFVC (ΔOFV = 26.705), baseline FVC (ΔOFV = 22.015), supplemental oxygen use (ΔOFV = 13.823), $\%pDL_{CO}$ (ΔOFV = 9.481), and age (ΔOFV = 6.779). Change in FVC or %pFVC from baseline at prespecified time points (4, 6, 12, 24, 36, and 52 weeks) were all significant predictors. Incorporating changes in FVC or %pFVC from baseline to 4, 6, and 12 weeks was associated with less significant drop in ΔOFV (ranging from 4.837 to 14.89) than incorporating baseline FVC into the model, whereas changes in FVC or %pFVC from baseline to 24, 36, and 52 weeks improved the model fit more significantly (ΔOFV ranging from 26.426 to 55.728) than baseline FVC. Of all variables, the most significant drop in OFV was seen with change in FVC from baseline to week 52 ($\Delta FVC_{baseline \rightarrow wk52}$, ΔOFV = 55.728), followed by change in %pFVC from baseline to week 52 ($\Delta\%pFVC_{baseline \rightarrow wk52}$, ΔOFV = 55.133). The effect of nintedanib treatment was associated with a HR of 0.64; however, this reduction in hazard was not statistically significant.

Multivariate analysis

Model with baseline variables. Baseline %pFVC, baseline FVC, supplemental oxygen use, $\%pDL_{CO}$, and age were baseline variables that were significant in univariate analysis. As baseline %pFVC and baseline FVC were highly correlated (R^2 = 0.6) and baseline %pFVC was associated with a more significant decrease in OFV; only baseline %pFVC, oxygen use, $\%pDL_{CO}$, and age were included in the SCM.

In the forward inclusion step, age, baseline %pFVC, and oxygen use were selected. Oxygen was removed in the backward elimination step, with age and baseline %pFVC retained in the model.

Stratified VPC plots of this model on supplemental oxygen revealed that the prediction interval did not cover the observed data for subjects receiving supplemental oxygen toward the end of the study (**Figure S2**). This observation supported the incorporation of supplemental oxygen use into the final baseline covariate model despite the lack of statistical significance in the backward step of the SCM.

The final baseline covariate model is, therefore, described according to Eq. 7:

$$h(t) = \lambda e^{\theta_{AGE} \times (AGE-67) + \theta_{B0FVCPP} \times (B0FVCPP-77.36) + \theta_{OXYGEN} \times OXYGEN} \quad (7)$$

where AGE represents age in years, B0FVCPP represents baseline %pFVC, and OXYGEN equals 1 for supplemental oxygen use and 0 for no supplemental oxygen use. Stratified VPCs for the included baseline covariates shown in **Figure 3** demonstrate an adequate predictive performance of the model.

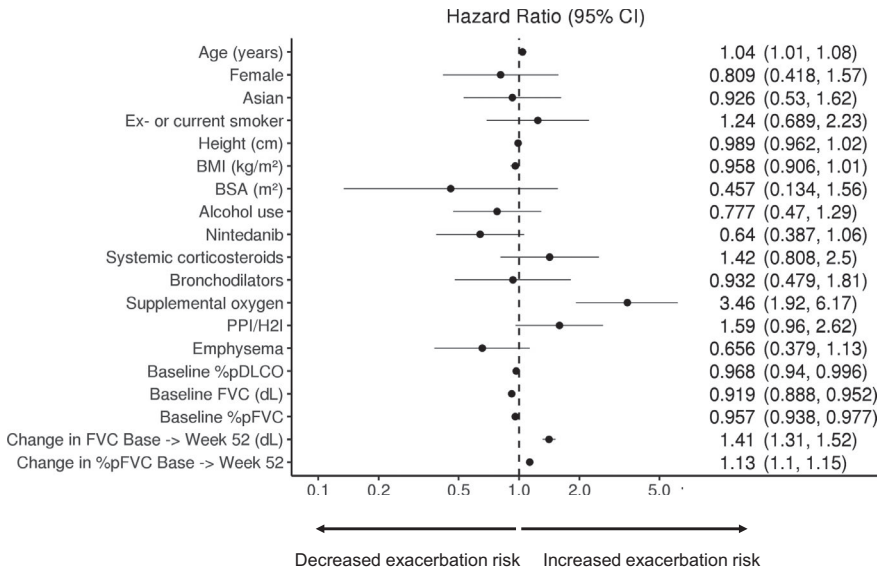

Figure 2 Associations of covariates with risk of acute exacerbations in the univariate analysis. For a dichotomous variable, the hazard ratio (HR) represents the change in probability of event for a patient with the variable compared with a patient without the variable. For a continuous variable, the HR represents the change in probability of event for every unit of increase above the median value. BMI, body mass index; BSA, body surface area; CI, confidence interval obtained from standard error of parameter estimates; H2I, histamine receptor-2 inhibitor; $\%pDL_{CO}$, percent-predicted diffusing capacity of the lung for carbon monoxide; FVC, forced vital capacity; %pFVC, percent-predicted forced vital capacity; PPI, proton pump inhibitor.

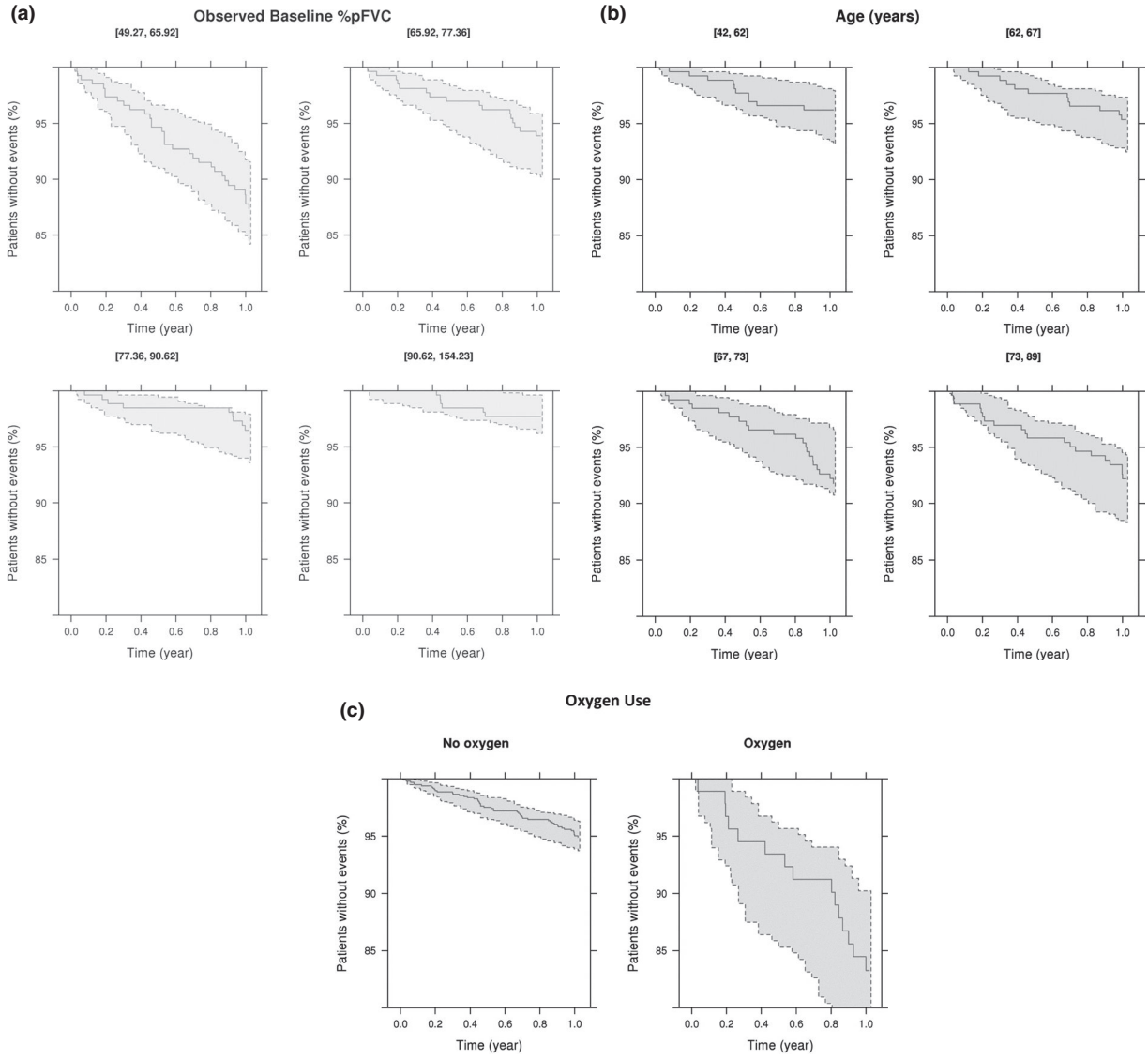

Figure 3 Stratified visual predictive check plots for the baseline covariate model. Continuous covariates were stratified based on quartiles of the observed demographics. The solid line represents the Kaplan–Meier curve of the observed data and the shaded area represents the 95% prediction interval. %pFVC, percent-predicted forced vital capacity. (**a**) Stratification by observed baseline %pFVC quartiles, (**b**) stratification by age quartiles, (**c**) stratification by use of supplemental oxygen.

Model with baseline variables and longitudinal change in pulmonary function. Model predicted changes in FVC or %pFVC from baseline to prespecified time points could be divided into two groups based on their correlations: changes in FVC or %pFVC from baseline to weeks 4, 6, and 12 were highly correlated, and changes in FVC or %pFVC from baseline to weeks 24, 36, and 52 were highly correlated ($R^2 > 0.5$). The most significant predictor in the first group ($\Delta FVC_{baseline \rightarrow wk6}$) and the most significant predictor in the second group ($\Delta FVC_{baseline \rightarrow wk52}$) were included in the SCM in addition to baseline variables included in the final baseline covariate model.

In the forward inclusion step, age, baseline %pFVC, supplemental oxygen use, and $\Delta FVC_{baseline \rightarrow wk52}$ were selected, and no covariate was removed in the backward elimination step. This final covariate model is described in Eq. 8:

$$h(t) = \lambda e^{\theta_{AGE} \times (AGE-67) + \theta_{B0FVCPP} \times (B0FVCPP-77.36) + \theta_{OXYGEN} \times OXYGEN + \theta_{PFW52} \times (PFW52-0.15)} \quad (8)$$

where PFW52 represents $\Delta FVC_{baseline \rightarrow wk52}$ in liters. The corresponding NONMEM control stream is provided as Supplementary Material.

Stratified VPC plots for this covariate displayed in **Figure 4** demonstrated that incorporating $\Delta FVC_{baseline \rightarrow wk52}$ into the covariate model further improved the model's predictive

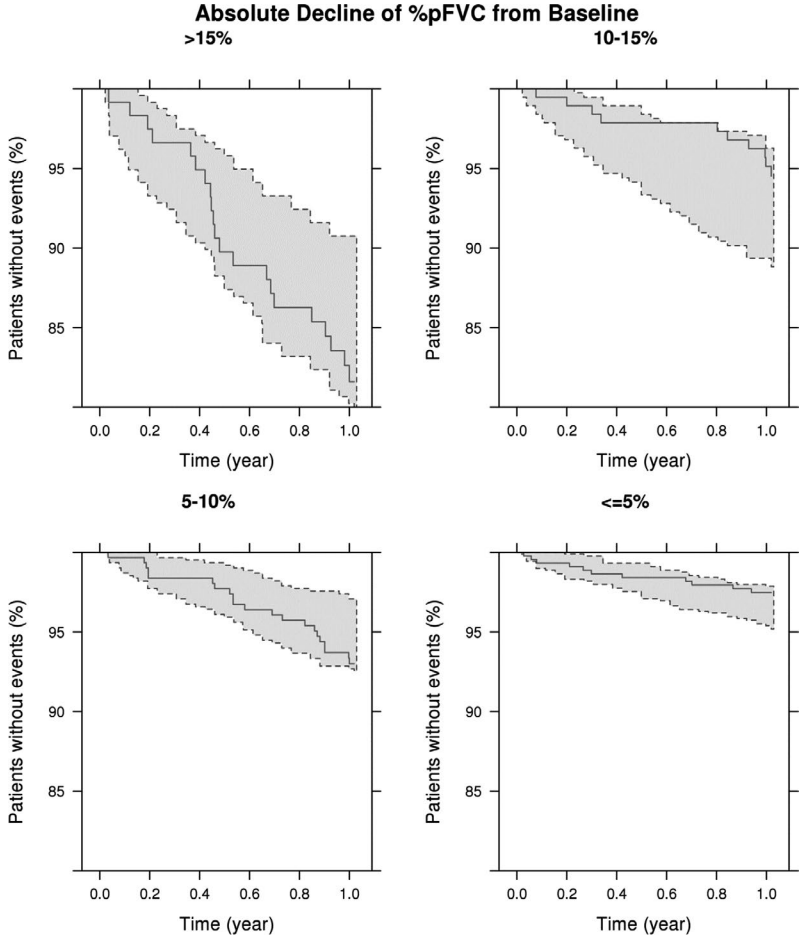

Figure 4 Visual predictive check plot stratified by quartiles of the absolute decline of %pFVC from baseline for the final covariate model. The solid line represents the Kaplan–Meier curve of the observed data and the shaded area represents the 95% prediction interval. %pFVC, baseline percent-predicted forced vital capacity.

performance. Stratified VPCs for all baseline demographics are shown in **Figure S3**. No discrepancies between observed data and predictions from the final model are seen in these plots.

Parameter estimates for both covariate models described in Eqs. 7 and 8 are summarized in **Table 3**. The 95% CIs of the parameter estimates were obtained from 1,000 bootstrap estimations. Based on these parameter estimates, a 67-year-old patient with IPF who has no supplemental oxygen use at baseline, has a baseline %pFVC of 77.36% and a decline of FVC of 150 mL from baseline to 52 weeks, and has a 3% risk of experiencing an acute exacerbation within the first year. The risk of acute exacerbations increases by 46% with every 100 mL increase of FVC decline in 52 weeks above 150 mL, decreases by 3.7% with every percent increase in baseline %pFVC above 77.36%, and increases by 5% with every year increase in age above 67 years. Additionally, the risk of acute exacerbations increases by 182% for a patient who had supplemental oxygen use at baseline compared with one who did not, when adjusting for baseline %pFVC, the amount of FVC declines in 52 weeks and age.

DISCUSSION

In this work, the hazard of acute exacerbations in IPF was quantified and the effect of potential predictors was evaluated in a parametric TTE analysis. An exponential model was selected as the base hazard model based on predetermined criteria. The base hazard was estimated to be ~ 0.06 year^{-1} from an observed 1-year incidence of 6% in our study population. The fact that the observed data from INPULSIS supported a constant hazard model was consistent with the clinical observation that acute exacerbation could occur at any point of time in the course of disease.[4]

Of the significant baseline variables in univariate analysis, the most predictive variable was baseline %pFVC, followed by absolute baseline FVC, %pDL_{CO}, supplemental oxygen use, and age. This study confirmed the predictive value of absolute baseline FVC or %pFVC, which has been consistently shown in the literature.[11] This finding suggested that acute exacerbations are more likely to occur in patients with more advanced disease, and a similar conclusion was drawn from a meta-analysis of placebo-controlled trials that acute

Table 3 Parameter estimates for covariate models

Parameter	Parameter estimate (RSE (%))	Bootstrap results[a] Median (95% CI)	HR (95% CI)
Model with baseline variables (OFV = 435.411)			
λ (year^{-1})	0.0458 (16.5%)	0.0454 (0.0313, 0.0590)	
θ_{AGE} (year^{-1})	0.0431 (34.4%)	0.0428 (0.0122, 0.0744)	1.04 (1.01, 1.08)
$\theta_{B0FVCPP}$ (%$^{-1}$)	−0.0435 (23.3%)	−0.0429 (−0.0667, −0.0253)	0.958 (0.935, 0.975)
θ_{OXYGEN}	0.763 (38.2%)	0.0755 (0.156, 1.32)	2.13 (1.17, 3.74)
Model with baseline variables + ΔFVC (OFV = 378.511)			
λ (year^{-1})	0.0300 (17.8%)	0.0286 (0.0193, 0.0391)	
θ_{AGE} (year^{-1})	0.0474 (36.2%)	0.0493 (0.0120, 0.0857)	1.05 (1.01, 1.09)
θ_{OXYGEN}	1.06 (28.7%)	1.04 (0.373, 1.65)	2.82 (1.45, 5.21)
$\theta_{B0FVCPP}$ (%$^{-1}$)	−0.0366 (28.5%)	−0.0372 (−0.0616, −0.0175)	0.963 (0.940, 0.983)
θ_{PFW52} (dL^{-1})	0.369 (12.3%)	0.378 (0.293, 0.480)	1.46 (1.34, 1.62)

λ, base hazard; CI, confidence interval; FVC, forced vital capacity; θ_{AGE}, effect of age (per year above the median of 67 years) on hazard; $\theta_{B0FVCPP}$, effect of baseline percent-predicted forced vital capacity (per percent above the median of 77.36%) on hazard; θ_{OXYGEN}, effect of supplemental oxygen use on hazard; θ_{PFW52}, effect of model predicted change in forced vital capacity from baseline to week 52 (per deciliter above the median of 1.5 dL) on hazard; HR, hazard ratio; OFV, objective function value; RSE, relative standard error.
[a]Obtained from 1,000 bootstrap runs; 983 and 995 runs out of 1,000 bootstrap runs terminated successfully for the baseline covariate and final covariate model, respectively.

exacerbations were less commonly observed in trials that excluded severe disease than those that did not.[24] The parameter %pDL$_{CO}$ was shown to be a significant predictor of acute exacerbations in some studies, although this finding was not confirmed in several other reports.[12,13,15,21] In our multivariate analysis, %pDL$_{CO}$ did not significantly improve the model fit when added on top of baseline %pFVC. The most likely interpretation for the significance of supplemental oxygen use in our analysis is that it serves an indicator for low oxygenation level at baseline, which was consistent with the observation that higher A_aDO_2 has been previously reported as a significant risk factor for acute exacerbations.[13,18] In contrast to previous studies, age was shown to be a significant factor in our study, albeit with a smaller effect on exacerbation risk than other significant baseline variables. Some of the previously proposed predictive clinical factors and biomarkers (e.g., dyspnea, A_aDO_2, and the baseline KL-6 level) were not available in the current data set, so they were not tested for their predictive performance in this analysis.

Univariate analysis also showed changes in FVC/%pFVC from baseline to specified time points were significant risk factors. Comparison of OFV indicated that decline in FVC/%pFVC within the first 12 weeks might not be as informative as baseline FVC/%pFVC values. In comparison, decline in FVC/%pFVC from baseline to 24 weeks and later time points improved the model fit more significantly than baseline FVC. However, it must be noted that although the decline in FVC/%pFVC from baseline to 52 weeks was the most informative factor among all significant predictors, using this information to predict acute exacerbations that occurred within the same time frame could be considered self-fulfilling as exacerbations could be a driver for increased decline in lung function.

Randomization to nintedanib treatment was associated with a trend toward lower exacerbation risk, although this effect was not statistically significant in this analysis (HR 0.640; 95% CI 0.387, 1.06). [Correction added on 4th February, 2020, after first online publication: In the preceding sentence, punctuation was missing in between the values 0.387 1.06, it should be 0.387, 1.06]. One possible explanation is that, as mentioned earlier, occurrence of acute exacerbations can be affected by disease severity and, therefore, be sensitive to the specific patient population in the analysis. For instance, significant difference in time to the first acute exacerbation was found in INPULSIS-2 but not INPULSIS-1, whereas a pooled analysis of TOMORROW and both INPULSIS trials reported significant benefit of nintedanib (150 mg twice daily) on time to the first acute exacerbation.[9] Nonetheless, our analysis indirectly supports an effect of nintedanib treatment on the exacerbation risk as nintedanib has been shown to reduce the annual rate of FVC decline significantly.[5]

Collard *et al*.[25] have previously published a risk factor analysis on time to first acute exacerbation also using data from the INPULSIS trials. Their final Cox proportional hazard model included baseline %pFVC, supplemental oxygen, use of antacid medications, and randomization to nintedanib as risk factors for investigator-reported acute exacerbations. Although their findings were in general agreement with ours, there are several important differences between the two studies. First, Cox proportional hazard models were developed in the previous study, whereas a parametric TTE analysis was adopted in this study to allow characterization of the base hazard of acute exacerbations over time. In contrast to Cox regression, parametric TTE analysis enables calculation of survival time distribution and simulation of outcomes in future clinical trials. Second, right censoring was applied at 372 days in this analysis but not in the previous study. Third, Collard *et al*. used forward stepwise selection with a cutoff *P* value of 0.2, resulting in the inclusion of antacid medication ($P = 0.0873$) and randomization to nintedanib ($P = 0.115$) in their final model. In this analysis, more stringent *P* values of 0.05 and 0.01 were used in forward selection and backward elimination of SCM, respectively. Fourth, in addition to the baseline variables that were included in the previous study, longitudinal changes in FVC/%pFVC were also considered in this analysis.

There were several limitations to this study. First, a linear disease progression model developed from all available

phase II and III nintedanib data was used to simulate individual subject level FVC and %pFVC response and calculate FVC/%pFVC decline over time at discrete predetermined time points to avoid missing values and to eliminate residual unexplained variability from the observed FVC data. However, a more rigorous approach might be to combine the longitudinal FVC disease progression model in IPF directly with the parametric TTE model and to evaluate the longitudinal change in FVC as time-varying covariate on the risk of acute exacerbations. Second, the study duration in this analysis was 52 weeks, so the characterization of exacerbation risk and predictors in this study might not be extrapolated to longer periods of time. Studies with longer follow-up may be needed to quantify how the base hazard of acute exacerbations changes in the long-term and to evaluate the long-term effect of potential predictors.

In summary, a parametric TTE model was developed to quantify the risk of developing acute exacerbations in IPF within 52 weeks. In a multivariate analysis, decline in FVC, baseline %pFVC, supplemental oxygen use, and age were identified as significant predictors. At present, there is no treatment that has proven efficacy for acute exacerbations in IPF,[11] in part due to the lack of randomized clinical trials comparing different treatment agents.[26] Whereas managing acute exacerbations has been recognized as an important unmet medical need,[11] due to their relatively low incidence in IPF, conducting clinical trials that target reduction of these events can be very challenging because of the limited power to detect effect of potential treatments.[3] It can be foreseen that better understanding of predictors of acute exacerbations could greatly contribute to more efficient clinical trial design and patient selection. In addition, as prevention of acute exacerbations is vital given the high risk of morbidity and mortality and the poor efficacy of current treatment options,[3] identification of patients at high risk of acute exacerbations will aid patient management and timely initiation of prevention strategies in clinical practice in this vulnerable patient population.

Supporting Information. Supplementary information accompanies this paper on the *CPT: Pharmacometrics & Systems Pharmacology* website (www.psp-journal.com).

Figure S1.
Figure S2.
Figure S3.
Table S1.
Final Model.

Acknowledgments. The authors would like to acknowledge Ulrike Schmid and Matthias Freiwald for the development of the longitudinal FVC disease progression models for IPF.

Funding. This work as well as the INPULSIS trials were funded by Boehringer Ingelheim.

Conflict of Interest. F.T. was an employee of Boehringer Ingelheim at the time some of this work was carried out, and B.W., S.S., and J.K. are employees of Boehringer Ingelheim.

Author Contributions. F.T., B.W., S.S., and J.K. wrote the manuscript. F.T., B.W., and J.K. designed the research. F.T. and J.K. performed the research.

1. Lederer, D.J. & Martinez, F.J. Idiopathic pulmonary fibrosis. *N. Engl. J. Med.* **378**, 1811–1823 (2018).
2. Brownell, R. *et al.* Precision medicine: the new frontier in idiopathic pulmonary fibrosis. *Am. J. Respir. Crit. Care Med.* **193**, 1213–1218 (2016).
3. Ryerson, C.J., Cottin, V., Brown, K.K. & Collard, H.R. Acute exacerbation of idiopathic pulmonary fibrosis: shifting the paradigm. *Eur. Respir. J.* **46**, 512–520 (2015).
4. Collard, H.R. *et al.* Acute exacerbations of idiopathic pulmonary fibrosis. *Am. J. Respir. Crit. Care Med.* **176**, 636–643 (2007).
5. Richeldi, L. *et al.* Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. *N. Engl. J. Med.* **370**, 2071–2082 (2014).
6. Richeldi, L. *et al.* Long-term treatment of patients with idiopathic pulmonary fibrosis with nintedanib: results from the TOMORROW trial and its open-label extension. *Thorax* **73**, 581–583 (2018).
7. Noble, P.W. *et al.* Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. *Lancet* **377**, 1760–1769 (2011).
8. King, T.E.J. *et al.* A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *N. Engl. J. Med.* **370**, 2083–2092 (2014).
9. Richeldi, L. *et al.* Nintedanib in patients with idiopathic pulmonary fibrosis: combined evidence from the TOMORROW and INPULSIS((R)) trials. *Respir. Med.* **113**, 74–79 (2016).
10. Raghu, G. *et al.* An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am. J. Respir. Crit. Care Med.* **183**, 788–824 (2011).
11. Collard, H.R. *et al.* Acute exacerbation of idiopathic pulmonary fibrosis. An international working group report. *Am. J. Respir. Crit. Care Med.* **194**, 265–275 (2016).
12. Judge, E.P., Fabre, A., Adamali, H.I. & Egan, J.J. Acute exacerbations and pulmonary hypertension in advanced idiopathic pulmonary fibrosis. *Eur. Respir. J.* **40**, 93–100 (2012).
13. Mura, M. *et al.* Predicting survival in newly diagnosed idiopathic pulmonary fibrosis: a 3-year prospective study. *Eur. Respir. J.* **40**, 101–109 (2012).
14. Luppi, F., Cerri, S., Taddei, S., Ferrara, G. & Cottin, V. Acute exacerbation of idiopathic pulmonary fibrosis: a clinical review. *Intern. Emerg. Med.* **10**, 401–411 (2015).
15. Song, J.W., Hong, S.B., Lim, C.M., Koh, Y. & Kim, D.S. Acute exacerbation of idiopathic pulmonary fibrosis: incidence, risk factors and outcome. *Eur. Respir. J.* **37**, 356–363 (2011).
16. Ley, B., Collard, H.R. & King, T.E. Jr. Clinical course and prediction of survival in idiopathic pulmonary fibrosis. *Am. J. Respir. Crit. Care Med.* **183**, 431–440 (2011).
17. Reichmann, W.M., Yanni, F.Y., Macaulay, D., Wu, E.Q. & Nathan, S.D. Change in forced vital capacity and associated subsequent outcomes in patients with newly diagnosed idiopathic pulmonary fibrosis. *BMC Pulm. Med.* **15**, 167 (2015).
18. Kondoh, Y. *et al.* Risk factors for acute exacerbation of idiopathic pulmonary fibrosis–extended analysis of pirfenidone trial in Japan. *Respir. Investig.* **53**, 271–278 (2015).
19. Kondoh, Y., Taniguchi, H. & Katsuta, T. Risk factors of acute exacerbation in idiopathic pulmonary fibrosis. *Sarcoidosis Vasc. Diffuse Lung Dis.* **27**, 103–110 (2010).
20. Schupp, J.C. *et al.* Macrophage activation in acute exacerbation of idiopathic pulmonary fibrosis. *PLoS One* **10**, e0116775 (2015).
21. Ohshimo, S. *et al.* Baseline KL-6 predicts increased risk for acute exacerbation of idiopathic pulmonary fibrosis. *Respir. Med.* **108**, 1031–1039 (2014).
22. Lee, J.S. *et al.* Bronchoalveolar lavage pepsin in acute exacerbation of idiopathic pulmonary fibrosis. *Eur. Respir. J.* **39**, 352–358 (2012).
23. Schmid, U. *et al.* Relationship between nintedanib exposure, patient characteristics and clinical efficacy in patients with idiopathic pulmonary fibrosis. *Eur. Respir. J.* **193**, A5000 (2016).
24. Atkins, C.P., Loke, Y.K. & Wilson, A.M. Outcomes in idiopathic pulmonary fibrosis: a meta-analysis from placebo controlled trials. *Respir. Med.* **108**, 376–387 (2014).
25. Collard, H.R. *et al.* Acute exacerbations in the INPULSIS trials of nintedanib in idiopathic pulmonary fibrosis. *Eur. Respir. J.* **49,** pii: 1601339 (2017).
26. Bhatti, H., Girdhar, A., Usman, F., Cury, J. & Bajwa, A. Approach to acute exacerbation of idiopathic pulmonary fibrosis. *Ann. Thorac. Med.* **8**, 71–77 (2013).