Dynamic prediction of treatment response and probability of exacerbation in COPD using joint modeling

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Objectives: To evaluate the association, using joint modelling, between baseline-adjusted forced expiratory volume in one second (ΔFEV1) and the risk of exacerbation in COPD patients receiving treatment with inhaled long-acting β2 agonists and corticosteroids.

Methods: ΔFEV1 and time-to-first exacerbation were jointly modeled using the JM-package [1] and data from a one-year COPD trial [2], including 1964 COPD patients randomized to Symbicort®pMDI 2x160/4.5μg twice-daily, Symbicort®pMDI 2x80/4.5μg twice-daily, Formoterol Turbuhaler® 2x4.5μg twice-daily or placebo. A flexible linear mixed-effects model based on a cubic polynomial function of time, including the interaction of treatment with time, was used to describe patient-specific longitudinal changes in ΔFEV1. For the survival submodel, several baseline covariates were evaluated together with the longitudinal trajectory and slope of ΔFEV1. The baseline risk function was modeled using B-spline basis functions for cubic splines.

Results: The current value and slope of ΔFEV, baseline FEV1 and breathlessness score were found to be strongly associated with the risk of exacerbation. A 100-ml increase in baseline FEV1 or ΔFEV1 was estimated to decrease the risk of exacerbation by 11.0% and 13.8% respectively, while a 1-unit worsening of baseline breathlessness score corresponded to an 18.8% increase in risk. In addition, treatment was found to directly influence the hazard function, reducing the risk of exacerbation.

Model diagnostics indicate an adequate fit to the data. The mean exacerbation-free probability curve overlaps with the Kaplan-Meier curve (Figure 1) and the model can distinguish patients with low vs. high risk of exacerbations within the prediction time window.

Conclusions: Joint modeling of ΔFEV1 and time-to-first exacerbation in COPD patients treated with long-acting β2 agonists and inhaled corticosteroids showed an association between exacerbation risk and ΔFEV1, suggesting that ΔFEV1 response is predictive of treatment effect on exacerbations.