Journal of Cystic Fibrosis
The Official Journal of the European Cystic Fibrosis Society

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Citation:

Andrinopoulou, ER, et al. Multivariate joint modeling to identify markers of growth and lung function decline that predict cystic fibrosis pulmonary exacerbation onset. BMC Pulm Med. 2020.

What was your research question?

In this paper, we focus on multiple assessment measures taken over a period of time and look to see if they can be used in such a way to predict pulmonary exacerbation (PE) onset in children with CF. The main factors we consider are FEV1 and nutritional status, but we also make allowances for genotype, sex, ethnicity, socioeconomic status, insurance, CF related diabetes, pancreatic sufficiency and positive cultures for certain bacterial infections. Using this, we can create different statistical models to show how these factors change through the clinical course of CF. We also, compare results from these models to see if they can help us predict when children might start having pulmonary exacerbations.

Why is this important?

Although past statistical models show us how CF disease progresses into its end stage, little is known about the value of joint models in assessing onset of PEs; these events may start earlier in life but could be attributed to other factors that occurred later. Furthermore, to our knowledge, the association of one or more longitudinal outcomes with onset of PE has not yet been addressed. The simpler models used in the past potentially ignores the fact that different markers of interest, specifically those related to growth and nutrition status, could also have an influence on PE.

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What did you do?

Using a longitudinal cohort of 17,100 patients aged 6-20 years (US Cystic Fibrosis Foundation Patient Registry; 2003-2015), we fit a univariate joint model of lung-function decline and PE onset and contrasted its predictive performance with a class of multivariate joint models that included combinations of growth markers as additional sub models. Outcomes were longitudinal lung function (forced expiratory volume in 1 s of % predicted), percentiles of body mass index, weight-for-age and height-for-age and PE onset. Relevant demographic/clinical covariates were included in sub models. We compared a simpler joint model of lung function and time-to-PE and four more complex joint models including growth outcomes.

What did you find?

All five joint models showed that declining lung function corresponded to slightly increased risk of PE, and all had reasonable predictive accuracy. None of the growth markers alongside lung function as outcomes in the more complex joint modelling appeared to have an association with hazard of PE. Jointly modelling only lung function and PE onset gave us the most accurate and precise (narrowest interquartile range) predictions. The accuracy of the models improved as children with CF grew older.

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What does this mean and reasons for caution?

Including growth markers in the more complex joint models did not improve prediction performance, compared to a simpler joint model with lung function. Individualized dynamic predictions from joint modelling could enhance physician monitoring of CF disease progression by providing PE risk assessment as people with CF grow older.

What's next?

Modify the joint model by including recurrent events of pulmonary exacerbation and test this model to see if it helps us more accurately predict PE patterns.