From the authors:

We thank the authors for raising two questions concerning our recent paper that proposed alternative ways for expressing forced expiratory volume in 1 s (FEV_1) patient data [1]. First was about the possible adverse effect on our conclusions from the statistical modelling for deriving the prediction equations we used. Our work used established equations supplied from other sources. The prerequisites for linear regression are that: 1) the dependent variable, which in our case is FEV_1, is normally distributed with respect to the independent or predictor variables; 2) any errors in the dependent variable are not related to the independent variables; 3) the scatter of the dependent variable is uniform and independent of the predictor variables (*i.e.* the data are homoscedastic); and 4) the relationship is linear.

The overwhelming majority of reference equations have found that the scatter of normal lung function data does not violate homoscedasticity, that is, the scatter is unchanging with regard to changes in the predictor variables. The residual standard deviation supplied for the equation is thus a constant. If the scatter varied in a predictable way with one or more of the predictors then more complex regression can be undertaken and the residual standard deviation would be quoted as an expression related to the predictor variables. None of the commonly used prediction equations for adults are like this. However, for children, as they grow the scatter does seem to increase with age.

FEV_1 declines with age and so the predicted FEV_1 tends to approach zero with advancing age. This is not a statistical quirk, just a fact. However, it would present a problem for linear regression if the data from normal subjects did encroach on a limit. This is true for FEV_1/FVC, which has a fixed upper bound of unity, but is not true for FEV_1. The authors quote lung function indices that do have poor characteristics in normal subjects for undertaking linear regression to produce prediction equations, and these indices are not recommended by the American Thoracic Society/European Respiratory Society for use in clinical decision making, and are not pertinent to our paper.

The fact that older people when they deteriorate can never have an FEV_1 standardised residual as low as a younger person is not a fault of the statistical reasoning behind the regression equation used for the prediction, but is a natural fact given there is a lower bound that subjects with disease (not normal subjects) will approach. This fact does not render the prediction equation invalid. This is a main reason why we offer alternative strategies for expressing severity of FEV_1 abnormality that are independent of prediction equations. We have proposed that for looking at severity of disease it is better to consider how far subjects are above some lower boundary rather than how far they have dropped from a suggested predicted value.

The second question raised was about the method used for ranking the models. Each Cox regression model was tested against the others (likelihood ratio test) and each model presented was significantly better or worse than other models, as shown by their Chi-squared result. During the review process, a reviewer requested we produce a receiver operating characteristic (ROC) plot, which was not in the original submission of the paper as we do not think it especially helps. The results from the ROC analysis were not used to discriminate between models. Whilst FEV_1 is the best predictor of all-cause and respiratory mortality in the general population, and also in patients with lung disease, we agree with the authors that it is not a strong or powerful predictor. However, if FEV_1 is being used in a research or a clinical setting there are various ways the FEV_1 result can be expressed. Our paper raised awareness of alternative manipulations of FEV_1 that can influence how good the variable is at relating to survival. Mortality is a well-defined end-point that both patients and clinicians appreciate is important. In the research setting it is a good idea to enhance any possible signal from data, whereas reducing any possible signal by inadvertently adding noise is not recommended. Our paper was aimed at encouraging clinicians and researchers to think about ways to enhance the signal inherent within FEV_1. We proposed possibly better ways to use FEV_1 data to the best advantage for patients and research and this may also help the research community in deciding on how best to define, stage and treat chronic obstructive pulmonary disease.

M.R. Miller* and O.F. Pedersen#

*Dept of Medicine, University Hospitals Trust, Selly Oak Hospital, Birmingham, UK. #Dept of Environmental and Occupational Medicine, University of Aarhus, Aarhus, Denmark.

Correspondence: M.R. Miller, Dept of Medicine, Queen Elizabeth Hospital Birmingham, 5th Floor Nuffield House, Birmingham, B15 2TH, UK. E-mail: martin.miller@uhb.nhs.uk

Statement of Interest: None declared.

REFERENCES

1 Miller MR, Pedersen OF. New concepts for expressing forced expiratory volume in 1 s arising from survival analysis. *Eur Respir J* 2010; 35: 873–882.

DOI: 10.1183/09031936.00086510