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From the authors:

We would like to thank D. Liu and S. Menjoge. Their letter has raised some statistical issues regarding the Poisson model with overdispersion correction and analysis of time-to-first event.

For the Poisson model with overdispersion correction, they state that this model "can also be viewed as equivalent to each individual having their own rate of exacerbations and the rate varying across the population following a gamma distribution" and provide two references for this statement. Unfortunately neither reference actually supports this view. In the first, MCCULLAGH and NELDER [1] specifically state that a mixture of a Poisson rate for each individual with a gamma distribution across the population "leads to the negative binomial distribution". In the second, LIU and DEY [2] briefly mention using a Poisson model with overdispersion correction as a simple approach but again do not place the quoted interpretation on this model. In fact, most of the paper is devoted to the negative binomial model and states "we confirm that negative binomial regression usually accounts for microlevel heterogeneity (overdispersion) satisfactorily" [2].

D. Liu and S. Menjoge further state that in order to decide between the Poisson model with overdispersion correction and the negative binomial model "one should compare model fitting to select a better model". This advice is contrary to the need in clinical trials to pre-specify the statistical analysis ahead of unblinding the data. In another cited paper, VER HOEF and BOVENG [3] discuss difficulties in determining the best model based on the model fit and advise that "a good understanding of the theoretical differences between them can form the basis for an *a priori* decision based on scientific purposes".

For the time-to-first event analysis, D. Liu and S. Menjoge state that this assumes a "constant hazard ratio between treatments over time but that is a much weaker assumption than the assumptions for Poisson and negative binomial models". Our study [4] clearly states that the time-to-first event approach is a simpler analysis than that involving the negative binomial model and we acknowledge the extra assumptions needed by the more sophisticated model. However, use of time-to-first event analysis requires that data collected on exacerbations beyond the first exacerbation be explored. The analysis of time-to-first exacerbation leads to a hazard ratio for the risk of experiencing an exacerbation in any given time interval. This is not as easy to interpret clinically as the reduction in exacerbation rates from the negative binomial model.

Therefore, we maintain our view that, currently, negative binomial regression is the method of choice for analysing exacerbation rates. In contrast to the overdispersed Poisson model, this model does not assume one single rate and then introduce an arbitrary correction for overdispersion. As we have stated, it can be useful to supplement the primary analysis with secondary sensitivity analysis using time-to-first event methods.

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Is air travel safe for those with lung disease?

To the Editors:

We are grateful to MARCHAND [1] for his interest in our report, "Is air travel safe for those with lung disease?" [2], and we would like to make the following response to the interesting questions he posed [1].

A total of 464 patients had resting sea-level arterial oxygen saturation measured by pulse oximetry (S_{p,O_2}) of 92–95%. Out of these, 132 (28%) underwent hypoxic challenge testing (HCT). Current British Thoracic Society (BTS) guidelines on air travel and lung disease [3] do not recommend HCT in all of these patients, but only in those with an additional risk factor,

for example forced expiratory volume in one second (FEV1) <50% predicted, restrictive lung disease or comorbidity with cardiovascular or cerebrovascular disease.

The BTS guidelines recommend that patients with arterial oxygen tension (P_{a,O_2}) <6.6 kPa (49.6 mmHg) during HCT should fly with supplementary oxygen [3]. Not all patients who underwent HCT underwent arterial blood gas estimations in addition to S_{p,O_2} monitoring during the test. Out of the 275 patients who underwent HCT, 162 had their P_{a,O_2} recorded. Out of these, 66 had P_{a,O_2} <6.6 kPa (49.6 mmHg) during HCT, and the majority were either advised to fly only with supplementary oxygen or not to fly. However, it is not possible to confirm whether all the patients who were advised to fly with oxygen actually used it.

As far as we are able to ascertain, all patients with S_{p,O_2} <92% were recommended to have in-flight oxygen. We are, however, unable to confirm whether all those patients recommended to take in-flight oxygen used it.

Out of the 275 patients who underwent HCT, 82 (nearly 30%) patients had a resting sea-level S_{p,O_2} of >96%. Out of these, 19 experienced severe hypoxaemia during HCT (as defined by P_{a,O_2} <6.6 kPa (49.6 mmHg) or S_{p,O_2} ≤85%). All of these 19 patients either had comorbidity, restrictive or parenchymal lung disease or FEV1 <1.00 L. In total, 10 patients had chronic obstructive pulmonary disease (COPD), of whom three had FEV1 ≤0.89 L. The other seven COPD patients had comorbidity (cardiac disease in four, pulmonary fibrosis in one, and malignancy in two). One patient had asthma with cardiac disease and two patients had chest wall disease, both of whom had FEV1 of ≤0.75 L. Five patients had diffuse parenchymal lung disease, and one patient had *Mycobacterium avium intracellulare* infection with Aspergilloma. Three patients did not fly.

Out of the 63 patients who did not experience severe hypoxaemia during HCT, incomplete data were available in eight. Out of the remaining 55 patients, 35 (64%) had comorbidity, restrictive or parenchymal lung disease, or FEV1 <1.00 L. The numbers are limited, and it is therefore difficult to draw any firm conclusions, but it would appear that the presence of comorbidity, restrictive or parenchymal lung disease or FEV1 <1.00 L does not reliably predict hypoxaemia during HCT. Our additional finding that there was no correlation between FEV1 (% pred) and S_{p,O_2} (r^2=0.0224) supports this observation.

Incomplete data are available for four patients with very severe COPD and S_{p,O_2} ≥96% who underwent HCT. Six COPD patients with FEV1 <30% pred and S_{p,O_2} ≥96% underwent HCT; one of these did not fly.

Only two patients with COPD and FEV1 <30% pred did not undergo HCT. The first patient had flown several times in the previous year and reported having been asymptomatic; he declined HCT and was advised not to fly. The second patient declined medical advice to undergo HCT or to fly with supplemental oxygen.

Since the original British Thoracic Society recommendations [3], a number of relevant studies have been published. For example, CHRISTENSEN *et al.* [4] have clearly shown that resting arterial oxygen tension >9.3 kPa (69.9 mmHg) at sea level does not preclude development of severe hypoxaemia in chronic obstructive pulmonary disease patients travelling by air, and that light exercise can worsen it. Consequently, we are currently planning a revision of the British Thoracic Society guidelines.

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STATEMENT OF INTEREST
None declared.

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