Reviewer's report

Title: Seasonal variation of serum KL-6 levels is greater in patients with hypersensitivity pneumonitis

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Reviewer: Chris Grainge

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Review of Ohnishi et al Seasonal variation of serum KL-6 levels is greater in patients with hypersensitivity pneumonitis

Many thanks for asking me to review this interesting manuscript examining the seasonal variability of serum KL-6 in patients with interstitial lung disease of varying aetiology. The manuscript has value as it examines for the first time the seasonal variation in KL-6 concentrations and also compares various ILDs of various aetiologies. The manuscript demonstrates that there are larger alterations in serum KL-6 concentrations in cases of HP where antigen load varies seasonally.

There are several points which could be addressed to improve the manuscript;

Major Compulsory revisions;

1. How were the patients identified and classified into each of the groups, and exactly which diagnostic criteria were used? This is important as the criteria have changed between the dates given for the study (mid 2009 to early 2014). The gold standard is multidisciplinary discussion based on the ATS/ERS consensus statement. Was this performed? What proportions of the patients had tissue diagnoses in each of the groups? Currently it isn’t possible to ascertain, for example, how many NSIP patients had a surgical lung biopsy. Perhaps this data would be best given in a table. This information is vital as when comparing groups of ILD it is essential the groups are correctly identified.

2. ‘House’ HP is not a disease classification that is recognised in Europe / Australia (and I don’t think in America), what is the antigen (is it the Trichosporon?) or is it a diagnosis used where there is no identifiable antigen found? This needs to be made clearer for an International audience.

3. There were 21 p values presented from a single set of data, were any corrections done to account for multiple analyses? This is important to reduce the possibility of Type I error. The data should be re-analysed using a Bonferonni correction or similar to reduce this possibility, or at least the increased risk of Type I error be acknowledged and discussed.

4. The differences between groups in terms of variation of KL-6 concentrations is statistically significant, however there is considerable variability within groups and overlap between groups which would make comparing individuals difficult. Do the authors consider this an issue clinically? This should be discussed.
5. The authors used non-parametric methods for statistical analysis, presumably as the data were not normally distributed, however the values are presented as mean +/- SD. The data should either be presented as median (IQR) or a reason given for the discrepancy between data presented as if parametric but analysed using non parametric testing.

6.

Minor Essential revisions

1. Figure 2B needs units for the serum KL6, also this is a concentration, not a level (similar comment for figure 2C)
2. The variation of KL-6 DURING the summer does not suggest that the KL-6 concentrations were significantly increased in the Summer, just that variability increased (line 18 page 11).
3. Throughout the manuscript, KL-6 concentrations are referred to as ‘levels’ this should be changed.

Discretionary revisions

1. The changes in KL-6 concentrations in the House HP group are significant, however examining the figure (2B) there were only 2 from 5 seasons when the difference between summer and winter was apparent visually. Similarly in the Bird HP only 2 of at best 4 seasons showed much change. Presumably these were the most apparent changes between seasons and hence chosen for the figures. In order for this testing to be useful clinically, the change would need to occur in a single year or so reliably. The data do not look like this would be the case. If the data are re-examined in a ‘real world’ manner (ie within a year) are they still helpful?

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
'I declare that I have no competing interests'