Author’s response to reviews

Title: Serum concentrations of Krebs von den Lungen-6, surfactant protein D, and matrix metalloproteinase-2 as diagnostic biomarkers in patients with asbestosis and silicosis: a case-control study

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Reply to reviewers’ comments

Minor revision

We thank the reviewers for their valuable comments which surely helped to improve the manuscript.

Brian Oliver (Reviewer 1):

Can the Authors please provide some data on the recruitment period for the patients (i.e. were they all recruited over the 2 years, or were the Asbestosis all recruited 1 month prior to measurement?) Similar were the HCs recruited and stored for the same amount of time as the patient samples.

Answer: We thank the reviewer’s suggestive comments. The outpatients with newly diagnosed asbestosis, silicosis or dust-exposed workers (DEWs) without pneumoconiosis were sequentially recruited during a 2-year period (January 2015 to December 2016). The healthy controls (HCs) comprised 45 age-, sex-, and smoking status-matched healthy volunteers from the health examination center during the same period of time. The HCs group was recruited in eight batches. The serum samples were collected from each participant and stored at −80°C until
serum analysis. The samples were measured within two weeks of the storage. (Methods section, line 19-20, page 5 and line 9, page 7).

Is there any influence on the storage time on measurement of any of the factors?

Answer: The all serum samples were collected from each participant once he or she recruited and stored at −80°C. To avoid any influence of the storage time on measurement the serum samples were measured within two weeks of the storage.

Is table 2 needed? (isn't it shown in figure 1).

Answer: The review is right. We deleted table 2.

Were any of the the datasets parametrically distributed?

Answer: The parameters of age, duration of exposure and pulmonary function were normal distribution and the differences were tested using one-way analysis of variance. The serum concentrations of KL-6, SP-D and MMP-2, -7 and -9 were non-normal distribution and the differences were tested using Kruskal–Wallis test.

What were samples diluted in for assay?

Answer: The samples were measured in accordance with the operating procedures of the instruction of these kits strictly. Firstly, a standard curve was developed and the samples were diluted in the sample dilution of the kits respectively.

Mary Gulumian (Reviewer 2):

The authors have evaluated the potential diagnostic biomarkers of asbestosis and silicosis and have proposed that KL-6, SP-D and MMP-2 may be used as such diagnostic biomarkers. They have conducted case-control study with appropriate statistical analysis but albeit on very small number of patients. They have then concluded that KL-6, SP-D and MMP-2 may be used as such diagnostic biomarkers for asbestos and silicosis.

This reviewer questions as to the benefits of measuring the levels of KL-6, SP-D and MMP-2 as diagnostic biomarkers for the following reasons:

1. Increased serum concentrations of KL-6, SP-D and MMP-2 are already reported for other fibrotic lung diseases and therefore by measuring their concentration may not be specific diagnostic biomarkers for asbestosis or silicosis.

Answer: We thank the reviewer’s suggestive comments. The serum concentrations of KL-6, SP-D and MMP-2 were reported to be nonspecific increased in other fibrotic pulmonary diseases. In this study, we further showed that KL-6, SP-D, and MMP-2 are available biomarkers for the
diagnosis of asbestosis and silicosis in addition to the occupational exposure and radiological abnormalities.

2. The levels of KL-6, SP-D and MMP-2 may increase upon the presence of fibrosis and therefore they will be considered as late biomarkers rather than early biomarkers for the onset of disease. What will then be the benefit of measuring late biomarkers of lung fibrosis if the possibility of intervention or prevention of disease will be minimal?

Answer: We thank the reviewer’s suggestive comments. The asbestosis or silicosis has a long latency since dust exposure. The significance of KL-6, SP-D and MMP-2 as early diagnostic markers remains unclear. It was reported that in the workers being exposed to indium, a significant dose–response relationship was found between the serum indium levels and KL-6 or SP-D[1]. Therefore, the detection of these markers for early diagnosis of occupational fibrotic lung diseases is rational. In particular, the concentrations of KL-6, SP-D and MMP-2 are correlated with lung function values and the extent of lung fibrosis on HRCT in our study. The biomarkers may be available in the evaluation of disease activity and progression in asbestosis and silicosis.

Reference:


3. The authors should be cognisant of the fact that prior to proposing any biomarker there should be a validation process of the said biomarker.

The authors should therefore give further justification for their proposal prior to consideration of measuring the levels KL-6, SP-D and MMP-2 as confirmation of fibrosis rather than diagnostic biomarkers for asbestosis and silicosis.

Answer: The review is right. Our data showed that serum levels of KL-6, SP-D, and MMP-2 are nonspecific elevated in asbestosis and silicosis in comparison with those in DEWs and HCs. KL-6, SP-D, and MMP-2 may be available biomarkers for the adjuvant diagnosis of asbestosis and silicosis in addition to occupational exposure and chest images (Conclusions section, line 8, page 3; line 7, page 14). We are planning to further justify KL-6, SP-D and MMP-2 as confirmation of early occupational lung fibrosis in the workers exposure to dusts for the possibility of intervention or prevention of the diseases (Conclusions section, line 9-11, page 14).