Author's response to reviews

Title: Clinical impact of high-attenuation and cystic areas on computed tomography in fibrotic idiopathic interstitial pneumonias

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Author's response to reviews: see over
Responses to the reviewers

We thank the reviewers for their helpful and insightful comments, and we revised the manuscript according to the suggestions and comments. Our responses to the questions and comments are as follows, and our changes are presented in red in the revised manuscript.

Reviewers' Comments to Author:

Reviewer #1
Major Compulsory revisions
This manuscript has many interesting results and worth publishing in BMC Pulmonary Medicine if appropriate revise will be done.
Major Points.
1. Confirm the reproducibility of the evaluation methods using Blant-Altoman Plots, kappa statistics, and Spearman’s rank correlation.
>>We appreciate your comment. We added the following in the Results section. We used Blant-Altoman Plots and Spearman’s rank correlation, but not kappa statistics, to test the reproducibility of the visual scoring, because we dealt with the visual scores as continuous variables. Quantitative CT analysis is essentially an automated procedure using whole-lung data. Therefore, we did not examine the reproducibility.

Revised (page 7, lines 31)
The interobserver correlation coefficients of the GGO and fibrosis scores calculated by the Blant-Altoman method were 0.72–0.83 and 0.77–0.95, respectively. The interobserver Spearman’s rank correlation coefficients (r_s) of the GGO and fibrosis scores were 0.66–0.77 and 0.77–0.96, respectively.

2. Describe the pathological background of HAA, LAA, kurtosis, and skewness in fibrotic lung diseases in Discussion paying special attention to the difference of UIP and NSIP.
>>We thank you for your comment. We added the following paragraph to the Discussion section.
The pathological background of these CT indices has been investigated in prior studies. Do et al. reported that kurtosis and skewness were higher in patients with pathological UIP than in those with NSIP [3]. Sumikawa et al. revealed that the histograms of GGA and fine reticulation patterns were similar, while the honeycombing pattern showed less kurtosis and skewness and a higher contrast and variance [19]. On the other hand, they also showed that the histogram of the whole lung was similar between UIP and NSIP, although an analysis of cubic regions of interest (ROIs) demonstrated differences between UIP and NSIP [20]. Those findings suggest that the whole lungs of patients with ILD are combinations of various ILD-characteristic regions. Although the histogram of each region can reflect the differences among the regions, the features of different ROIs offset each other in the histogram analysis of the whole lung, leading to conflicting results of comparisons between different pathological patterns [3, 21]. Indeed, our results showed no significant differences in densitometric parameters between the IPF and non-IPF groups. Given the significant association between densitometric parameters and physiological impairments and long-term outcomes, the densitometric parameters of the whole lung might represent the physiological burdens of disease rather than pathological patterns. The novel CT indices used in this study, %HAA and %CA, are presumed to reflect the fibrotic and honeycombing lesions, respectively. The %HAA was similar between the IPF and non-IPF groups. Although a different definition was used, the percentages of low, intermediate, and high CT density areas did not differ between UIP and NSIP in a previous study [21]. Similar to the densitometric parameters, the %HAA or high-density area might not be an index for morphological characteristics but might instead be an index for the extent and severity of disease. Of note, the %CA was higher in patients with IPF and correlated with the extent of honeycombing by visual scoring in our study. Those results suggest the possibility that the %CA can detect the pathological features of IPF/UIP even in whole-lung analyses.

3. Clearly define MLD, SD-LD, kurtosis, and skewness in Methods.

>> We appreciate your comment. We revised the Methods section.
MLD, SD-LD, kurtosis, and skewness likewise were calculated automatically from CT attenuation histograms as follows:

\[
MLD = \frac{\sum_{l = l_{\text{min}}}^{l_{\text{max}}} \ln(l)}{N}
\]

\[
SD-LD = \sqrt{\frac{\sum_{l = l_{\text{min}}}^{l_{\text{max}}} n(l)(l - MLD)^2}{N}}
\]

\[
\text{Kurtosis} = \frac{\sum_{l = l_{\text{min}}}^{l_{\text{max}}} [n(l)(l - MLD)^4]/N(SD)^4}{3} - 3
\]

\[
\text{Skewness} = \frac{\sum_{l = l_{\text{min}}}^{l_{\text{max}}} [n(l)(l - MLD)^3]/N(SD)^3}{3}
\]

\(l\) = CT value
\(n(l)\) = number of pixels in each CT value
\(N\) = number of pixels in all CT values
\(SD\) = SD-LD

MLD and SD-LD represent the average and standard deviation of the HU of each pixel, respectively. Kurtosis describes how sharply peaked a histogram is when compared with the histogram of a normal distribution. Skewness describes the degree of asymmetry of a histogram, and a long right tail indicates positive skewness.

4. Introduce the following manuscripts and compare your methods with ones in these manuscripts.


Sumikawa H, et al. Pulmonary adenocarcinomas with ground-glass attenuation on

We thank you for your comment. We added the following paragraphs and descriptions in the Discussion section. We also referred to the first article in another added paragraph in the Discussion section to respond to your major comment 2.

Revised (page 11, lines 28)

Quantitative CT analysis of the lung has been performed for COPD, bronchial asthma, and ILDs [6, 14, 22-27]. Histogram analysis of fibrotic ILDs has been conducted for IPF, asbestosis, and scleroderma [1, 2, 4, 5]; and MLD, SD-LD, kurtosis, and skewness were employed as CT indices in those studies. Sumikawa et al. added contrast, variance, and entropy to the repertory of CT indices used to discriminate the different ILD-characteristic abnormalities more precisely [21]. In contrast to those for COPD and bronchial asthma, the standard CT indices remained to be elucidated for ILDs. In addition to the histogram indices, we calculated the %HAA and %CA. As aforementioned, the analysis of whole-lung histograms might not be able to detect the extents of different disease-characteristic lesions sufficiently, because each lesion can offset other lesions in a single histogram. Therefore, we sought to measure the areas of fibrotic lesions and honeycombing directly and automatically. Although such a cut-off approach using CT values has been well established in COPD and emphysema, its utility and limitations in ILDs should be examined in further studies.

Original (page 10, lines 8)

Recently, texture analysis has emerged as a novel method for quantifying fibrotic IP on CT. The expanse of honeycombed areas and serial changes in abnormalities (reticular and total interstitial) in texture analysis reportedly are significant predictors of mortality in IPF [17, 19].

Revised (page 12, lines 9)

Recently, texture analysis has emerged as a novel method for quantifying fibrotic IP by CT [18, 28]. Texture analysis is based on the histogram analysis of characteristic ILD findings in small ROIs. That method segments the whole lung into small ROIs, classifies each ROI into one CT pattern such as GGA, reticulation, or
honeycombing determined through histogram analysis, and calculates the extent of each CT pattern automatically. As a result, the CT data of the whole lung are converted into a combination of the ROI percentages of the histogram-based CT patterns. Texture analysis aims to overcome the limitations of whole-lung histogram analysis by dividing the whole lung into small ROIs, thus avoiding the summation of the whole lung CT data into a single histogram.

Revised (page 13, line 1)

Another issue in quantitative CT analysis is the selection of ROIs. Sumikawa et al. reported that three-dimensional (3D) histogram analysis using cubic ROIs is superior to two-dimensional histogram analysis with square ROIs for assessing various CT patterns of ILDs [19]. They applied a similar method to quantify pulmonary adenocarcinoma with GGA and demonstrated the utility of 3D histogram analysis in small lung cancer [30]. In addition, a 3D approach was used in a recent texture analysis [28]. We used CT scans with a 2 mm thickness obtained at 10 mm intervals and therefore could not apply a 3D analysis. Those differences in CT scanning conditions might have influenced our results.

Minor points

1. Describe the numbers of patients with IPF, NSIP, unclassifiable IPF, respectively.
>>We thank you for your comment. We described the numbers of patients with IPF, NSIP, and unclassifiable IIP in the Results section.

Original (page 6, lines 31) and revised (page 7, lines 21)

Among the 75 patients with fibrotic IIPs, the diagnoses were IPF (n=36, 12 biopsy proven), non-specific interstitial pneumonia (NSIP; n=9, all biopsy proven), and unclassifiable IIP (n=29).

2. Depict the method for diagnosis of IPF/UIP.
>>We appreciate your comments. We revised the method for diagnosis of IPF/UIP in the Methods section more precisely.

Original (page 4, lines 32)
IPF and NSIP were diagnosed according to recent guidelines [9, 10]. If HRCT showed possible or inconsistent usual interstitial pneumonia (UIP) pattern and a pathologic diagnosis was unavailable, the case was interpreted as unclassifiable IIP.

Revised (page 4, lines 31)
IPF and NSIP were diagnosed according to the 2002 American Thoracic Society (ATS)/European Respiratory Society (ERS) IIP statement [9], and HRCT patterns were classified based on the 2011 American Thoracic Society (ATS)/European Respiratory Society (ERS)/Japanese Respiratory Society (JRS)/Latin American Thoracic Association (LATA) IPF guidelines [10]. If HRCT showed a possible or inconsistent usual interstitial pneumonia (UIP) pattern, and a pathologic diagnosis was unavailable, the case was interpreted as unclassifiable IIP according to the 2013 ATS/ERS IIP statement [11].

Reviewer #2
In their manuscript „Clinical impact of high-attenuation and cystic 1 areas on computed tomography in fibrotic idiopathic interstitial pneumonias“ by Tanizawa et al., the authors describe various CT indices and their correlation to functional and prognostic parameters. While the intention of this analysis has to be highly valued there are a couple of points which might have influenced the results of the analyses to a significant proportion.

1. Patients were retrospectively recruited with a HRCT between 2004 and 2006. However, in the methods section the authors state that they were classified according to the proposals in 2011 and 2013. Does this mean that all patients had been reclassified in an experienced multidisciplinary team? if not, the diagnoses have to be questioned.>>We appreciate your comment. As you pointed out, the patients were classified basically according to the 2002 ATS/ERS IIP statement throughout daily practice. On the other hand, we also used the 2011 ATS/ERS/JRS/ LATA IPF guideline and the 2013 ATS/ERS IIP statement to define those without pathological diagnosis. The HRCT pattern was reclassified into UIP, possible and inconsistent UIP, and, if HRCT showed a possible or inconsistent UIP pattern and a pathologic diagnosis was unavailable, unclassifiable IIP. In our cohort, all patients with IPF who were clinically diagnosed
without pathology according to the 2002 statement also had UIP pattern based on the 2011 IPF guideline. To clarify the procedure, we revised the Methods section.

Original (page 4, lines 32)
IPF and NSIP were diagnosed according to recent guidelines [9, 10]. If HRCT showed possible or inconsistent usual interstitial pneumonia (UIP) pattern and a pathologic diagnosis was unavailable, the case was interpreted as unclassifiable IIP.

Revised (page 4, lines 31)
IPF and NSIP were diagnosed according to the 2002 American Thoracic Society (ATS)/European Respiratory Society (ERS) IIP statement [9], and HRCT patterns were classified based on the 2011 American Thoracic Society (ATS)/European Respiratory Society (ERS)/Japanese Respiratory Society (JRS)/Latin American Thoracic Association (LATA) IPF guidelines [10]. If HRCT showed a possible or inconsistent usual interstitial pneumonia (UIP) pattern, and a pathologic diagnosis was unavailable, the case was interpreted as unclassifiable IIP according to the 2013 ATS/ERS IIP statement [11].

2. The definition of unclassifiable disease in this cohort is not supported by the literature. Especially should clinical parameters be taken into account. Therefore there could be a significant proportion of patients with IPF, iNSIP etc. in the cohort of unclassifiable ILD. The definition used by the authors might be the reason of this unexpected high number of patients with unclassifiable disease. This could be a significant bias of this analysis.

>> We thank you for your comment. As you pointed out, unclassifiable IIP in our cohort could be IPF or NSIP if the pathology was available, and that was among the major limitations of our study. We added the following statements at the end of the Discussion section.

Revised (page 13, lines 21)
Additionally, our cohort included several patients with unclassifiable IIP because of a lack of pathological diagnoses. Those patients can be potentially diagnosed with IPF or NSIP, and such diagnoses might influence the results of comparisons between IPF and
non-IPF and multivariate survival analyses.

3. The method used for HRCT might not reflect the standard of multi slice thin section CT being used nowadays. Especially the 10 mm intervals in CT might have influenced the results in this manuscript to a significant amount.

>> We appreciate your comment. We added the following description in the Discussion section.

Revised (page 13, lines 7)
We used CT scans with a 2 mm thickness obtained at 10 mm intervals and therefore could not apply a 3D analysis. Those differences in CT scanning conditions might have influenced our results.

4. Treatment issues might also have influenced the survival analysis (e.g. immunosuppressive treatment in IPF as a parameter with a more detrimental survival effect). At least this point is discussed by the authors.

>> We thank you for your comment. We addressed the possible impact of immunosuppressive therapies on the survival of patients with IPF in the Discussion section.

Original (page 10, lines 25)
First, the subjects did not receive uniform treatment such as corticosteroids, immunosuppressive agents, or pirfenidone, because evidence-based guidelines for IPF were just published recently [7]. Hence, we could not address the impact of therapeutic regimens on survival.

Revised (page 13, lines 10)
First, the subjects did not receive uniform treatment such as corticosteroids, immunosuppressive agents, or pirfenidone, because evidence-based guidelines for IPF were just published recently [7]. Given the relatively poor outcomes of the patients with IPF who received the combination therapy of prednisone and azathioprine in the PANTHER-IPF study [31], different therapeutic strategies might have affected the long-term outcomes of patients with IPF. In addition, our cohort included several
patients with non-IPF IIPs, whose responses to treatment could be more variable. Hence, we could not address the impact of therapeutic regimens on survival.

5. figures with CT examples of their analyses are missing.
>> We appreciate your comment. We added Figure 1 as an example of our CT analysis.