EUROPEAN RESPIRATORY journal

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Correspondence

Reply to: The potential and challenges of radiomics in uncovering prognostic and molecular differences in interstitial lung disease associated with systemic sclerosis

Janine Schniering, Malgorzata Maciukiewicz, Stephanie Tanadini-Lang, Britta Maurer

Please cite this article as: Schniering J, Maciukiewicz M, Tanadini-Lang S, *et al*. Reply to: The potential and challenges of radiomics in uncovering prognostic and molecular differences in interstitial lung disease associated with systemic sclerosis. *Eur Respir J* 2022; in press (https://doi.org/10.1183/13993003.00303-2022).

Reply to: The potential and challenges of radiomics in uncovering prognostic and molecular differences in interstitial lung disease associated with systemic sclerosis

Janine Schniering[1,2], Malgorzata Maciukiewicz[1,4], Stephanie Tanadini-Lang[3], Britta Maurer[1,4]

[1]Center of Experimental Rheumatology, Department of Rheumatology, University Hospital Zurich, University of Zurich, Zurich, Switzerland
[2]Institute of Lung Biology and Disease and Comprehensive Pneumology Center, Helmholtz Zentrum München, Member of the German Center for Lung Research (DZL), Munich, Germany,
[3]Department of Radiation Oncology, University Hospital Zurich, University of Zurich, Zurich, Switzerland,
[4]Department of Rheumatology and Immunology, University Hospital Bern, University Bern, Switzerland

*Corresponding Author: Britta Maurer, MD, Department of Rheumatology and Immunology, University Hospital Bern, University Bern, Switzerland, Phone +41 31 632 98 40, e-mail britta.maurer@insel.ch

Conflicts of Interests: J.S., M.M., S.T. have no competing interests to declare. B. M. has consultancies with Novartis, Boehringer Ingelheim, Janssen-Cilag, had grant/research support from AbbVie, Protagen, Novartis Biomedical Research, received speaker fees from Boehringer-Ingelheim and Novartis as well as congress support from Medtalk, Pfizer, Roche, Actelion, mepha, and MSD. In addition, B.M. has a patent mir-29 for the treatment of systemic sclerosis issued (US8247389, EP2331143).

We thank Zhang *et al.* for their correspondence to our manuscript.

In interstitial lung disease associated with systemic sclerosis (SSc-ILD), the lack of valid prognostic biomarkers hampers individualized patient management. Our study introduces radiomics as a novel non-invasive tool to acquire phenotypic, prognostic and molecular information derived from standard-of-care HRCT images with great potential to support clinical decision making in SSc-ILD [1].

The reproducibility of radiomic models is significantly dependent on image acquisition and reconstruction methodologies as well as the intra-/inter-observer variability during image segmentation. Therefore, in 2017 Lambin *et al.* [2] proposed the Radiomics Quality Score (RQS) to support the scientific community in assessing the quality and clinical value of radiomics studies. Our study scored 16 out of 36 possible points (Table 1), which is an excellent result compared to other studies [3–9]. In a recent systematic review on neuro-oncology the mean RQS was 11, ranging between 3 and 12 [9]. Similarly, in the review by Sanduleanu *et al.* on the correlation between tumor biology and radiomics, only 2 out of 41 studies had an RQS larger or equal to 16 [8].

The definitions of radiomic features of our in-house developed software Z-rad are - same as other software solutions such as pyradiomics - based on the image biomarker standardization initiative (IBSI) and therefore follow state-of-the-art standards [10]. Image pre-processing before extracting radiomics features has been performed as described in van

Timmeren *et al.,* including interpolation to isotropic voxels and discretization of intensities. CT images have the advantage that intensity values are standardized; therefore, image normalization is not needed and might even lead to loss of information [11].
In the present study, we first filtered out not associated features (Cox regression) followed by LASSO to select our final features out of a set of correlated features.
We, however, agree with Zhang *et al.* that filtering out highly correlated features, e.g. with a Spearman's correlation coefficient of 0.9, followed by association analysis (i.e. Cox regression) or penalized regression (e.g. LASSO), makes an attractive, alternative approach.

As stated by Zhang *et al.,* understanding the biological underpinnings of radiomic features and prediction models is key to enabling the application of radiomics in clinical routine [12].
Given the scarce availability of matched imaging data and tissue biosamples in SSc-ILD, we conducted in the present study a cross-species approach using the well-characterized bleomycin-induced lung fibrosis mouse model to define the biological basis of qRISSc.
Bleomycin is the most commonly used agent to replicate interstitial lung disease *in vivo* as it recapitulates major hallmarks of the human disease such as remodeling of the pulmonary architecture, fibroblast and macrophage activation and increased deposition of extracellular matrix proteins [13–15].
Using a combination of multiple and complementary experimental techniques, including unbiased whole-tissue proteomic profiling and validation by gene expression profiling and immunostainings of established pathophysiologically relevant fibrotic and inflammatory markers, we found that qRISSc was associated with the fibrotic remodeling yet not inflammatory processes in experimental ILD.

To model different disease stages and address the molecular heterogeneity of human ILD, we incorporated and pooled imaging and molecular data from different time points after bleomycin instillation, thereby covering inflammatory (day 3/7), fibrotic (day14/21) and remodeling phases (day28/35) of experimental ILD. We decided against using different bleomycin dosages since the effects on pulmonary fibrosis are often incremental / insignificant except when using dosages that lead to unacceptably high morbidity and mortality rates [16]. Additionally, arguing for an even more heterogeneous animal model implicitly means a (further) increase in animal numbers to reach statistical significance. Since the ultimate aim is not to prove that radiomic prediction modelling works in mice, with respect to animal welfare, such an approach seems not advisable.

In the future, further validation of our molecular correlation analysis in human tissue biosamples is warranted, which, however, is complicated by the limited access to lung biopsies in SSc-ILD.
The fact, however, that in SSc-ILD, a high qRISSc score was associated with progressive as opposed to stable lung disease as assessed by HRCT and lung function tests supports the potential merit of future radiomics research in SSc-ILD and other types of fibrosing ILDs.

References

1. Schniering J, Maciukiewicz M, Gabrys HS, Brunner M, Blüthgen C, Meier C, Braga-Lagache S, Uldry A-C, Heller M, Guckenberger M, Fretheim H, Nakas CT, Hoffmann-Vold A-M, Distler O, Frauenfelder T, Tanadini-Lang S, Maurer B. Computed tomography-based radiomics decodes prognostic and molecular differences in

interstitial lung disease related to systemic sclerosis. *Eur. Respir. J.* [Internet] 2021; Available from: http://dx.doi.org/10.1183/13993003.04503-2020.

2. Lambin P, Leijenaar RTH, Deist TM, Peerlings J, de Jong EEC, van Timmeren J, Sanduleanu S, Larue RTH, Even AJG, Jochems A, van Wijk Y, Woodruff H, van Soest J, Lustberg T, Roelofs E, van Elmpt W, Dekker A, Mottaghy FM, Wildberger JE, Walsh S. Radiomics: the bridge between medical imaging and personalized medicine [Internet]. Nature Reviews Clinical Oncology 2017. p. 749–762Available from: http://dx.doi.org/10.1038/nrclinonc.2017.141.

3. Wang Q, Li C, Zhang J, Hu X, Fan Y, Ma K, Sparrelid E, Brismar TB. Radiomics Models for Predicting Microvascular Invasion in Hepatocellular Carcinoma: A Systematic Review and Radiomics Quality Score Assessment. *Cancers* [Internet] 2021; 13Available from: http://dx.doi.org/10.3390/cancers13225864.

4. Kendrick J, Francis R, Hassan GM, Rowshanfarzad P, Jeraj R, Kasisi C, Rusanov B, Ebert M. Radiomics for Identification and Prediction in Metastatic Prostate Cancer: A Review of Studies. *Front. Oncol.* 2021; 11: 771787.

5. Wang H, Zhou Y, Li L, Hou W, Ma X, Tian R. Current status and quality of radiomics studies in lymphoma: a systematic review. *Eur. Radiol.* 2020; 30: 6228–6240.

6. Kao Y-S, Hsu Y. A Meta-Analysis for Using Radiomics to Predict Complete Pathological Response in Esophageal Cancer Patients Receiving Neoadjuvant Chemoradiation. *In Vivo* 2021; 35: 1857–1863.

7. Lee S, Han K, Suh YJ. Quality assessment of radiomics research in cardiac CT: a systematic review. *Eur. Radiol.* [Internet] 2022; Available from: http://dx.doi.org/10.1007/s00330-021-08429-0.

8. Sanduleanu S, Woodruff HC, de Jong EEC, van Timmeren JE, Jochems A, Dubois L, Lambin P. Tracking tumor biology with radiomics: A systematic review utilizing a radiomics quality score. *Radiother. Oncol.* 2018; 127: 349–360.

9. Park JE, Kim HS, Kim D, Park SY, Kim JY, Cho SJ, Kim JH. A systematic review reporting quality of radiomics research in neuro-oncology: toward clinical utility and quality improvement using high-dimensional imaging features. *BMC Cancer* 2020; 20: 29.

10. Zwanenburg A, Vallières M, Abdalah MA, Aerts HJWL, Andrearczyk V, Apte A, Ashrafinia S, Bakas S, Beukinga RJ, Boellaard R, Bogowicz M, Boldrini L, Buvat I, Cook GJR, Davatzikos C, Depeursinge A, Desseroit M-C, Dinapoli N, Dinh CV, Echegaray S, El Naqa I, Fedorov AY, Gatta R, Gillies RJ, Goh V, Götz M, Guckenberger M, Ha SM, Hatt M, Isensee F, et al. The Image Biomarker Standardization Initiative: Standardized Quantitative Radiomics for High-Throughput Image-based Phenotyping. *Radiology* 2020; 295: 328–338.

11. van Timmeren JE, Cester D, Tanadini-Lang S, Alkadhi H, Baessler B. Radiomics in medical imaging—“how-to” guide and critical reflection [Internet]. Insights into Imaging 2020.Available from: http://dx.doi.org/10.1186/s13244-020-00887-2.

12. Tomaszewski MR, Gillies RJ. The Biological Meaning of Radiomic Features. *Radiology* 2021; 299: E256.

13. Scotton CJ, Chambers RC. Bleomycin revisited: towards a more representative model of IPF? Am. J. Physiol. Lung Cell. Mol. Physiol. 2010. p. L439–L441.

14. Mouratis MA, Aidinis V. Modeling pulmonary fibrosis with bleomycin. *Curr. Opin. Pulm. Med.* 2011; 17: 355–361.

15. Perelas A, Silver RM, Arrossi AV, Highland KB. Systemic sclerosis-associated interstitial lung disease [Internet]. The Lancet Respiratory Medicine 2020. p. 304–320Available from: http://dx.doi.org/10.1016/s2213-2600(19)30480-1.

16. Ravanetti F, Ragionieri L, Ciccimarra R, Ruscitti F, Pompilio D, Gazza F, Villetti G, Cacchioli A, Stellari FF. Modeling pulmonary fibrosis through bleomycin delivered by osmotic minipump: a new histomorphometric method of evaluation. *Am. J. Physiol. Lung Cell. Mol. Physiol.* 2020; 318: L376–L385.

Table 1. Radiomics Quality Score Assessment of the present study [1].

Criteria		Points possible	Points achieved
1	Image protocol quality - well-documented image protocols (for example, contrast, slice thickness, energy, etc.) and/or usage of public image protocols allow reproducibility/replicability	+ 1 (if protocols are well-documented) + 1 (if public protocol is used)	1
2	Multiple segmentations - possible actions are: segmentation by different physicians/algorithms/software, perturbing segmentations by (random) noise, segmentation at different breathing cycles. Analyse feature robustness to segmentation variabilities	+ 1	1
3	Phantom study on all scanners - detect inter-scanner differences and vendor-dependent features. Analyse feature robustness to these sources of variability	+ 1	0
4	Imaging at multiple time points - collect images of individuals at additional time points. Analyse feature robustness to temporal variabilities (for example, organ movement, organ expansion/shrinkage)	+ 1	0
5	Feature reduction or adjustment for multiple testing - decreases the risk of overfitting. Overfitting is inevitable if the number of features exceeds the number of samples. Consider feature robustness when selecting features	− 3 (if neither measure is implemented) + 3 (if either measure is implemented)	2
6	Multivariable analysis with non radiomics features (for example, EGFR mutation) - is expected to provide a more holistic model. Permits correlating/inferencing between radiomics and non radiomics features	+ 1	1
7	Detect and discuss biological correlates - demonstration of phenotypic differences (possibly associated with underlying gene–protein expression patterns) deepens understanding of radiomics and biology	+ 1	1
8	Cut-off analyses - determine risk groups by either the median, a previously published cut-off or report a continuous risk variable. Reduces the risk of reporting overly optimistic results	+ 1	1
9	Discrimination statistics - report discrimination statistics (for example, C-statistic, ROC curve, AUC) and their statistical significance (for example, p-values, confidence intervals). One can also apply resampling method (for example, bootstrapping, cross-validation)	+ 1 (if a discrimination statistic and its statistical significance are reported) + 1 (if a resampling method	1

		technique is also applied)	
10	Calibration statistics - report calibration statistics (for example, Calibration-in-the-large/slope, calibration plots) and their statistical significance (for example, *P*-values, confidence intervals). One can also apply resampling method (for example, bootstrapping, cross-validation)	+ 1 (if a calibation statistic and its statistical significance are reported) + 1 (if a resampling method technique is also applied)	0
11	Prospective study registered in a trial database - provides the highest level of evidence supporting the clinical validity and usefulness of the radiomics biomarker	+ 7 (for prospective validation of a radiomics signature in an appropriate trial)	0
12	Validation - the validation is performed without retraining and without adaptation of the cut-off value, provides crucial information with regard to credible clinical performance	- 5 (if validation is missing) + 2 (if validation is based on a dataset from the same institute) + 3 (if validation is based on a dataset from another institute) + 4 (if validation is based on two datasets from two distinct institutes) + 4 (if the study validates a previously published signature) + 5 (if validation is based on three or more datasets from distinct institutes) *Datasets should be of comparable size and should have at least 10 events per model feature	3
13	Comparison to 'gold standard' - assess the extent to which the model agrees with/is superior to the current 'gold standard' method (for example, TNM-staging for survival prediction). This comparison shows the added value of radiomics	+ 2	2
14	Potential clinical utility - report on the current and potential application of the model in a clinical setting (for example, decision curve analysis)	+ 2	2
15	Cost-effectiveness analysis - report on the cost-	+ 1	0

	effectiveness of the clinical application (for example, QALYs generated)		
16	Open science and data - make code and data publicly available. Open science facilitates knowledge transfer and reproducibility of the study	+ 1 (if scans are open source) + 1 (if region of interest segmentations are open source) + 1 (if code is open source) + 1 (if radiomics features are calculated on a set of representative ROIs and the calculated features and representative ROIs are open source)	1
Total points possible (36 = 100%)			**Total points (16/36 = 44%)**