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

Received: 25 Oct 2021
Accepted: 17 Nov 2021

To the Editor:

We read with great interest the study by Schniering *et al.* [1], recently published in the *European Respiratory Journal*. This study highlighted the potential of radiomics as a non-invasive tool for disease characterisation, prognosis stratification and lung pathophysiology evaluation in systemic sclerosis-associated interstitial lung disease (SSc-ILD). The results demonstrated that quantitative radiomic risk score (qRISSc) could accurately predict survival in SSc-ILD cohorts and was reverse translatable from human to animal ILD and correlated with fibrotic pathway activation. To the best of our knowledge, this is the first landmark study to validate the biological meaning of radiomic biomarkers through a cross-species approach, which may provide new insights into future radiomic works to break through the current bottleneck of traditional radiomics.

Despite the promising results, we are concerned about key aspects of the analysis. A series of standard radiomic processes is very crucial for reliable and reproducible radiomic biomarkers [2]. According to the methodological quality assessed by the radiomics standard scoring (RQS) (maximum score of 36) [2], this study scored 16 points, *i.e.* below 50%. The workflow of radiomics is complex, and its robustness and reproducibility can be affected by each step of the workflow, such as image acquisition, image pre-processing, feature extraction, feature selection and modelling. Several methodological limitations should be pointed out. First, the image pre-processing can reduce the density variations among different CT scanners and thus is a crucial step before feature extraction, which was not conducted in this study. Second, this study applied in-house developed radiomics software instead of well-validated software (*e.g.* PyRadiomics) to extract radiomic features; the reliability of the extracted features warrants future testing. Third, more sophisticated and rigorous dimensionality reduction techniques (*e.g.* Pearson correlation coefficient analysis) before LASSO need to be implemented to ensure the independence of the identified radiomic features. Finally, as the qRISSc was developed and externally validated in two small cohorts, the generalisation of the prognostic score remains unclear. Thus, the procedures of this study may not be rigorous enough to obtain robust radiomic feature representation.

Biological interpretability is a vital but challenging issue for radiomic features [3]. A disconnect between radiomic features and biological meaning will inherently limit broad clinical translation [3]. Efforts to introduce biological meaning into radiomics are gaining traction in this field with distinct emerging approaches available, including correlation with digital pathology features, radiology–pathology co-registration and analysis of biological pathways or genomic correlations in humans or animals [4–8]. Nevertheless, the biological cause of patient outcome remains poorly understood. Unlike past studies, Schniering *et al.* [1] defined the biological basis of the qRISSc from human to mice; however, we have doubts regarding the experimental ILD model and experimental process (figure 1). The prognostic value of qRISSc was expected to be validated in the mice dataset; however, this important part was not performed in this study. Because the experimental ILD was established with the same dosage of bleomycin, it thus failed to fully reflect the considerable heterogeneity of SSc-ILD. We are not sure if there are survival differences between mice with low qRISSc and those with high qRISSc. If the survival of mice with low qRISSc is significantly longer than those mice with high qRISSc, the within-group error will be large and this difference could be attributed to random factors. If there is no significant survival difference between the two clusters, qRISSc will be invalid and the translation of radiomic signatures between experimental ILD and SSc-ILD patients will be unsuccessful. Thus, the mouse modelling method needs to be improved.

Shareable abstract (@ERSpublications)
The radiomic risk score is promising but challenging in the evaluation of prognostic and molecular differences in interstitial lung disease associated with systemic sclerosis. https://bit.ly/3oWg4UO

Cite this article as: Zhang L, Zheng J, Jin Z, *et al*. The potential and challenges of radiomics in uncovering prognostic and molecular differences in interstitial lung disease associated with systemic sclerosis. *Eur Respir J* 2022; 59: 2102792 [DOI: 10.1183/13993003.02792-2021].

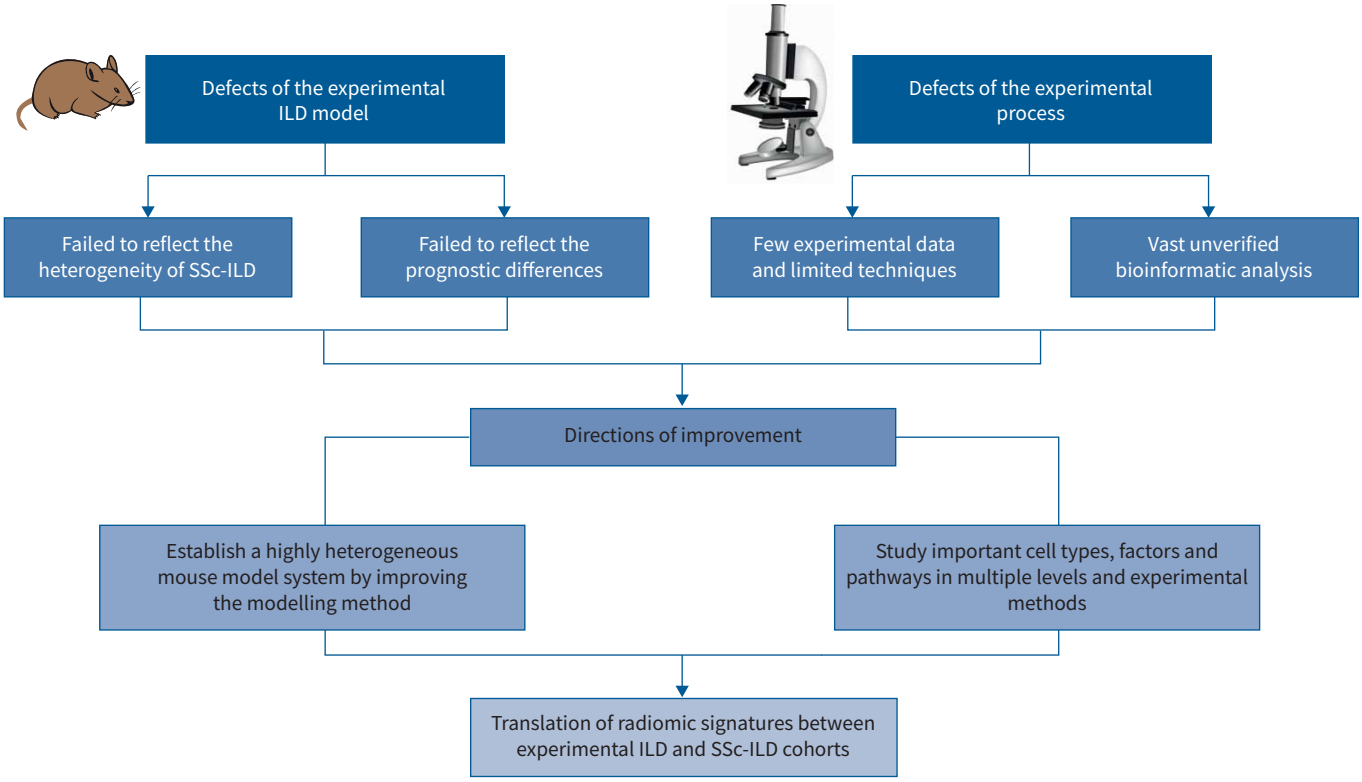

FIGURE 1 Main defects of the interstitial lung disease (ILD) mouse model and experimental process, as well as directions of improvement. The experimental ILD failed to reflect the considerable heterogeneity of systemic sclerosis (SSc)-associated ILD and provide survival data for prognostic analysis. The solution to this problem is to establish a highly heterogeneous mouse model system of bleomycin-induced lung fibrosis by changes of modeling methods. The conclusions from experimental ILD might be overstated due to few experimental data, limited techniques and vast unverified bioinformatic analysis. To solve this issue, important cell types, factors and pathways that are closely associated with SSc-ILD need to be investigated by more experimental methods at different molecular levels for providing reasonable evidence.

Given that the radiomic clusters determined by qRISSc showed no differences in the clinical, demographic and serological characteristics of SSc, we advise the authors to establish a highly heterogeneous mouse model of bleomycin-induced lung fibrosis for simulating the individual differences of SSc-ILD cohorts. For example, C57BL/6J-rj mice at different weeks of age can be treated with bleomycin in different doses and at different times.

Besides the ILD modelling, the experimental scheme also requires improvement. It is proved that specific cell types, cellular factors and extracellular matrix components can mediate the pathophysiology of ILD [9]. In this study, the inflammatory pathway activation explored by the $CD45^+$ cells and mRNA expression of *Il6* and *Mcp1* seems superficial and not quite relevant. The investigation of important cell types, cellular factors and pathways is a tremendous priority in the experimental ILD; for instance, neutrophils and macrophages, which are involved in the process of fibrosis *via* secretion of TGF-β, PDGF and IL-6 [10]. The cell counts and subtype ratios can be detected by flow cytometry while the cytokines can be detected by ELISA. Last but not least, the primary results of experimental ILD were based on bioinformatic analysis, which had an inadequate evidence base. Given the above-mentioned limitations, this study may overstate the conclusions and we should interpret the findings with caution. We are looking forward to furthering investigations for validation.

Lu Zhang[1,2], Jieling Zheng[1,2], Zhe Jin[1], Qiuying Chen[1], Shuyi Liu[1] and Bin Zhang[1]

[1]Dept of Radiology, the First Affiliated Hospital of Jinan University, Guangdong, China. [2]Lu Zhang and Jieling Zheng contributed equally to this work.

Corresponding author: Bin Zhang (xld_Jane_Eyre@126.com)

Conflict of interests: No competing financial interests exist.

References

1 Schniering J, Maciukiewicz M, Gabrys HS, *et al.* Computed tomography-based radiomics decodes prognostic and molecular differences in interstitial lung disease related to systemic sclerosis. *Eur Respir J* 2022; 59: 2004503.

2 Lambin P, Leijenaar RTH, Deist TM, *et al.* Radiomics: the bridge between medical imaging and personalized medicine. *Nat Rev Clin Oncol* 2017; 14: 749–762.

3 Tomaszewski MR, Gillies RJ. The biological meaning of radiomic features. *Radiology* 2021; 298: 505–516.

4 Khorrami M, Prasanna P, Gupta A, *et al.* Changes in CT radiomic features associated with lymphocyte distribution predict overall survival and response to immunotherapy in non-small cell lung cancer. *Cancer Immunol Res* 2020; 8: 108–119.

5 Vaidya P, Bera K, Gupta A, *et al.* CT derived radiomic score for predicting the added benefit of adjuvant chemotherapy following surgery in stage I, II resectable non-small cell lung cancer: a retrospective multicohort study for outcome prediction. *Lancet Digit Health* 2020; 2: e116–e128.

6 Sun R, Limkin EJ, Vakalopoulou M, *et al.* A radiomics approach to assess tumour-infiltrating CD8 cells and response to anti-PD-1 or anti-PD-L1 immunotherapy: an imaging biomarker, retrospective multicohort study. *Lancet Oncol* 2018; 19: 1180–1191.

7 Hosny A, Parmar C, Coroller TP, *et al.* Deep learning for lung cancer prognostication: a retrospective multi-cohort radiomics study. *PLoS Med* 2018; 15: e1002711.

8 Aslan K, Turco V, Blobner J, *et al.* Heterogeneity of response to immune checkpoint blockade in hypermutated experimental gliomas. *Nat Commun* 2020; 11: 931.

9 Spagnolo P, Distler O, Ryerson CJ, *et al.* Mechanisms of progressive fibrosis in connective tissue disease (CTD)-associated interstitial lung diseases (ILDs). *Ann Rheum Dis* 2021; 80: 143–150.

10 Kolahian S, Fernandez IE, Eickelberg O, *et al.* Immune mechanisms in pulmonary fibrosis. *Am J Respir Cell Mol Biol* 2016; 55: 309–322.