Early View

Correspondence

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

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

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To the editor: We read with great interest the study by Dr. Janine and colleagues [1], recently published in *European Respiratory Journal.* This study highlighted the potential of radiomics as a non-invasive tool for disease characterization, 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 are 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 that 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 preprocess, feature extraction, feature selection, and modeling. Several methodological limitations should be pointed out. First, the image preprocess can reduce the density variations among different CT scanners

and thus is a crucial step before feature extraction, which wasn't conducted in this study. Second, this study applied in-house developed radiomics software instead of well-validated softwares (e.g. PyRadiomics) to extract radiomic features, the reliability of the extracted features warrants to be tested in the future. 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, the qRISSc was developed and externally validated in two small cohorts, the generalization of the prognostic score remains unclear. Thus, the procedures of this study maybe not 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 coregistration, 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, Janine et al. defined the biological basis of the qRISSc from human to mice; however, we doubt 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 done in this study. Because the experimental ILD was established with the same dosage of bleomycin, thus it 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 modeling method needs to be improved. 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 ages can be treated with bleomycin in different doses and at different times.

Besides the ILD modeling, 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.

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Figure legends

Figure 1. Main defects of the ILD mouse model and experimental process, as well as directions of improvement. The experimental ILD failed to reflect the considerable heterogeneity of SSc-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.