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Early View

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Radiomics derived morphological features predict pulmonary function response under lumacaftor-ivacaftor in patients with cystic fibrosis

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To the editor: We read with great interest the study by Dr. Alienor and colleagues [1], recently published in European Respiratory Journal. Lumacaftor/ivacaftor combination therapy has achieved clinical benefits in patients with cystic fibrosis homozygous for the Phe508del CFTR mutation. The authors used traditional morphological features on chest computed tomography (CT) to evaluate one year of treatment with lumacaftor-ivacaftor and applied pretherapy radiomics morphological features to identify distinct disease phenotypes that were related to treatment response. The results demonstrated that the mean Bhalla total score and subscores significantly reduced after one year of treatment, and three clusters could be identified with distinct treatment responses. Notably, patients from cluster C with younger age and less severe lung structural abnormalities, achieved a better response rate as compared to other clusters. Despite the promising and well-presented findings, we are concerned about several issues below.

Current radiomic features suffer from poor reproducibility and generalizability, because most features are dependent on imaging modality, making them susceptive to variations in scan protocol [2]. In this study, chest CT scans were performed on 14 different machines with various parameters and acquisitions, thus the extracted radiomic features maybe not reproducible and representative enough. As a result, the three morphological phenotypes identified based on the radiomic features maybe

not objective, which hinders the generalization of the findings to other institutions. Unlike previous radiomic works, this study did not adhere to a standard radiomic workflow and skipped the steps of feature selection and radiomic modeling. Most radiomic features were redundant and not associated with the treatment response. However, as a coin has two sides, this study may evade the uncertainty caused by feature selection and provides us a new insight into the direct application of radiomic features into identifying morphological phenotypes of diseases without feature selection. Considering the high-dimensional property of radiomic features, t-distributed stochastic neighbor embedding (t-SNE) is recommended to conduct after K-means clustering analysis. The t-SNE has been widely accepted as a method for dimensionality reduction and visualization of high-dimensional data [3]. By using t-SNE plots, we can visualize the three clusters and their differences in the treatment response.

This study was also limited by the significant selection bias and confounding factors. Except for the exclusion of patients who discontinued lumacaftor-ivacaftor therapy, the patient's age, baseline lung function, and lumacaftor-ivacaftor dose could also affect the analysis results. The proportion of $ppEFV_1$ < 40 (advanced lung disease) was significantly higher in adults than in adolescents (19.9% vs. 5.2%, P<0.001) [4]. A pooled analysis of two clinical trials showed that lumacaftor-ivacaftor was effective in patients with different degrees of lung function impairment [5]; however, initial lung function is a confounding factor that potentially influences the efficacy and safety of this therapy. Burgel PR et al. [6] found the percentage of $ppFEV_1$ increase ≥ 5% in patients with baseline $ppFEV_1$ of 40–90 was 1.5 to 2 fold higher than in patients with baseline $ppFEV_1$ < 40 or ≥ 90, indicating that the treatment response depends on $ppFEV_1$ at baseline. Aalbers BL et al. showed that patients starting lumacaftor-ivacaftor at $ppFEV_1$ ≥ 90 didn't respond in $ppFEV_1$ [7]. Compared with patients with $ppFEV_1$ > 40, patients with $ppFEV_1$ < 40 had a higher rate of adverse respiratory events, worse nutritional status, and an increased risk of mortality [8]. Additionally, the treatment dose also affects the response to lumacaftor-ivacaftor. Amongst patients who received continuous or intermittent treatment with

lumacaftor-ivacaftor, the rate of responders was significantly lower in the latter [4]. Somayaji R et al. [9] showed that using half-dose lumacaftor-ivacaftor at the beginning and gradually increased to the full dose resulted in fewer respiratory adverse events and no treatment discontinuations, indicting patients with $ppFEV_1 < 40$ may benefit from therapy initiation at a lower dose with close monitoring before increasing to the full dose. Table 3 shows that clusters A and B both included patients with $ppFEV_1 < 40$ while cluster C included all patients with $ppFEV_1 > 40$. Thus, the results of unsupervised K-means clustering were significantly affected by the patient's age and $ppEFV_1$ at baseline. It is not surprising that a better response rate was observed in cluster C in which the patients had younger age and less severe morphological and functional abnormalities. From this perspective, the radiomics analysis was bothersome and not important as expected. A more meaningful action could be the development of a response prediction model. Although the authors stated that they failed to use deep learning to predict response to lumacaftor-ivacaftor because of the limited data size, they might select radiomic features and then build a radiomic model via traditional machine learning (eg, random forest and Support Vector Machine) [10] combing the modified Bhalla score and CT-derived radiomic features at baseline. However, external validations are warranted to test the robustness and generalization of the prediction model.

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