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Commentary

Fibrotic lung disease: A molecular glimpse into severe Covid-19?

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Covid-19, the clinical syndrome caused by the novel severe acute respiratory syndrome (SARS)-CoV2 virus, is primarily a respiratory condition that can range in severity from asymptomatic infection to acute respiratory distress syndrome (ARDS), leading to respiratory failure and death [3]. While the majority of patients recover, the prognosis of Covid-19 is unpredictable and influenced by a number of factors, mainly older age and age-related comorbidities [5]. In addition, there is concern that some organs, particularly the lungs, may suffer persistent damage. Indeed, the majority of hospitalized Covid-19 survivors have persistent functional and radiographic abnormalities at the initial follow-up [8], suggesting there may exist shared pathobiology between fibrotic lung disease and Covid-19-related lung disease. However, the proportion of cases of asymptomatic interstitial lung disease (ILD) that were simply unmasked by SARS-CoV2 infection is unknown.

Because there is an urgent need to better understand drivers of severe Covid-19 and predict outcomes in these patients, the work of Juan-Guardela and colleagues, published in this issue of EBioMedicine, is timely and provides potential molecular insight into this devastating disease. In a retrospective, multicentre cohort study, investigators determined peripheral blood expression of 50 genes comprising a known transcriptomic signature of idiopathic pulmonary fibrosis (IPF) survival to assess whether a similar signature would predict mortality in patients with Covid-19 [6]. A Scoring Algorithm of Molecular Subphenotypes (SAMS) was used to classify patients in a derivation cohort (n = 8) as having a high-risk (Up score >0.41) versus low-risk (Down score <-0.41) signature, which effectively discriminated severe from mild Covid-19 - according to the National Early Warning Score (NEWS; severe ≥5, mild <5).

When applying this signature in a validation cohort (n = 100), authors found it to predict intensive care unit (ICU) admission, need for mechanical ventilation, and in-hospital mortality in individuals with Covid-19. As expected, high-risk subjects were significantly older, and had higher APACHE-II severity score and Charlson Comorbidity Index. Notably, only 1/41 (2.4%) patients in the 50-gene low-risk profile group died compared to 23/59 (39%) in the high-risk group. Refractory respiratory failure secondary to ARDS was the cause of death in all deceased patients in the validation cohort. To determine the cellular source of genes comprising this 50-gene risk profile, authors performed a cell type-specific analysis using single-cell RNA sequencing data from seven subjects with Covid-19. They found that cells with a high-risk profile were mainly CD14+ monocytes, dendritic cells and neutrophils, suggesting that specific cell types are critical regulators of the high-risk profile and may contribute to the increased risk of mortality and other poor outcomes in patients with Covid-19.

Finally, authors showed that this 50-gene signature developed in patients with Covid-19 predicted differential survival in two independent cohorts of patients with IPF, consistent with previous findings using a similarly derived signature from this group of genes [4]. IPF is a chronic and inexorably progressive interstitial lung disease of unknown cause with a median survival of 3-4 years if untreated [7] and provides a reference group

The clinical implications of the study by Juan-Guardela and colleagues are potentially relevant, as the identification of 50-gene risk profiles in Covid-19 may allow early identification of patients more likely to progress, enabling timely optimization of care. However, measurement of RNA biomarkers is costly and, at present, generally available only in the setting of research laboratories. In addition, while the predictive model based on this 50-gene expression signature performed relatively well, an unbiased approach using transcriptomic or other molecular data would likely perform better. At present, the significance of the transcriptomic overlap between Covid-19 and IPF remains speculative and it remains to be seen whether Covid-19 itself causes progressive pulmonary fibrosis. Indeed, while pulmonary fibrosis is a well-known complication of ARDS [1], Covid-19-related pulmonary fibrosis and IPF differ significantly with regard to their clinical, radiological and histopathologic features. However, patients with IPF may experience episodes of acute worsening (termed “acute exacerbations”), which, similar to ARDS, are characterized histologically by diffuse alveolar damage (DAD) and have a poor prognosis [9].

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If a causal link between Covid-19 and progressive pulmonary fibrosis is established, shared transcriptomic profiles between Covid-19 and IPF may lend support to the hypothesis that antifibrotic drugs approved for IPF [2] may help prevent long-term pulmonary sequelae of Covid-19. Indeed, several studies are currently investigating this approach. The study by Juan-Guardela and colleagues calls for further research, including, as highlighted by the investigators themselves, validation of their findings in larger, prospective studies of fibrotic lung diseases other than IPF, identification of additional genes associated with outcomes in both Covid-19 and IPF through unbiased -omics-based analyses of peripheral blood, and single-cell RNA sequencing analyses. Such analyses may determine whether the cellular origins of these diseases are shared. Addressing some of these points is instrumental to developing further molecular and genetic blood markers as predictors of outcomes in patients with Covid-19, Covid-19-related pulmonary fibrosis, and IPF.

Contributors

PS and JO co-wrote this commissioned Commentary.

Declaration of Competing Interest

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