MMP-1 AND MMP-7 AS BIOMARKERS FOR IDIOPATHIC PULMONARY FIBROSIS

COVID-19 SURVIVORS HAVE HIGH RISK OF DEVELOPING IPF

Studies have as of Jan 26, 2021, nearly 99.5 million people have been infected and around 2.13 million people have died from the coronavirus disease 2019 (Covid-19) worldwide. In the United States alone, 25.1 million people have infected and 419,827 people died from Covid-19. Almost all serious Covid-19-related consequences feature pneumonia[1]. To date, about 55 million people worldwide, and 15.7 million in the U.S. have recovered from Covid-19, but there remains concern that some organs, including the lungs, might have long-term impairment following the infection[1]. One of the major risk factors for severe Covid-19 is shared with idiopathic pulmonary fibrosis (IPF) which is recognized as a potential sequelae among the survivors[2]. IPF is a progressive, fibrotic, and irreversible interstitial lung disease[3]. Even a relatively small degree of residual but non-progressive fibrosis could result in considerable morbidity and mortality in an older population of patients who have had Covid-19.

An early analysis from patients with Covid-19 on hospital discharge suggests that more than a third of recovered patients develop fibrotic abnormalities[4]. Therefore, it is important to rapidly identify whether the development of pulmonary fibrosis occurs in the survivor population so as to aid physicians in providing Covid-19 survivors with timely and effective antifibrotic therapies[1,2,4,5]. Though chest CT is an effective diagnostic tool for pulmonary fibrosis, it is too expensive for screening and long term monitoring. A blood test using a set of sensitive and specific biomarkers can be a cost effective aid to the early diagnosis of IPF in COVID-19 survivors. The most clinically established biomarkers for IPF are blood levels of matrix metalloproteinases, especially MMP-1 and MMP-7[6-10].

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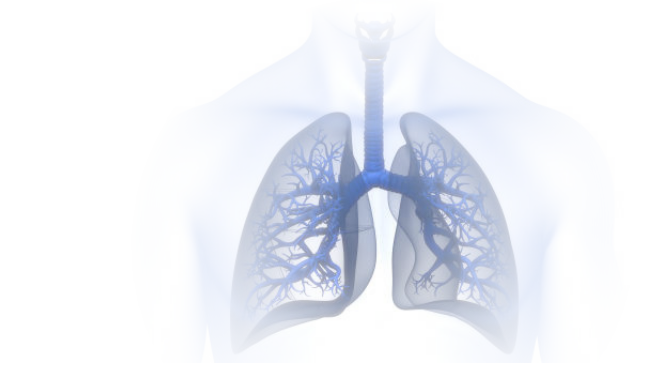
MMP-1 AND MMP-7 ASSAYS



MMP FAMILY EXPRESSION ARE HIGHLY UPREGULATED IN IPF LUNGS

Idiopathic pulmonary fibrosis (IPF) is assumed to be caused by aberrant tissue repair and remodeling following recurrent alveolar epithelial injury leading to a persistent and progressive disordered fibroproliferation3. In the process of lung tissue repair and remodeling, metalloproteinases are overexpressed to digest and remove fibrotic scar tissues in the lungs. Among the metalloproteinases, Matrix metalloproteinase-7 and Matrix metalloproteinase-1 (MMP-1 and MMP-7) are the most significantly overexpressed proteins in the lungs of patients with IPF compared with healthy controls[6-10].

Rosas et al. from the University of Pittsburgh, School of Medicine found the concentrations of both MMP-1 and MMP-7 in peripheral blood samples of IPF patients were significantly higher compared to the levels in samples from hypersensitivity pneumonitis (HP) patients. This suggests not only a determinant role in IPF pathogenesis, but also potential utility as biomarkers in the differential diagnosis of this disease7. The combination of high plasma concentrations of both MMP-7 (≥ 1.99 ng/mL) and MMP-1 (≥ 2.15 ng/mL) excludes all controls7. The diagnostic sensitivity and specificity of the combined biomarkers are 98.6% (95% confidence interval [CI] 92.7%–100%) and 98.1% (95% CI 89.9%–100%), respectively[7].

MMP-7 AND MMP-1 IN COMBINATION

The receiver operating characteristic curves (ROCs) (figure 1) confirm that MMP-7 is the best univariate classifier, although the combination of MMP-7 and MMP-1 is better in identifying IPF from controls (data not shown)7. Additionally, the combination of high MMP-7 and high MMP-1 peripheral blood concentrations distinguish IPF from HP with 96.3% sensitivity (95% CI 81.0%–100%) and 87.2% specificity (95% CI 72.6%–95.7%), further supporting that MMP-1 in combination with MMP-7 distinguishes IPF from HP.

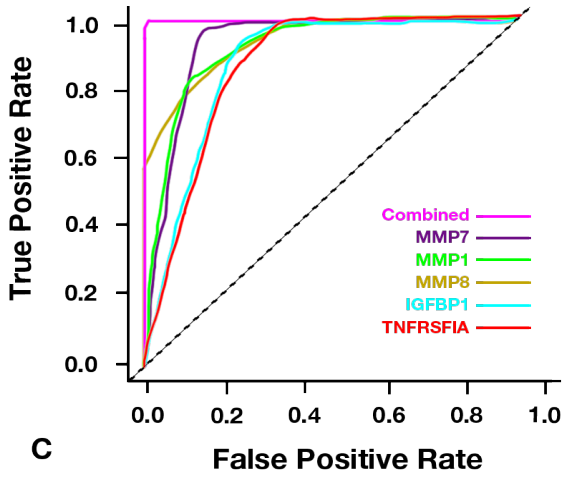


Figure 1. Data from Rosas I at al. PLoS Medicine, April 2008 | Volume 5 | Issue 4 | e93

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