# Cluster analysis to identify long COVID phenotypes using $^{129}$Xe magnetic resonance imaging: a multicentre evaluation

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**Cluster analysis of $^{129}$Xe MRI metrics identifies 4 phenotypes of long COVID with distinct functional MRI and clinical characteristics. MRI-based clusters can be used to dissect long COVID heterogeneity, enabling personalised clinical care and treatment.** https://bit.ly/42uia1J

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## Abstract

***Background*** Long COVID impacts ∼10% of people diagnosed with coronavirus disease 2019 (COVID-19), yet the pathophysiology driving ongoing symptoms is poorly understood. We hypothesised that $^{129}$Xe magnetic resonance imaging (MRI) could identify unique pulmonary phenotypic subgroups of long COVID. Therefore, we evaluated ventilation and gas exchange measurements with cluster analysis to generate imaging-based phenotypes.

***Methods*** COVID-negative controls and participants who previously tested positive for COVID-19 underwent $^{129}$Xe MRI ∼14 months post-acute infection across three centres. Long COVID was defined as persistent dyspnoea, chest tightness, cough, fatigue, nausea and/or loss of taste/smell at MRI; participants reporting no symptoms were considered fully recovered. $^{129}$Xe MRI ventilation defect percent (VDP) and membrane-to-gas (Mem/Gas), red blood cell-to-membrane (RBC/Mem) and red blood cell-to-gas (RBC/Gas) ratios were used in k-means clustering for long COVID, and measurements were compared using ANOVA with post-hoc Bonferroni correction.

***Results*** We evaluated 135 participants across three centres: 28 COVID-negative (mean±SD age 40±16 years), 34 fully recovered (42±14 years) and 73 long COVID (49±13 years). RBC/Mem (p=0.03) and forced expiratory volume in 1 s ($FEV_1$) (p=0.04) were different between long COVID and COVID-negative; $FEV_1$ and all other pulmonary function tests (PFTs) were within normal ranges. Four unique long COVID clusters were identified compared with recovered and COVID-negative. Cluster 1 was the youngest with normal MRI and mild gas trapping; Cluster 2 was the oldest, characterised by reduced RBC/Mem but normal PFTs; Cluster 3 had mildly increased Mem/Gas with normal PFTs; and Cluster 4 had markedly increased Mem/Gas with concomitant reduction in RBC/Mem and restrictive PFT pattern.

***Conclusions*** We identified four $^{129}$Xe MRI long COVID phenotypes with distinct characteristics. $^{129}$Xe MRI can dissect pathophysiological heterogeneity of long COVID to enable personalised patient care.