Title: Mediation of the effect of airflow obstruction upon six minute Walking distance (6MWD) by cytokine IL6 plasma levels in chronic obstructive pulmonary disease (COPD)

Body: To explore the causative role of cytokine IL6 blood levels on the relationship between FEV₁ and 6 minute walking distance (6MWD), 153 patients (GOLD [Global Initiative for Chronic Obstructive Lung Disease] stages I–IV) underwent measurement of fasting plasma levels of IL6, together with pulmonary function tests, standardized six minute walking test, and EuroQoL 5D questionnaire at the start of respiratory rehabilitation program at our Institution. We hypothesized a mediation model were effect of the initial variable X (FEV₁) upon the outcome variable Y (6MWD) is caused by the intervening variable M (IL6). A four steps causal approach was used by conducting three separate regression analyses. Out of 153 patients (120 males) 54, 28, 34, 37 were in GOLD stage I, II, III, and respectively IV. Mean age was 69.7±9.0 years. Mean FEV₁ averaged 54.3±23.5% of predicted, and 6MWD 295.6±135.7 meters (66.4±41.3% of predicted). Median cytokine IL6 was 6.68 (IQR: 5.87). Raw correlation coefficients for association of 6MWD on FEV₁ was: 0.518, of IL6, in log units, on FEV₁: -0.283, and of 6MWD on IL6, in log units, -0.447, (p<0.0001 for all). Indirect effect, i.e. the portion of total effect upon Y accounted for by M when controlling for X, was 0.52. A full mediation of LnIL6 on the X-Y relationship exists (Sobel z= 2.899247, p=0.0037). In conclusion, mediation of the effect of FEV₁ upon walking performance decline by a systemic immune activation biomarker stands for a underlying pathological process that makes up heterogeneity of the syndrome of COPD, and might enable tailoring rehabilitation strategies to individual patients.