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Title: Inflammatory markers and COPD phenotypes as predictors of COPD exacerbations

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Body: Background: COPD exacerbations accelerate disease progression. Aims: To examine if COPD phenotypes and systemic inflammatory markers predict the risk for COPD exacerbations, defined as requiring treatment with either systemic steroids or antibiotics. Methods: 433 COPD patients, GOLD stage II-IV, aged 40-76 yrs were included in the Bergen COPD Cohort Study in 2006/07, and followed for 3 years. Examined baseline predictors were sex, age, body composition, smoking habits, exacerbations the last year prior to baseline, GOLD stage, Charlson comorbidity score (CCS), presence of hypoxemia (PaO2<8 kPa), chronic cough, use of inhaled steroids and/or tiotropium, and the inflammatory markers C-reactive protein (CRP), neutrophil gelatinase associated lipocalin (NGAL), soluble tumor necrosis factor receptor 1 (sTNF-R1), and osteoprotegrin (OPG). Univariate and multivariable Poisson models with random effects were fitted to estimate the yearly incidence rate ratios (IRR). Results: Univariately, all variables except sex and CCS were significantly associated with the outcome. Higher levels of the inflammatory markers each predicted an increased yearly IRR (95% CI) per unit increase of the markers with IRR 1.03 (1.01-1.05), 1.07 (1.03-1.13), 1.06 (1.001-1.13), and 1.08 (1.01-1.16), respectively. Multivariately, significant predictors of COPD exacerbations were: age [IRR per 1 yr increase:1.02 (1.003-1.04)], female sex [1.35 (1.06-1.73)], >1 exacerbations last year before baseline [1,58 (1.17-2.13)], GOLD III [1.28 (1.01-1.64)], GOLD IV [2.73 (1.85-4.05)], chronic cough [1.61 (1.28-2.03)], use of inhaled steroids [1.67 (1.29-2.17)]. Conclusion: Clinical COPD characteristics were independent predictors of exacerbations.