Protocol: The Association Between Frequent Acute Exacerbations of COPD and Risk of Chronic Kidney Disease

Background and Rationale

Chronic obstructive pulmonary disease (COPD) is associated with systemic inflammation, cardiovascular comorbidity, and recurrent acute exacerbations (AECOPD). Each exacerbation triggers transient hypoxia, systemic inflammatory responses (e.g., elevated IL-6, TNF-α, CRP), and hemodynamic stress, which may cumulatively damage other organs, including the kidneys. Furthermore, repeated systemic corticosteroid therapy and other medications during exacerbations may increase the risk of renal injury. Observational data suggest that repeated inflammatory insults could accelerate the decline in renal function. This study aims to quantify the relationship between the frequency of AECOPD and incident chronic kidney disease (CKD) using Danish nationwide registers.

Hypothesis

Frequent AECOPD (≥1 per year) among patients with COPD increases the risk of developing chronic kidney disease (CKD; defined as eGFR <60 mL/min/1.73 m² or new CKD diagnosis).

Study Design

- Type: Retrospective register-based cohort study
- Data Sources
    - Danish COPD Registry (baseline characteristics, FEV1, comorbidities)
    - LAB-register (serial eGFR measurements)
    - National Patient Register (CKD diagnoses: ICD-10 N18.x)
    - Civil Registration System (date of death, emigration)
    - Prescription registries for NSAID, systemic steroids, and other medications

Study population

Inclusion criteria:

- Patients registered in the Danish COPD Registry from 2010–2022
- At least one follow-up measurement of renal function in the year before inclusion
- Age ≥ 40 years

Exclusion criteria:

- Pre-existing CKD at baseline.

Exposure

- Primary Exposure: Number of AECOPD per year, categorized as:
    - No hospitalizations with primary diagnosis of COPD or less than two systemic steroid or antibiotic prescription for acute worsening of respiratory symptoms. **(reference)**
    - At least one hospitalization with primary diagnosis of COPD or two or more systemic steroid or antibiotic prescription for acute worsening of respiratory symptoms. **(frequent)**

- Definition of AECOPD: Hospitalization with primary diagnosis of COPD exacerbation or systemic steroid or antibiotic prescription for acute worsening of respiratory symptoms.
    - Hospital admission with primary diagnosis of COPD: ICD-10: J441+ J440+ J44.9 with duration of at least 24 hours
    - Systemic steroid prescription: H02AB0 with strength > 5mg and pack size smaller than 100, to avoid prescriptions for maintenance treatment. Prescriptions must be at least 30 days apart to count as two separate exacerbations.
    - Antibiotic prescription: J01CA04, J01CR02, J01FA09, J01FA06, J01FA10. Prescriptions must be at least 14 days apart to count as two separate exacerbations.

- At index date, phenotype is determined by number of exacerbations 1 year prior to baseline. Each year after baseline, phenotypes are revalued by considering number of exacerbations in the past year. Thus, exacerbation frequency is a time varying variable.

Outcome

- Primary Outcome: Incident CKD during follow-up, defined as:

    1. New ICD-10 CKD diagnosis (N18.x) OR
    2. eGFR <60 mL/min/1.73 m² on at least two consecutive measurements ≥90 days apart (overensstemmelse med KDIGO-definitionen af CKD)

Covariates

- Age, sex, baseline eGFR, COPD severity (FEV1 % predicted), body mass index (BMI), smoking status.
- Comorbidities:
    - Hypertension I10–I15.
    - Diabetes mellitus E08-E13
    - Cardiovascular disease I00-I99
        - Ischemic heart disease (I20–I25
        - Heart failure (I50)
        - Cerebrovascular disease (I60–I69)
        - Peripheral arterial disease (I70–I79)
- Medications:
    - NSAIDs ATC code M01A
    - ACE inhibitors/ARBs C09
    - Systemic corticosteroids H02AB0

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Statistical Analysis

1. Descriptive statistics for baseline characteristics by exacerbation frequency

2. Primary Analysis: Cox proportional hazards regression
    - Exposure: AECOPD as a time-varying covariate
    - Outcome: Time to incident CKD
    - Competing risk: Death
    - Adjusted for all covariates listed above. Systemic corticosteroid is included as a time varying confounder.
    - Index date: First entree in Danish COPD registry
3. Secondary Analyses:
    - Moderate exacerbation vs. no moderate exacerbations
    - Severe exacerbators vs. no severe exacerbation.
    - Dose-response: Number of exacerbations as continuous variable
    - Subgroup analyses: age (<65 vs ≥65), sex, baseline eGFR categories
    - Sensitivity: lagging exposure by 30–90 days to reduce reverse causation
4. Test proportional hazards assumption using Schoenfeld residuals
5. Multiple imputation for missing covariate data

Strengths

- Nationwide register ensures large sample size and long-term follow-up
- Time-varying exposure accounts for changes in exacerbation frequency over time
- Clinically relevant outcome with strong mechanistic rationale

Limitations

- Incomplete laboratory data for all patients (eGFR measurements may be missing)
- Potential residual confounding from unmeasured variables (e.g., alcohol, diet, adherence to medications)

- Possible misclassification of AECOPD or CKD outcomes

Ethics and Data Management

- Approval from relevant Danish data authorities (Sundhedsdatastyrelsen / Data Protection Agency) required
- Secure handling of personal data according to Danish legislation
- Data linkage performed via personal identification number (CPR)