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Rheumatoid Arthritis and Bronchiectasis: Hospital-treated Pneumonia and Mortality in a Nationwide Population-Based Cohort Study

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Background

Bronchiectasis is a chronic airway disease characterized by irreversible bronchial dilatation, persistent airway inflammation, and recurrent respiratory infections. Rheumatoid arthritis (RA) is a systemic autoimmune disease frequently involving the lungs, and bronchiectasis is among the most common pulmonary manifestations of RA. The coexistence of RA and bronchiectasis is clinically important, as both conditions are associated with chronic inflammation, impaired host defense, and increased susceptibility to infections.

Previous studies have demonstrated that patients with RA-associated bronchiectasis have increased mortality compared with patients with idiopathic bronchiectasis. However, it remains unclear whether RA independently contributes to an increased risk of severe respiratory outcomes, including pneumonia, and death among patients with bronchiectasis.

Understanding the prognostic impact of RA in bronchiectasis is essential for optimizing preventive strategies, immunosuppressive treatment decisions, and clinical monitoring in this vulnerable patient population.

Hypotheses

1. Patients with bronchiectasis and rheumatoid arthritis have a higher risk of hospital-treated pneumonia than patients with bronchiectasis without rheumatoid arthritis.

2. Patients with bronchiectasis and rheumatoid arthritis have a higher risk of all-cause mortality than patients with bronchiectasis without rheumatoid arthritis.

Study Design

Nationwide, population-based, observational cohort study with prospective follow-up using routinely collected healthcare registry data.

Data Sources

The study will be conducted using linked data from the following Danish national registries:

1. **The Danish National Patient Registry (DNPR)**
    - Dates of hospital admissions and outpatient visits, primary and secondary diagnoses, and procedure codes coded according to ICD-10 (DJ479).
2. **The Danish Civil Registration System (CRS)**
    - Date of birth, sex, migration, and complete information on vital status, ensuring full mortality follow-up.
3. **The Danish National Prescription Registry**
    - Information on redeemed prescriptions including drug class, dispensing date, and quantity.
    - Medications of interest include inhaled corticosteroids, systemic corticosteroids, long-acting beta2 agonists, long-acting muscarinic antagonists, short-acting beta2 agonists and muscarinic antagonist and azithromycin

Study Population

Inclusion Criteria

- Adults aged ≥18 years.
- Diagnosis of bronchiectasis, defined as:
    - at least one hospital-based diagnosis of bronchiectasis (ICD-10 DJ479)
- Index date defined as the first hospital-based inpatient or outpatient contact with bronchiectasis during the study period.

Exposure Groups

- Bronchiectasis with rheumatoid arthritis (RA-BE)
    - Patients with bronchiectasis and a diagnosis of rheumatoid arthritis defined as ICD-10 codes M05 (seropositive RA) or M06 (other RA), registered at a minimum of two separate hospital contacts prior to the index date.

- Bronchiectasis without rheumatoid arthritis (BE alone)
    - Patients with bronchiectasis and no recorded diagnosis of RA before index date.

Study Period and Follow-Up

The study period will span from January 1st, 2010 to December 31st, 2024. Patients will be followed until the end of the study period.

Follow-up will be censored at death, emigration, or completion of the study period, whichever occurs first.

Outcomes

Primary outcome

The primary outcome was hospital-treated pneumonia, defined as the first hospital admission with pneumonia recorded as the primary discharge diagnosis (ICD-10 codes J13–J18) after index date within the study period.

Secondary outcome

The secondary outcome was all-cause mortality, defined as death from any cause occurring after index date within the study period**.**

Outcomes were compared between patients with bronchiectasis with and without rheumatoid arthritis.

For each outcome, only the first event during follow-up will be considered.

Covariates

Potential confounders selected a priori based on clinical relevance and prior literature include:

- Age (categorized by quartiles)
- Sex
- Charlson Comorbidity Index (excluding RA)
- Use of inhaled corticosteroids in the year before baseline (No use, low dose ≤400 µg/day, moderate dose 401–999 µg/day or high dose ≥1000 µg/day)
- Use of systemic corticosteroids in the year before baseline (No use, low dose and high dose characterized by median dose)

Statistical Analysis

Primary Analysis

Multivariable regression analyses will be conducted as the primary analytical approach. Models will adjust for all predefined covariates, including age, sex, Charlson Comorbidity Index (excluding RA), use of inhaled corticosteroids and use of systemic corticosteroids

Outcome Analyses

- Cox regression models will be used to estimate the hazard rates of hospital-treated exacerbations and pneumonia, accounting for death as a competing risk. Absolute risk will be assessed with cumulative incidence plots.
- Cox proportional hazards regression will be used to estimate the risk of all-cause mortality.

Results will be reported as hazard ratios (HRs) with 95% confidence intervals (CIs) and illustrated using cumulative incidence curves.

Sensitivity Analyses

- Inverse probability of treatment weighting (IPTW) based on propensity scores will be applied as a sensitivity analysis to assess the robustness of the primary findings.
- Propensity scores will be estimated using gradient boosted models including all predefined covariates. Covariate balance between exposure groups will be evaluated using standardized mean differences.
- Stratified analyses according to:
    - inhaled corticosteroid use

Proportional hazards assumptions will be evaluated using standard diagnostic methods.

All analyses will be carried out using R version 4.3. The r-packages survival and twang will be used to fit survival models, and to calculate propensity weights respectively.

Ethics and Data Protection

The study will be conducted using pseudonymized registry data. According to Danish legislation, informed consent and ethical committee approval are not required for retrospective register-based studies. Approval from the relevant regional data protection authority will be obtained prior to data access.

Perspectives

This study will clarify the independent prognostic impact of rheumatoid arthritis in patients with bronchiectasis. Improved understanding of the interaction between systemic autoimmune disease and chronic airway infection may inform clinical risk stratification, preventive strategies, and tailored management of patients with bronchiectasis and concomitant RA.