Supplementary Materials

An Expanded View of Disease Continuum Centered on Rheumatoid Arthritis: From Single to Systemic Perspectives

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Supplementary Material and Methods

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Study Population of Rheumatoid Arthritis Cohort

This study leveraged data from the extensive FinnGen cohort, which comprises 392,423 participants, including 12,555 individuals diagnosed with rheumatoid arthritis (RA). The cohort offers a rich dataset, encompassing 1,289 distinct medical events and clinical outcomes, allowing for a detailed investigation of comorbidities associated with RA. Data were sourced from several national health registries in Finland, providing a comprehensive, longitudinal view of participants' health statuses over time.[1] These registries' data included the Care Register for Health Care (HILMO), which captures inpatient and outpatient visits; the Population Register (DVV) for demographic details; the Death Registry; the Finnish Cancer Registry; and the Drug Purchase and Reimbursement Database (Kela), which tracks prescribed medications and reimbursements. Each registry was meticulously linked to create a longitudinal profile for every participant. This integration of clinical, demographic, and mortality data allowed for an in-depth assessment of both pre- and post-RA diagnosis comorbidities. Follow-up for each participant began on January 1, 1998, and extended until the end of the study period on December 31, 2021, or until death, whichever came first.

Comorbidity Analysis

To identify comorbidities associated with RA, we employed Cox proportional hazards regression models. These models were adjusted for sex and age, addressing potential confounders.[2] A medical event was considered an RA comorbidity if it showed a statistically significant association with RA, determined by a false discovery rate (FDR)-adjusted p-value of less than 0.05. Our analysis focused on identifying comorbidities both before and after RA diagnosis. By distinguishing pre-RA comorbidities (comorbidities that may contribute to the development of RA) from post-RA comorbidities (comorbidities emerging after RA diagnosis), we aimed to map a broader health continuum centered around RA. High-Risk Comorbidities: Defined by an FDR-adjusted p-value < 0.05, an absolute log10-hazard ratio (HR) > 1.5, and a prevalence exceeding 1.0% in the RA population. High-risk comorbidities represent comorbidities with the strongest associations and the highest occurrence rates within the cohort. This risk identification allowed us to prioritize the most clinically relevant comorbidities for further investigation.

Disease Taxonomy and Classification

For systematic classification, we utilized the International Statistical Classification of Diseases and Related Health Problems (ICD-10) and the International Classification of Diseases for Oncology (ICD-O-3) frameworks. Additionally, the FinnGen study's disease classification system was applied to maintain consistency across the diverse range of medical conditions analyzed. We categorized RA comorbidities by their disease type and temporal relationship to RA onset. This dual approach enabled us to: Group comorbidities by disease category (e.g., cardiovascular, metabolic, neoplastic) to understand the broad health domains affected by RA. Segment comorbidities temporally into pre-RA and post-RA groups, revealing comorbidities that may predispose individuals to RA versus those that develop as a consequence of the disease. This structured classification provided a detailed view of the interconnectedness of RA with other diseases, enabling us to uncover patterns within the RA disease continuum. Through this approach, we aimed to shed light on how different comorbidities interact with RA, influencing its onset, progression, and patient outcomes.[3]

Statistical Analysis

Statistical analyses were conducted in the R version 3.6.1 environment (Copyright 2019; The R Foundation for Statistical Computing). Cox models provided insights into the hazard ratios associated with each comorbidity,[2] in order to explore potential interactions between comorbidities to assess their collective impact on unipolar depression. Correction for multiple testing was performed using the false discovery rate (FDR) method.[4] The significance threshold was set at an FDR-adjusted p-value of less than 0.05 for all tests.

Reference

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