Gender Differences and Comorbidities in Rheumatologic Diseases

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Disclosures

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Objectives:

• Recognize Gender differences that occur in Rheumatic Diseases
  • Rheumatoid Arthritis, Systemic Lupus, Axial Spondyloarthitis

• Recognize Comorbidities that occur with, and complicate Rheumatic Diseases
  • Cardiovascular, Malignancy, Depression, Osteoporosis

• Recognize the impact of Menopause
Autoimmune disease have a well-known female preponderance.

Approximately 78% of patients with autoimmune diseases such as multiple sclerosis, scleroderma, systemic lupus, Sjogren syndrome, and rheumatoid arthritis are women. "Sex contributes to several differences in RA disease aspects like epidemiology, disease course, and management, making the experience different for affected males and females. This should be taken into account while personalizing management of RA to a specific patient." - Namrata Singh, MD, MSCI, FACP.
LUPUS
Systemic Lupus Erythematosus (SLE) is a chronic inflammatory disease

• Affects predominantly women, with men ranging from (4–22%) in various studies.
• Sex differences may influence clinical and serological manifestations, and outcomes in disease.
• Current results vary among different countries and different ethnic groups (1-3)
Differences Between Male And Female Patients With Systemic Lupus Erythematosus: A Single Center Experience Over 20 Years Of Follow-up, Brescia, Italy

METHODS:

• Cumulative clinical, serological manifestations, concomitant diseases of patients belonging to the historical SLE cohort with at least one evaluation in the past 15 months were collected from clinical charts

• Collected data regarding the overall and ongoing treatments

• Outcomes:
  • Damage index (SDI)
  • Activity index (SLEDAI-2K) during the last 12 months

Differences Between Male And Female Patients With Systemic Lupus Erythematosus: A Single Center Experience Over 20 Years Of Follow-up

RESULTS:

• 31 Males and 314 Females (male to female ratio of 1:10)

• Disease onset after age 60:
  • male, female (13% vs 1.6%) (p=0.001; OR 9.1; 95%CI 1.92-42.56)

• Diagnosis after age 60:
  • male, female: (16% vs 1.6%); (p<0.0001; OR11.8; 95% CI 2.73-51.56

RESULTS:

Males compared to female SLE, more frequently presented with
- discoid lesions, renal involvement, polyneuropathy, leukopenia

SLEDAI: no difference regarding disease activity during the last 12 m
SDI damage index: males compared to female,
- higher mean SDI
- higher number of patients with a severe damage (SDI > 2)
Potential Implications for Clinical Care

Patient:

• Social hindrances to seek early medical care after symptom onset
• Lack of education regarding disease in men

Physician:

• Implicit bias in accurately referring and diagnosing male patients

End Result:

• Greater damage accrual with more severe organ damage at time of diagnosis
AXIAL SPONDYLOARTHRITIS
Gender Differences in Axial Spondyloarthritis: Women Are Not So Lucky

- Had different disease manifestations due to different immunological, hormonal, and genetic responses.
- Had different allelic frequencies of the AHNK-gene and tissue non-specific alkaline phosphatase (TNAP) haplotypes in ankylosing spondylitis (AS).
- Show a higher diagnostic delay compared to males
- Have a higher frequency of extra-articular manifestations (EAM), such as enthesitis, psoriasis, and inflammatory bowel disease (IBD), whereas acute anterior uveitis is more prevalent in male patients.
- Have higher disease activity (BASDAI) and quality of life (AsQol) scores are significantly higher in women, and more importantly,
- Have significantly lower response rates to treatment with TNF inhibitors (TNFi) and a significantly lower drug adherence.
- Have different levels of tumor necrosis factor (TNF), interleukins IL-6, IL-17, and IL-18.

Gender Differences in Axial Spondyloarthritis: Women Are Not So Lucky

Male AS patients more frequently have higher radiological damage and radiographic progression.

Different levels of tumor necrosis factor (TNF), interleukins IL-6, IL-17, and IL-18, were found between the two sexes.

Despite the fact that men with Axial SpA have a worse radiologic prognosis, women have a high disease burden, in part because they have a longer delay in diagnosis, higher disease activity, and significantly less responsiveness to treatment with TNFi.
The most typical symptom of AxSpA is inflammatory back pain. Thoracic spine, cervical spine, and chest can be affected.

Female patients compared to males present inflammatory back pain at a lower frequency. Axial pain in thoracic, lumbar, and SIJ tends to be more common in women.

Women with AxSpA have a Unique Burden of Disease

More diagnosis delay\(^1\)

Poorer quality of life\(^8\)

Women with axSpA are less likely to have children than women in the general population\(^2\)

Misdiagnoses of fibromyalgia and psychosomatic disorder\(^7\)

More pronounced enthesitis, disease severity, and peripheral symptoms\(^3-6\)

Lower inflammatory markers despite comparable or higher disease severity score\(^6\)


axSpA, axial spondyloarthritis.
RHEUMATOID ARTHRITIS
Comorbidities:
Population Studies
CARDIOVASCULAR COMORBIDITIES IN RA

CHARACTERISTICS AND CARDIOVASCULAR COMORBIDITIES IN PATIENTS WITH RHEUMATOID ARTHRITIS IN A LOCAL PATIENT COHORT IN RUSSIA

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Background: Patients with Rheumatoid Arthritis (RA) have an increased risk for cardiovascular disease (CVD).

COMORBIDITIES AND RISK FACTORS OF CARDIOVASCULAR DISEASES IN RHEUMATOID ARTHRITIS PATIENTS

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Background: It is well known, that atherosclerosis associated cardiovascular diseases in many cases determine the life expectancy in RA patients. At the same time, risk factors which promote the development of premature atherosclerosis, including comorbidities, remain uncertain.

Prevalence of Evaluated Comorbidities in 3920 Patients with RA: Results Of An International, Cross-sectional Study (COMORA)

Depression 15.0% [13.8-16.1]
- Most commonly observed
- Varied widely among countries (Morocco 2% - USA 33%)

Ischemic Cardiovascular disease: MI, Stroke 6.0% [5.3-6.8]
- Varied among countries (Morocco 1%, Hungary 17%)

Solid Tumors (excl Basal cell ca.) 4.5% [3.9-5.2]

Hepatitis B 2.8% [2.3-3.3]
- Highest in Italy 9%, Taiwan 7%
- Hepatitis C highest in Italy 6.6%, Egypt 6.8%, Taiwan 4.8%

GI Ulcers 10.8% [9.8-11.8]
- Varied among countries (Morocco 1%, Egypt 22%)

Diverticulitis (requiring surgery) 0.4% [0.2-0.6]

Pulmonary Diseases
- Lowest in Japan 1.4%, Korea 1.3%, Taiwan 0.3%
- Highest in Hungary 8%, USA 7.5 %
Prevalence And Pattern Of Comorbidities In Chronic Rheumatic And Musculoskeletal Diseases: The COMORD Study

COMORD is an observational, cross-sectional, multicentric national study. Consecutive RMD patients (RA), (OA), (SLE), (AxSpA) and (pSpA)

Location:
Lebanon: 6 practices (university hospitals and private clinics)

Demographics:
515 patients: 196 RA, 161 OA, 75 AxSpA, 45 SLE, 40 pSpA
Mean age: 56y, 76% female.

Most common comorbidities:
• Cardiovascular diseases
• Depression
• Osteoporosis
Cross sectional analyses performed on 962 RA patients from the French cohort study of comorbidities COMEDRA

Assessment tools:
RAID3 0-10, Class (acceptable <3, moderate 3-4, severe 5-10)

Demographics:
57.7 + 11.1 yrs, Disease duration 11.1 [6.2-19.1], 79% female, DAS28 3.1 +1.3

Severe fatigue:
Associated with HTN, COPD, Fracture Hx, RA-related surgery

More severe:
Current NSAID, steroid, bDMARD Rx (Not assoc with MTX or type of bDMARD)
Comorbidities Of Rheumatoid Arthritis: Results From The Korean National Health And Nutrition Examination Survey

Adjusted ORs (95% CI) for medical comorbidities among patients with RA compared with non-RA.1

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>0.97 (0.67–1.36)</td>
<td>0.873</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>1.11 (0.78–1.57)</td>
<td>0.581</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.33 (0.87–2.02)</td>
<td>0.189</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.27 (0.65–2.47)</td>
<td>0.490</td>
</tr>
<tr>
<td>Myocardial infarction or angina</td>
<td>1.86 (1.17–2.96)</td>
<td>0.009</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1.67 (0.73–3.83)</td>
<td>0.228</td>
</tr>
<tr>
<td>Angina</td>
<td>1.88 (1.11–3.17)</td>
<td>0.018</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>7.61 (0.92–63.28)</td>
<td>0.060</td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>1.29 (0.43–3.84)</td>
<td>0.648</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>0.95 (0.28–3.20)</td>
<td>0.928</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>2.06 (0.72–5.90)</td>
<td>0.179</td>
</tr>
<tr>
<td>Stomach cancer</td>
<td>0.72 (0.14–3.67)</td>
<td>0.689</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>1.28 (0.90–1.81)</td>
<td>0.173</td>
</tr>
<tr>
<td>Pulmonary tuberculosis</td>
<td>1.95 (1.24–3.09)</td>
<td>0.004</td>
</tr>
<tr>
<td>Asthma</td>
<td>1.97 (1.05–3.71)</td>
<td>0.036</td>
</tr>
<tr>
<td>Thyroid disease</td>
<td>1.71 (1.05–2.77)</td>
<td>0.030</td>
</tr>
<tr>
<td>Depression</td>
<td>2.38 (1.47–3.85)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Atopic dermatitis</td>
<td>0.99 (0.41–2.40)</td>
<td>0.987</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>1.96 (0.73–5.25)</td>
<td>0.180</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>2.34 (1.15–4.80)</td>
<td>0.020</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>1.47 (0.18–11.80)</td>
<td>0.714</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td>1.22 (0.16–9.38)</td>
<td>0.846</td>
</tr>
</tbody>
</table>

Adjusting for age, sex, income, region, education, marriage, drink, smoking, body mass index

Comorbidities:

- Cardiovascular Disease
- Malignancy
- Depression
### Relative Risk of Selected Comorbidities in RA Patients

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>RA vs Controls Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiovascular</strong></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1.35 (0.92–1.97)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>1.60 (1.12–2.27)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>1.51 (0.91–2.30)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>0.90 (0.61–1.32)</td>
</tr>
<tr>
<td><strong>Chronic pulmonary disease</strong></td>
<td>2.33 (1.44–3.77)</td>
</tr>
<tr>
<td><strong>Liver disease</strong></td>
<td>1.84 (0.77–4.41)</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>1.24 (0.73–2.12)</td>
</tr>
</tbody>
</table>

*aStatistically significant comparisons.*

Comorbidities were selected based on an adequate number of events observed to support the analysis in a US cohort of residents including patients with RA and age- and sex-matched controls without arthritis. Control subjects were age- and sex-matched Rochester, MN residents who did not have an arthritis diagnosis during the 10-year period prior to the prevalence date.

Cardiovascular Risk in RA

RA is Associated with Increased Risk of Cardiovascular Disease Events, Cardiovascular Mortality, and Subclinical Atherosclerosis.

• Cardiovascular mortality 50% in RA compared with matched non-RA controls ¹

• Burden of atherosclerosis is higher in RA
  • More coronary calcium in multiple studies using cardiac CT ²,³,⁴
  • More calcified, mixed, and noncalcified plaques by CT angiography⁵

Arterial Inflammation is Increased in RA

• RA patients without CVD, diabetes, kidney disease (n=17) vs. age-matched nonRA controls with known CAD (n=34) ¹

• Aortic FDG-PET CT
  • Mean TBRmax higher in RA than control (2.02 vs. 1.74; p=0.0001)
  • Proportion of “hot slices” (TBRmax>2.0) higher in RA than control (50% vs. 23%; p=0.001)

Atherogenicity of Lipoproteins Change in Systemic Inflammation

More small LDL particles

• Passive diffusion across endothelium increased

Oxidized LDL

• Scavenged by macrophage foam cells
• Initiates an cytokine/chemokine cascade in the vessel wall, and vascular remodeling

“Pro-inflammatory” HDL

• Oxidized Apolipoprotein A1
  • Defective reverse cholesterol transport
• Loss of anti-atherogenic cargo
• Gain of pro-atherogenic cargo
  • Serum amyloid A, sPLA2, others
Carotid atherosclerosis was 3-fold more prevalent in patients with RA (44% vs 15%, $P<0.001$)

Error bars indicate 95th percentiles.

98 consecutive patients with RA were matched for age, sex, and ethnicity with 98 normotensive and hypertensive controls from longitudinal studies from the NIH. Both extracranial carotid systems were monitored by carotid ultrasonography.

71% of patients reported current or past corticosteroid use; 63% reported current or past methotrexate use, and 46% reported current or past use of anti-TNF agents.

## Risk of Stroke in Patients with RA Compared to Patients with Noninflammatory Rheumatic Diseases

<table>
<thead>
<tr>
<th></th>
<th>Strokes (n)</th>
<th>Patients (n)</th>
<th>RA cases/Non-cases</th>
<th>NIRD cases/Non-cases</th>
<th>OR(^a) (95% CI)</th>
<th>(p) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All strokes</td>
<td>269</td>
<td>5640</td>
<td>226/4125</td>
<td>43/1246</td>
<td>1.64 (1.16–23.0)</td>
<td>0.005</td>
</tr>
<tr>
<td>Ischemic strokes</td>
<td>67</td>
<td>1405</td>
<td>59/996</td>
<td>8/342</td>
<td>2.66 (1.24–5.70)</td>
<td>0.012</td>
</tr>
</tbody>
</table>

\(^a\)Comparison group consists of patients with NIRDS, matched for age, sex, and time of study entry.

No information on glucocorticoid or NSAID use was available in the publication.

NIRD = noninflammatory rheumatic disorder.

## Risk of Ischemic Stroke in RA Patient

<table>
<thead>
<tr>
<th>RA variable</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI</td>
<td>2.58 (1.22–5.47)</td>
<td>0.013</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.98 (1.16–3.37)</td>
<td>0.012</td>
</tr>
<tr>
<td>First comorbidity index&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.69 (1.44–1.99)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Comorbidity index at time of event&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.42 (1.20–1.64)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

### RA variable

- **Lifetime total joint replacement**: 2.13 (1.14–3.95) 0.017
- **Index HAQ score**: 2.04 (1.40–2.97) <0.001
- **HAQ score**: 1.43 (0.98–2.11) 0.067

<sup>a</sup>Conditions in the comorbidity index include pulmonary disorders, MI, other CV disorders, stroke, hypertension, diabetes, spine/hip/leg fracture, depression, gastrointestinal ulcer, other gastrointestinal disorders, and cancer.

No information on glucocorticoid or NSAID use was available in the publication.

Myocardial Dysfunction is Increased in RA

Danish population-based study (entire population)\(^1\)

- 24,343 RA patients; 4,280,882 non-RA controls
- 6.64/1000 patient years in RA vs. 2.43/1000 patient years in control group
- *Adjusted incidence of hospitalized heart failure 1.30 for RA vs. control (p<0.001)*

Predominant phenotype is **diastolic dysfunction**

- Faster progression in RA vs. non-RA control\(^2\)

Subclinical **myocardial fibrosis and inflammation common in RA**\(^3\)

- MRI late gadolinium enhancement in 32% of RA patients with no known CVD or risk factors
- T2 enhancement observed in 12%

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Calculations included 575 patients with RA and 583 non-RA subjects followed for 8107 and 9521 person-years, respectively. CHF was defined by the Framingham Heart Study Criteria. CV risk factors that remained in the model were smoking, hypertension, and diabetes.


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**Risk of CHF in RA Patients**

- All patients with RA vs all non-RA subjects
- RF-negative patients with RA vs non-RA subjects
- RF-positive patients with RA vs non-RA subjects

<table>
<thead>
<tr>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>Adjusted for age and sex</th>
<th>Adjusted for age, sex, CV risk factors, and ischemic heart disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>a</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.54–2.49</td>
<td>a</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.03–1.96</td>
<td>a</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.90–3.26</td>
<td>a</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>a</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.47–2.39</td>
<td>a</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.92–1.78</td>
<td>a</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.95–3.43</td>
<td>a</td>
<td></td>
</tr>
</tbody>
</table>

\( ^{a} P \leq 0.05. \)
Clinical Features of CHF Differ in Patients with RA Compared with non-RA Patients

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>RA (n = 103)</th>
<th>Non-RA (n = 852)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptom</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orthopnea</td>
<td>22 (21%)</td>
<td>271 (34%)</td>
<td>0.53 (0.32–0.87)</td>
</tr>
<tr>
<td>One or more symptoms&lt;sup&gt;b&lt;/sup&gt;</td>
<td>76 (74%)</td>
<td>681 (84%)</td>
<td>0.54 (0.33–0.87)</td>
</tr>
<tr>
<td><strong>Signs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Rales</strong></td>
<td>95 (92%)</td>
<td>522 (84%)</td>
<td>2.24 (1.04–4.81)</td>
</tr>
<tr>
<td>Hepatojugular reflux</td>
<td>11 (11%)</td>
<td>153 (20%)</td>
<td>0.50 (0.26–0.96)</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP ≥140 mm Hg</td>
<td>48 (47%)</td>
<td>468 (60%)</td>
<td>0.58 (0.38–0.89)</td>
</tr>
<tr>
<td>Diastolic BP ≥90 mm Hg</td>
<td>15 (15%)</td>
<td>271 (34%)</td>
<td>0.34 (0.19–0.60)</td>
</tr>
</tbody>
</table>

<sup>a</sup>P <0.05.

<sup>b</sup>Excluding swollen extremities which are an unreliable sign of heart failure in patients with RA.

Study included 103 patients with RA and 852 sex- and age-matched controls from Rochester, Minnesota. There were no significant differences in paroxysmal nocturnal dyspnea, cough, dyspnea on exertion, swollen extremities, engorged jugular veins, S3 gallop, hepatomegaly, tachycardia, cardiomegaly, acute pulmonary edema, or pleural effusion.

## Risk of MI in Female RA Patients

<table>
<thead>
<tr>
<th></th>
<th>RA</th>
<th>No RA</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Person-years of follow-up</strong></td>
<td>6259</td>
<td>2,381,418</td>
<td></td>
</tr>
<tr>
<td><strong>MI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence/100,000 person-years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No of cases</td>
<td>272</td>
<td>96</td>
<td></td>
</tr>
<tr>
<td>Age-adjusted relative risk&lt;sup&gt;a&lt;/sup&gt; (95% CI)</td>
<td>2.07 (1.28–3.34)</td>
<td>1.0</td>
<td>0.002</td>
</tr>
<tr>
<td>Multivariable relative risk&lt;sup&gt;b&lt;/sup&gt; (95% CI)</td>
<td>2.00 (1.23–3.29)</td>
<td>1.0</td>
<td>0.005</td>
</tr>
</tbody>
</table>

<sup>a</sup> Relative risk compared with participants without RA. Adjusted for age in 5-year categories.

<sup>b</sup> Relative risk compared with participants without RA. Adjusted for age in 5-year categories, hypertension, diabetes, high cholesterol level, parental history of MI before age 60 years, body mass index, cigarette use, physical activity, alcohol use, aspirin use, menopausal status, hormone replacement therapy use, oral glucocorticoid use, nonsteroidal anti-inflammatory drug use, folate intake, omega-3 fatty acid intake, and vitamin E supplement intake.

Compared with patients without RA, women with RA were significantly more likely to be using glucocorticoids (1.5% vs 30.2%; P<0.001).

Comorbidities:

- Cardiovascular Disease
- Malignancy
- Depression
## Risk of Malignancy in RA Patients

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Number</th>
<th>SIR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solid cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>1311</td>
<td>1.19 (1.13–1.26)</td>
</tr>
<tr>
<td>Women</td>
<td>2068</td>
<td>0.97 (0.93–1.02)</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>471</td>
<td>0.83 (0.76–0.91)</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>342</td>
<td>0.74 (0.66–0.84)</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>330</td>
<td>1.48 (1.33–1.65)</td>
</tr>
<tr>
<td>Non-melanoma skin cancer</td>
<td>374</td>
<td>1.66 (1.50–1.84)</td>
</tr>
</tbody>
</table>

The Swedish Inpatient Register RA cohort includes 53,067 patients with RA based on inpatient care countywide since 1964 and nationwide since 1987 and is estimated to include more than 50% of all Swedish RA patients in 2003. The risk was compared with the total Swedish population.

## Risk of Lung Cancer in RA Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Patients</th>
<th>No. of Controls</th>
<th>OR(^a) (95% CI)</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>232</td>
<td>7393</td>
<td>1.48 (1.27–1.73)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Females</td>
<td>15</td>
<td>628</td>
<td>2.91 (1.63–5.17)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Age, years</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;55</td>
<td>18</td>
<td>1690</td>
<td>1.59 (0.95–2.67)</td>
<td>0.08</td>
</tr>
<tr>
<td>55-65</td>
<td>47</td>
<td>2118</td>
<td>1.40 (1.01–1.95)</td>
<td>0.047</td>
</tr>
<tr>
<td>65-75</td>
<td>87</td>
<td>2262</td>
<td>1.50 (1.17–1.93)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>&gt;75</td>
<td>95</td>
<td>2451</td>
<td>1.61 (1.27–2.05)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Tobacco exposure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>153</td>
<td>4233</td>
<td>1.59 (1.35–1.88)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>No</td>
<td>38</td>
<td>2387</td>
<td>1.36 (0.98–1.88)</td>
<td>0.07</td>
</tr>
<tr>
<td>Missing</td>
<td>56</td>
<td>1901</td>
<td>1.72 (1.32–2.26)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

\(a\)Adjusted for effects of age, race, sex, tobacco, and asbestos exposure.

Retrospective case-control study nested in a cohort from the VA Health Care System between October 1, 1998 and June 1, 2004.

Comorbidities:

- Cardiovascular Disease
- Malignancy
- Depression
• Depression is 2-3 times more common in RA than in the general population 1-3
• Prevalence of 9.5 – 41.5 %
• Associated with 2,3
  • Increased Pain, Fatigue, Physical disability
  • Reduced QOL
  • Increased mortality rates
  • More Comorbidities
• Affects all disease activity measures except DAS4,5
• May influence the longitudinal changes in RA disease activity4,5

Bidirectional Associations Between Rheumatoid Arthritis And Depression: A Nationwide Longitudinal Study (Taiwan)

Incidence of Depression in RA vs non-RA (per 1000 PYs)

<table>
<thead>
<tr>
<th></th>
<th>RA</th>
<th>Non-RA</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>15.9</td>
<td>8.95</td>
<td>1.69 (1.51-1.87)</td>
</tr>
</tbody>
</table>

Incidence of RA in Depressed vs non-Depressed (per 1000 PYs)

<table>
<thead>
<tr>
<th></th>
<th>Depressed</th>
<th>Non-Depressed</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>2.07</td>
<td>1.21</td>
<td>1.65 (1.41-1.77)</td>
</tr>
</tbody>
</table>

- National Health Insurance Research Database of Taiwan Claims-based Study
- One cohort was included to analyze RA predicting the onset of depression and a second cohort for analysis of depression predicting RA. A sex- and age-matched control group was included for both.
- **This population-based cohort study suggested strong bidirectional relationships between RA and Depression**

**Gender Associated Comorbidities in RA and their Impact on Outcome: data from GENIRA**

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Women, $n = 70$</th>
<th>Men, $n = 70$</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>21 (30.0)</td>
<td>19 (27.1)</td>
<td>0.70</td>
</tr>
<tr>
<td>Hypertension</td>
<td>23 (32.8)</td>
<td>18 (25.7)</td>
<td>0.35</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>6 (8.5)</td>
<td><strong>16 (22.8)</strong></td>
<td>0.02</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>19 (27.1)</td>
<td>21 (30.0)</td>
<td>0.70</td>
</tr>
<tr>
<td>Depression</td>
<td><strong>20 (28.5)</strong></td>
<td>2 (2.8)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Solid neoplasia</td>
<td>1 (1.4)</td>
<td>4 (5.7)</td>
<td>0.17</td>
</tr>
<tr>
<td>Hematologic neoplasia</td>
<td>0 (0.0)</td>
<td>1 (1.4)</td>
<td>0.31</td>
</tr>
<tr>
<td>IHD</td>
<td>1 (1.4)</td>
<td><strong>7 (10.0)</strong></td>
<td>0.02</td>
</tr>
<tr>
<td>COPD</td>
<td>2 (2.8)</td>
<td><strong>12 (17.1)</strong></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Other CV</td>
<td>4 (5.7)</td>
<td>5 (7.1)</td>
<td>0.73</td>
</tr>
<tr>
<td>PUD</td>
<td>4 (5.7)</td>
<td><strong>13 (18.5)</strong></td>
<td>0.02</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td><strong>13 (18.5)</strong></td>
<td>4 (5.7)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

**Cross-sectional study**
University Hospital in Northern Spain

**MEN** more likely to have:
- History of smoking
- Diabetes mellitus
- Peptic ulcer disease
- Ischemic CV disease
- COPD

**WOMEN** more likely to have:
- Depression
- Higher BDI score (more intense depression)
- Osteoporosis

*COPD* chronic obstructive pulmonary disease, *IHD* ischemic heart disease, *other CV* other cardiovascular manifestations, *PUD* peptic ulcer disease

Aurrecoechea E et. al. Rheumatol Int (2017) 37:479-485
MENOPAUSE
The impact of menopause on functional status in women with rheumatoid arthritis

Elizabeth Mollard¹, Sofia Pedro², Eliza Chakravarty³, Megan Clowse⁴, Rebecca Schumacher⁵ and Kaleb Michaud⁴,⁵

Abstract

Objective. The aim of this study was to investigate the association of menopause with functional status outcomes in women with RA.

Methods. Participants were women in a US-wide observational cohort who developed RA before menopause. The HAQ measured functional status. We controlled for confounding variables and used univariate and multivariable generalized estimating equation methods with the sandwich estimator of variance. Best models were selected using the quasi-likelihood under the independence model criterion. A sensitivity analysis was performed using linear mixed effects regression models.

- US-wide observational cohort who developed RA before menopause
- Functional status was measured by HAQ
- Univariate and Multivariate analyses with sandwich estimator of variance.
- Sensitivity analysis performed using linear mixed effects regression models
IMPACT OF MENOPAUSE ON FUNCTIONAL STATUS IN WOMEN WITH RA: Demographics

<table>
<thead>
<tr>
<th>Menopausal State</th>
<th>Number of Women with RA (n = 8189)</th>
<th>Percent of total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-menopausal at enrollment</td>
<td>2005</td>
<td>24.5</td>
</tr>
<tr>
<td>Transitioned through menopause</td>
<td>611</td>
<td>7.5</td>
</tr>
<tr>
<td>Post-menopausal at enrollment</td>
<td>5573</td>
<td>68.1</td>
</tr>
</tbody>
</table>
• Pre-menopausal women had less functional decline as measured by the HAQ when compared with post-menopausal women.

• Less functional decline was noted in women with:
  • Ever using hormone replacement therapy
  • Ever having a pregnancy
  • Longer length of reproductive life

• After menopause the trajectory of decline worsened and accelerated in women with RA.
IMPACT OF MENOPAUSE ON WOMEN WITH RA

Study confounders:

• Menopause is associated with depression and decreased QoL. This may have changed patients perceptual experience of their functional status

• Study participants had a higher socioeconomic status than RA and may have been more compliant than patients in the general population

• Depression is associated with autoimmune disease

Further study is needed to understand the relationship of menopause and functional decline

Mollard E et al Rheumatology 2018;57:798-802
OSTEOPOROSIS
The Impact of Menopause

There are significant hormonal changes leading up to menopause.


- **Postmenopausal women are at higher risk for osteoporosis**
  - Women with a longer disease duration of RA tend to have higher risk of bone mineral loss.
    - The use of biologic drugs is not significantly associated with bone mineral density.
    - Osteoporosis is a complication of corticosteroid use and may impact rheumatic treatment considerations.

Risk of Fracture In RA Patients

- GPRD database *
- 30,262 patients with RA
- 2460 patients with at least 1 incident fracture

* GPRD, General Practice Research Database, UK
Risk of Vertebral Fracture Before and During the First Year of Corticosteroid therapy

Distribution Of Second Fracture Type Within 1 Year Of Index Hip, Shoulder Or Wrist Fracture

Observational Cohort Study of Medicare Patients in 2009
Age >65 yrs
N = 273,330
1 year rate = 4.3 %

SUMMARY:

- Gender can impact disease prevalence and expression
- Gender differences occur in, and complicate Rheumatoid Arthritis, Systemic Lupus, AxSpA and other IMIDs

Comorbidities occur in Rheumatic diseases and may vary by gender
- Cardiovascular, Malignancy, Depression, Osteoporosis
- Menopause is an important consideration during disease assessment and management
Thank You!