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RHEUMATOID ARTHRITIS, ANKYLOSING SPONDYLITIS AND HOSPITALIZATION WITH PNEUMONIA

PhD dissertation

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Health

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This PhD thesis is based on the following studies:

1. RHEUMATOID ARTHRITIS; MEDICAL TREATMENT AND DISEASE ACTIVITY: RISK OF HOSPITALIZED PNEUMONIA. A NESTED CASE-CONTROL STUDY

2. PROGNOSIS OF PNEUMONIA IN PATIENTS WITH RHEUMATOID ARTHRITIS: THE ROLE OF PREADMISSION MEDICATION AND DISEASE ACTIVITY. A POPULATION-BASED COHORT STUDY

3. ANKYLOSING SPONDYLITIS AND MORTALITY OF HOSPITALIZED PNEUMONIA; A POPULATION-BASED COHORT STUDY.

List of abbreviations

ACR: American College of Rheumatology

Anti-CCP: Anti-bodies to Cyclic Citrullinated Peptide

AS: Ankylosing Spondylitis

ASAS: Assessment of SpondyloArthritis international Society

ASDAS: Ankylosing Spondylitis Disease Activity Score

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index

BASFI: Bath Ankylosing Spondylitis Functional Index

BASMI: Bath Ankylosing Spondylitis Metrology Index

DAS28: Disease Activity Score 28 joints

CAP: Community Acquired Pneumonia

CCI: Charlson Comorbidity Index

CDAI: Clinical Disease Activity Index

CI: Confidence Interval

COPD: Chronic Obstructive Pulmonary Disease

CRP: C-Reactive Protein

CsDMARD: Conventional synthetic Disease Modifying AntiRheumatic Drug

CSR: Civil Registration System

CVE: CardioVascular Event

DNDRP: Danish National Database of Reimbursed Prescriptions

DNPR: Danish National Patient Registry

EULAR: The European League against Rheumatism

HAQ: Health Assessment Questionnaire

HR: Hazard Ratio

ICD: International Classification of Diseases and Related Health Problems

IQR: Inter Quartile Range

MRR: Mortality Rate Ratio

OR: Odds Ratio

PN: Pneumonia

PPV: Positive Predictive Value

PROM: Patient Reported Outcome Measure

RA: Rheumatoid Arthritis

RCT: Randomized Controlled Trial

RF: Rheumatoid Factor

SIR: Standardized Incidence Ratio

SJC: Swollen Joint Count

SMR: Standardized mortality ratio

SpA: Spondyloarthritis

SR: Sedimentation Rate

TCZ: Tocilizumab

TJC: Tender Joint Count

VAS: Visual Analogue Scale

Preface

This PhD thesis is based on studies carried out during my employment at The Department of Rheumatology, Aalborg University Hospital during the period 2012-2018 in collaboration with The Department of Clinical Epidemiology, Aarhus University.

This work was made possible due to a number of people who supported and guided me through the process. I have been blessed with a true "Dream team" of supervisors. Mette Nørgaard has been a superb scientific mentor, all ways giving constrictive feedback and never tiring of going over the manuscripts once more. Her encouragement, inspiration and patience with my never ending questions have been invaluable, and I am thankful for all of her help, guidance and believing in me. Reimar W. Thomsen initially introduced me to the world of epidemiology and has patiently tried to teach me, what clinical epidemiology is all about and has helped with both methodological challenges and keeping up good spirits. Ulrik Tarp provided me with the reumatologists' perspective, knowledge on the art of scientific writing and some sound discussions on the bigger things in life.

I want to express my sincere gratitude to all of my colleagues at the Department of Rheumatology in Aalborg for giving me the time and space to conduct these studies and creating a pleasant atmosphere. I am grateful to my Manager Vivian Kjær Hansen and Head of Research Annette Schlemmer for having allocated time and money, which made this project possible

I wish to thank biostatisticians Uffe Heide-Jørgensen and Frank Mehnert who provided help with data management and Søren Kjærgaard Boldsen who patiently answered my questions.

A special thanks to all of my patients, who inspired me to do this work!

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Finally, I cannot thank my friends and family enough. Mette Yde – thank you for doing all of my "chores" in DSIM; so I could put all of my energy into finalizing this dissertation. Mom and Dad – thank you for all helping with everything I asked for.

I am especially grateful to my husband Peter for his love, support, patience and believing in me, even when I did not. My warmest thank to my children Emily and Frederik for their love and understanding.

Mette Holland-Fischer

CONTENT

1. INTRODUCTION AND BACKGROUND:

Rheumatoid arthritis and ankylosing spondylitis are common chronic rheumatic diseases. These diseases are associated with not only discomfort and functional disability, but also with the likelihood of physical disability, especially if treatment is not efficient or well tolerated. Most patients need lifelong monitoring and are seen on a regular basis in outpatient clinics. The patients are often treated with pharmacotherapy affecting the immune system, presumably leaving them more prone to infections. This thesis aims to examine the risk for and prognosis after pneumonia, which is one of the most common infections leading to hospitalization among these patients. We aim to study the effect of disease activity and pharmacotherapy on both the risk for and prognosis after pneumonia among patients with RA and the prognosis after pneumonia among patients with AS.

1.1. PNEUMONIA

1.1.2. PNEUMONIA: INCIDENCE, RISK FACTORS AND PROGNOSIS

Pneumonia is an acute respiratory infection of the lungs associated with high hospitalization rate. Pneumonia remains a common cause of morbidity and mortality worldwide. On the World Health Organisation published top ten causes of death lower respiratory infection came in fourth in 2016, causing 3 million deaths worldwide.[1] It also results in considerable economic burden.

A Danish study from 2013 showed that total pneumonia hospitalizations in Denmark increased from 4.96/1000 population in 1997 to 8.09 in 2011[2], which is most likely due to the increasing number of elderly. In addition to older age, other known risk factors for pneumonia include chronic obstructive pulmonary disease, alcoholism, smoking, asthma, cancer, heart disease, and treatment with immunosuppressive therapy.[3-6] Pneumonia prognoses seem, however, unchanged. In the Danish study, the 30-day mortality of hospitalized pneumonia remained at approximately 13% between 1997 and 2011. Pre-existing diseases have been shown to be predictors of poorer pneumonia outcome.[7-10] A newly published study, including 9,580 pneumonia patients, found, that any single comorbid condition was associated with a 9% greater risk of death.[11]

1.2. RHEUMATOID ARTHRITIS

1.2.1. RHEUMATOID ARTHRITIS: DEFINITION AND EPIDEMIOLOGY

RA is a chronic, inflammatory disease characterised by peripheral symmetric polyarthritis particularly affecting the small joints and extra-articular manifestations. Morning stiffness and swelling of the small joints of the hands and feet is the typical symptoms of RA. The extra–articular manifestations include rheumatoid nodules, haematological abnormalities (anaemia, thrombocytosis, lymphadenopathy), rheumatoid lung disease (e.g. pleuritis, parenchymal pulmonary nodules, diffuse interstitial pulmonary fibrosis, bronchiolitis obliterans organizing pneumonia), pericarditis, neuropathy, vasculitis, glomerulonephritis, Felty's Syndrome and ophthalmologic manifestations.[12] A majority of the patients will have rheumatoid factor (RF) and/or anti-bodies to cyclic citrullinated peptide (anti-CCP).

RA is a clinical diagnosis. No single laboratory test or physical finding is pathognomic for the disease. Classification criteria exist and are widely used. The American Rheumatism Association 1987 revised Criteria for the Classification of RA [13] were developed from a computerized analysis of 262 RA patients and 267 controls and compared to prior sets of classification criteria from 1958 and 1966. The set from 1987 consist of seven criteria (see table 1 in the appendix). They have been criticized for their lack in ability to identify early stages of RA. In 2010 a working group from ACR (American College of Rheumatology) and EULAR (The European League Against Rheumatism) presented the 2010 ACR/EULAR classification criteria for RA. The aim was "focusing on features at earlier stages of disease that are associated with persistent and/or erosive disease, rather than defining the disease by its late-stage features".[14] The classification criteria consist of an obligatory criteria of at least one joint with synovitis and a total score of 6 or greater in 4 domains (for details – please see table 2 in the appendix).

RA is the most common inflammatory arthritis among adults. The prevalence of RA in most western countries is relatively constant, at 0.3-1.0%.[15-20] Higher rates have been describes in several Alaska and American Indian populations. In a study from 1989 the age-adjusted prevalence among female Pima Indians was 6.95.[21] Lower prevalence of RA have been described in cohorts from rural areas of Africa.[22] Most studies on prevalence show a male-female ratio between 1:2 and 1:4. Age-specific prevalence rates increases with age. No studies on the prevalence of RA in Denmark exist. But the estimated point prevalence in the southern part of Denmark in 2004 was 0.30 (95% CI: 0.17-0.50) while the cumulative prevalence was 0.75 (95% CI: 0.52-0.97).[23] The mean incidence rate of RA in the southern part of Denmark from 1995 to 2001 was estimated to be 35/100,000 years (95% CI: 32-38).[24]

RA is most likely caused by a complex interplay between genetic and environmental factors. New understanding of the complex changes in the immune system of patients with RA, have led to new treatments for RA. While some decades ago, the aim was primarily symptom relief we are now able to offer targeted treatments aiming to stop disease progression.

1.2.2. RHEUMATOID ARTHRITIS: DISEASE ACTIVITY

Different research groups have identified variables to assess disease activity in patients with RA and several indices for disease activity in RA have been developed.[25-28] Most of these indices contain one or more of the following components:

- Joint counts – number of swollen joints, number of tender joints
- Markers of inflammation – CRP or SR (sedimentation rate)
- Information on pain – often on a VAS
- Patients assessment of global disease activity – often measured on a VAS using the question" Considering all the ways your arthritis affects you, mark "X" on the scale for how well you are doing)
- Doctor's assessment of global disease activity

The Disease Activity Score 28 (DAS 28) is the most commonly disease activity index in Denmark, where it is an integrated part of the monitoring of RA patients in DANBIO. It is a composite score including tender and swollen joint count, patients assessment and CRP and is calculated as[28]:

$$DAS28 = 0.56\sqrt{\text{TJC28}} + 0.28\sqrt{\text{SJC28}} + 0.36\ln(\text{CRP} \times 10 + 1) + 0.014\text{PtGH} + 0.96$$

(TJC: tender joint count, SJC: swollen joint count, PtGH: patient assessment of disease activity using a 100 mm visual analogue scale (VAS) with 0=best, 100=worst).

A DAS28 value > 5.1 corresponds to high disease activity, a DAS28 value between 3.2 and 5.1 corresponds to moderate, a DAS28 value between 2.6 and 3.2 corresponds to a low disease activity while a DAS28 value < 2.6 corresponds to remission.

Previous studies have shown that elevated CRP levels and elevated platelet counts are valid markers of RA disease activity.[29-32] Clinicians evaluate these measurements as an integrated part of daily clinical practice, when monitoring patients with RA. Mild normocytic hypochromic anaemia which

correlates with the activity of the disease is common – but other causes of anaemia in RA patients should be considered.

1.2.3. RHEUMATOID ARTHRITIS: COMORBIDITY

In addition to the extra–articular manifestations that can occur in patients with RA the inflammation per se also promote other conditions and diseases. It is well known that patients with RA have an increased risk of cardiovascular events (CVE).[33;34] A Danish study from 2011 found the overall incidence rate ratio (IRR) of myocardial infarction in RA to be 1.7 (95% CI: 1.5-1.9) compared to the general population.[35] Another Danish study found a 30% increase in risk for stroke among patients with RA compared to the general population.[36] Systemic inflammation is one of the mechanism believed to promote atherogenesis[37], which can lead to CVE. But other risk factors for cardiovascular events such as smoking, diabetes mellitus or lower HDL cholesterol levels are also found more frequently among patients with RA.[38-40] The increased risk of CVE among patients with RA is most likely due to a combination of systemic inflammation and a higher frequency of "classic" risk factors.

Patients with RA have increased risk of osteoporosis.[41;42] This risk is not only due to corticosteroid therapy but also due to functional impairment and the systemic effects of the disease itself. Other conditions linked to RA is hypothyroidism,[43] congestive heart failure, chronic pulmonary disease, dementia, and peptic ulcer disease.[44] A Swedish study from 2016 found that within the first 5 years after being diagnosed with RA, 41.0 % developed at least one new comorbidity, the most common being: hypertension (15.1 %), malignancy (7.6 %), stroke/transient ischemic accident (5.1 %), myocardial infarction (4.3 %) and osteoporosis (3.7 %).[39]

1.2.4. RHEUMATOID ARTHRITIS: PROGNOSIS

Prognostic factors for joint damage and ultimately disability include presence of early erosions, elevated acute phase reactant levels, presence of RF and/or anti-CCP (especially high levels), moderate to high disease activity and failure of two or more conventional synthetic DMARDs (csDMARDs). [45]

Extensive research into prognostication in individual patients is ongoing, and is expected to lead to personal treatment strategies. There is an ongoing need to assess the risk:benefit ratio of pharmacotherapy in order to optimize the outcome and minimize adverse effects and complications

including infections. Balancing the risks of comorbidities against the anticipated benefits of treatment is also an essential part of this equation.

1.2.5. RHEUMATOID ARTHRITIS: MORTALITY

Rheumatoid Arthritis (RA) is associated with higher mortality rates compared with the general population. [46-52] In studies with cohorts of newly diagnosed RA patients the mortality is generally lower than in studies concerning non-inception-cohorts.[53-55] As in the general population cardiovascular disease is a major source of morbidity and mortality for patients with RA.[56-58] Other important causes include increased risk of lung fibrosis, cancer – especially haematological cancers and infections - particularly pneumonia. [49;50;52;59-61] Data from the Nurses' Health Study presented in an abstract by Sparks et al. in 2014, showed that in a 34 years prospective follow-up, women with RA had increased all-cause mortality compared to women without RA (HR: 2.07, 95% CI: 1.83-2.35). Women with RA had increased risk of dying from respiratory causes (HR: 4.50, 95% CI: 3.28-6.17), cardiovascular disease (HR: 1.87, 95% CI: 1.44-2.43), and cancer (HR: 1.35, 95% CI: 1.07-1.69) compared to women without RA.[62]

Table 1. Studies on mortality among patients with rheumatoid arthritis						
Author, year, country	Title	Design	Included individuals	Mean duration of follow-up	Number of deaths	Results (95% CI)
Cobb et al., 1953, USA[63]	Length of life and cause of death in RA	Observational	583 RA patients hospitalized at the Massachusetts General Hospital		137	Mortality rate per year: RA patients: Overall:24.4 Women: 23.6 Men: 25.7 Non-RA (general population): 18.9
Symmons et al., 1998, UK[64]	Long-term mortality outcome in patients with RA: early presenters continue to do well	Cohort	489 consecutive RA patients seen between 1964 and 1978	21.5 years	266	Standardized mortality ratios among RA patients compared with expected rates in general population: Women, SMR: 3.0 (2.6-3.5) Men, SMR: 2.4 (1.9-2.9) Overall, SMR: 2.7 (2.3-3.1) RA patients with disease duration<5 years when first had lower SMRs - also at the end of the study
Riise et al., 2001, Norway[46]	Total Mortality is Increased in RA. A 17-year Prospective study.	Prospective study Case control	187 RA patients 903 population-control matched for age, gender and municipality	RA patients: 12 years Controls: 14 years	RA patients: 91 (49%) Controls: 178 (30%)	MRR: 2.0 (1.6-2.5)
Goodson et al., 2002, UK[65]	Mortality in Early inflammatory arthritis	Cohort	1,236 patients from the Norfolk Arthritis Register diagnosed with polyarthritis between 1990 and 1994	Median: 6.9 years	160	Standardized mortality ratios among arthritis-patients compared with expected rates in general population: Women: 1.01 (0.80-1.26) RF-positive: 1.41 (0.93-2.05) Men: 1.13 (0.90-1.10) RF-Positive: 1.51 (1.06-2.08) Cardiovascular disease was the most common cause of death
Peltomaa et al., 2002, Finland[66]	Mortality in patients with RA treated actively from the time of diagnosis	Cohort	2 cohorts: 87 RA patients diagnosed between 1986 and 1989 63 RA patients diagnosed between 1993 and 1996	Cohort 1: 12.2 years Cohort 2: 7.7 years	24	Standardized mortality ratios Cohort 1: 0.93 (0.37-1.92) Cohort 2: 1.62 (0.95-2.60) Total: 1.33 (0.85-1.98)

Table 1. Studies on mortality among patients with rheumatoid arthritis						
Author, year, country	Title	Design	Included individuals	Mean duration of follow-up	Number of deaths	Results (95% CI)
Gabriel et al., 2003, USA[47]	Survival in RA. A population-based analysis of trends over 40 years.	Population-based cohort study	609 RA patients diagnosed with RA in Rochester between 1955 and 1994 General population	14.2 years	NA	Standardized mortality ratios among RA patients compared with expected rates in general population: Women, SMR:1.41 (1.22-1.61) Men, SMR: 1.08 (0.86-1.32) Overall, SMR: 1.27 (1.13-1.41)
Thomas et al., 2003, Scotland[50]	National study of cause-specific mortality in RA; Juvenile Chronic Arthritis and other rheumatic conditions	Population-based cohort study	All RA patients (33,318) with a Scottish hospital inpatient record between 1981 and 2000	6.9 years	Males: 4,406 Females: 11,471	Standardized mortality ratios among RA patients compared with expected rates in general population: Women: 1.97 (1.93-2.01) Men: 2.07 (1.67-4.62)
Book et al., 2004, Sweden[67]	Prediction of Mortality in RA based on disease activity markers	Cohort	152 consecutive RA outpatients seen in a 2 months period February and March 1978	12.4 years	111	Standardized mortality ratios among RA patients compared with expected rates in general population: Women, SMR:161 (129-199) Men, SMR:152 (99-223) Overall, SMR: 156(128 -1.88)
Sihvonen et al., 2004, Finland[49]	Death rates and causes of death in patients with RA; a population-based cohort study	Cohort	Cross-sectional population-based cohort of RA patients (604), age and sex-matched control prospectively and 438 RA patients (non-participants) retrospectively		384	Standardized mortality ratios among RA patients compared with expected rates in general population: Women: 2.53 (2.52-2.54) Men: 3.0 (3.11-3.30) Overall: 2.64 (2.63-2.68)

Table 1. Studies on mortality among patients with rheumatoid arthritis						
Author, year, country	Title	Design	Included individuals	Mean duration of follow-up	Number of deaths	Results (95% CI)
Jacobsson et al., 2006, Sweden[68]	Treatment with TNF-blockers and mortality risk in patients with RA	Cohort	1,430 from a national RA-register, 921 of the patients received treatment with TNF-blockers	4,95 years	188	Adjusted HR for death in Anti-TNF-treated vs. non-treated: Men: 0.95 (0.52-1.71) Women: 0.52 (0.33-0.82) Overall: 0.65 (0.46-0.93)
Young et al., 2006, UK[52]	Mortality in RA. Increased in early course of disease, in ischaemic heart disease and in pulmonary fibrosis	Cohort	1,429 RA patients from a UK inception cohort of RA patients recruited from 1986-1997	Median follow-up: 9.1 years	459	All-cause SMR: 1.27 (1.04-1.46) SMR for ischaemic heart disease: 1.49 (1.21-1.77). Baseline predictors of mortality: men, older age, poor function, comorbidity, rheumatoid factor, erosion on X-rays, high ESR, low haemoglobin, extra-articular features, lower socio-economic status
Bergström et al., 2009, Sweden[59]	Cardiovascular morbidity and mortality remain similar in two cohorts of patients with long-standing RA seen in 1978 and 1995 in Malmö, Sweden	Cohort	Two cohort of consecutive RA patients seen at outpatient clinics in Malmö: 1978: 148 RA patients 1995: 161 RA patients	8 years	1978 cohort: 36 1995 cohort: 34	Standardized mortality ratios among RA patients compared with expected rates in general population: 1978 cohort: 161 (116-223) 1995 cohort: 115 (82-160)
Radovits et al., 2009, The Nederlands[60]	Excess mortality emerges after 10 years in an inception cohort of early RA	Cohort	1,049 RA patients diagnosed from 1985 to 2007	9 years	207	Standardized mortality ratios among RA patients compared with expected rates in general population: SMR after 20 years:140 (1.09-1.77) Excess mortality in RA emerged after 10 years of disease duration. Higher levels of DAS 28 over time were associated with lower survival rates.

Table 1. Studies on mortality among patients with rheumatoid arthritis						
Author, year, country	Title	Design	Included individuals	Mean duration of follow-up	Number of deaths	Results (95% CI)
Mikuls et al., 2010, USA[69]	Associations of disease activity and treatments with mortality in men with RA: Results from the VARA registry	Cohort	1,015 enrolled in the VARS registry from 2002 to 2009	2.3 years	138	Standardized mortality ratios among RA patients compared with expected rates in general population: 2.1 (1.8-2.5) Factors independently associated with higher mortality. Older age, Caucasian race, low body weight, higher ESR, higher RF, increased DAS 28, subcutaneous nodules, prednisolone use. MTX use: HR: 0.63 (0.42-0.96)
Michaud et al., 2011, USA[70]	Mortality risk by functional status and health-related quality of life in patients with RA	Cohort	10,319 RA patients selected from the National Data Bank for Rheumatic Diseases	6.2 years	1317	The HAQ and SF-36 are strongly associated with mortality risk
Kapetanovic et al., 2011, Sweden[53]	Long-term mortality rate in RA patients with disease onset in the 1980s	Cohort	183 RA patients with disease duration< 2 years recruited 1985-1989	13 years	69	Standardized mortality ratios among RA patients compared with expected rates in general population: 1.23 (0.97-1.55)
Krause et al., 2014, Germany[71]	The positive influence of MTX on the mortality of patients with RA is partly independent of its effect on disease activity: results of re-evaluation 18 years after baseline	Cohort	Cohort from Ratingen starting treatment (n=271) with MTX between 1980 and 1987		147	Standardized mortality ratios among RA patients compared with expected rates in general population: Response group: 1.6 (1.25-1.95) Non-responders: 3.2 (2.16-4.14) Continued MTX-treatment, mortality 10-18 years after baseline, HR: 0.63 (0.43-0.92)
Listing et al., 2015, Germany[72]	Mortality in RA: the impact of disease activity, treatment with glucocorticoids, TNFα inhibitors and rituximab	Cohort	8908 RA patients from the German biologic register enrolled between 2001 and 2011	3.5 years	463	Standardized mortality ratios among RA patients compared with expected rates in general population: 1.49 (1.36-1.63) Hazard ratios: High disease activity (DAS 28>5.1): 2.43(1.64-3.61) Effective control of disease activity decreases mortality. TNFα inhibitors and rituximab reduces the risk.

Table 1. Studies on mortality among patients with rheumatoid arthritis						
Author, year, country	Title	Design	Included individuals	Mean duration of follow-up	Number of deaths	Results (95% CI)
Widdifield et al., 2015, Canada[73]	Trends in excess mortality among patients with RA in Ontario, Canada	Population-based	RA patients (97.499 in 2009) from the Ontario from 1996 to 2009 RA administrative Database General population (11,595,951 in 2009)			Standardized mortality ratios among RA patients compared with expected rates in general population: 1996-1997: 1.51 (1.43-1.59) 2000-2001: 1.50 (1.43-1.57) 2004-2005: 1.43 (1.37-1.50) 2008-2009: 1.41 (1.35-1.47)
Sparks et al., 2016, USA	RA and mortality among women during 36 years of prospective follow-up: results from the nurses' health study		964 incident RA-cases among 121.700 female registered nurses		RA: 307 Non-RA: 28,501	Mortality RA patients compared with non-RA, HR: 1.40 (1.25-1.57) Respiratory disease mortality, HR: 2.06 (1.51-2.80) Cardiovascular mortality, HR: 1.45 (1.14-1.83)
Movahedi et al., 2016, UK[74]	Oral glucocorticoid therapy and all-cause mortality and cause-specific mortality in patients with RA: Retrospective cohort study	Cohort	16,762 RA patients from the Clinical Practice Research Datalink database from 1998- 2011	Median: 6.1 years	2,996	Association between oral glucocorticoid use and mortality, HR: All-cause mortality: 1.77 (1.62-1.93) CVD-mortality: 1.58 (1.37-1.83) Neoplasms: 2.22 (1.84-2.68) Respiratory causes: 1.92 (1.57-2.36)
Lacaille et al., 2016, Canada[54]	Improvement in 5-year mortality in incident RA compared with the general population – closing the mortality gap	Cohort	Two incident RA-cohorts diagnosed in 1996-2000 (10,798 patients) 2001-2006 (14,116 patients) Compared to general population controls	5 years	RA: 2,747 Non-RA: 2,332	All-cause mortality adjusted HR for RA compared to control: Early cohort: 1.40 (1.30-1.51) Late cohort: 0.97 (0.89-1.05)

Table 1. Studies on mortality among patients with rheumatoid arthritis						
Author, year, country	Title	Design	Included individuals	Mean duration of follow-up	Number of deaths	Results (95% CI)
Van den Hoek et al., 2016, The Nederlands	Mortality in patients with RA: a 15 year prospective cohort study[75]	Cohort	A sample of 1,222 RA patients randomly selected I 1997 compared to the general population	15 years	540 RA patients	Standardized mortality ratios among RA patients compared with expected rates in general population: All-cause mortality: 1.54 (1.14-1.67). There was a trend to decreasing SMR (2% annually)
Zhang et al., 2017, USA[55]	Improved survival in RA: a general population-based cohort study	Cohort	Early RA-cohort diagnosed between 199 and 2006: 10,126 Late RA-cohort diagnosed between 2007 and 2014:10,769 Non-RA individuals matched on age, sex	Early cohort: 3.2 years Late cohort: 3.3 years	Early cohort: 936 Late cohort: 605	Mortality rate differences: Early: 9.5/1000 person-years (7.5-11.6) Late: 3.1/1000 person-years (1.5-4.6) Mortality HR: Early: 1.56 (1.44-1.69) Late: 1.29 (1.17-1.42)
Holmquist et al., 2017, Sweden[76]	Mortality following new-onset RA: Has modern Rheumatology had an impact	Cohort	17,512 patients with new-onset RA (1997-2014) 78,847 matched general population comparator subjects	RA, median: 6.2 years Non-RA, median: 6.1 years	RA: 2,386 Non-RA: 9,850	Risk of death for RA: HR:1.01 (0.96-1.59) Excess mortality was present in the RA cohort 5 years after diagnosis: 1.43 (1.28-1.59), across all calendar periods of RA diagnosis

Table 2. Studies on causes of death in RA patients						
Author, year, country	Title	Design	Included individuals	Mean duration of follow-up	Number of deaths	Results (95% CI)
Watson et al., 2002, UK[51]	All-cause mortality and vascular events among patients with RA, steoarthritis or no arthritis in the UK General Practice Reseach Database	Cohort	Retrospective cohort of patients 40 years and older from GPRD practices Women: 1.263.977 (8123 diagnosed with RA) Men: 1.109.574 (3510 diagnosed with RA)	Women: 4.8 years Men: 4.7 years		Standardized incidence rates (per 1000 patient-years) All-cause mortality: Women: RA: 27.7 Non-RA: 17.3 Men: RA:32.1 Non-RA: 20.6 Vascular death: Men: RA: 5.3 Non-RA: 3.6 Women: RA: 4.6 Non-RA: 3.1
Thomas et al., 2003, Scotland[50]	National study of cause-specific mortality in RA; Juvenile Chronic Arthritis and other rheumatic conditions	Population-based cohort study	All RA patients (33318) with a Scottish hospital inpatient record between 1981 and 2000	6.9 years	Males: 4,406 Females: 11,471	Standardized mortality ratios among RA patients compared with expected rates in general population: Coronary artery disease: Women: 1.95 (1.87-2.02) Men:1.63 (1.54-1.72) Stroke: Women: 1.73 (1.63-1.83) Men: 1.36 (1.21-1.52) Respiratory infection: Women: 1.92 (1.72-2.15) Men: 2.42 (2.28-2.57)
Maradit-Kremers et al., 2003, USA[77]	Cardiovascular death in RA	Population-based cohort study	Cohort of 603 RA patients who first fulfilled the ACR criteria for Ra between 1955 and 1995	15 years	354	Cause of death: Cardiovascular: 49.7% Likelihood (Hazard ratio) of dying of cardiovascular causes: RF-seropositivity:1.62 (1.15-2.27) Treatment with corticosteroids: 1.70 (1.26-2.29)

Table 2. Studies on causes of death in RA patients						
Author, year, country	Title	Design	Included individuals	Mean duration of follow-up	Number of deaths	Results (95% CI)
Sihvonen et al., 2004, Finland[49]	Death rates and causes of death in patients with RA; a population-based cohort study	Cohort	Cross-sectional population-based cohort of RA patients (604) and age and sex-matched control prospectively and 438 RA patients (non-participants) retrospectively		384	Causes of death among RA patients (SMR compared to general population): Cardiovascular: 42.7% (1.91 (1.89-1.92)) Cancer: 17.9% (2.40 (2.38-2.42)) Respiratory: 8.1% (2.51 (2.49-2.55))
Young et al., 2006, UK[52]	Mortality in RA. Increased in early course of disease, in ischaemic heart disease and in pulmonary fibrosis	Cohort	1429 RA patients from a UK inception cohort of RA patients recruited from 1986-1997	Median follow-up: 9.1 years	459	All-cause SMR: 1.27 (1.04-1.46) SMR for ischaemic heart disease: 1.49 (1.21-1.77) Causes of death (SMR): Cardiovascular: 31% (149 (124-173)) Respiratory: 22% (188 (136-241)) Solid tumours: 20% (113 (92-134)) Cerebrovascular: 10% (110 (79-110)) Septicaemia: 5% (682 (422-1,043))
Koivuniemi et al., 2006, Finland[78]	Infectious causes of death in patients with RA: an autopsy study		369 consecutively autopsied RA and 371 non-RA patients	-	all	Death from infection: RA: 36%, Non-RA: 26% Death from pyelonephritis: RA: 8%, Non-RA: 3% Death from respiratory infection: RA: 22%, Non-RA: 22% Infection was unmentioned on the autopsy remittance in 55% of the RA patients that died from infection

Table 2. Studies on causes of death in RA patients						
Author, year, country	Title	Design	Included individuals	Mean duration of follow-up	Number of deaths	Results (95% CI)
Bergström et al., 2009, Sweden[59]	Cardiovascular morbidity and mortality remain similar in two cohorts of patients with long-standing RA seen in 1978 and 1995 in Malmö, Sweden	Cohort	Two cohort of consecutive RA patients seen at outpatient clinics in Malmö: 1978: 148 RA patients 1995: 161 RA patients	8 years	1978 cohort: 36 1995 cohort: 34	Standardized mortality ratios among RA patients compared with expected rates in general population: 1978 cohort: 161 (116-223) CVD related mortality: 175 (100-284) 1995 cohort: 115 (82-160) CVD related mortality:172 (100-276)
Kapetanovic et al., 2011, Sweden[53]	Lon-term mortality rate in RA patients with disease onset in the 1980s	Cohort	183 RA patients with disease duration< 2 years recruited 1985-1989	13 years	69	Standardized mortality ratios among RA patients compared with expected rates in general population: 1.23 (0.97-1.55) Causes of death: CVD: 46% Malignancies: 29% Infections: 13%
Sparks et al., 2016, USA	RA and mortality among women during 36 years of prospective follow-up: results from the nurses' health study		964 incident RA-cases among 121.700 female registered nurses		RA: 307 Non-RA: 28501	Mortality RA patients compared with non-RA, HR: 1.40 (1.25-1.57) Causes: Cancer: 26.1% Cardiovascular disease: 22.8% Respiratory disease: 14.3%
England et al., 2016, USA[79]	Cause-specific mortality in male in US veterans with RA	Cohort	1652 RA patients - enrolled in the VARA register initiated in 2003	3.7 years	332	Causes of death: CVD: 31.6%, SMR: 1.77 (1.46-2.14) Cancer: 22%, SMR: 1.50 (1.20-1.89) Respiratory disease: 15.1%, SMR: 2.90 (2.20-3.83)
Avouac et al., 2017, France[80]	Mortality profile in patients with RA in France and its change in ten years	Population-based	All deaths (2000-2011) where RA was mentioned as an underlying cause of death (UCD) or as an associated cause of death (ACD)		13208 UCD: 4597 ACD: 8611	When RA was the UCD – causes of death: Cardiovascular: 29% Infectious: 22% When RA was ACD – causes of death: Cardiovascular: 35% Neoplasms: 14% Respiratory: 9% Infectious: 7%

1.2.6. Rheumatoid arthritis: Treatment, adverse events and complications to treatment

Studies have shown that a target oriented treatment approach leads to lower disease activity, less cardiovascular risk and comorbidities and better work productivity than conventional care.[81] This approach has been called the treat to target or T2T strategy. In the 2014 update of the recommendations of an international task force for "treating RA to target" it is stated that "The primary target should be a state of clinical remission, but low-disease activity may be an acceptable alternative therapeutic goal, particularly in long-standing disease".[82] The Danish guideline on treatment of RA also recommends the T2T strategy. Since treatment with csDMARDs, glucocorticoid and biologics has many potential adverse advents and complications, it is essential to balance the risks of complications against the expected benefits of treatment. Since this thesis concern the risk and outcome after pneumonia, the following section will focus on both the literature regarding treatment and its impact on infections and outcome as well as other factors with potential impact.

1.2.7. Rheumatoid arthritis: Risk of infection

Infections are a major problem in patients with RA and several studies have shown an increased risk of serious infections in RA patients compared with persons without RA with hazard ratios ranging from 1.83 to 2.03.[83;84] Risk factors for infections are either exposures or characteristics of the patient associated with an adverse outcome of the infection. When considering risk of infections in RA patients, the disease per se, comorbidities and the use of immunosuppressive therapy all play a role.

Doran et al. followed 609 RA patients for 12.7 years and compared the risk of infection to age and sex-matched subjects without RA. Patients with RA had an increased risk of infections - especially infections requiring hospitalization (HR: 1.83, 95% CI: 1.52-2.21).[83] Other studies confirm these findings. Smitten et al. found the rate of first hospitalization higher in a cohort of RA patients compared to a cohort of non-RA patients with an adjusted HR of 2.03 (95% CI: 1.93-2.13).[84] Coyne et al. found an annual incidence of lower respiratory tract infection in patients with RA of 2.3%, with a mortality rate of 22.5%.[85]

Risk factors for infections in RA patients include age, extra-articular manifestations, leukopenia, chronic obstructive pulmonary disease, kidney disease and diabetes mellitus.[86;87] Functional

impairment in RA patients is also a known risk factor for infection.[88;89] Since comorbidities are risk factors for infections – focusing on these when studying infection among RA patients is essential.

Evidence suggests that high RA disease activity is associated with increased probability of developing infections.[88;90] Au et al. found with each 0.6 unit increase in DAS28 score the rate of outpatients infections increased with 4% and the rate of infections resulting in admission to hospital increased by 25%[88], while Emery et al. found a linear relationship existed between the serious infection rate and disease activity, measured by DAS28.[90]

csDMARDs and biologics

Current data supports an increased risk of infections in RA patients treated with biologics.[91] In a meta-analysis based on 106 trials that included RA patients on biologics and reported on serious infections both standard-dose biologic (OR: 1.31 (95% CI: 1.09-1.58)) and high-dose biologic medication (OR: 1.90 (95% CI: 1.50-2.39)) compared to traditional csDMARDs, were associated with an increased risk of serious infections, while low-dose biologics (OR: 0.93 (95% CI: 0.65-1.33)) were not. [92] The increased risk of infection when treated with biologics is time-dependent, and seems to decline over time.[93] Clinical response, efficacy and the risk of adverse events of biologics vary among different individuals. Therefore, more information on predictive markers of clinical response is needed to guide treatment decisions.

Although most existing studies report no increased risk for infections in RA patients treated with csDMARDs, mainly methotrexate, sulfasalazine and hydroxychloroquine.[87;94], an American study from 2006 found that leflunomide treatment was associated with a 20% increased risk of pneumonia hospitalisation (HR: 1.2 (95% CI: 1.0-1.5).[89] Some studies have evaluated the effect on treatment on mortality. Choi et al. prospectively assessed the effect on mortality of methotrexate in a cohort of 1,240 patients with RA. The results indicate that methotrexate may provide a substantial survival benefit, largely by reducing cardiovascular mortality.[95] Another study found no increased mortality among patients treated with anti-TNF therapies compared with standard csDMARD therapy.[96]

Glucocorticoids

Several studies have examined the association between use of glucocorticoids and risk of infection in RA patients. Dixon et al. conducted a nested case control study and found increased risk of non-serious infection in RA patients treated with glucocorticoids with RR of 1.20 (95% CI: 1.15-1.25).

A dose response was seen with adjusted relative risk (RR) for less than 5 mg glucocorticoid/day of 1.10 and RR for more than 20mg glucocorticoid/day of 1.85.[97] The study included 16,207 RA patients aged over 65 years making the results only representative for this age group. No information on RA disease activity was included. Smitten et al. similarly found a dose-related risk of first-time hospitalization with infection in RA patients. For RA patients treated with oral corticosteroids RR for risk of hospitalized infection was 1.92 (95% CI: 1.67–2.21) compared with patients not treated with corticosteroids, and the relative effect varied by corticosteroid dose (≤ 5 mg/day: RR = 1.32 (95% CI: 1.06–1.63); 6–10mg/day: RR = 1.94 (95% CI: 1.53–2.46); > 10 mg/day: RR = 2.98 (95% CI: 2.41–3.69).[84] Wolfe et al. found a dose-related relationship between use of prednisolone and risk of pneumonia in RA patients.[89] This study followed 16,788 RA patients 3.5 years with semi-annual questionnaires – but no objective measures of disease activity were included. Despite the well documented risk of infections in patients with RA treated with prednisolone, there is a paucity of studies considering the effect of therapy while taking disease activity into account.

Risk scores predicting the 1 year risk of serious infections has been developed.[98;99] The risk scores calculates the risk using several well-known risk factors: older age, previous serious infection, corticosteroid use, number of treatment failures, elevated erythrocyte sedimentation rate, extra-articular manifestations, functional status and comorbidities (coronary heart disease, heart failure, peripheral vascular disease, chronic lung disease, diabetes mellitus, alcoholism and renal disease).[98;99]

Table 3. Selected studies on RA and the risk of infection						
Author, year, country	Title	Design	Included individuals	Mean follow-up	Number of infections	Results (95% CI)
Doran et al., 2002, USA[83]	Frequency of infection in patients with RA compared with controls	Population-based cohort study	609 members of a population-based incidence-cohort diagnosed with RA between 1955 and 1994 609 non-RA controls matched on sex and age	RA patients: 12.7 years Controls: 15.0 years	RA patients: 1481 Non RA patients: 1137	Rate of infection per 100 person-years: RA patients: 19.64 Non-RA patients: 12.87 Rate ratio: 1.53 (1.41-1.65) Infection requiring hospitalization: RA patients: 9.57 Non-RA patients: 5.09 Rate ratio: 1.88 (1.71-2.07) HR after adjustment: 1.83 (1.52-2.21) The rate of infection was higher among RA patients than non-RA patients in each of the 11 infection categories studied
Doran et al., 2002, USA[87]	Predictors of infections in RA	Cohort	609 members of a population-based incidence-cohort diagnosed with RA between 1955 and 1994	12.7 years	740 requiring hospitalization	Predictors of infection requiring hospitalization: Extra-articular RA, HR: 3.0 (2.17-4.77) Alcoholism, HR: 2.0 (1.27-3.16) Leukopenia, HR:2.17 (1.58-2.98) Chronic Lung disease, HR: 2.83 (2.15-3.72) Diabetes mellitus, HR: 2.83 (2.15-3.72) Organic brain disease, HR: 2.94 (2.08-4.16) Corticosteroids, HR: 1.90 (1.47-2.47)
Listing et al., 2005, Germany[100]	Infections in Patients with RA treated with biologic agents	Prospective cohort (RABBIT) Nested case-control	Cases: 928 RA patients started on infliximab, etanercept, anakinra or adalimumab 2003- 2004 Controls: 601 RA patients started on additional DMARD or another DMARD after the failure of at least one DMARD	74% completed the 12 months of follow-up	204	Relative risk of infection compared with controls: Patients treated with etanercept, RR: 2.2 (0.9-5.4) Patients treated with infliximab, RR: 2.1 (0.8-5.5)

Table 3. Selected studies on RA and the risk of infection						
Author, year, country	Title	Design	Included individuals	Mean follow-up	Number of infections	Results (95% CI)
Dixon et al., 2006, UK[101]	Rates of serious infection, including Site-specific and Bacterial Intracellular Infection in RA patients receiving Anti-TNF α therapy	Prospective observational study	7,664 anti-TNFα treated and 1,354 DMARD-treated patients with severe RA from the British Society for Rheumatology Biologics register	9,67 years in the anti-TNFα treated cohort 1.35 years in the DMARD-treated patients	525 in the anti-TNFα treated cohort 56 in the DMARD-treated patients	Incidence rate ratio (IRR)for the anti-TNFα treated cohort compared with the DMARD-treated patients: 1.03(0.68-1.57) Soft tissue infections, IRR: 4.28 8.06-17.17)
Schneeweiss et al., 2007, USA[102]	Anti-TNFα Therapy and the Risk of Serious Bacterial Infection in Elderly Patients With RA	Cohort	15,597 RA Medicare beneficiaries ≥65 years Whom a DMARD was initiated between 1995 and 2003	From 0.2-1.29 in the different drug exposure groups	Bacterial infections: MTX-treated: 41 TNF-treated: 29 Glucocorticoid-treated: 196	Incidence of serious bacterial infection: 2.02 per 100 patient-years (CI: 2.0-2.4) No increase in serious bacterial infection among users of anti-TNFα therapy compared with user of MTX , RR: 1.0 (0.6-1.7) Glucocorticoid compared to MTX, RR: 2.1 (CI: 1.5-3.1)
Bernatsky et al., 2007, Canada[103]	Anti-rheumatic drug use and risk of serious infection in RA	Nested case-control	Cohort of 23,733 RA patients studied between 1980 and 2003	6.3 years	1970 serious infections (requiring hospitalization)	Glucocorticoid, RR: 2.56 (2.29-2.85) Azathioprine, RR: 1.52 (1.18-1.97) anti-TNFα, RR: 1.93 (0.70-5.34) Cyclophoshamide, RR: 3.26 (2.28-4.67)
Coyne et al., 2007,UK[85]	Acute lower respiratory tract infections in patients with RA	Cohort	1522 RA patients seen in 2002	1 year	36	Annual incidence of acute lower respiratory tract infection: 2.3% Mortality rate: 22.5%
Lacaille et al., 2008, Canada[94]	Use of Non-biologic DMARDs and risk of infection in patients with RA	Cohort	22.710 RA patients who received care for their RA between 1996 and 2000	5.9 years	25,680 (96%) had a least 1 mild infection 4941 (18%) had at least one serious infection	Rate ratios for serious infections (vs no DMARD and no glucocorticoid): DMARD + glucocorticoid: 1.63 (1.5-1.7) DMARD alone: 0.92 (0.85-1.0) Glucocorticoid: 1.9 (1.75- 2.05)
Smitten et al., 2008, USA[84]	The Risk of Hospitalized Infection in Patients with RA	Cohort and nested case-control	245,30 RA –patients with data in a medical and pharmacy database from 199-2006 and a random sample of non-RA patients (n=500,000)	RA: 26.6 months Non-RA: 23.4 months	1993 among RA patients 11,977 among non- RA patients	Rate of first hospitalized infection, HR: 2.03 (9.93-2.13) Corticosteroid, RR: 1.92 (1.67-2.21) Biologics, RR: 1.21 (1.02-1.43) Methotrexate, RR: 0.81 (1.02-1.43)

Table 3. Selected studies on RA and the risk of infection						
Author, year, country	Title	Design	Included individuals	Mean follow-up	Number of infections	Results (95% CI)
Grijalva et al., 2009, USA[104]	Initiation of RA treatments and the risk of serious infections	Cohort	14,586 RA patients with a new episode of DMARD use (started when a RA patient filled a prescription for a DMARD or glucocorticoid from 1995-2005)	180 days for each new episode of use	Infections requiring hospitalization: Pneumonia: 192 Any: 307	The risk of pneumonia hospitalization was consistently increased with initiation of glucocorticoids, HR: Low dose: 2.30 (1-2-4.41) Medium dose: 2.36 (1.44-3.87) High dose: 4.33 (2.49-7.54) Same pattern for "any infection" Hospitalizations due to infections were not significantly increased among initiators of anti-TNFα-therapy.
Greenberg et al., 2010, USA[105]	Association og MTX and anti-TNFα-therapy with the risk of infectious outcomes including opportunistic infections in the CORRONA registry	Cohort	7,971 RA patients enrolled in the CORRONA registry	1.4 years	MTX: 1714 anti-TNFα-therapy: 890 MTX+TNF: 1514 Other DMARDS:447	Adjusted rate of infection per 100-patient-years: MTX: 30.9 (29.2-32.7) TNF: 40.1 (37.0-43.4) MTX+TNF: 37.0 (34.9-39.3) Other DMARDs: 24.5 (21.8-27.5) Adjusted incidence rate ratio: MTX: 1.30 (1.12-1.50) TNF: 1.52 (1.30-1.78)
Au et al., 2011, USA[88]	High disease activity is associated with an increased risk of infection in patients with RA	Cohort	6,242 RA patients enrolled in the CORRONA registry from 2002-2007 on stable therapy for at least 6 months	1.2 years	2,282	Overall out-patient infection event rate per 100 patient-years: 31.2 Disease activity was associated with an increased rate of infections. Each 0.6 unit increase in DAS28 score corresponded to a 4% increased rate of outpatient infections (IRR: 1.04., p= 0.01)
Dixon et al., 2011, Canada[97]	The influence of systemic glucocorticoid therapy upon the risk of non-serious infections in older patients with RA: a nested case-control study	Nested case control	16,207 RA patients aged>65 years	28,695 person years of follow-up	13,634 non-serious infections	Glucocorticoid treatment was associated with an adjusted RR of 1.20 (95% CI: 1.15-1.25). A dose response was seen: adjusted RR for <5mg/day: 1.10, RR for >20mg/day: 1.85
Dixon et al., 2011[106]	The association between systemic glucocorticoid and the risk of infection in patients with RA: systemic review and meta-analyses	Meta-analyses	21 RCT and 42 observational trials	-	-	RCT: GC therapy was not associated with risk of infection Observational studies: Rr: 1.67 (95% CI:1.49-1.87). A positive dose response was seen

Table 3. Selected studies on RA and the risk of infection						
Author, year, country	Title	Design	Included individuals	Mean follow-up	Number of infections	Results (95% CI)
Hoshi et al., 2011, Japan[107]	Incidence of serious respiratory infections in patients with RA treated with tocilizumab	Cohort	Comparison of two independent cohorts: 601 RA patients from TCZ controlled trails 601 PA-patients age and sex-matched from a large observational cohort of RA patients	9 years	51	The standardized incidence ratio (SIR) of serious respiratory infection: Standardized for age, sex and corticosteroid use: 1.85 (1.30-2.55) Standardized for age, sex and disease activity: 2.41 (1.68-3.34)
Weaver et al., 2013 USA[108]	RA disease activity and disability affect the risk of serious infection events in RADIUS 1	Cohort	4,084 RA patients from the RADIUS 1 cohort (enrolled from 2001-2003)	3.0 years	347 serious infections	A 5-unit CDAI increase corresponded with a 7.7% increase serious infection risk (HR: 1.077 (1.044-1.112)) A 0.4-unit HAQ-DI increase corresponded with a 30.1% increase serious infection risk (HR: 1.3001 (1.225-1.381)
Widdifield et al., 2013, Canada[109]	Serious infections in a population-based cohort of 86039 seniors with RA	Cohort	86,039 ≥ 66 years RA patients from the Ontario health adm. data from 1992-2010 Cases: – RA patients with serious infection Control: RA patients matched on age, sex, and date of cohort entry	5.2 years	20.575 requiring hospitalization or ER-visit	Rate of infections: 46.4 events/1,000 person-years OR for infection: MTX: 2.97 (1.90-4.64) Sulfasalazine: 1.16 (0.98-1.37) Anti-TNF: 1.60 (1.19- 2.15) Corticosteroids- Low: 3.96 (3.67-4.27) Corticosteroids- Medium: 4.28 (3.70-4.96) Corticosteroids – past use: 2.28 (2.17-2.39)
Yun et al., 2014, USA[110]	Risk of hospitalised infection in RA patients receiving biologics following a previous infection while on treatment with Anti-TNF therapy	Cohort Nested case control	2006-2010 Medicare data – 10,794 among 10,183 unique RA patients index hospitalized infections	7,807 person-years	2666	Risk of subsequent infection compared to infliximab-user, HR: Abatacept: 0.83 (0.64-0.99) Etanercept: 0.83 (0.72-0.96)
Emery et al., 2014, UK[90]	Association between disease activity and risk of serious infections in subjects with rheumatoid arthritis treated with etanercept or disease-modifying anti-rheumatic drugs	Prospective observational study	Patients with active RA treated with etanercept, were used and data were compared with a cohort of patients receiving DMARDs with active RA	19,964 patient-years	651 first-recorded serious infections	7.5% increase in serious infection for each unit increase of DAS28 score at baseline. A DAS28 change of 1 unit during follow-up predicted a 27% increase in serious infection rates. No significant increase in the risk of serious infection was observed with ETN versus DMARDs over the 5-year study

Table 4. Selected studies on RA and the risk of pneumonia						
Author, year, country	Title	Design	Included individuals	Mean follow-up	Number of infections	Results (95% CI)
Coyne et al., 2007, UK[85]	Acute lower respiratory tract infections in patients with RA	Cohort	1,522 RA patients seen in 2002	1 year	36 (hospitalized)	Annual incidence of acute lower respiratory tract infection: 2.3% Mortality rate: 22.5% Oral Steroids and not Taking csDMARDs were associated with increased of hospital admission
Smitten et al., 2008, USA[84]	The Risk of Hospitalized Infection in Patients with RA	Cohort and nested case-control	24,530 RA patients with data in a medical and pharmacy database from 1999-2006 and a random sample of non-RA patients (n=500,000)	RA: 26.6 months Non-RA: 23.4 months	434 among RA patients 2,261 among non-RA patients	Incidence rates of hospitalized pneumonia per 100.000 person-years: RA: 841,5 Non-RA: 362.4
Grijalva et al., 2009, USA[104]	Initiation of RA treatments and the risk of serious infections	Cohort	14,586 RA patients with a new episode of DMARD use (started when a RA patient filled a prescription for a DMARD or glucocorticoid from 1995-2005)	180 days for each new episode of use	Infections requiring hospitalization: Pneumonia: 192	The risk of pneumonia hospitalization was consistently increased with initiation of glucocorticoids, HR: Low dose: 2.30 (1-2-4.41) Medium dose: 2.36 (1.44-3.87) High dose: 4.33 (2.49-7.54) Hospitalizations due to pneumonia were not significantly increased among initiators of anti-TNFα-therapy.
Hoshi et al., 2011, Japan[107]	Incidence of serious respiratory infections in patients with RA treated with tocilizumab	Cohort	Comparison of two independent cohorts: 601 RA patients from TCZ controlled trails 601 PA-patients age and sex-matched from a large observational cohort of RA patients	9 years	51	The standardized incidence ratio (SIR) of serious respiratory infection: Standardized for age, sex and corticosteroid use: 1.85 (1.30-2.55) Standardized for age, sex and disease activity: 2.41 (1.68-3.34)

1.2.8. RHEUMATOID ARTHRITIS: PROGNOSIS AFTER INFECTION

In contrast to the many studies focusing on the risk of infection s in RA patients, there is a paucity of studies considering the prognosis after infection. A German study investigated the outcome of serious infections in RA patients observed in the German biologics register. Among 1,017 patients with serious infection, 135 developed sepsis and of these 85 patients died. Risk factors of a fatal serious infection included use of corticosteroids at higher doses, heat failure and higher age. RA patients with better functional level and those treated with biologics (compared to csDMARDs) had lower risk of mortality following serious infection.[111]A British study from 2007 found an overall annual incidence of lower respiratory tract infections in patients with RA of 2.3% and a mortality rate for RA patients hospitalized with acute lower respiratory tract infections of 22.5%.[85] Due to lack of power (36 patients were admitted with lower respiratory tract infections and 8 patients died) nothing could be concluded on the prognostic effects of prior medication, comorbidity etc.

It remains unclear if the increased mortality due to infections in RA can be explained solely by the increased risk of acquiring infections or if RA patients have worse infection outcomes as well. RA may influence the outcome of infections due to the use of immunosuppressive therapy, the RA disease activity *per se* or the related comorbidities. To our knowledge no studies have evaluated the prognosis among RA patients following pneumonia while taking these factors into account.

1.2.9. RHEUMATOID ARTHRITIS: RECENT INFECTIONS AND THE RISK OF CARDIOVASCULAR EVENTS

Several studies have shown an increased risk for cardiovascular events following infection.[112-115] A case-control study from 2006 showed an increased risk for both myocardial infarction (OR: 2.0 (95% CI: 1.38-3.21)) and stroke (OR: 1.92 (95% CI: 1.24-2.97)) within 7 days following the respiratory infection.[113] Another study including 50,119 patients hospitalized due to pneumonia found the 90-day incidence of myocardial infarction and stroke to be 1.5% and 0.2%, respectively.[116] Pneumococcal pneumonia increases the risk for a concurrent acute cardiac event. Musher et al. found that 19.4% of patients with pneumococcal pneumonia had a major cardiac event.[117] A newly published study followed 1,182 patients hospitalized with community acquired pneumonia or (CAP) and of these 380 (32.2%) experienced cardio vascular events (CVE). The 30 day mortality was higher (17.6% vs 4.5%) in patients who developed a CVE compared with those who did not. [118] To our knowledge no study exists on RA patients and their risk of cardiovascular events following pneumonia.

1.3. Ankylosing Spondylitis

1.3.1. Ankylosing Spondylitis: Definition, prevalence, treatment, comorbidity and mortality

Ankylosing spondylitis is the most classic representative of the family of spondyloarthritis (SpA). It is a chronic systemic inflammatory rheumatic disease characterised by axial skeleton involvement. It can affect the peripheral joints and may be complicated by extra-articular manifestations such as uveitis and inflammatory bowel disease.

The diagnosis requires fulfilment of New York Classification Criteria including radiological evidence of sacroiliitis.[119] Most patients with AS are HLA-B27-positive.[120;121] The prevalence of AS varies and depends on the prevalence of HLA-B27, ethnicity, gender and diagnostic criteria.[22;120-129] No studies exist on the AS prevalence in Denmark, but in the southern part of Sweden the prevalence was 0,12 %,[130] in one study, while a Swedish nationwide, register-based study found a prevalence of AS of 0.18%.[131]

The medical treatment of AS includes non-steroidal anti-inflammatory drugs (NSAID) as first line treatment and biologics (including anti-TNF-alfa therapy and IL-17-inhibitors) as second line.

Comorbidity

Lung disease is associated with AS. It includes apical fibrosis, interstitial lung disease and chest wall abnormalities.[132] A recent study including 4,076 patients with AS and 20,290 age- and sex-frequency matched controls also links chronic obstructive pulmonary disease (COPD) to AS. A higher proportion of COPD in AS patients than in controls (46% vs. 18%, respectively) was found.[133] A systematic review which included 10 articles (303 patients) found a high prevalence of lung abnormalities on thoracic HRCT in AS. A total 61% of the patients had an abnormal thoracic HRCT: emphysema in 55 (18.1%), ground glass attenuation in 34 (11.2%), bronchiectasis in 33 (10.8%), and upper lobe fibrosis in 21 (6.9%). In 101 (33%) patients non-specific interstitial abnormalities were observed.[134]

Patients with AS have a 30%–50% increased risk of incident CV events.[135] In a recent meta-analysis of seven longitudinal studies showed an increase in myocardial infarction (OR = 1.60 (95% CI: 1.32-1.93)) in AS patients and an increase in stroke with an OR = 1.50 (95% CI: 1.39-1.62) in AS patients.[136] Another study investigating CVE-related comorbidities found an increase in

hypertension among AS patients compared to non-AS patients.[137] A cross-sectional international study with 22 participating countries and 3,984 patients with spondyloarthritis, examined the prevalence of comorbidities and risk factors. The most frequent risk factors were hypertension (34%), smoking (29%) and hypercholesterolemia (27%), while the most frequent comorbidity was were osteoporosis (13%) followed by gastroduodenal ulcer (11%).[138]

Other chronic diseases known to be associated with AS include renal disease and osteoporosis.[139;140] Patient with AS are also at higher risk of vertebral fractures and spinal injury.[132]

Mortality

Patients with AS have an increased risk of death compared to the general population and cardiovascular disease is the major cause of death.[141-143] Earlier studies found an increased mortality and researchers speculated that radio therapy treatment might be the cause. This therapy, now obsolete, increased the number of deaths due to lymphoma, leukaemia and aplastic anaemia.[144;145] However, studies done on AS patients who have not been given radiation therapy still find increased mortality. Cardiovascular and cerebrovascular disease has been identified as significant causes of mortality.[141;146] Increased mortality in AS also seems related to disease activity.[147] An increased risk of death from infections including respiratory tract infections has also been identified, please see table 7 for details.[148]

Table 5: Studies on Ankylosing spondylitis and mortality						
Author, year, country	Title	Design	Included individuals	Mean duration of follow-up	Number of deaths	Results (95% CI)
Kaprove et al., 1980, Canada[144]	Ankylosing spondylitis. Survival in men with and without radiotherapy	Prospective cohort	151 AS patients – Canadian war veterans – entered between 1947 and 1949 – followed until 1976	Minimum 27 years	54	Male AS population had a survival of 60.9% (expected survival =77.0% in the general population) AS-men receiving radiotherapy: 55.3 % survival, vs 79.6% expected AS-men not receiving radiotherapy: 67.7% vs 74.0% expected
Smith et al., 1982, United Kingdom[145]	Mortality among patients with ankylosing spondylitis after a single treatment course with x-rays	Cohort	14,560 AS patients given a single course of x-ray treatment during 1935-1954	16.2 years	1759	66% excess of deaths compared to the general population Five-fold excess of deaths from leukaemia Higher than expected death rates due to AS itself and non-malignant causes
Lehtinen, 1993, Finland[141]	Mortality and causes of death in 398 patients admitted to hospital with AS	Cohort	398 AS patients treated for the first time at The Rheumatism Foundation Hospital in 1961-1969	25.7 years	152	1.5 times higher overall mortality in the AS patients compared with the general population (same age and sex)
Bakland et al., 2011, Norway[147]	Increased mortality in AS is related to disease activity	Cohort	677 AS patients followed from 1977 2,031 control matched by gender, age and postal code	31.9 years	98 AS patients	Standardized mortality ratios among RA patients compared with expected rates in general population: SMR: 1.61 (1.29-1.93) Increasing levels of CRP, diagnostic delay, not using NSAIDs and work disability were independent predictors for increased mortality

Table 5: Studies on Ankylosing spondylitis and mortality						
Author, year, country	Title	Design	Included individuals	Mean duration of follow-up	Number of deaths	Results (95% CI)
Haroon et al., 2011, Canada[146]	Patients with AS have increased cardiovascular and cerebrovascular mortality	Population-based cohort	21,473 AS patients 86,606 comparators without AS, matched for age, sex and location of residence	AS: 7.8 years Non-AS: 7.9	AS: 170 vascular deaths Non-AS: 594 vascular deaths	Adjusted HR for vascular death: Overall:1.36 (1.13-1.65) Men: 1.46 (1.13-1.87) Women: 1.24 (0.92-1.67)
Exarchou et al., 2016, Sweden[143]	Mortality in ankylosing spondylitis: results from a nationwide population-based study	Population-based cohort	Nationwide cohorts of patients with AS: 8,600, 40,460 age-, sex- and county-matched general population comparators		AS: 496 Non-AS: 1533	Age-adjusted and sex-adjusted HR of 1.60 (95% CI 1.44 to 1.77) Men: HR=1.53 (95% CI 1.36 to 1.72) Women HR=1.83 (95% CI 1.50 to 2.22).
Buschiazzo et al., 2016, Argentina[149]	Mortality in patients with ankylosing spondylitis in Argentina	Cross-sectional, retrospective	127 AS patients from a local clinic in Buenos Aires	10 years	9	AS overall mortality in 10 years: 7.1% Population average gross death rate: 7.76/1,000
Prati et al., 2017, France[148]	Deaths associated with AS in France from 1969-2009		Deaths certificates in which AS was indicated were evaluated Compared to general population		2940 death certificates	When AS was stated as an non-underlying cause of death, the SMR for the following causes was: Infectious disease: 2.1 (1.46-2.91) Neoplasm: 0.43 (0.36-0.51) Disease of the circulatory system: 1.06 (0.93-2.06) Disease of the respiratory system:1.66 (1.31-1.06) External cause:1.91 (1.57-2.29)

1.3.2. Ankylosing Spondylitis: Disease activity and functional status

Several measurements have been developed to evaluate disease activity. Commonly used are the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)[150], the AS Disease Activity Score (ASDAS)[151] and Patient and Physician Global Assessments on Visual Analog Scales. The BASDAI consists of six horizontal Visual Analogue Scales (VAS) measuring severities of fatigue, back pain, peripheral joint pain, localized tenderness and morning stiffness (both qualitative and quantitative). The mean of the answers gives the BASDAI with a score range between 0 and 10. In Denmark a BASDAI over 4 usually indicates that the patient is a candidate for treatment with biologics. The BASDAI has a good test-retest ($r= 0.93$; $p < 0.001$) reliability, reflects the entire spectrum of disease and is sensitive to change.[150]

The Bath Ankylosing Spondylitis Functional Index (BASFI) and the Bath AS Metrology Index (BASMI) can be used to evaluate functional status. BASFI consist of 8 questions regarding function in AS and two questions concerning the patients' ability to cope with everyday life. The answers are given on a 10 cm horizontal visual analogue scale. The mean of the answers gives the BASFI score (0-10).[152] BASMI is a composite index consisting of five clinical measurements reflecting the axial status of the AS patients and has been found reproducible and sensitive to change across the AS disease spectrum.[153] Measures of disease activity and severity (BASDAI, BASMI and BASFI) are registered in daily clinical practice in DANBIO.

1.3.3. Ankylosing Spondylitis: Risk of infection and prognosis after infection

The risk of infections during treatment with biologics has been investigated in several randomised controlled trials (RCT). A systematic review a meta-analysis including 14 RCTs with AS patients treated with NSAIDs or TNF-alfa-blocker and monitoring serious infections found, that the absolute risk of serious infection in patients receiving TNF-alfa blockers was higher compared to NSAID/placebo but the difference was not significant.[154] A later meta-analysis of RCTs with larger sample size found a RR of 2.02 (95% CI: 0.57-7.13) for serious infections among AS treated with TNF-alfa blocker compared to controls treated with placebo/NSAIDs.[155] Continued monitoring of the potential increased risk of infections in AS patients treated with biologics is necessary to gather enough data to confirm the current results with more exact estimates.

In contrast, only a few studies examined the risk of infections in AS patients compared to patients without AS. A German study examined the cumulative prevalence of *self-reported* infections in the previous 12 months among 1,080 AS patients and 102 patients with disc herniation. The proportion

of AS patients with a symptomatic infection was 65.5% in comparison with 25.5% among patients with disc herniation. Respiratory infections were reported more frequently (OR 5.83 (95% CI: 3.38-10.08)) among patients with AS.[156]

Little is known about the *prognosis* of infections in AS patients compared to members of the general population without AS. It therefore remains unclear, if the increased risk of dying from infections in AS, can be explained solely by an increased risk of acquiring infections, or if AS patients might have worse infection outcomes.

A study focusing on diagnoses associated with in-hospital mortality in AS patients identified 12,484 admissions and 267 deaths between 2007 and 2011. Spinal fracture with spinal cord injury had the highest OR of death followed by sepsis. They also reported that pneumonia was associated with increased mortality with an OR of 1.94 (95% CI: 1.42-2.65).[157] The study only included in-hospital mortality, and deaths related to the admission but deaths occurring after discharge were not included and no non-AS controls were included.

Since an increased risk of death from infections including respiratory tract infections has been identified, gaining knowledge about the infection outcome among AS patients and prognostic factors is essential to prevent excess mortality. To our knowledge no study exists on AS as a predictor of outcome of infection, including pneumonia.

1.4 Conclusion of the literature review and implications for the studies in the thesis

Although studies have demonstrated an increased risk of infections in RA patients treated with biologics[92 93] and glucocorticoids[97] and high RA disease activity additionally seems associated with increased risk of developing infections,[88;90] there is a paucity of studies considering the effect of anti-rheumatic therapy while taking disease activity into account and including all age groups. Also, it remains unclear if the increased mortality due to infections in RA, can be explained solely by the increased risk of acquiring infections or if RA patients have worse infection outcomes compared with the general population. Since Pneumonia is one of the most common infections requiring hospitalization, we wanted to examine if there was an increase in the risk of pneumonia hospitalization in RA patients depending on anti-rheumatic therapy and whether RA was associated with increased mortality in patients who are hospitalized with pneumonia, and to evaluate whether

preadmission RA disease activity with or without preadmission treatment with csDMARDs, biologics, or prednisolone influenced the prognosis.

Little is known about the prognosis of infections in AS patients compared to members of the general population without AS. It therefore remains unclear, if the increased risk of dying from respiratory and other infections in AS[146;148], can be explained by an potential increased risk of acquiring infections, or if AS patients have worse infection outcomes as well. We wanted to examine whether AS is associated with worse outcomes in patients who are hospitalized with pneumonia.

2. AIM OF THE THESIS

To improve our understanding of infection risk and prognosis in patients with RA and AS this thesis used Danish medical databases to examine the risk of, and prognosis after pneumonia among these patients taking disease activity and pharmacotherapy into account. The aims of the thesis were:

- To investigate the association between anti-rheumatic therapy, disease activity, and risk of hospitalized pneumonia in patients with RA across all age groups (paper I)
- To examine whether RA is associated with increased mortality in patients hospitalized with pneumonia and to assess the validity of RA diagnoses in the Danish National Patient Registry (DNPR) (paper II).
- To examine whether AS is associated with increased mortality, complications and readmission in patients who are hospitalized with pneumonia (paper III).

3. SUBJECTS AND METHODS

3.1. SETTING

All studies were conducted in Denmark. Study1 was a case-control study of pneumonia nested in a cohort of patients diagnosed with incident RA between January 2004 and December 2016. Study 2 was a population-based cohort study in the northern and central regions of Jutland, with approximately 1.8 million inhabitants, while study 3 was a population-based study which included data from all regions of Denmark (Table 8). The studies were based on data from medical databases and administrative registries and were conducted through linkage at the individual level.

3.2. DATA SOURCES

The civil registration system

The civil registration system (CRS) assigns unique CPR numbers to the entire Danish population and does daily updates of information on migration and vital status.[158] The CRS records information on name, address, birth (date, place and sex), civil status (single, married, divorced, widow/widower, registered partnership, dissolved partnership), citizenship, kinship (CPR numbers of parents, siblings and children) and status.[158] Since the CPR number is unique and permanent it allows linkage of data from different registries at the individual level.

The Danish National Patient Registry

The Danish National Patient Registry (DNPR) has a record of all inpatient hospitalizations in the entire Danish population since 1977 and all instances of contact with hospital outpatient clinics since 1995, including admission and discharge dates and up to 20 discharge diagnoses per contact coded according to the International Classification of Diseases, edition 10 (ICD-10) during the period of this study and ICD-8 during earlier periods.[159] Since 1995 contacts to the emergency rooms have been included and from 2003 onwards all private hospitals have been obligated to report to the DNPR. The DNPR has records of patients' municipalities, CPR numbers, identification of the hospital wards, and dates and times of activities performed, including information on the type of examinations, surgeries and treatments. For RA and AS outpatient the use and types of csDMARDs and/or biologics is recorded in relation to the patients' visits to the hospitals' outpatient clinics. Many diagnoses have been validated for research purposes. Of interest,

the validity of a pneumonia diagnosis has been evaluated and found to be very good, with a positive predictive value (PPV) of 90% (95% CI: 82-95%).[160]

The Danish National Database of Reimbursed Prescriptions

The Danish National Database of Reimbursed Prescriptions (DNDRP) has recorded data on all reimbursed prescriptions redeemed at Danish community pharmacies and hospital-based outpatient pharmacies since 2004.[161] The information includes the patients CPR number, date of dispensing, product name, and the WHO-defined Anatomical Therapeutical Chemical code (ATC).

The Aarhus University Prescription Database

In Denmark most prescription medications are eligible for full or partial general reimbursement by the National Health Service.[162] The Aarhus University Prescription Database records information on prescriptions filled for all reimbursed medications including the CPR number, type of drug and date of sale. The database receives data from all of the community pharmacies in the northern and central regions of Jutland and have complete coverage since 1998.[162] CsDMARDs, NSAIDs and prednisolone are eligible for reimbursement. Non-reimbursable medications are not registered, this include low dose NSAIDs in small packages (max 20 tablets) which can also be purchased outside pharmacies. Non-reimbursable medications are not registered.

DANBIO

DANBIO is a Danish nationwide clinical quality register recording clinical data on patients with rheumatic diseases. DANBIO was initiated in 2000 as a nationwide voluntary register focusing on patients who received biologics, and recording information regarding the indications for treatment, treatment efficacy and adverse events. In 2006, DANBIO was approved by the Danish National Board of Health as a clinical quality register, and since then, reporting of patients treated with biologics and newly referred RA patients, regardless of the treatment and disease duration, has been mandatory.[163] Since 2006 it has been mandatory to register all AS patients treated with biologics and since 2015 all newly diagnosed AS patient. Patients are registered in DANBIO, when they are seen by a rheumatologist in hospital or private outpatient clinics. Each time an RA/AS patient is seen by a rheumatologist, a visit is recorded in DANBIO including information regarding the disease activity, treatment, current functional status and visual analogue scale (VAS) scores of pain,

fatigue, and of the patient and physician's global assessment. RA patients' disease activity is measured and recorded using DAS28 and CDAI, and AS patients by BASDAI or ASDAS.

The LABKA database

The LABKA database contains results from every analysed blood sample for patients living in the northern region of Jutland since 1997 and for the central region since 2000. Data collected in the database include the CPR number, date the blood sample analysis was performed, test results and an identification code for the physician/department requesting the analysis.[164]

3.3. STUDY DESIGN AND DEFINITION OF EXPOSURES, OUTCOMES AND CONFOUNDING FACTORS

Table 6 below provides an overview of the study designs used in the three studies.

Table 6	**Study 1**	**Study 2**	**Study 3**
Design	Case-control study	Cohort study	Cohort study
Setting, period	Denmark 2004-2016	North Denmark and central Denmark Regions 1997-2011	Denmark 1997-2017
Study population	6,672 incident RA cases with a first-time pneumonia hospitalization and 32,483 incident RA controls without pneumonia matched by age, sex, and RA duration	52,577 patients with a first time pneumonia hospitalization	387,796 patients with a first time pneumonia hospitalization
Exposure	RA therapy, RA disease activity	Rheumatoid arthritis	Ankylosing spondylitis
Outcome	Pneumonia hospitalization	30- and 90-day all-cause mortality	90-day all-cause mortality, 90-day readmission, 90-day complication rate

3.3.1. STUDY 1

To examine, if there is an increase in the risk of pneumonia hospitalization in RA patients treated with certain anti-rheumatic therapy regimens, we conducted a case-control study nested in a cohort of patients diagnosed with incident RA (ICD10 codes: M05 and M06) between January 2004 and

December 2016 according to the DNPR. We identified RA cases admitted with pneumonia defined as the first primary hospital discharge diagnosis of pneumonia recorded after the RA diagnosis between January 2004 and end of December 2016 through the DNPR, thus excluding patients with a pneumonia discharge diagnosis recorded between 1977 and their RA diagnosis. For each pneumonia case, we randomly selected up to 5 RA controls with no hospitalization for pneumonia matched on age, sex and RA duration using incidence density sampling. The controls were adult RA patients who were still at risk for becoming a pneumonia-case at the index date (the date of the admission for pneumonia). A subgroup of the included cases and control were registered in DANBIO. For this subgroup we could obtain additional information on disease activity and treatment with biologics. Please see Figure 1 for details concerning the routine registry cohort and the DANBIO cohort.

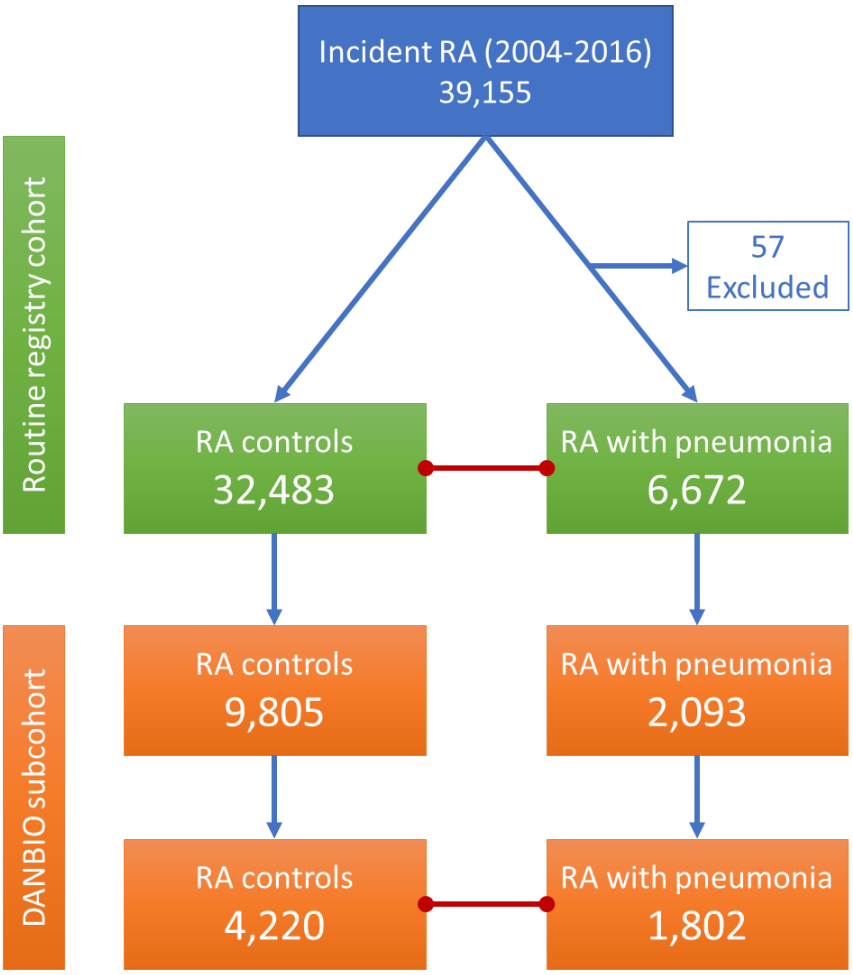

Figure 1. Flowchart for Study I. The registry cohort consists of patients diagnosed with RA between 2004 and 2016. RA cases and controls were matched on age, sex and disease duration. 57 pneumonia cases had no matched control subjects and were excluded. DANBIO sub-cohort refers to the subgroup registered in DANBIO 0 to 180 days prior to the index date. In the DANBIO sub-cohort 1,802 cases had matched DANBIO controls.

We retrieved data on medication from the DNPR, DNDRP and DANBIO 0-180 days prior to the index date. Treatment with prednisolone was defined as a prescription for prednisolone reimbursed

0-90 days prior to the index date. In the primary analysis we compared anti-rheumatic therapy regimens containing prednisolone with non-prednisolone therapy regimens both for the routine registry cohort and the DANBIO cohort.

We also divided RA therapy into mutually exclusive categories and compared these to each other. For the patients in the routine registry cohort we used the following categories: prednisolone monotherapy, prednisolone in combination with one or more csDMARDs, methotrexate monotherapy, sulfasalazine monotherapy, other csDMARD monotherapy, csDMARD combination therapy and finally a group not treated with csDMARDs or prednisolone. In the DANBIO cohort we also included information on biologics and expanded the categories to the following: Prednisolone monotherapy, prednisolone in combination with one or more csDMARDs, prednisolone in combination with TNF inhibitors, prednisolone in combination with other biologics, TNF inhibitor monotherapy, TNF-alfa monotherapy, other csDMARD monotherapy, csDMARD combination therapy and finally a group not treated with either csDMARDs, biologics or prednisolone.

Finally we compared patients currently using prednisolone (prescription 0-90 prior to the index date) and patients previously using prednisolone with patients who had never used prednisolone.

Covariates

We used the Charlson Index to adjust for existing comorbidities in the analysis and considered the 19 conditions included in the original Charlson Index[165] (excluding RA diagnoses) and we additionally considered alcohol-related conditions as potential confounders. We obtained information on the conditions included in the Charlson Index and alcohol-related conditions based on ICD-8 and ICD-10 codes recorded in DNPR within 10 years before the pneumonia hospitalization (please see appendix for codes included). In a previous study, the coding in the DNPR for the 19 Charlson conditions was found to have an overall PPV of 98%.[166] We used incidence density sampling and matched cases and controls on sex, age and disease duration. To address possible *confounding by indication* (i.e. prednisolone treated patients may have been prescribed prednisolone due to high disease activity which in itself could increase pneumonia risk) we included disease activity when analysing the subgroup registered in DANBIO.

3.3.2. STUDY 2

In order to examine whether RA is associated with increased mortality in patients who are hospitalized with pneumonia and to evaluate whether preadmission RA disease activity with or without preadmission treatment with csDMARDs, biologics, or prednisolone influences the prognosis, we conducted a population-based cohort study in the northern and central regions of Jutland, with approximately 1.8 million inhabitants.

DNPR was used to identify patients with pneumonia. We included all adult patients (≥ 16 years) with a first-time primary hospital discharge diagnosis of pneumonia between January 1997 and December 31, 2011; thus, patients with a prior discharge diagnosis of pneumonia were excluded. Data on RA were also obtained from the DNPR. To quantify the occurrence of potential coding errors, we reviewed a sample of 190 medical records of pneumonia patients with one or more previous RA registrations in the DNPR from the northern region of Jutland (100 patients with one registration, 45 patients with two registrations, and 45 patients with three or more previous RA registrations). A trained rheumatologist confirmed the diagnosis using three definitions of RA: clinically confirmed RA based on a rheumatologist's expert opinion, fulfilment of the American College of Rheumatology (ACR) 1987 criteria for RA, or fulfilment of the 2010 ACR/EULAR classification criteria for RA, for patients diagnosed in 2010 or later. We confined the validation to the North Jutland Region.

The study outcome was death from any cause within 30 and 90 days from the pneumonia hospitalization. We ascertained the date of eventual death from the Danish Civil Registration System.

Covariates

Previous studies have shown that elevated CRP levels and elevated platelet counts are valid markers of RA disease activity.[29-32] We obtained data on CRP and platelets measured 30-90 days before pneumonia hospitalization from LABKA. In cases of more than one measurement made 30-90 days before hospitalization, the most recent value was selected. We omitted measurements from 1 to 30 days before admission, to avoid any influence from the subsequent infection. A minor proportion of the RA patients were registered in DANBIO, and had a visit recorded in DANBIO 0-90 days prior to admission. We used information on disease activity from the latest visit for this subgroup of patients and stratified analyses by level of activity (using DAS28 = 3.2 as threshold between low and high disease activity).

Data on RA treatment were obtained from the DNPR, the Aarhus University Prescription Database and DANBIO. All of the RA patients were categorized according to the type of preadmission RA medication into the following groups: any prednisolone treatment, any biologic treatment, methotrexate-monotherapy, other csDMARDs monotherapy, csDMARDs combination therapy, and no RA medication. We categorized the patients using this hierarchy according to the registration for the last known therapy before the instance of pneumonia hospitalization. A hierarchical structure was used, if a patient was treated with therapies from several groups. Patients treated with either prednisolone therapy or biologic therapy, regardless of any other therapies they were receiving, were assigned to those groups. Patients treated with both biologics and prednisolone were categorized as prednisolone users. In addition we examined the prognostic effect of prednisolone separately stratified by low or high CRP levels before the pneumonia admission using patients with no prescriptions for prednisolone and low CRP levels as a reference.

To adjust for existing comorbidities in the analysis of prognosis we considered the 19 conditions in the Charlson Index (excluding RA diagnoses) and alcoholism-related diagnoses as described above for study 1. We also considered age and sex to be potential confounders. For this study we also collected information on use of antibiotics prior to the admission. We obtained information on redeemed prescription for antibiotics within 30 days prior to the admission from the Aarhus University Prescription Database.

3.3.3. STUDY 3

To examine, whether AS is associated with increased mortality in patients who are hospitalized with pneumonia, we initially conducted a population-based cohort study in the northern and central regions of Jutland, with approximately 1.8 million inhabitants. However, between 1997 and 2011 only 82 AS patients were admitted with a first time pneumonia. The low number hampered our possibilities to conduct the planned analyses and we decided to do national population-based cohort study in Denmark with approximately 5.8 million inhabitants.

The primary outcome was death from any cause within 90 days from the pneumonia hospitalization. We ascertained the exact date of eventual death from the Danish Civil Registration System.[158] Other outcomes were all-cause readmission rate within 90 days after initial pneumonia hospitalization discharge, and hospital diagnoses of pulmonary complications associated with the initial hospitalization or up to 90 days after the admission date. We defined complications as pulmonary

embolism, empyema or pulmonary abscess (please see appendix for ICD10 codes). In addition we examined the prognostic effect of AS functional status, disease activity and therapy.

We used the DNPR to identify patients with pneumonia. We included all adult patients with a first-time primary hospital discharge diagnosis of pneumonia between January 1997 and 31 July 2017. Data on AS were obtained from the DNPR and DANBIO.

We obtained information on the latest registration of BASDAI and BASFI from DANBIO. Data on AS treatment were assessed from both DNPR and DANBIO. We retrieved DNPR information on all treatments registered within 12 months prior to pneumonia hospitalization. For the subgroup of pneumonia patients who were registered in the DANBIO database, we also retrieved information from the last visit within 12 months before the pneumonia hospitalization. If the patient had more than one registration in DANBIO or the DNPR within that year, the latest visit data was used. We categorized all AS patients according to the type of preadmission AS medication into the following groups: treatment with csDMARD (either as monotherapy or as csDMARD combination therapy), anti-TNFα treatment as monotherapy, anti-TNFα treatment in combination with one or more csDMARDs, and no recorded AS therapy.

Covariates

To adjust for existing comorbidities in the analysis of prognosis we used previous alcoholism-related diagnoses and the Charlson Index as described for study 1. We also considered age and sex to be potential confounding factors

3.3.4. ADDITIONAL MATERIAL

To examine whether RA patients have increased risk of cardiovascular events (CVE) following hospitalized pneumonia compared to patients with pneumonia without RA, we conducted a population-based cohort study of adults with a first-time hospitalization with pneumonia between 1997 and 2011 in Northern Denmark. Information on RA, comorbidity, pneumonia and CVE was obtained from medical databases.

We defined CVE as stroke or acute myocardial infarction. Data on mortality was ascertained from the Danish Civil Registration System.

We considered sex, age, the 19 conditions in the Charlson Index, alcoholism and previous diagnosis of CVE to be possible confounders.

3.4. STATISTICAL ANALYSIS

3.4.1. STUDY 1

We used conditional logistic regression to compute unadjusted and adjusted odds ratios (ORs) with 95% CIs as a measure of the relative risks of pneumonia hospitalization. The primary analysis compared users of prednisolone containing anti-rheumatic therapy regimens with non-prednisolone therapy regimens for all the patients and for the DANBIO patients. In addition, we stratified the analysis by age groups (16-29, 30-44, 45-59, 60-74 and ≥75 years).

Analysis of the impact of csDMARDs and prednisolone (and biologics in the DANBIO cohort) were performed after dividing the patients into therapy groups as previously described comparing the different treatment regimens to all the other regimens. We adjusted for level of comorbidity and alcohol-related conditions and in the DANBIO sub-cohort also for disease activity.

Unadjusted ORs were computed according to treatment with prednisolone comparing patients currently using prednisolone (prescription 0-90 prior to the index date), patients previously using prednisolone (prescription more than 90 days before index date) with patients who had never used prednisolone (reference), overall and stratified by sex and age groups. We adjusted for comorbidities and alcohol-related conditions. The analyses were repeated for the DANBIO sub-cohort, but in this group, we were able to adjust for disease activity as well.

3.4.2. STUDY 2

We calculated the PPV of an RA diagnosis as the percentage of RA diagnoses in the reviewed hospital record samples that fulfilled the criteria for confirmed RA for each of the three RA definitions previously described.

In the main analysis, follow-up began at the date of pneumonia-admission and continued until migration, death, or 90 days after the admission date, whichever came first. We estimated 30- and 90-day mortality for both RA and non-RA patients. To compare mortality in RA patients with non RA patients, we used Cox regression to compute the crude and adjusted hazard ratios (HRs) for death within 30 and 90 days following hospital admission, controlling for level of comorbidities, alcoholism, sex, age and use of antibiotics within 30 days before admission. In addition we stratified the analysis by calendar time for the pneumonia diagnosis (1997-2001, 2002-2006 and 2007-2011) and for chronic lung disease.

We compared 30- and 90-day mortality according to preadmission CRP levels (CRP <8 mg/L (reference), 8 – 19.9 mg/L, > 20 mg/L) using Cox regression. Similar analyses were performed for platelet levels (<$350 \cdot 10^9$/L (reference), 350 – $400 \cdot 10^9$/L, > $400 \cdot 10^9$/L) in pneumonia patients with RA. We additionally estimated the effect on mortality with numerical increase in CRP levels by 10 mg/L and an increase in platelet count by $20 \cdot 10^9$/L. In order to examine if an association between high RA disease activity and mortality could be explained by a higher prevalence of prednisolone use, we adjusted for prednisolone use in addition to level of comorbidity, alcoholism, sex, age, and prescribed antibiotics. Patients were identified as prednisolon users if they filled a prescription within 3 months prior to admission.

We compared the mortality between high and low disease activity (using DAS28 = 3.2 as threshold) among RA patients with a visit registered in DANBIO 0-90 days prior to pneumonia admission, adjusting for sex, age and level of comorbidity.

Effect of RA-therapy on pneumonia outcome was evaluated by categorizing RA patients according to preadmission anti-rheumatic therapy. Since MTX was frequently used and is regarded as a cornerstone of RA treatment[45], we computed the 30- and 90-day HRs for mortality by type of anti-rheumatic therapy using methotrexate users as reference. We adjusted for sex, age, level of comorbidities, alcoholism, and antibiotic use before admission.
We wanted to evaluate potential biological interaction between use of prednisolone and disease activity and examined the prognostic effect of prednisolone stratified by low or high CRP levels before the pneumonia admission. Next, we used patients with no prescriptions for prednisolone and low CRP levels as a reference and computed the HRs for mortality in patients with prescriptions for prednisolone and low CRP levels, patients without prescriptions for prednisolone and elevated CRP levels, and patients with prescriptions for prednisolone and elevated CRP levels.

3.4.3. STUDY 3

Follow-up began at the date of pneumonia-admission and continued until death, migration, or 90 days after the discharge date, whichever came first. Mortality was estimated after 90 days for AS and non-AS patients. We used cox regression to compute crude and adjusted hazard ratios (HRs) for death within 90 days following admission for pneumonia while comparing AS and non-AS patients, controlling for age, sex and level of comorbidities. We stratified the analysis by calendar year for pneumonia diagnosis (1997-2006 and 2007-2017) to evaluate if the prognostic impact of AS on pneumonia changed over time. We estimated rates for readmission and pulmonary complications

after 90 days for AS and non-AS patients, respectively. We used cox regression to compute crude and adjusted HRs for readmission within 90 days following discharge and pulmonary complications within 90 days following admission for pneumonia while comparing AS and non-AS patients, controlling for age, sex and level of comorbidities. These analyses were also stratified by calendar time for pneumonia diagnosis (1997-2006 and 2007-2017).

3.4.4. ADDITIONAL MATERIAL

Follow-up for CVE started the discharge for pneumonia and continued until CVE, death or 90 days after the discharge. Cox regression was used to compute Hazard Ratios (HR) for CVE after being discharged following hospitalization comparing patients with and without RA, controlling for sex, age, level of comorbidity, prior CVE, alcoholism, and antibiotic therapy before admission

3.5. SOFTWARE

Statistical analyses were performed using the Stata V12.1 statistical software package (StataCorp, College Station, Texas, USA).

3.6. ETHICS

The studies were approved by the Danish Data Protection Agency (record numbers (2008-58-0028 and 2013-41-2663). Patient consent and approval by an ethics committee were not required according to Danish legislation.

4. RESULTS

4.1. STUDY 1

The study included 6,672 patients with first-time pneumonia and 32,483 RA matched controls (Figure1). Pneumonia cases had more comorbidities than controls; 28.6% had a high Charlson index score compared with 12.2% of RA controls.

Anti-rheumatic therapy regimens containing prednisolone were associated with increased risk of pneumonia hospitalization compared with non-prednisolone therapy regimens with crude OR of 6.23 (95% CI: 5.77-6.72) and OR adjusted for level of comorbidity and alcoholism–related conditions prior to admission of 5.62 (95% CI: 5.20-6.08) **.** We found a similar pattern in the DANBIO cohort with unadjusted OR of 4.88 (95% CI: 4.13-5.77). Adjusting for disease activity, comorbidity and alcohol-related conditions reduced the OR to 4.11 (95% CI: 3.28-5.16). The

increased risk of hospitalization due to pneumonia among patients treated with prednisolone was present in patients aged 30 and above and increased with age.

OR for hospitalization with pneumonia according to medication prior to admission for the routine registry cohort and the DANBIO cohort are presented in Figure 2.

Compared with patients with no prior prednisolone use, both current and former users of prednisolone had increased risk of pneumonia hospitalization with adjusted ORs of 9.03 (95% CI: 8.23-9.90) and 1.96 (95% CI: 1.96-2.04), respectively. Similarly in the DANBIO cohort,, current and former users of prednisolone had increased risk of pneumonia hospitalization with unadjusted ORs of 7.93 (95% CI: 6.26-10.05) and 1.73 (95% CI: 1.48-1.79) and after adjusting for comorbidity ORs of 6.91 (95% CI: 5.43-8.79) and 1.70 (95% CI: 1.57-1.83), respectively. Adjusting for disease activity did not lower the risk.

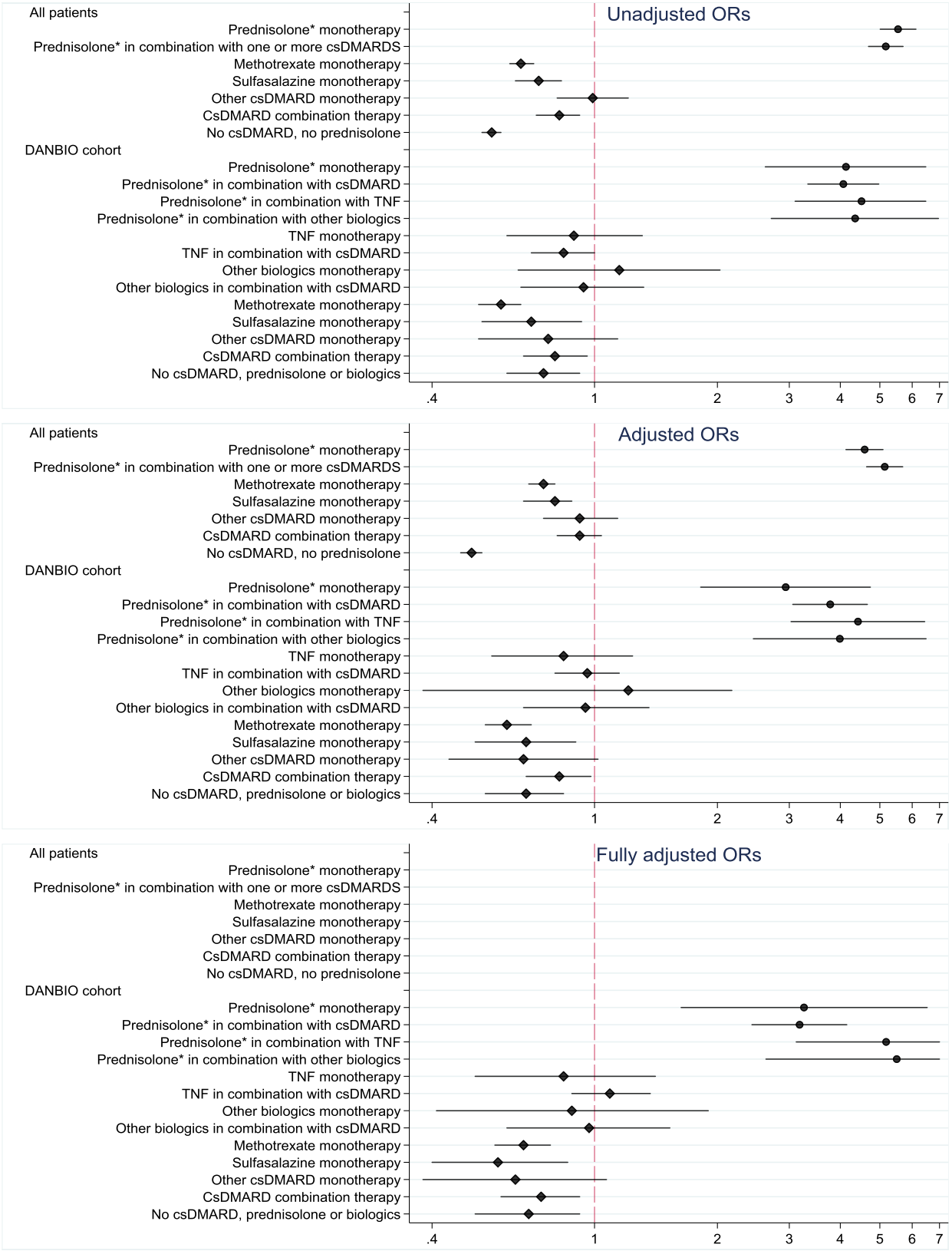

Figure 2. ORs and 95% CIs for hospitalization with pneumonia according to preadmission RA therapy. Middle panel adjusted for comorbidity and alcoholism (adjusted). Lower panel adjusted for disease activity as well (fully adjusted).

4.2. Study 2

A total of 52,577 patients were hospitalized for pneumonia between 1997 and 2011. Among these, 1,220 (2.3%) had a diagnosis of RA. Of the 1,220 RA patients, 637 had a single hospital contact registered with a diagnosis of RA, 255 patients had two registrations and 328 patients had three or more registrations in the DNPR. The PPV of an RA diagnosis was 88% (95% CI: 83-93%). In patients with three or more registrations, 98% of the RA diagnoses were confirmed, whereas the proportion of patients with a confirmed diagnosis among those with only one registration was 83%. The ACR 1987 criteria for RA were fulfilled by 81 (42.6%) patients.

Mortality rates and crude and adjusted HRs for 90-day morality following hospitalized mortality are presented in Figure 3.

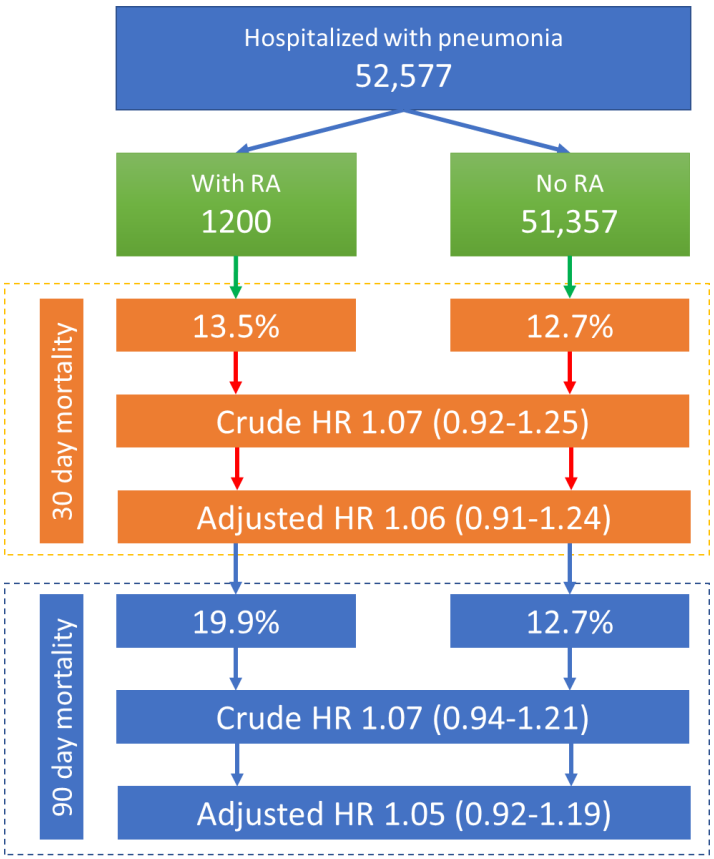

Figure 3: Hazard ratios (HR) shown with 95% confidence intervals were calculated using cox proportional hazards model. If indicated adjusted for comorbidity, alcoholism and antibiotic use prior to admission to hospital.

Among RA patients, the 90-day pneumonia mortality decreased from 22.0% in 1997-2001 to 19.2% and 19.4% in 2002-2006 and 2007-2011, respectively. A similar decrease was found among non-RA patients, suggesting an overall improved prognosis for pneumonia over time. In the stratified analysis of patients with or without lung disease, no increased mortality was found neither when comparing RA patients with chronic lung disease with non-RA patients with chronic lung disease,

nor when comparing RA patients without chronic lung disease with non-RA patients without chronic lung disease.

CRP measurements within 30-90 days prior to admission were available for 704 (58%) RA patients. When categorized according to CRP level 90-day mortality in the low-CRP group was 5.7% compared with 9.7% and 28.1% in the groups with intermediate or high CRP levels, respectively. Using low-CRP group as reference, we found crude 90-day HRs for mortality in the intermediate and high CRP groups to be 1.74 (95% CI: 0.70-4.33) and 5.58 (95% CI: 2.45-12.69), respectively. When adjusted for prednisolone prescriptions filled within 3 months prior to admission, sex, age, level of comorbidity, alcoholism, and prescribed antibiotics, 90-day HR was 1.68 (95% CI: 0.67-4.18) and 4.91(95% CI:2.15-11.2). A numerical increase in CRP by 10 mg/L predicted an increase in mortality of 4% (95% CI: 2-6%).

Data on platelet counts measured 30-90 days prior to admission were available for 681 (56%) RA patients. Compared with patients with normal platelet counts, the crude 90-day HR for mortality was 1.84 (95% CI: 1.28-2.66) in patients with platelet count $\geq 400 \cdot 10^9$/L with a corresponding adjusted 90-day HR of 1.84 (95% CI: 1.27-2.66). An increase in platelet count of $20 \cdot 10^9$/L predicted an increase in 90-day mortality of 3% (1-5%).

RA patients with at least one prescription for prednisolone within 3 months prior to hospitalization had a more than 40% increased 90-day all-cause mortality compared with RA patients treated with methotrexate. Compared with RA patients treated with methotrexate as monotherapy, RA patients who did not receive any RA therapy had a crude 90-day HR for mortality of 1.60 (95% CI: 0.93-2.76) and when adjusted for sex, age, level of comorbidity, alcoholism and antibiotic use prior to admission 90-day HR for mortality was 1.35 (95% CI: 0.85-2.14). Treatment with biologics did not increase mortality.

Ninety-day all-cause mortality in patients with rheumatoid arthritis following hospitalization for pneumonia according to disease activity and treatment with prednisolone are presented in Table 7.

Table 7	No prednisolone + low CRP[2]	No prednisolone + high CRP[2]	Prednisolone[1] + low CRP[2]	Prednisolone[1] + high CRP[2]
Number of patients (N)	64	310	42	288
All-cause mortality at 90 days, n (%)	5 (7.8%)	56 (18.1%)	1 (2.4%)	74 (25.7%)
Crude HR for 90-day mortality	1 (ref)	2.46 (0.98-6.14)	0.29 (0.03-2.55)	3.57 (1.44-8.83)
Adjusted[3] HR for 90-day mortality	1 (ref)	2.35 (0.94-5.87)	0.29 (0.03-2.52)	3.09 (1.25-7.65)

Data are presented as hazard ratios (HR) with 95% CI for all-cause mortality.
1 Treatment with prednisolone 0-3 months prior to admission.
2 CRP levels were measured 30-90 days prior to pneumonia admission with a value of 8 mg/L used threshold.
3 Adjusted for sex, age, level of comorbidity, alcoholism, and antibiotic use before admission

4.3. STUDY 3

A total of 387,796 patients (median age 71 years) were hospitalized for pneumonia in Denmark between 1997 and 2017. Among these 842 (0.2%) had AS. AS patients were younger than non-AS patients (median age 65 vs. 71 years) and had higher comorbidity including higher prevalence of chronic lung disease. Among AS patients, 57.6% had one or more comorbidities compared to 53.3% among non-AS patients. The median duration of hospital stay for patients with AS was 6 days (IQR: 3-15) compared to 7 days (IQR: 4-12) for non-AS patients.

Mortality rates and crude and adjusted HRs for 90-day morality following hospitalized mortality are presented in figure 4.

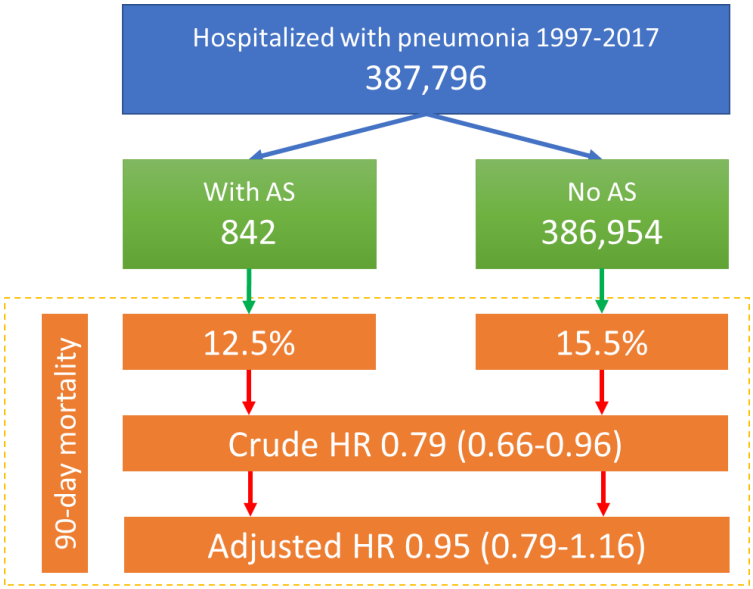

Figure 4: 90-day mortality. Hazard ratios (HR) with 95% CI. If indicated adjusted for sex, age and level of comorbidity.

The 90-day mortality in AS patients tended to be highest in the first period with a rate of 13.9 (95% CI: 10.0-18.5) compared to 11.8% (95% CI: 9.3-14.7) in the second period, while among non-AS patients, the 90-day mortality remained steady across the two calendar periods with rates of 15.6 and 15.4%,respectively.

The 90-day post-discharge readmission rates were 27.3% in AS and 25.4% in non-AS patients, with a corresponding adjusted HR of 1.12 (95% CI: 0.98-1.27). The risk of pulmonary complications among AS patients compared to non-AS patients decreased over time with adjusted HRs of complications for the first and second period of 1.63 (95% CI: 0.82-3.27) and 0.62 (95% CI: 0.31-1.23), respectively.

Prior to admission, 185 (22%) of the AS patients had at least one registration in DANBIO. In 133 patients, the last registration was within one year prior to admission. BASDAI measurements within one year prior to admission were available for 110 patients. High preadmission BASDAI was not associated with increased mortality following pneumonia. Compared with the group with low BASDAI (< 4), we found crude and adjusted 90-day HR for mortality with BASDAI >4 of 1.00 (95% CI: 0.95-1.05) and 0.99 (95% CI: 0.94-1.05), respectively.

Among AS patients 18 (2%) were treated with one or more csDMARDs, 87 (10.3%) were treated with anti-TNFα monotherapy and 44 (5.2%) received a combination of anti-TNFα and csDMARDs. The 90-day mortality rate was higher among non-treated (13.6%) than patients treated with csDMARD (5.6%), Anti-TNF (5.8%) or anti-TNFα and csDMARD in combination (6.8%),

respectively. Neither anti-TNFα monotherapy, treatment with csDMARDs or anti-TNFα therapy in combination with one or more csDMARDs were associated with increased mortality. The low number of exposed hampered our ability to do adjust for potential confounding factors.

4.4. ADDITIONAL MATERIAL

At pneumonia admission, a larger proportion of the RA patients had prior CVE 17.9% (95% CI: 15.8-20.1) vs 14.9% (95% CI: 14.9-15.2) of non-RA patients. The risk of new CVE 1-7 days after being discharged following hospitalization for pneumonia was increased in RA patients with corresponding crude and adjusted HRs for CVE of 2.50 (95% CI: 1.27-4.89) and 2.30 (95% CI: 1.17-4.50), respectively. The risk declined over time and after 90 days we found corresponding crude and adjusted HRs for CVE of 1.26 (95% CI: 0.82-1.92) and 1.18 (95% CI: 0.78-1.81), respectively. The data are presented in table 8.

Table 8. CVE following hospitalized pneumonia

	RA N (%)	Non-RA N (%)	Crude HR (95%CI)	Adjusted HR[2] (95%CI)
N	1220	51172		
Patients with CVE on or 1-7 days after admission[1]	9 (0.74)	170 (0.33)	2.50 (1.27-4.89)	2.30 (1.17-4.50)
Patients with CVE 1-30 days after admission	14 (1.15)	427 (0.83)	1.56 (0.91-2.65)	1.40 (0.82-2.39)
Patients with CVE 1-90 days after admission	22 (1.8)	818 (1.59)	1.26 (0.82-1.92)	1.18 (0.78-1.81)

1 Admission for pneumonia
2 Adjusted for sex, age, level of comorbidity, prior cardiovascular events, alcoholism and antibiotics before admission
CVE: cardiovascular event

5. STRENGTHS AND WEAKNESSES OF THE STUDIES

Observational studies are prone to bias, which broadly can be classified as selection bias, information bias, and confounding. Below, we discuss potential sources and directions of bias in the three studies.

5.1. SELECTION BIAS

"Selection biases are distortions that results from procedures used to select subjects and from factors that influence study participation".[167] As a result, the association between exposure and outcome is different among the study participants compared with non-participants.

Study 1

Selection bias could have occurred if the inclusion of cases and controls depended on their exposure. Both cases and controls were diagnosed with incident RA between January 2004 and December 2016 and the controls were sampled using the density sampling technique. We had 57 unmatched cases and the loss of these cases from the analysis could have reduced the precision of the estimates. However, the number of excluded cases is small, and we have no reason to suspect the lacking controls was dependent on exposure status and therefore introduced selection bias. We can't rule out that RA patients with high disease activity and pneumonia were more likely to be admitted for pneumonia, since the combination of high disease activity an infection might make it harder for them to cope at home, whereas RA patients with low disease activity and pneumonia might be treated by their general practitioner (GP). This could lead to an exaggerated estimate of the effect of disease activity on pneumonia risk.

For the sub-group registered in DANBIO it's possible that they differed from the rest of the RA patients. Since patients registered in DANBIO are required to fill out patient reported outcome measures (PROM), when seen at the outpatients clinics, patients who are not able to do this, for instance because of dementia, are not all ways included in DANBIO. In addition registration of patients treated with biologics has been mandatory for several years, so the completeness of data concerning patients treated with biologics is likely to be more complete, than for other therapies. However, since controls also had to be registered in the DANBIO and therefore would represent exposure status in the subgroup that gave rise to the DANBIO pneumonia cases, we do not expect selection bias because of this.

Studies 2 and 3

In cohort studies, selection bias can occur if loss to follow-up depends on exposure and/or outcome. In our two populations based cohort studies the participants were defined by a first-time primary diagnosis of pneumonia in the DNPR. It is unlikely that any coding errors in the DNPR, leading to inclusion into the cohort or exclusion from the cohort were related to exposure and thus will not

give rise to selection bias. However, patients with mild RA or AS mild disease might have been missed if they were not seen at hospital clinics and therefore not given the diagnoses in the DNPR. Since the treatment guidelines for RA treatment advocate early treatment with csDMARDs, which are usually administered at hospital clinics, these patients most likely account for only a limited number of patients. There is however, no reason to suspect that their mortality following pneumonia hospitalization should be higher than those of the AS or RA patients that we captured by our data sources and thus included in the studies.

Since the studies in this thesis were done using data from population-based medical and administrative registries with virtually complete follow-up, selection-bias due to loss-of follow up was not a concern.

5.2. INFORMATION BIAS

Information bias is caused by measurement errors in the information needed to estimate an effect.[167] These errors may result in misclassification of the exposure, the outcome, or the confounders and can be either evenly distributed among comparison groups (non-differential misclassification) or unevenly distributed among comparison groups (differential misclassification).

Study 1

In our case-control study, data on RA was ascertained in the same way for cases and controls, as were information on RA therapy and disease activity. Ibfelt et al. found a high proportion of true RA cases (96%) in DANBIO, while the proportion of true RA cases in the DNPR was 79% (if the patients were diagnosed at a department of rheumatology and had two registrations within 90 days).[168] Cases included in the study were identified using hospital diagnoses of pneumonia. A previous study found a PPV of 90% (95% CI: 82-95%) for pneumonia if the diagnosis were recorded in the DNPR .[160] However, since RA patients receiving csDMARDs and/or anti-TNFα therapy are closely monitored (both with clinical controls and with regular lab tests) they may have been more likely to be admitted with pneumonia than RA patients being managed without these treatments (differential misclassification). This could lead to an overestimation of the risk for being hospitalized with pneumonia when treated with CSDMARDs and/or biologics.

Misclassification of exposure (the different RA therapies) could have influenced our results. But data on medication was ascertained from the DNPR, the DNDRP and DANBIO in the same way for

both cases and controls. We used prospectively collected data thereby eliminating the risk of recall bias.

Studies 2 and 3

Both studies were population based cohort studies including all patients hospitalized with a first-time primary pneumonia. The diagnosis of pneumonia was based on discharge diagnosis from the DNPR, where this diagnose have been found to have a PPV of 90% (95% CI: 82-95%).[160] We have no reason to believe that the PPV differs in RA and non-RA patients. In our validation study the PPV of an RA diagnosis in the DNPR was 88% (95% CI: 83-93%). To our knowledge no validation of the AS diagnosis in the DNPR exists. The diagnosis of AS requires x-rays and clinical assessment by a rheumatologist and we believe that the PPV for AS in the DNPR is at least as high as for RA. However, if the completeness of AS in DNPR is low, some of the non-AS pneumonia could have an unregistered AS which could lead to a more conservative estimate– however since AS is a relatively rare disease we do not expect this to be a substantial problem.

Misclassification of mortality is unlikely. The CRS is updated daily and contains the exact date of death.

In study 3 we evaluated the 90-day complication rate. Information on complications was retrieved form DNPR and may not be entirely correctly coded. However, a PPV of 90.6% (95% CI: 86.0–94.1) has been found for pleural empyema[169]. We do not expect complications to be coded differently among AS patients and non-AS patients. It is however, possible - due to increased surveillance - that patients with AS were more likely to have pulmonary complications diagnosed compared to non-AS patients. This could have resulted in an overestimation these complications among the AS patients.

Finally, the diagnosis of comorbidities and registration of these in the DNPR may have differed between the RA/AS patients and the non-RA/AS patients in the two cohort studies if the RA/AS patients had been more frequently hospitalized prior to the admission for pneumonia, and as a consequence had their comorbidity coded more completely. On the other hand, it is also possible that patients with other chronic conditions and contact to the health care system due to these conditions might get diagnosed with RA or AS earlier than others. Such misclassification of potential confounders would result in residual confounding (see below).

5.3. CONFOUNDING

Confounding is a distortion of the estimates, which is induced by a third factor associated with both the exposure and the outcome, but which is not an intermediate between the exposure and the outcome on the causal pathway.[170]

We considered sex and age to be potential confounders. In **study 1** we controlled for the effect of these variables by matching cases and control on age and sex and using conditional logistic regression for analysis. In addition we stratified analyses by both sex and different age groups. In **study 2 and 3** we adjusted for both age and sex.

For all three studies we considered comorbidities as potential confounding factors. To control for comorbidity we used the Charlson morbidity index, which has been validated for the prediction of mortality following hospitalization.[165;171] Residual confounding may exist due to misclassification of the conditions included in the CCI due to erroneous coding or from differences in coding related to RA or AS status. As mentioned above, in a previous study, the coding in the DNPR for the 19 Charlson conditions was found to have an overall PPV of 98%.[166] Still, the index has not been validated for predicting the occurrence of subsequent diseases and may therefore not be considered optimal for adjustment of comorbidities in our studies assessing pneumonia risk.

Unfortunately we did not have data regarding lifestyle factors such as smoking, body mass index, and alcohol use. Smoking is linked to the development and severity of RA.[172] Since smoking is associated with increased risk of mortality following hospitalization for pneumonia among smokers[173], this could lead to an overestimation of the relative mortality when comparing RA patients to non-RA patients. However, it also possible that the prevalence of smoking was high among the non-RA patients in **study 2**, since smoking is an important risk factor for pneumonia.[4] Still, the possible confounding role of tobacco smoking was reduced by controlling for chronic obstructive pulmonary disease in both **studies 1 and 2**. In **study 2** we also stratified the analysis according to the presence of chronic lung disease. We also adjusted for alcoholism-related diagnoses. Inclusion of these diagnoses into our model did however, not affect our estimates materially.

In study 1, *confounding by indication* may have influenced our result. Prednisolone treated patients appears to have higher risk of pneumonia hospitalisation. But the patients may have been prescribed prednisolone due to high disease activity, making them more susceptible to pneumonia. To further

examine the association between this potential confounder and risk of pneumonia, we examined how the risk of pneumonia varied depending on time since prednisolone prescription. If no *confounding by indication* was present we would expect a gradual decline to the risk observed among non-prednisolone users as the period from prescription to admission increased. We did find a gradual decline, but the risk, even when patients where prescribed prednisolone more than 180 days prior to admission, did not reach the level of non-prednisolone users. This may suggest some element of *confounding by indication.*

Importantly, we were able to adjust for disease activity in our analysis in the DANBIO subgroup – and except for patients between 30 and 44 years – the risk in prednisolone users remained substantially increased after adjusting for disease activity. This speaks against confounding by indication as the only explanation of our convincing estimates.

In **study 3**, neither treatment with anti-TNFα and csDMARDs nor disease activity was associated with increased pneumonia mortality. But the low number of exposed hampered our ability to adjust for potential confounding factors.

Recent studies have indicated that NSAID exposure at the early stage of community-acquired pneumonia is associated with a more complicated course and worse outcomes, probably because NSAIDs mask initial symptoms and delay therapy.[174;175] Since NSAIDs are considered first line treatment in AS, it is likely that a large proportion of AS patients in our study received NSAIDs. Unfortunately, we lacked information on use of NSAIDs and we were unable to examine whether pneumonia prognosis varied by use of these drugs. However, we did not find an increased mortality among AS patients compared to patients without AS, which makes it unlikely that NSAIDs causes significantly increased mortality among AS patients following pneumonia.

5.4. RANDOM ERROR

Random error relates to statistical precision and may be reduced by averaging over many observations. We presented all estimates in these studies accompanied by 95% CI (meaning that if the study was unbiased and was repeated numerous times, 95% of the times the estimate would be located within the confidence interval). The large size of our studies reduces the impact of random error. However, estimates from some of the smaller subgroup analysis should be interpreted with care as indicated by wide CIs. In the additional material concerning CVE after hospitalized pneumonia, the number of events is low and the results likewise should be interpreted with care.

6. DISCUSSION

RA: Risk of infection

In study 1, which included more than 6,500 RA pneumonia patients and 32,000 RA controls, we found that RA patients treated with prednisolone had an increased risk of hospitalization with pneumonia compared to RA patients not treated with prednisolone.

These findings are consistent with previous studies [94;97;103], which show that prednisolone increase the risk of infection in RA patients. We add to this knowledge by showing, that this risk was present regardless of concomitant csDMARD or biologics and also after adjustment for comorbidities. In addition, by showing that the increased risk was present across age groups from 30 years and above we provide evidence that this risk is also present among younger RA patients. High RA disease activity has previously been associated with increased infection risk.[88;90] We thus add to previous findings of an association between glucocorticoid therapy and both serious and non-serious infections[94;97;103] by showing that even after adjusting for RA disease activity prior to admission, treatment with prednisolone increases the risk of pneumonia hospitalization substantially.

RA: Prognosis after infection

In study 2 including more than 50,000 patients hospitalized due to pneumonia, we found that active arthritis negatively influenced the outcome.

RA patients with high disease activity are more likely to undergo intensive treatment with prednisolone, combination therapy with csDMARDs and/or biologics. This leads to concerns about the risk of severe infections associated with intensive treatment with corticosteroids and biologics.[84] On the other hand, if patients with untreated RA disease activity have similar or even worse infection outcomes as patients receiving immunosuppressive drugs, this would support the strategy of intensive treatment even in RA patients prone to infections. Since flares of RA are often treated with prednisolone, it may be difficult to separate the effect of prednisolone from the effect of disease activity. In this study, we were able to compare pneumonia outcomes in RA patients with and without prednisolone treatment within strata of patients with similar disease activity. Prednisolone treatment in patients with low disease activity was not associated with increased mortality, in contrast to patients with high disease activity who had increased mortality irrespective

of prednisolone use, thus providing new evidence that high RA disease activity not only increases the risk of pneumonia, but also predicts poorer outcome following pneumonia.

AS: Prognosis after infection

Despite the association between AS and lung diseases such as COPD, interstitial lung disease and chest wall abnormalities[132;133], study 3, to our knowledge, is the first to investigate the influence of AS on the prognosis of pneumonia. In this population-based study including 842 AS patients and more than 350,000 non-AS patients hospitalized due to pneumonia, we found no increased pneumonia mortality among AS patients. In addition, no increased risk of complication or readmission was detected from 2007-2017.

Among AS patients internally, neither treatment with anti-TNFα and csDMARDs nor disease activity was associated with increased pneumonia mortality. But the numbers of exposed were low and larger studies are needed to confirm these findings.

RA: Recent pneumonia and the risk of CVE

We found an increased risk of new CVE 1-7 days after being discharged following hospitalization for pneumonia in RA patients. The risk declined over time. To our knowledge no other studies exist on RA patients and their risk of cardiovascular events following pneumonia, but several studies have shown an increased risk for cardiovascular events following infection in patients in general[112-115]and others studies have found an increased risk of CVE following pneumonia.[116-118] This needs to be studied further: It is likely that recent infection may trigger myocardial infarction and stroke, and this mechanism may be particularly important in patients with underlying low-grade inflammation such as RA.

7. MAIN CONCLUSIONS

7.1. STUDY 1

Treatment with prednisolone both as monotherapy and in combination with biologics or csDMARDs was associated with substantially increased risk of pneumonia hospitalization, even after adjusting for both RA disease activity and comorbidity. The risk of for pneumonia hospitalization among current users of prednisolone increased with age but was present across all age groups from the age of 30 and above. In contrast, we found no increased risk for pneumonia in

patients treated with csDMARDs and/or biologics without prednisolone. This indicates that concerns about the risk RA disease activity poses regarding infection, should not lead to treatment with prednisolone but rather seek other therapy strategies.

7.2. STUDY 2

RA patients do not have a higher mortality following hospitalization than patients without RA. However, high preadmission RA disease activity predicts increased mortality following hospitalized pneumonia in patients with or without prednisolone use. This suggests that high RA disease activity per se is an important *prognostic* factor in RA patients with pneumonia and should be controlled. RA patients with at least one prescription for prednisolone within 3 months prior to hospitalization had a more than 40% increased 90-day all-cause mortality compared with RA patients treated with methotrexate. Reassuringly, treatment with biologics and csDMARDs, either as a monotherapy or in combination, did not predict increased pneumonia mortality.

7.3. STUDY 3

Despite the association between AS and lung disease, AS patients did not have higher mortality than non-AS patients following hospitalized pneumonia after adjustment for confounding factors. In addition, no increased risk of complication or readmission was detected from 2007-2017. Reassuringly, among AS patients internally, neither treatment with anti-TNFα and csDMARDs nor disease activity was associated with increased pneumonia mortality, but the numbers of exposed were low and larger studies are needed to confirm our results.

8. PERSPECTIVES

Our findings have potential impact on daily clinical practice. Our data provide strong evidence that treatment with prednisolone both as monotherapy and in combination with biologics or csDMARDs are associated with substantially increased risk of pneumonia hospitalization, even after adjusting for both comorbidity and RA disease activity. The results indicate that to prevent severe infections such as pneumonia, the clinician should avoid the use of prednisolone. Concerns about the risk RA disease activity poses in regard to infection, should not lead to treatment with prednisolone but rather seek other therapy options.

To prevent poorer outcomes following hospitalized pneumonia, clinical focus should be on the risk of uncontrolled disease activity. Our study reveals that high preadmission RA disease activity

predicts increased mortality following hospitalized pneumonia regardless of prednisolone use. If RA patients with high disease activity are treated more aggressively to obtain remission/low grade disease activity, this might lead to better outcomes for RA patients with infections. Our data were unable to answer whether or not immunosuppressive RA medications should be stopped in case of severe infection, since we did not have information on in-hospital treatment following admission.

Despite the association between AS and lung disease, we found no increased pneumonia mortality among AS patients and no increased risk of complication or readmission. The relatively low number of patient for whom we had information on disease activity should lead to caution when interpreting the results. Future studies should focus on disease activity and on incorporating information on NSAID and prednisolone into the analysis.

9. SUMMARY

Rheumatoid Arthritis (RA) and Ankylosing Spondylitis (AS) are common chronic diseases requiring lifelong regular monitoring. Most patients receive disease modifying anti-inflammatory treatment presumably leaving them more prone to infections. However, few data have described the influence of RA or AS on pneumonia risk and outcome. To improve our understanding of infection risk and prognosis in patients with RA and AS this thesis used Danish medical databases to examine the risk for, and prognosis after, pneumonia among these patients taking disease activity and pharmacotherapy into account.

Particularly, we examined if RA was associated with increased mortality in patients hospitalized with pneumonia, and how pre-admission RA disease activity and pharmacotherapy influenced prognosis (study 2). We examined how RA treatment affected risk of hospitalization for pneumonia (study 1) and we examined if AS was associated with increased mortality, complications and readmission in patients hospitalized with pneumonia (study 3).

In study 1, we included 6,672 RA patients with a first-time hospitalization for pneumonia and 32,483 RA patients matched on gender, age and disease duration without pneumonia as controls. Of these, 2,093 cases and 9,805 controls had detailed information on both treatment and disease activity though a registration in DANBIO prior to pneumonia admission. Preadmission use of prednisolone, was associated with an increased risk of hospitalization for pneumonia compared with other therapy groups. ORs adjusted for level of comorbidity and alcoholism–related conditions were

4.59 (95% CI: 4.1-5.09) for prednisolone as monotherapy and 5.14 (95% CI: 4.64-5.69) for prednisolone in combination with other conventional synthetic Disease Modifying Anti-Rheumatic Drugs (csDMARDs). Among patients registered in DANBIO, prednisolone in combination with TNF-inhibitors or other biologics was associated with increased risk compared to the other therapy regimens. Adjusting for comorbidity and disease activity did not change the ORs substantially. Reassuringly, we found no increased risk for pneumonia in patients treated with csDMARDs and/or biologics without prednisolone.

In study 2, we included 52,577 patients with first-time hospitalized pneumonia of whom 1,220 (2.3%) had RA. The 30- and 90-day mortality did not differ substantially between patients with and without RA. Among RA patients, however, preadmission RA activity (measured either as CRP or platelet levels 30-90 days before pneumonia admission) was associated with increased mortality. RA patients with low preadmission CRP who used prednisolone had lower mortality than patients with low preadmission CRP without prednisolone use (adjusted HR for 90-day mortality was 0.29 (95% CI: 0.03-2.52)). In contrast, patients with high disease activity and use of prednisolone and patients with high disease activity and no prednisolone had 2- and 3-fold higher 90-day mortality, respectively.

In study 3 we included 387,796 patients with first-time hospitalized with pneumonia in Denmark of whom 842 (0.2%) had AS. Patients with AS did not have increased pneumonia mortality compared with non-AS pneumonia patients. The 90-day mortality in pneumonia patients was 12.5% in AS patients and 15.5% in non-AS pneumonia patients, with crude and adjusted 90-day HRs of 0.79 (95% CI: 0.66-0.96), and 0.95 (95% CI: 0.79-1.16), respectively. The 90-day post-discharge readmission rates were 27.3% in AS patients and 25.4% in non-AS patients, with a corresponding adjusted HR of 1.12 (95% CI: 0.98-1.27). The risk of pulmonary complications among AS patients compared to non-AS patients decreased over time and no increased risk of complication was detected from 2007-2017.

10. DANSK RESUME

Leddegigt og rygsøjlegigt (morbus Bechterew) er kroniske lidelser, der kræver livslang monitorering og behandling med lægemidler som kan øge risikoen for infektioner. Der eksisterer kun sparsom viden om den betydning, det at have enten leddegigt eller rygsøjlegigt, har for risikoen for at få lungebetændelse og prognosen, hvis man får lungebetændelse. For at få en større forståelse

for risiko og prognose for infektion blandt disse patienter, har vi i denne afhandling brugt danske registre og databaser til at undersøge risikoen for at få lungebetændelse og prognosen, hvis man får det, inklusiv den betydning behandlingen af gigtsygdommen og sygdomsaktiviteten har.

Vi undersøgte om leddegigt var forbundet med øget dødelighed hos patienter indlagt med lungebetændelse og om gigtpatienternes gigtaktivitet og den behandling de havde fået for deres leddegigt op til indlæggelsen havde betydning for dødeligheden (studie 2). Vi undersøgte om den medicin patienter med leddegigt får for deres sygdom øger risikoen for lungebetændelse (studie 1) og om patienter med rygsøjlegigt har højere dødelighed, når de bliver indlagt med lungebetændelse end patient er der ikke har rygsøjlegigt og højere risiko for komplikationer og genindlæggelse (studie 3).

I studie 1 inkluderede vi 6.672 leddegigt patienter indlagt med lungebetændelse for første gang og 32.483 kontroller (leddegigtpatienter der ikke var indlagt med lungebetændelse) matchet på køn, alder og sygdomsvarighed. For 2.093 af de indlagte og for 9.805 af kontrollerne havde vi deltaljeret information om sygdomsaktivitet of medicin op til indlæggelsen fra DANBIO. Behandling med prednisolon var associeret med øget risiko for at blive indlagt med lungebetændelse sammenlignet med behandling uden prednisolon. Efter justering for komorbiditet og alkohol-relaterede tilstande fandt vi en OR på 4,59 (95% CI: 4,1-5,09) for behandling med prednisolon alene og 5,14 (95% CI: 4,64-5,69) for prednisolon behandling i kombination med csDMARDs. Blandt de patienter der var registeret i DANBIO var prednisolon alene og i kombination med biologiske præparater også associeret med øget risiko for at blive indlagt med lungebetændelse – og justering for komorbiditet og sygdomsaktivitet ændrede ikke risikoen markant. Vi fandt ingen øget for risiko for at blive indlagt med lungebetændelse blandt patienter behandlet med biologisk medicin eller csDMARDs.

I studie 2 inkluderede vi 52,577 patienter med som var indlagt med lungebetændelse for første gang. Blandt dem havde 1.220 (2,3%) leddegigt. Hverken 30- eller 90 dages dødeligheden blandt patienter med leddegigt var væsentlig forskellig fra patienter uden leddegigt. Blandt patienterne med leddegigt var høj sygdomsaktivitet – bedømt ved tilstedeværelse af forhøjet CRP eller forhøjet antal blodplader 30-90 dage før indlæggelsen - associeret med øget dødelighed. Leddegigtpatienter med lav CRP og som havde fået prednisolon havde lavere dødelighed end patienter med lav CRP, der ikke fik prednisolon (justeret HR for 90-dages dødelighed: 0,29 (95% CI: 0,03-2,52). Mens patienter med høj sygdomsaktivitet før indlæggelsen, som havde fået prednisolon havde en 2 gange

højere dødelighed og patienter med høj sygdomsaktivitet som ikke havde fået prednisolon havde en 3 gange øget dødelighed.

I studie 3 inkluderede vi 387.796 patienter som var indlagt med lungebetændelse for første gang. Af disse havde 842 (0,2%) rygsøjlegigt. Patienterne med rygsøjlegigt havde ikke en højere 90-dages dødelighed efter lungebetændelse sammenlignet med patienterne uden rygsøjlegigt. Efter 90 dage var 12,5% af patienterne med rygsøjlegigt døde mod 15,5% af patienterne uden rygsøjlegigt med justeret HR for 90-dages dødelighed på 0,95 (95% CI: 0,79-1,16). Blandt patienterne med rygsøjlegigt var 27,3 % blevet genindlagt indenfor 90 dage efter udskrivelsen mod 25,4% blandt patienter uden rygsøjlegigt og en justeret HR for genindlæggelse inden for 90 dage på 1,12 (95% CI: 0,98-1,27). Risikoen for lungekomplikationer faldt i undersøgelsesperioden og vi fandt ingen øget risiko for lungekomplikationer blandt patienter indlagt med lungebetændelse i årene 2007 til 2017.

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12. APPENDICES

12.1. CLASSIFICATION CRITERIA

Table 1. The 1987 revised criteria for the classification of RA[13]	
Criterion	Definition
Morning stiffness	Morning stiffness in and around joints lasting at least 1 hour before improvement
Arthritis of 3 or more joint areas	At least 3 joint areas simultaneously have had soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician. The 14 possible areas are right or left PIP, MCP, wrist, elbow, knee, ankle and MTP joints
Arthritis of hand joints	At least 1 area swollen (as defined above in a wrist, MCP or PIP joint
Symmetric arthritis	Simultaneous involvement of the same joint areas (as defined in 2) on both sides of the body (bilateral involvement of PIPs, MCPs, or MTPs is acceptable without symmetry)
Rheumatoid nodules	Subcutaneous nodules, over bony prominences, or extensor surfaces, or in juxtaarticular regions, observed by a physician
Serum rheumatoid factor	Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive in <5% of normal controls
Radiographic changes	Radiographic changes typical of RA on posteroanterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localized in most marked adjacent to the involved joints (osteoarthritis changes alone do not qualify)
For classification purposes, a patient shall be said to have rheumatoid arthritis if he/she has satisfied at least **4 of** these **7** criteria. Criteria **1**through **4** must have been present **for** at least **6** weeks. Patients with **2** clinical diagnoses are not excluded. Designation as classic, definite, or probable rheumatoid arthritis is ***not*** to be made.	

Table 2.The 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis[14]

Target population (Who should be tested?): Patients who
1) have at least 1 joint with definite clinical synovitis (swelling)*
2) with the synovitis not better explained by another disease†
Classification criteria for RA (score-based algorithm: add score of categories A–D;
a score of _6/10 is needed for classification of a patient as having definite RA)‡

Points	
A. Joint involvement§	
1 large joint¶	0
2-10 large joints	1
1-3 small joints (with or without involvement of large joints)#	2
4-10 small joints (with or without involvement of large joints)	3
>10 joints (at least 1 small joint)**	5
B. Serology (at least 1 test result is needed for classification)††	
Negative RF *and* negative ACPA	0
Low-positive RF *or* low-positive ACPA	2
High-positive RF *or* high-positive ACPA	3
C. Acute-phase reactants (at least 1 test result is needed for classification)‡‡	
Normal CRP *and* normal ESR	0
Abnormal CRP *or* abnormal ESR	1
D. Duration of symptoms§§	
_6 weeks	0
_6 weeks	1

* The criteria are aimed at classification of newly presenting patients. In addition, patients with erosive disease typical of rheumatoid arthritis (RA) with a history compatible with prior fulfillment of the 2010 criteria should be classified as having RA. Patients with longstanding disease, including those whose disease is inactive (with or without treatment) who, based on retrospectively available data, have previously fulfilled the 2010 criteria should be classified as having RA.
† Differential diagnoses vary among patients with different presentations, but may include conditions such as systemic lupus erythematosus, psoriatic arthritis, and gout. If it is unclear about the relevant differential diagnoses to consider, an expert rheumatologist should be consulted.
‡ Although patients with a score of _6/10 are not classifiable as having RA, their status can be reassessed and the criteria might be fulfilled cumulatively over time.
§ Joint involvement refers to any *swollen* or *tender* joint on examination, which may be confirmed by imaging evidence of synovitis. Distal interphalangeal joints, first carpometacarpal joints, and first metatarsophalangeal joints are *excluded from assessment*. Categories of joint distribution are classified according to the location and number of involved joints, with placement into the highest category possible based on the pattern of joint involvement.
¶ "Large joints" refers to shoulders, elbows, hips, knees, and ankles.
# "Small joints" refers to the metacarpophalangeal joints, proximal interphalangeal joints, second through fifth metatarsophalangeal joints, thumb interphalangeal joints, and wrists.
** In this category, at least 1 of the involved joints must be a small joint; the other joints can include any combination of large and additional small joints, as well as other joints not specifically listed elsewhere (e.g., temporomandibular, acromioclavicular, sternoclavicular, etc.).
†† Negative refers to IU values that are less than or equal to the upper limit of normal (ULN) for the laboratory and assay; low-positive refers to IU values that are higher than the ULN but ≤ 3 times the ULN for the laboratory and assay; high-positive refers to IU values that are >3 times the ULN for the laboratory and assay. Where rheumatoid factor (RF) information is only available as positive or negative, a positive result should be scored as low-positive for RF. ACPA: anti-citrullinated protein antibody.
‡‡ Normal/abnormal is determined by local laboratory standards. CRP =C-reactive protein; ESR =erythrocyte sedimentation rate.
§§ Duration of symptoms refers to patient self-report of the duration of signs or symptoms of synovitis (e.g., pain, swelling, tenderness) of joints that are clinically involved at the time of assessment, regardless of treatment status.

12.2. DIAGNOSTIC CODES FOR EXPOSURES AND OUTCOMES

Codes for RA:

- ICD-8 codes: 712 excluding 712.09 and 712.49
- ICD-10 codes: M05 and M06

Codes for AS:

- ICD-8 code: 712.4
- ICD-10 code: M45*

Codes for pneumonia:

- ICD 8: 480.xx-486.xx, 0.73.xx, 471.xx
- ICD10: J12.x-J18.x, A481x, A709.x

ICD-10 codes for complication:

- Empyema: DJ86
- Pulmonary embolism: DI26
- Pulmonary abscess: DJ85

ICD-10 codes for CVE:

- I21.x-I23.x
- I63.x except I63.6
- I64.x

12.3. CODES FOR PHARMACEUTICALS

Drug Category	**ATC classification code**	
Antibiotics	J01	
DMARDs	Sulfasalazin	A07EC01
	Leflunomid	L04AA13
	Aurothiomalat-natrium	M01CB01
	Penicillamin	M01CC01
	Chloroquin	P01BA01
	Hydroxychloroquin	P01BA02
	Methotrexat	L01BA01, L04AX03
	Cyklophosphamid	L01AA01
	Ciclosporin	L04AD01
	Azathioprin	L04AX01
	Cellcept	L04AA06
Steroid	H02AB06, H02AB07	
Biologics	L04AB02, L04AB01, L04AB04, L01XC02, L04AA24, L04AB05, L04AB06, L04AC07	
NSAIDs	Etoricoxib	M01AH05
	Naproxen	M01AE02
	Ibuprofen	M01AE01
	Celecoxib	M01AH01
	Indometacin	M01AB01
	Diclofenac	M01AB05
	Parecoxib	M01AH04
	Phenylbutazon	M01AA01
	Dexketoprofen	M01AE17
	Meloxicam	M01AC06
	Tolfenamsyre	M01AG02
	Ketoprofen	M01AE03
	Piroxicam	M01AC01
	Nabumeton	M01AX01
	Dexibuprofen	M01AE14
	Tiaprofensyre	M01AE11
	Tenoxicam	M01AC02
	Etodolac	M01AB08
	Ketorolac	M01AB15
	Lornoxicam	M01AC05
The Anatomical Therapeutic Chemical (ATC) Classification System is used for the classification of drugs according to the system/organ on which they act. Pharmaceuticals are coded in the NPR, DNPR and The Aarhus University Prescription Database according to the ATC.		

12.4. CHARLSON'S INDEX AND ALCOHOL RELATED DISORDERS

Codes used for identifying alcohol related disorders:

ICD8: 291, 303,57710, 57109, 57110

ICD10: F10, G312, G621, G721, I426,K292, K70, K860, Z721

Charlson Index			
Disease category	**ICD8**	**ICD10**	**Score**
Myocardial infarction	410	I21;I22;I23	1
Congestive heart failure	427.09; 427.10; 427.11; 427.19; 428.99; 782.49	I50; I11.0; I13.0; I13.2	1
Peripheral vascular disease	440; 441; 442; 443; 444; 445	I70; I71; I72; I73; I74; I77	1
Cerebrovascular disease	430-438	I60-I69; G45; G46	1
Dementia	290.09-290.19; 293.09	F00-F03; F05.1; G30	1
Chronic pulmonary disease	490-493; 515-518	J40-J47; J60-J67; J68.4; J70.1; J70.3; J84.1; J92.0; J96.1; J98.2; J98.3	1
Connective tissue disease	*712*; 716; 734; 446; 135.99	*M05*; *M06*; M08; M09;M30;M31; M32; M33; M34; M35; M36; D86	1
Ulcer disease	530.91; 530.98; 531-534	K22.1; K25-K28	1
Mild liver disease	571; 573.01; 573.04	B18; K70.0-K70.3; K70.9; K71; K73; K74; K76.0	1
Diabetes type1 Diabetes type2	249.00; 249.06; 249.07; 249.09 250.00; 250.06; 250.07; 250.09	E10.0, E10.1; E10.9 E11.0; E11.1; E11.9	1
Hemiplegia	344	G81; G82	2
Moderate to severe renal disease	403; 404; 580-583; 584; 590.09; 593.19; 753.10-753.19; 792	I12; I13; N00-N05; N07; N11; N14; N17-N19; Q61	2
Diabetes with end organ damage Type 1 Type 2	 249.01-249.05; 249.08 250.01-250.05; 250.08	 E10.2-E10.8 E11.2-E11.8	2
Any tumour	140-194	C00-C75	2
Leukaemia	204-207	C91-C95	2
Lymphoma	200-203; 275.59	C81-C85; C88; C90; C96	2
Moderate to severe liver disease	070.00; 070.02; 070.04; 070.06; 070.08; 573.00; 456.00-456.09	B15.0; B16.0; B16.2; B19.0; K70.4; K72; K76.6; I85	3
Metastatic solid tumour	195-198; 199	C76-C80	6
AIDS	079.83	B21-B24	6

In study 1 and 2 the RA diagnoses marked above under the disease category "Connective tissue disease" are not included when calculating the Charlson Index Score.