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ORIGINAL RESEARCH

Prognosis of pneumonia in patients with rheumatoid arthritis: the role of medication and disease activity prior to admission a population-based cohort study

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ABSTRACT

Objective Patients with rheumatoid arthritis (RA) experience an increased risk of infections, but the prognosis of infections is unclear. We examined if patients with RA have worse outcomes from pneumonia than non-RA individuals.

Methods In a population-based cohort study, we computed 90-day mortality rates and crude and adjusted HRs comparing pneumonia patients with and without RA. Among patients with RA, we evaluated prognostic effects of RA medications including prednisolone and disease activity as assessed by C reactive protein (CRP) or platelet levels measured 30–180 days before admission to avoid any influence from the subsequent infection.

Results Among 52 577 patients hospitalised for the first time with pneumonia, 1220 (2.3%) had RA. The 90-day mortality was 19.9% for patients with RA and 18.9% for non-RA patients (adjusted 90-day HR of 1.05 (95% CI 0.92 to 1.19)). Compared with CRP levels <8 mg/L, CRP levels ≥20 mg/L predicted increased mortality in patients with RA with adjusted 90-day HRs of 4.98 (95% CI 2.19 to 11.36). Compared with methotrexate monotherapy, both prednisolone (HR 1.43 (95% CI 0.91 to 2.22)) and no RA therapy (HR 1.35 (95% CI 0.85 to 2.14)) tended to increase 90-day mortality. Compared with patients who used prednisolone and had low CRP levels, high CRP predicted increased mortality both in patients who used prednisolone (HR 3.09, 95% CI 1.25 to 7.65) and those who did not (HR 2.35, 95% CI 0.94 to 5.87).

Conclusions Overall, RA does not increase mortality following hospitalisation for pneumonia. However, high RA disease activity prior to admission predicts increased pneumonia mortality in patients regardless of prednisolone use.

Key messages

What is already known about this subject?

- Patients with rheumatoid arthritis (RA) have an increased risk of infections, but the prognosis of infections is unclear.

What does this study add?

- In this large population-based cohort study, the overall mortality after hospitalised pneumonia among RA patients was not increased compared with non-RA patients.
- However, we identified a higher mortality among patient with high disease activity prior to pneumonia hospitalisation.
- Reassuringly, treatment with biologics and conventional synthetic disease-modifying antirheumatic drugs, either as a monotherapy or in combination, did not predict increased pneumonia mortality.

How might this impact on clinical practice?

- High RA disease activity rather than RA medication is associated with poorer prognosis after hospitalised pneumonia.

INTRODUCTION AND AIMS

Patients with rheumatoid arthritis (RA) have increased mortality compared with the general population, with age-standardised mortality ratios of 1.2–2.6.[1–6] Major causes of death include cardiovascular disease, lung fibrosis and infections, particularly pneumonia.[4 5 7 8] Thomas *et al* found a standardised mortality ratio for respiratory infections among patients with RA compared with the general population of 1.92 (1.72–2.15) for women and 2.42 (2.28–2.57) for men.[2] Several studies have shown an increased risk of other serious infections requiring hospitalisation in patients with RA.[9–11]

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 patients with RA have worse infection outcomes as well. RA may influence the outcomes of pneumonia and other infections due to the RA disease activity per se, the related comorbidities or the use of

immunosuppressive therapy. Patients with RA with high disease activity are more likely to undergo intensive treatment with prednisolone, combination therapy with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) and biologics. This leads to concerns about the risk of severe infections associated with intensive treatment with corticosteroids and biologics.[11] 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 patients with RA prone to infections.

The purpose of the present study was to examine whether RA is associated with increased mortality in patients who are hospitalised with pneumonia and to evaluate whether RA disease activity with or without treatment with csDMARDs, biologics or prednisolone prior to admission influences the prognosis. We hypothesised that patients with RA have worse outcomes from pneumonia than non-RA individuals and that both high disease activity and the use of prednisolone worsen the prognosis.

PATIENTS AND METHODS

Setting and study population

We conducted a population-based cohort study in the northern and central regions of Jutland, with approximately 1.8 million inhabitants. Data were obtained from medical registries, and since all Danish citizens are assigned a unique personal identification number (CPR) at birth, the data from different registries can be cross-linked at the individual level.[12] The Danish National Patient Register (DNPR) was used to identify patients with pneumonia. Please see the online supplementary file for a thorough description of the DNPR. We included all adult patients (≥16 years) with a first-time primary hospital discharge diagnosis of pneumonia (ICD10: J12.x-J18.x, A481x, A709.x) between January 1997 and 31 December 2011; thus, patients with a prior discharge diagnosis of pneumonia were excluded. The validity of a pneumonia diagnosis in this register has previously been evaluated and found to be high, with a positive predictive value (PPV) of 90% (95% CI 82% to 95%).[13]

Data on RA and validation of the diagnosis

Data on RA were obtained from the DNPR (ICD-8 codes: 712 excluding 712.09 and 712.49, ICD-10 codes: M05 and M06). We reviewed medical records of 190 patients with RA diagnosis and found a PPV of 88% (95% CI 83% to 93%) for true RA; see online supplementary file for more details.

Data on medication

Data on RA treatment were assessed from three healthcare registries: The DNPR, the Aarhus University Prescription Database[14] and DANBIO.[15] Please see the online supplementary file for a thorough description of these databases.

In the DNPR, treatment with csDMARDs and biologics were coded in relation to visits to hospital outpatient clinics. Most of the patients with RA were seen at least annually; therefore, we retrieved information on all the treatments registered within 12 months prior to pneumonia hospitalisation.

From the Aarhus University Prescription Database,[14] we obtained information on filled community pharmacy prescriptions for csDMARDs (see online supplementary file for all of the Anatomical Therapeutic Chemical Classification System codes) within 12 months before pneumonia hospitalisation and prescriptions for prednisolone filled within 3 months before pneumonia hospitalisation. In addition, we obtained information on filled prescription for Non Steroidal Anti-Inflammatory Drugs (NSAIDs).

When a patient with RA is seen by a rheumatologist, a 'visit' is created in DANBIO. A visit consists of information regarding the current functional status, disease activity, treatment, and Visual Analogue Scale scores of pain, fatigue and of the patient and physician's global assessment. For the subgroup of pneumonia patients who were registered in the DANBIO database, we retrieved information from the last visit within 0–180 days before the pneumonia hospitalisation. If the patient had more than one registration in DANBIO within the 180 days, the later instance was used.

Since some RA medications are dispensed at the hospital and some are written as prescriptions, we took this into account when defining RA treatment. A patient was defined as being treated with biologics if there was either a registration in DANBIO or the DNPR with this information. Since methotrexate (MTX) can be administered either orally (prescription) or subcutaneously (dispensed at the hospital), treatment with MTX was defined as a registration in either the DNPR or the Aarhus University Prescription Database. Treatment with leflunomide was similarly defined as a registration in either the DNPR or the Aarhus University Prescription Database. However, all the other csDMARDs and prednisolone treatments were defined as registrations in the Aarhus University Prescription Database.

We categorised all of the patients with RA according to the type of RA medication prior to admission into the following groups: (1) any prednisolone treatment, (2) any biological treatment, (3) MTX monotherapy, (4) other csDMARDs monotherapy, (5) csDMARDs combination therapy and (6) no RA medication. If a patient was treated with therapies from several groups, a hierarchical structure was used: if a patient had received a prescription for prednisolone in the period 0–3 months before pneumonia diagnosis, the patients was categorised in the 'any prednisolone group' irrespective of any other RA medication. Among the remaining patients, those who received any biologics (0–12 months) before the pneumonia diagnoses were categorised in the 'any biologic group'. Patients without prednisolone and biologics were categorised as either 'MTX monotherapy', 'other

csDMARD monotherapy', 'csDMARDs combination therapy' or 'no RA medication'. An overview is presented in online supplementary figure 1. We did not have information on doses for any DMARDs or prednisolone.

For all of the pneumonia patients, we also acquired data on filled prescriptions for antibiotics at any community pharmacy 0–30 days prior to their hospitalisation for pneumonia from the Aarhus University Prescription Database (see the online supplementary file for codes).

Data on disease activity

Previous studies have shown that elevated C reactive protein (CRP) levels and elevated platelet counts are valid markers of RA disease activity.[16–19] Information on CRP and platelets was obtained from the clinical laboratory information system research database. Please see the online supplementary file for a thorough description of this database.

We obtained data on CRP and platelets measured 30–90 days before pneumonia hospitalisation. In cases of more than one measurement made 30–90 days before hospitalisation, the most recent value was selected. Measurements from 1 to 30 days before admission were omitted to avoid any influence from the subsequent infection.

In the subgroup of patients with a visit recorded in DANBIO 0–90 days prior to admission, we used information on disease activity from the latest visit.

Comorbidity data

From the DNPR, we obtained information on previous alcoholism-related diagnoses and the 19 conditions included in the Charlson Comorbidity Index (excluding RA diagnoses) recorded within 10 years before the pneumonia hospitalisation. In a previous study, the coding in the DNPR for the 19 Charlson conditions was found to have an overall PPV of 98%.[20] The index has been validated for the prediction of mortality following hospitalisation.[21 22] We assessed the three comorbidity index levels according to the Charlson Comorbidity Index scores as follows: score of 0, low; score of 1–2, medium and score of 3+, high.

Pneumonia outcome

The primary outcome was death from any cause within 30 and 90 days from the pneumonia hospitalisation. The date of eventual death was ascertained from the Danish Civil Registration System.[12]

Statistical analysis

Pneumonia prognosis in patients with RA versus non-RA

Follow-up time was computed from the date of pneumonia admission until migration, death or 90 days after the admission date, whichever came first. Mortality after 30 and 90 days was estimated for both patients with RA and non-RA. We used Cox regression to compute the crude and adjusted HRs for death within 30 and 90 days following hospital admission to compare patients with RA and non-RA, controlling for sex, age, level of comorbidities, alcoholism and use of antibiotics within 30 days before admission. We additionally stratified the analysis by calendar time for the pneumonia diagnosis (1997–2001, 2002–2006 and 2007–2011) and for chronic lung disease.

Prognostic effect of RA disease activity

In pneumonia patients with RA, we compared 30-day and 90-day mortality according to CRP levels prior to admission (CRP <8 mg/L (reference), 8–19.9 mg/L, >20 mg/L) using Cox regression. Similar analyses were performed for platelet levels (<350×10^9/L (reference), 350–400×10^9/L, >400×10^9/L). To examine if an association between high RA disease activity and mortality could be explained by a higher prevalence of prednisolone use, we conducted disease activity analyses with and without adjustment for prednisolone prescriptions filled within 3 months prior to admission, in addition to sex, age, level of comorbidity, alcoholism and prescribed antibiotics. In addition, we estimated the effect on mortality with numerical increases in CRP levels by 10 mg/L and increases in platelet counts by 20×10^9/L.

In patients with RA with a visit registered in DANBIO 0–90 days prior to pneumonia admission, we compared the mortality between high and low disease activity (ie, those with a Disease Activity Score 28 joints (DAS28) >3.2 and those with a DAS28 <3.2) adjusting for sex, age and level of comorbidity.

Prognostic effect of prednisolone and other medications prior to admission in patients with RA

To evaluate the effect of RA therapy on pneumonia outcome, we categorised patients with RA according to type of RA medication prior to admission. We computed the crude HRs for mortality within 30 and 90 days of using MTX as a reference, since MTX was frequently used and is regarded as a cornerstone of RA treatment. We adjusted for sex, age, level of comorbidities, alcoholism and antibiotic use before admission.

Interaction between prednisolone and disease activity

We examined the prognostic effect of prednisolone separately 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.

Statistical analyses were performed using the Stata V.12.1 statistical software package (StataCorp). HRs are presented as point estimates with 95% CIs.

RESULTS

Descriptive data

A total of 52 577 patients were hospitalised for pneumonia between 1997 and 2011. Among these, 1220 (2.3%) had a diagnosis of RA. Patients with RA were slightly older, were

more often women and had higher comorbidity than non-RA patients. The proportion of patients receiving antibiotics prior to pneumonia admission did not differ by RA status, nor did the duration of the hospital stay (table 1). Prior to admission, 155 (12.7%) of the patients with RA had at least one registration in DANBIO. In 69 patients, the last registration was within 90 days prior to admission.

Mortality in patients with RA versus non-RA

We found a 90-day mortality in pneumonia patients with RA of 19.9% compared with 18.9% in non-RA pneumonia patients. Corresponding crude 90-day HR was 1.07 (95% CI 0.94 to 1.21), and adjusted HR was 1.05 (95% CI 0.92 to 1.19) (table 2).

Among patients with RA, 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. When comparing the 30-day mortality of the patients with RA with the non-RA patients we found adjusted HRs of 1.15 (95% CI 0.84 to 1.57) in 1997–2011, 1.03 (95% CI 0.78 to 1.35) in 2002–2006 and 1.08 (95% CI 0.85 to 1.36) in 2007–2011. The stratified analyses of patients with and without lung disease are presented in table 2.

In the adjusted model for both 30-day and 90-day mortality, the potential confounders male gender, increasing age, comorbidity level and an alcohol-related diagnosis was associated with increased mortality after pneumonia. HR for 90-day mortality for these variables was 1.19 (1.14–1.24) if patients were male, 1.05 (1.05–1.05) for an age increase by 1 year, 1.20 (1.19–1.21) for each increase in comorbidity level and 1.66 (1.51–1.83) if the patient had an alcohol related diagnosis. Prior use of antibiotics was not associated with change in mortality (HR 1.02 (0.98–1.07)). These HR estimates for 30-day mortality were almost identical. In addition, HR for these confounders were similar for patients with RA and non-RA.

Prognostic effect of disease activity in patients with RA

CRP measurements within 30–90 days prior to admission were available for 704 (58%) patients with RA (table 3). In these patients, CRP levels were <8 mg/L in 15.1% of patients, 8–19.9 mg/L in 29.4% of patients and ≥20 mg/L in 55.5% of patients. The 30-day mortality in the group with low CRP levels (<8 mg/L) was 4.7% compared with 6.8% and 17.9% in the groups with CRP levels ranging from 8 to 19.9 mg/L and CRP levels ≥20 mg/L, respectively. Compared with the group with low CRP (<8 mg/L), we found crude 30-day HRs for mortality in the groups with CRP levels ranging from 8 to 19.9 mg/L and CRP levels ≥20 mg/L of 1.45 (95% CI 0.52 to 4.01) and 4.03 (95% CI 1.63 to 9.99), respectively. When adjusted for prednisolone prescriptions filled within 3 months prior to admission, sex, age, level of comorbidity, alcoholism

Table 1 Characteristics of patients with and without rheumatoid arthritis (RA) who were hospitalised for pneumonia from 1997 to 2011 in northern Denmark

	RA	Non-RA
N	1220 (2.3%)	51 357 (97.7%)
Pneumonia 1997–2001	277 (1.8%)	15 011 (98.2%)
Pneumonia 2002–2006	411 (2.3%)	17 657 (97.7%)
Pneumonia 2007–2011	532 (2.8%)	18 674 (97.2%)
Age, median	74 (66–80)	72 (59–81)
16–39 years	18 (1.5%)	4406 (8.6%)
40–49 years	35 (2.9%)	3311 (6.5%)
50–59 years	120 (9.8%)	5739 (11.2%)
60–69 years	249 (20.4%)	8890 (17.3%)
70–79 years	454 (37.2%)	13 176 (25.7%)
80–89 years	306 (25.1%)	12 699 (24.7%)
90–105 years	38 (3.1%)	3136 (6.1%)
Sex		
Women	801 (65.7%)	24 018 (46.8%)
Men	419 (34.3%)	27 339 (53.2%)
Comorbidity		
Congestive heart failure	170 (13.9%)	5269 (10.3%)
Peripheral vascular disease	118 (9.7%)	3811 (7.4%)
Previous myocardial infarction	104 (8.5%)	3443 (6.7%)
Chronic pulmonary disease	291 (23.9%)	10 431 (20.3%)
Cerebrovascular disease	174 (14.3%)	6936 (13.5%)
Haemiplegia	5 (0.4%)	335 (0.7%)
Dementia	17 (1.4%)	1246 (2.4%)
Connective tissue disease	109 (8.9%)	1425 (2.8%)
Peptic ulcer disease	118 (9.7%)	3064 (6.0%)
Diabetes 1 and 2	106 (8.7%)	4024 (7.8%)
Diabetes with end organ damage	65 (5.3%)	2155 (4.2%)
Moderate to severe renal disease	83 (6.8%)	1967 (3.8%)
Any tumour	146 (12.0%)	6914 (13.5%)
Leukaemia	13 (1.1%)	670 (1.3%)
Lymphoma	21 (1.8%)	1160 (2.3%)
Metastatic solid tumour	32 (2.6%)	1568 (3.1%)
Mild liver disease	16 (1.3%)	757 (1.5%)
Moderate-to-severe liver disease	4 (0.3%)	231 (0.5%)
AIDS	<3	70 (0.1%)
Alcoholism-related disorders	17 (1.4%)	2411 (4.7%)

Continued

Table 1 Continued

	RA	Non-RA
Comorbidity Index (level of Charlson Index Score)		
Low (0)	391 (32.1%)	21 487 (41.8%)
Medium (1–2)	543 (44.5%)	19 514 (38.0%)
High (≥3)	286 (23.4%)	10 356 (20.2%)
Duration of hospital stay, median	6 (3–10)	6 (3–10)
Systemic antibiotic therapy before admission	445 (36.5%)	17 094 (33.3%)

and prescribed antibiotics, the 90-day HRs were 1.42 (95% CI 0.51 to 3.95) and 3.64 (95% CI 1.46 to 9.08), respectively. A numerical increase in CRP by 10 mg/L predicted an increase in mortality of 4% (95% CI 2% to 6%). Analyses without adjustment for prednisolone are presented in table 3. They did not differ materially from the above mentioned analyses.

Data on platelet counts measured 30–90 days prior to admission were available for 681 (56%) patients with RA (table 4). Of these, 60.8% had platelet counts $<350\times10^9$/L, 14.2% had platelet counts ≥350 $<400\times10^9$/L and 25% had platelet counts $\geq400\times10^9$/L. Compared with patients with normal platelet counts ($<350\times10^9$/L), the crude 90-day HR for mortality was 1.50 (95% CI: 0.94 to 2.41) in patients with platelet counts $\geq350<400\times10^9$/L and 1.84 (95% CI 1.28 to 2.66) in those with platelet counts $\geq400\times10^9$/L. The corresponding adjusted 90-day HRs were 1.54 (95% CI 0.95 to 2.48) and 1.84 (95% CI 1.27 to 2.66), respectively. An increase in platelet counts of 20×10^9/L predicted an increase in 90 day mortality of 3% (1%–5%).

In the subgroup of patients who had a visit recorded in DANBIO within 90 days prior to admission, mortality was higher in patients with DAS28 >3.2 compared with patients with DAS28 ≤3.2 with a crude HR of 1.57 (95% CI 0.26 to 9.38) and an adjusted HR of 2.29 (95% CI 0.38 to 13.86). However, only 57 patients were included in this analysis, and the precision of the estimates is therefore limited.

Prognostic effect of prednisolone and other medications prior to admission in patients with RA

Compared with patients with RA treated with MTX monotherapy, patients with RA who did not receive any RA therapy had 30-day and 90-day mortality with HRs of 1.60 (95% CI 0.93 to 2.76) and 1.40 (95% CI 0.89 to 2.23), respectively (table 4). When adjusted for sex, age, level of comorbidity, alcoholism and antibiotic use prior to admission, the 30-day and 90-day HRs for mortality were 1.49 (95% CI 0.86 to 2.57) and 1.35 (95% CI 0.85 to 2.14), respectively. Patients with RA with at least one prescription for prednisolone within 3 months prior to hospitalisation had a more than 40% increased 90-day all-cause mortality compared with patients with RA treated with MTX. Treatment with biologics did not increase mortality (table 4). Of the 1220 patients with RA, 394 did not receive RA therapy 0–12 months prior to admission. But 123 of these patients had previously (more than 1 year prior to the admission) been prescribed csDMARDS and 310 of them had been on NSAIDS. The number of patients presented in table 4 with a prescription for NSAID was: MTX monotherapy: 2, any prednisolone: 7, any biologics: 0, other DMARDS as monotherapy: 2, combination therapy (DMARDs): 1 and 19 in the 'No RA medication' medication group.

Table 2 Results of 30-day and 90-day all-cause mortality following hospitalisation for pneumonia in patients with and without rheumatoid arthritis (RA)

	All pneumonia patients		Pneumonia patients with chronic lung disease		Pneumonia patients without chronic lung disease	
	RA	Non-RA	RA	Non-RA	RA	Non-RA
N	1220	51 357	291 (23.9)	10 428 (20.3)	929 (76.1)	40 914 (79.7)
30-day mortality	165 (13.5%)	6521 (12.7%)	37 (12.7)	1335 (12.8)	128 (13.8)	5186 (12.7)
90-day mortality	243 (19.9%)	9679 (18.9%)	62 (21.3)	2118 (20.3)	181 (19.5)	7561 (18.5)
Crude 30-day HR	1.07 (0.92 to 1.25)	1.00 (ref)	1.00 (0.72 to 1.39)	1.00 (ref)	1.10 (0.92 to 1.30)	1.00 (ref)
Adjusted 30-day HR*	1.06 (0.91 to 1.24)	1.00 (ref)	1.04 (0.75 to 1.46)	1.00 (ref)	1.07 (0.90 to 1.28)	1.00 (ref)
Crude 90-day HR	1.07 (0.94 to 1.21)	1.00 (ref)	1.06 (0.82 to 1.36)	1.00 (ref)	1.07 (0.92 to 1.23)	1.00 (ref)
Adjusted 90-day HR*	1.05 (0.92 to 1.19)	1.00 (ref)	1.11 (0.86 to 1.42)	1.00 (ref)	1.03 (0.89 to 1.19)	1.00 (ref)

HRs with 95% CI were calculated using a Cox proportional hazards model.
*Adjusted for sex, age, level of comorbidity, alcoholism and antibiotic use before admission.

Table 3 Results of a subanalysis of 1220 patients with rheumatoid arthritis (RA)

	N	All-cause mortality at 30 days n (%)	HRs 30-day mortality			All-cause mortality at 90 days n (%)	HRs 90-day mortality		
			Crude	Adjusted*	Adjusted†		Crude	Adjusted*	Adjusted†
CRP <8 mg/L	106	5 (4.7)	1 (ref)	1 (ref)	1 (ref)	6 (5.7)	1 (ref)	1 (ref)	1 (ref)
CRP ≥8–19.9 mg/L	207	14 (6.8)	1.45 (0.52 to 4.01)	1.42 (0.51 to 3.95)	1.42 (0.51 to 3.95)	20 (9.7)	1.74 (0.70 to 4.33)	1.68 (0.69 to 4.18)	1.68 (0.67 to 4.18)
CRP ≥20 mg/L	391	70 (17.9)	4.03 (1.63 to 9.99)	3.56 (1.43 to 8.85)	3.64 (1.46 to 9.08)	110 (28.1)	5.58 (2.45 to 12.69)	4.98 (2.19 to 11.36)	4.91 (2.15 to 11.22)
CRP (increase by 10)	704	89 (12.6)	1.04 (1.02 to 1.06)	1.04 (1.02 to 1.06)	1.04 (1.02 to 1.06)	136 (19.3)	1.04 (1.03 to 1.06)	1.04 (1.02 to 1.06)	1.04 (1.02 to 1.06)
Platelets <350×10^9/L	414	48 (11.6)	1 (ref)	1 (ref)	1 (ref)	68 (16.4)	1 (ref)	1 (ref)	1 (ref)
Platelets 350–400×10^9/L	97	15 (15.5)	1.36 (0.76 to 2.43)	1.38 (0.77 to 2.49)	1.39 (0.77 to 2.49)	23 (23.7)	1.50 (0.94 to 2.41)	1.55 (0.96 to 2.50)	1.54 (0.95 to 2.48)
Platelets ≥400×10^9/L	170	27 (15.9)	1.40 (0.87 to 2.24)	1.41 (0.88 to 2.27)	1.42 (0.88 to 2.28)	49 (28.8)	1.84 (1.28 to 2.66)	1.87 (1.29 to 2.71)	1.84 (1.27 to 2.66)
Platelets (increase by 20)	681	90 (13.2)	1.01 (0.98 to 1.04)	1.02 (0.99 to 1.04)	1.02 (0.99 to 1.04)	140 (20.6)	1.03 (1.01 to 1.05)	1.03 (1.01 to 1.05)	1.03 (1.01 to 1.05)

HRs, including 95% CI, were calculated using a Cox proportional hazards model. CRP levels and platelet counts were measured 30–90 days prior to pneumonia admission
All-cause mortality in patients with RA following hospitalisation for pneumonia according to disease activity measured by CRP levels and platelet counts within 30–90 days before pneumonia hospitalisation.
*Adjusted for sex, age, level of comorbidity, alcoholism and antibiotic use before admission.
†Adjusted for sex, age, level of comorbidity, alcoholism, antibiotic use and prednisolone use before admission.
CRP, C reactive protein.

Table 4 Results of all-cause mortality following hospitalisation for pneumonia: a subanalysis of patients with rheumatoid arthritis (RA) and their preadmission treatments for RA with patients receiving methotrexate as a reference

RA therapy		Mortality at 30 days n (%)	HRs 30-day mortality		Mortality at 90 days n (%)	HRs 90-day mortality	
	N		Crude	Adjusted*		Crude	Adjusted*
All	1220	165 (13.5)			243 (19.9)		
Methotrexate monotherapy	143	16 (11.2)	1.0 (ref)	1.0 (ref)	23 (16.1)	1.0 (ref)	1.0 (ref)
Any prednisolone†	526	71 (13.5)	1.23 (0.72 to 2.12)	1.16 (0.68 to 2.01)	121 (23.0)	1.48 (0.95 to 2.31)	1.43 (0.91 to 2.22)
Any biologics	46	1 (2.2)	0.19 (0.02 to 1.42)	0.35 (0.05 to 2.66)	1 (2.2)	0.13 (0.02 to 0.94)	0.21 (0.03 to 1.56)
Other csDMARDS as monotherapy	63	8 (12.7)	1.17 (0.50 to 2.73)	1.24 (0.53 to 2.92)	10 (15.9)	1.01 (0.48 to 2.12)	1.09 (0.52 to 2.29)
Combination therapy (csDMARDs)	48	1 (2.0)	0.18 (0.02 to 1.34)	0.27 (0.36 to 2.06)	3 (6.2)	0.37 (0.11 to 1.22)	0.56 (0.17 to 1.87)
No RA medication	394	68 (17.3)	1.60 (0.93 to 2.76)	1.49 (0.86 to 2.57)	85 (21.6)	1.40 (0.89 to 2.23)	1.35 (0.85 to 2.14)

Patients categorised according to therapy registered within 1 year prior to pneumonia admission.
Each patient was assigned to one group using the hierarchy described in the text and shown in online supplementary figure 1.
*Adjusted for sex, age, level of comorbidity, alcoholism, and antibiotic use before admission.
†Prescriptions for prednisolone 0–3 months prior to admission.
csDMARDs, conventional synthetic disease-modifying antirheumatic drugs.

Interaction between prednisolone and disease activity in patients with RA

In estimating the prognostic effect of prednisolone stratified by disease activity before pneumonia admission, we found 90-day crude HRs of 0.30 (95% CI 0.04 to 2.59) in patients with low CRP levels and 1.45 (95% CI 1.02 to 2.05) in patients with elevated CRP levels prior to admission. When adjusting for sex, age, level of comorbidity, alcoholism and antibiotic use prior to admission, the 30-day and 90-day HRs for mortality were 0.24 (95% CI 0.03 to 2.10) and 1.32 (95% CI 0.91 to 2.22), respectively. The all-cause 30-day and 90-day mortality rates and the crude and adjusted HRs for 30-day and 90-day mortality were evaluated for the following four groups (with the first group as reference): (1) patients with no prescription for prednisolone and low CRP levels, (2) patients with no prescription for prednisolone and elevated CRP levels, (3) patients with a prescription for prednisolone and low CRP levels and (4) patients with a prescription for prednisolone and elevated CRP levels (table 5). In patients with high disease activity, 90-day mortality was 18.1% in non-prednisolone users and 25.7% in prednisolone users. Compared with non-users of prednisolone with low RA activity, the adjusted HRs were 2.35 (95% CI 0.94 to 5.87) for patients with high RA activity and no prednisolone use prior to admission and 3.09 (95% CI 1.25 to 7.65) for patients with high RA activity and prednisolone use prior to admission.

DISCUSSION

In this population-based study including more than 50 000 patients hospitalised due to pneumonia, we found that active arthritis negatively influenced the outcome. 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 patients with RA 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. Patients with RA did not, on average, have higher 30-day or 90-day mortality than individuals without RA.

To our knowledge, our study is the first to investigate the influence of RA disease activity per se on the prognosis of severe infection. Our results indicate that concerning severe infections, clinical focus should be on the risk of uncontrolled disease activity rather than just on potential dangers of RA medication. If patients with RA with high disease activity are treated more aggressively to obtain remission/low-grade disease activity, this might lead to better outcomes for patients with RA 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

Table 5 Results of all-cause mortality in patients with rheumatoid arthritis following hospitalisation for pneumonia according to disease activity and treatment with prednisolone

	No prednisolone +low CRP	No prednisolone +high CRP	Prednisolone treatment +low CRP	Prednisolone treatment +high CRP
No of patients (N)	64	310	42	288
All-cause mortality at 30 days, n (%)	4 (6.3)	41 (13.2)	1 (2.4)	43 (14.9)
Crude HR for 30-day mortality	1 (ref)	2.20 (0.78 to 6.13)	0.38 (0.04 to 3.37)	2.48 (0.89 to 6.91)
Adjusted HR for 30-day mortality	1 (ref)	2.08 (0.74 to 5.81)	0.36 (0.04 to 3.23)	2.11 (0.76 to 5.88)
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 to 6.14)	0.29 (0.03 to 2.55)	3.57 (1.44 to 8.83)
Adjusted HR for 90-day mortality	1 (ref)	2.35 (0.94 to 5.87)	0.29 (0.03 to 2.52)	3.09 (1.25 to 7.65)

Data are presented as HRs with 95% CIs for all-cause mortality.
Treatment with prednisolone 0–3 months prior to admission. CRP levels were measured 30–90 days prior to pneumonia admission with a value of 8 mg/L used as a division between low and high CRP levels.
Adjusted for sex, age, level of comorbidity, alcoholism and antibiotic use before admission.
CRP, C reactive protein.

on in-hospital treatment following admission, including information on in-hospital treatment with prednisolone

The strengths of this study include the size and accuracy of the data sources used. We had complete follow-up data from detailed, high-quality registries, which allowed for extensive control of confounders. However, we chose our potential confounders because we wanted to examine the association between RA and pneumonia outcome. We may not have included all needed confounders to examine the association between other chronic diseases and pneumonia outcome thus our estimates may be affected by residual confounding. Recall and selection bias were limited because of the prospectively recorded population-based data. However, the identification of patients with RA through the DNPR might have excluded patients with RA with mild disease (ie, patients who were not treated at a hospital clinic or admitted for another illness without concomitant registration of RA 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, who would not have influenced the results significantly.

Patients with RA who attend regular follow-up are informed of the importance of contacting a physician in case of infection. This could lead to an earlier diagnosis of pneumonia and possibly to a higher likelihood of being hospitalised, which may underestimate the impact of RA on pneumonia mortality. On that same note, patients with RA taking biologics may be hospitalised earlier and/or more frequently than patients being managed with other RA treatments when infection is suspected and thus are not as seriously affected, which may lead to an underestimation of mortality.

CRP measurements within 30–90 days prior to admission were available for 58% of the patients with RA. It is possible that patients with higher RA disease activity were more likely to have laboratory test done, but since most patients have laboratory test done at regular intervals—and we omitted measurements 0–30 days prior to admission to avoid any influence from the subsequent infection the number of laboratory test is to be expected.

By using MTX as a reference drug, we may have overestimated the influence of comparative drugs because the risks associated with comorbidities that prohibit the use of MTX or with MTX failure, rather than risk associated with other RA medications, was measured. However, we adjusted for comorbidities, including previous alcoholism related diagnoses.

Of 1220 patients with RA, 394 did not receive RA therapy 0–12 months prior to admission. But 123 of them had previously (more than 1 year prior to the admission) been prescribed csDMARDS and 310 of them had been on NSAIDS. It is likely that this group of patient are in remission or have low disease activity and therefore not on RA medication. Of the 1220 patients, 46 (3.8%) were on biologics. In the yearly rapport from DANBIO concerning 2005, 1390 patient with RA were treated with biologics. The estimated point prevalence in the southern part of Denmark in 2004 has been estimated to 0.30 (95% CI 0.17 to 0.50) while the cumulative prevalence was 0.75 (95% CI 0.52 to 0.97),[23] which means that 25.000–37.500 persons had RA at that time. Thus, the rates of RA treated with biologics match the number in our data.

We were able to adjust for a broad range of comorbidities using the Charlson Comorbidity Index, but not for lifestyle factors, such as smoking and body mass index. Smoking is linked to the development and severity of RA.[24] Bello *et al* found an increased risk of 30-day mortality following hospitalisation for pneumonia among smokers even after taking tobacco-related comorbidity, age and other comorbid conditions into account.[25] This could

lead to an overestimation of the relative mortality when comparing patients with RA to non-RA. However, it also possible that the prevalence of smoking was high among the non-RA patients in this study, since smoking is an important risk factor for pneumonia.[26]

In conclusion, patients with RA do not have a higher mortality following hospitalisation than patients without RA. However, high RA disease activity prior to admission predicts increased mortality following hospitalised pneumonia in patients with or without prednisolone use. This suggests that high RA disease activity per se is an important prognostic factor in patients with RA with pneumonia and should be controlled. Reassuringly, treatment with biologics and csDMARDs, either as a monotherapy or in combination, did not predict increased pneumonia mortality.

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