




## Original article

## Incidence and severeness of COVID-19 hospitalization in patients with inflammatory rheumatic disease: a nationwide cohort study from Denmark

René Cordtz <sup>1,2,\*</sup>, Jesper Lindhardsen<sup>3,\*</sup>, Bolette G. Soussi<sup>1</sup>, Jonathan Vela <sup>1</sup>, Line Uhrenholt <sup>1</sup>, Rasmus Westermann<sup>1</sup>, Salome Kristensen<sup>1,4</sup>, Henrik Nielsen<sup>5,4</sup>, Christian Torp-Pedersen<sup>6</sup> and Lene Dreyer<sup>1,4,7</sup>

## Abstract

**Objectives.** To estimate the incidence of COVID-19 hospitalization in patients with inflammatory rheumatic disease (IRD); in patients with RA treated with specific DMARDs; and the incidence of severe COVID-19 infection among hospitalized patients with RA.

**Methods.** A nationwide cohort study from Denmark between 1 March and 12 August 2020. The adjusted incidence of COVID-19 hospitalization was estimated for patients with RA; spondyloarthritis including psoriatic arthritis; connective tissue disease; vasculitides; and non-IRD individuals. Further, the incidence of COVID-19 hospitalization was estimated for patients with RA treated and non-treated with TNF-inhibitors, HCQ or glucocorticoids, respectively. Lastly, the incidence of severe COVID-19 infection (intensive care, acute respiratory distress syndrome or death) among hospital-admitted patients was estimated for RA and non-IRD individuals.

**Results.** Patients with IRD ( $n=58\,052$ ) had an increased partially adjusted incidence of hospitalization with COVID-19 compared with the 4.5 million people in the general population [hazard ratio (HR) 1.46, 95% CI: 1.15, 1.86] with strongest associations for patients with RA ( $n=29\,440$ , HR 1.72, 95% CI: 1.29, 2.30) and vasculitides ( $n=4072$ , HR 1.82, 95% CI: 0.91, 3.64). There was no increased incidence of COVID-19 hospitalization associated with TNF-inhibitor, HCQ nor glucocorticoid use. COVID-19 admitted patients with RA had a HR of 1.43 (95% CI: 0.80, 2.53) for a severe outcome.

**Conclusion.** Patients with IRD were more likely to be admitted with COVID-19 than the general population, and COVID-19 admitted patients with RA could be at higher risk of a severe outcome. Treatment with specific DMARDs did not affect the risk of hospitalization.

**Key words:** rheumatoid arthritis, epidemiology, viruses, DMARDs, biological therapies, immunosuppressants

## Rheumatology key messages

- Patients with IRD had higher incidence of COVID-19 hospitalisation compared with the general population of Denmark.
- Among patients with RA, the COVID-19 hospitalisation rates were not higher among those treated with hydroxychloroquine, TNF-inhibitor or glucocorticoids.
- COVID-19 admitted patients with RA had a tendency towards a higher incidence of severe outcome, but this was not statistically significant.

<sup>1</sup>Department of Rheumatology, Aalborg University Hospital, Aalborg, <sup>2</sup>Department of Rheumatology, Center for Rheumatology and Spine Diseases, Gentofte Hospital, Hellerup, <sup>3</sup>Lupus and Vasculitis Clinic, Center for Rheumatology and Spine Diseases, Rigshospitalet, Copenhagen, <sup>4</sup>Department of Clinical Medicine, Aalborg University, Aalborg, <sup>5</sup>Department of Infectious Diseases, Aalborg University Hospital, Aalborg, <sup>6</sup>Department of Cardiology, Nordsjællands Hospital, Hillerød and <sup>7</sup>The DANBIO Register, Denmark

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Correspondence to: René Cordtz, Department of Rheumatology, Aalborg University Hospital, Reberbansgade 15, DK-9000 Aalborg, Denmark. E-mail: r.cordtz@rn.dk/r.cordtz@gmail.com

\*René Cordtz and Jesper Lindhardsen contributed equally to this study.

## Introduction

The coronavirus disease 2019 (COVID-19) pandemic caused by the SARS-CoV-2 virus has challenged societies and health care systems globally. A major public health focus has been to protect high-risk individuals, but due to the novelty of SARS-CoV-2, it is, to some extent, still unclear who constitute the high-risk groups. Some clear risk factors for a serious outcome have been identified, of which age is by far the strongest, but obesity, cardiovascular, lung and renal diseases have also proven to be important risk factors [1].

Patients with inflammatory rheumatic diseases (IRDs) are generally at increased risk of acquiring infections [2]; however, some of the treatments used in routine care of these rheumatic diseases have also been proposed as potential treatments for those with severe COVID-19 infections, e.g. as HCQ, glucocorticoids, IL-6 inhibitors and TNF inhibitors (TNFi) [2–4]. For safe and efficient management, it is important to determine how patients with IRD are affected by the current pandemic. In the course of just a few months, case studies and cohort studies (without controls) have tried to investigate how patients with IRD have fared regarding COVID-19, but with considerable variation in study setting, size and results [4–10].

We used the nationwide registries in Denmark to investigate the incidence of hospitalization with COVID-19 among >58 000 patients with IRD compared with the adult population of 4.5 million people. We also assessed the impact of treatment with TNFi, HCQ and glucocorticoid on the incidence of COVID-19 hospitalization in patients with RA. Lastly, we studied the impact of having RA on the incidence of severe COVID-19 infection.

## Methods

### Study design

Based on the linkage of several Danish nationwide registers, we conducted a population-based observational cohort study investigating the incidence of COVID-19 hospitalization in patients with IRD from 1 March (start of epidemic in Denmark) to 12 August 2020. Secondary analyses focused on the incidence of severe outcomes among the hospitalized patients with RA.

### Data sources, study population and exposures

Residents of Denmark have a unique and permanent personal identifier, which allows for complete register-linkage [11]. The primary cohort was identified through the Civil Registration System (CRS) and consisted of the entire adult population of Denmark defined as individuals of age 18 years or older and alive on 1 March 2020 [11]. The nationwide rheumatology register *DANBIO* was used to identify patients with RA and SpA (axial spondyloarthritis and psoriatic arthritis) and to obtain information on ongoing treatments with disease-modifying antirheumatic drugs (DMARDs) including conventional

DMARDs, biologics and glucocorticoids [12]. Patients with CTD (SLE, Sjögren's disease, systemic sclerosis, and myositis) or vasculitis (e.g. giant cell arteritis, granulomatosis with polyangiitis and other vasculitides) were identified in The Danish National Patient Register (DNPR) [13, 14]. Case definitions for all four groups are provided in [Supplementary Table S1](#), available at *Rheumatology* online.

### Medicine exposure

For patients with RA, data on exposure to DMARDs was available from 1 March to 1 May 2020. Several drugs used in the treatment of RA have been proposed as potential treatments for severe COVID-19, including TNFi, HCQ, glucocorticoids and IL-6 inhibitors, and the impact of these drugs were explored in the present study except for IL-6 inhibitors which are not as frequently used as the others, thus prohibiting any meaningful analysis on that class of drug.

Two approaches were used to estimate the impact of treatment with TNFi, hydroxychloroquine or glucocorticoids on the incidence of hospitalization with COVID-19: a time-fixed and a time-dependent covariate adjustment in Cox models. The time-fixed exposure was defined as the ongoing treatment as per 1 March 2020. In the time-dependent exposure model, treatment status of each drug was updated during follow-up according to the entries in the *DANBIO* register.

### Outcome information

Outcome information on COVID-19 hospitalization and transfer to an intensive care unit (ICU) was also obtained in DNPR by use of ICD-10 codes created by the Danish Ministry of Health specifically for the pandemic in accordance with the definition established by the World Health Organization (ICD-10 codes B342A, B972 and B972A). These ICD-10 codes have been validated at Copenhagen University Hospital, and within that institution showed a positive predictive value of 99% of a patient having had a positive real-time reverse transcriptase-polymerase chain reaction (RT-PCR) test for SARS-CoV-2 [15].

In the primary analysis, hospitalization due to COVID-19 was defined as the listing of a hospital contact with a duration of >24 h and an associated ICD-10 code for COVID-19.

In the secondary analysis, a severe outcome was defined as the presence of a procedure code for mechanical ventilation, an ICD-10 code of B972A indicating acute respiratory distress syndrome (ARDS) due to COVID-19, or death following COVID-19.

### Covariates

Comorbidities including a history of chronic lung disease, diabetes mellitus (DM), cardiovascular disease (CVD) (ischemic heart disease, heart failure, hypertension and stroke), obesity and cancer were identified by use of diagnoses listed in the DNPR and/or redeemed

prescriptions registered in the Danish Prescription Register of relevant drugs for each comorbidity [14] (see [Supplementary Table S2](#), available at *Rheumatology* online for definitions of each comorbidity).

Information on age, sex and vital status was obtained in the CRS [11].

### Statistical analysis

*Incidence of hospitalization compared with the general population.* The cohort was followed from 1 March 2020 to the date of COVID-19 hospitalization, date of death or 12 August 2020, whichever occurred first. The age- and sex standardized incidence rate of hospitalization per 1000 person years was estimated for each group. Associations between exposure and time-to-admission were assessed by hazard ratios (HRs) using Cox-regression models with age as underlying time scale and stratified by sex. In additional models, we adjusted for the following comorbidities: chronic lung disease, CVD, DM, obesity and malignant disease.

To illustrate how age, sex and follow-up affected the cumulative probability of hospitalization in more absolute terms, we show the predicted incidence curves (1 – predicted survival function) for ages 40, 60 and 80 years in males and females, respectively. The predictions were based on a Cox model with time-on-study as time scale, stratified by sex, and included two covariates: IRD as main exposure variable of interest and age as a restricted cubic spline (4 degrees of freedom). Competing risk by death was ignored due to the short time period (deaths in the cohorts were <1%).

*Impact of treatment with HCQ, TNFi and glucocorticoids.* To assess the average treatment risk of COVID-19 hospitalization in patients with RA treated with HCQ, TNFi and glucocorticoids compared with non-HCQ, non-TNFi and non-glucocorticoid treated patients with RA, respectively, a Cox model adjusting for age, sex, comorbidities and treatment with, HCQ, TNFi, glucocorticoid and other conventional DMARDs was performed. The Cox model was then used to estimate the absolute standardized risks and risk differences using the g-formula and 95% CIs were determined by use of 1000 bootstrap samples [16].

An additional Cox model was performed with time-dependent exposure to the abovementioned treatments as the covariates of interest.

*Incidence of severe COVID-19 outcome.* For the subgroup of patients with RA and individuals from the general population who were hospitalized with COVID-19, we estimated the age- and sex standardized incidence rate per 100 person years, and HR for the composite outcome of death, ARDS or transfer to ICU. In this analysis, age was the underlying time scale and the model was adjusted for sex and the comorbidities listed in [Supplementary Table S2](#), available at *Rheumatology* online.

Data management and all analyses were performed in R version 3.6.1. The level of statistical significance was set at 5%.

## Results

A total of 58 052 patients with IRD were identified of whom 51% were patients with RA ([Table 1](#)). On average, patients with RA, CTD and vasculitis were older, more often female, and more frequently had comorbidities compared with the general population, while the characteristics of SpA patients resembled that of the background population.

During follow-up, 2536 admissions occurred in the general population and 69 among patients with IRD, the majority of the latter being patients with RA ( $n = 47$ ).

Incidence rates and associations between IRDs with COVID-19 hospitalizations are listed in [Table 2](#). As shown, suffering from an IRD was associated with a 46% increased hazard rate of hospitalization. Of note, the increased incidence was not uniform across the different IRD groups: while HRs were increased for patients with RA (1.72, 95% CI: 1.29, 2.30), CTD (1.38, 95% CI: 0.66, 2.91) and vasculitis (1.82, 95% CI: 0.91, 3.64), SpA patients were not more often hospitalized than individuals in the general population (HR 0.67, 95% CI: 0.32, 1.41). The Cox model that adjusted for comorbidities generally continued to show increased HRs for IRDs but with slightly lower effect size than observed in the Cox model solely adjusting for demographic characteristics. The predicted probability of hospitalization in men and women at ages 40, 60 and 80 years are shown in [Fig. 1](#), and it is seen that the predicted incidence increase with age, and men generally had a higher predicted incidence. It also suggests an increased effect of IRD on the absolute risk of hospitalization with increasing age in accordance with age being a strong risk factor of COVID-19 admission.

HRs and absolute standardized risks in RA patients treated with either TNFi, HCQ or glucocorticoids are shown in [Table 3](#). While the point estimates for both HRs and absolute risks associated with TNFi or HCQ treatment were lower than non-TNFi and non-HCQ treated patients, the confidence intervals included the possibility of no difference in both analyses. Treatment with glucocorticoids was also not associated with hospitalization (HR 1.22, 95% CI: 0.47, 3.15). The use of time-dependent adjustment for drug exposure did not alter the overall findings.

Among patients hospitalized with COVID-19, 47% ( $n = 22$ ) of patients with RA and 37% ( $n = 945$ ) from the general population suffered from a severe COVID-19 outcome ([Table 4](#)). In patients with a severe outcome, a higher proportion had preexisting cardiovascular and lung disease compared with those with non-severe outcomes. Adjusted for age, sex and comorbidities, this resulted in a HR of 1.43 (95% CI: 0.80, 2.53) for patients with RA compared with the general population.

## Discussion

The main finding in this nationwide cohort study was that patients with IRD had a moderately increased

**TABLE 1** Demographics and characteristics of patients with inflammatory rheumatic disease and the general population at start of follow-up

	RA	Spondyloarthritis <sup>a</sup>	Connective tissue disease <sup>b</sup>	Vasculitis <sup>c</sup>	General population
Total <i>n</i>	29 440	17 863	6677	4072	4 539 177
Age in years, median (interquartile range)	67.3 (56.7–75.7)	52.9 (41.8–63.3)	60.7 (48.7–71.9)	71.2 (59.6–77.5)	49.8 (33.6–65)
Women, <i>n</i> (%)	20 990 (71.3%)	8865 (49.6%)	5729 (85.8%)	2490 (61.1%)	2 291 573 (50.5%)
Cardiovascular disease, <i>n</i> (%)	10 101 (34.3%)	3957 (22.2%)	2734 (40.9%)	1874 (46.0%)	737 758 (16.3%)
Lung disease, <i>n</i> (%)	6468 (22.0%)	2769 (15.5%)	1853 (27.8%)	1014 (24.9%)	543 443 (12.0%)
Diabetes mellitus, <i>n</i> (%)	3169 (10.8%)	1610 (9.0%)	569 (8.5%)	588 (14.4%)	286 147 (6.3%)
History of or concurrent cancer, <i>n</i> (%)	3632 (12.3%)	1136 (6.4%)	811 (12.1%)	558 (13.7%)	292 879 (6.5%)
Diagnosed with obesity, <i>n</i> (%)	2670 (9.1%)	2151 (12.0%)	673 (10.1%)	305 (7.5%)	294 900 (6.5%)
Treated with HCQ, <i>n</i> (%)	2722 (9.2%)	37 (0.2%)	–	–	–
Treated with any other conventional synthetic DMARD, <i>n</i> (%)	20 217 (68.7%)	6232 (34.9%)	–	–	–
Treated with glucocorticoid, <i>n</i> (%)	2411 (8.2%)	269 (1.5%)	–	–	–
Treated with TNFi, <i>n</i> (%)	4110 (14.0%)	5014 (28.1%)	–	–	–
Treated with IL6 inhibitor, <i>n</i> (%)	728 (2.5%)	17 (0.1%)	–	–	–
Treated with other biological DMARD	1542 (5.2%)	611 (3.4%)	–	–	–

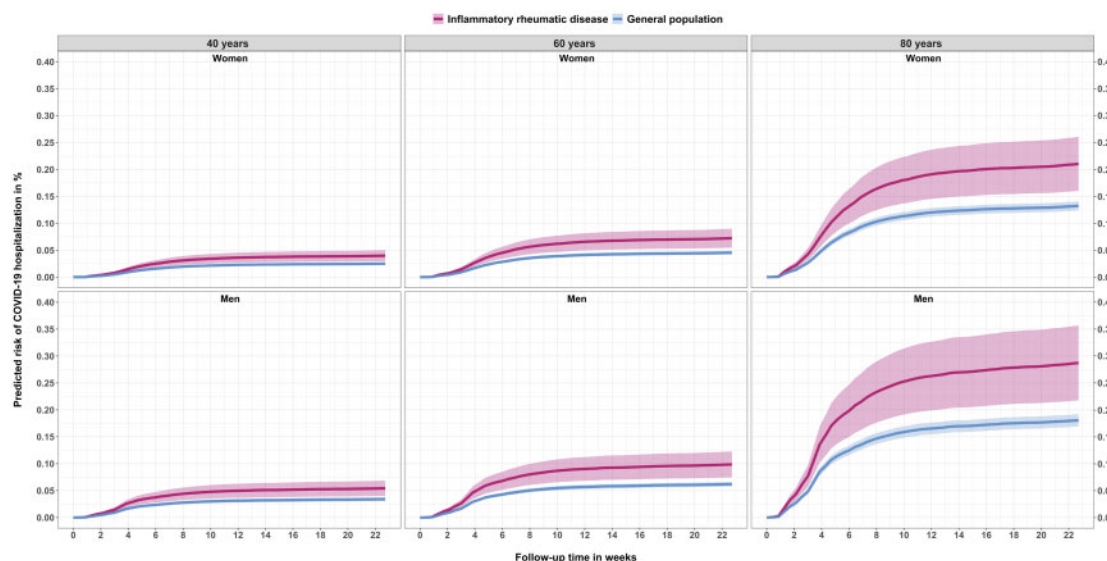
DMARD: Disease modifying anti-rheumatic drug; TNFi: TNF inhibitor. <sup>a</sup>Psoriatic arthritis (*n* = 10 349), axial spondyloarthritis (*n* = 7514). <sup>b</sup>SLE (*n* = 2505), Sjögren's disease (*n* = 2220), systemic sclerosis (*n* = 1230), other CTDs (*n* = 722). <sup>c</sup>Giant cell arteritis (*n* = 2149), other vasculitides (*n* = 1923).

**TABLE 2** Numbers, incidence rates and hazard ratios for hospitalization with COVID-19 infection among patients with inflammatory rheumatic disease and the general population

	All inflammatory rheumatic diseases	RA	Spondyloarthritis	Connective tissue disease	Vasculitis	General population
<i>n</i> hospitalised with COVID-19	69	47	7	7	8	2536
Person years of observation	25 919	13 119	8006	2982	1812	2 032 099
Incidence rates per 1000 person years (age and sex standardized)	1.73 (1.34–2.23)	1.97 (1.38–2.81)	0.76 (0.36–1.63)	2.30 (0.86–6.17)	1.99 (0.98–4.05)	1.26 (1.21–1.31)
Median (interquartile range)/mean duration of hospitalization in days	3.1 (1.2–7.9)/6.1	2.8 (1.1–7.9)/6.5	2.4 (1.1–4.5)/3.1	5.5 (3.4–7.4)/6.7	4.5 (1.7–8.8)/5.7	2.8 (0.8–6.8)/5.1
HR adjusted for sex with age as underlying time scale	1.60 (1.26–2.03)	1.84 (1.38–2.46)	0.75 (0.36–1.57)	1.63 (0.78–3.43)	2.03 (1.02–4.08)	1 (Ref.)
HR adjusted for sex and comorbidities <sup>a</sup> with age as underlying time scale	1.46 (1.15–1.86)	1.72 (1.29–2.30)	0.67 (0.32–1.41)	1.38 (0.66–2.91)	1.82 (0.91–3.64)	1 (Ref.)

HR: hazard ratio. <sup>a</sup>Comorbidities included lung disease, cardiovascular disease, diabetes mellitus and cancer.

**Fig. 1** Predicted probability of COVID-19 hospital admission in patients with inflammatory rheumatic disease and the general population



Follow-up started at 1 March 2020 and ended at date of admission with COVID-19, death or 12 August 2020, whichever occurred first.

**TABLE 3** Numbers, incidence rates, absolute risks, absolute risk differences and hazard ratios for hospitalization with COVID-19 by treatment among patients with RA

	TNFi treated	Non-TNFi treated	HCQ treated	Non-HCQ treated	Glucocorticoid treated	Non-glucocorticoid treated
N	4110	25 330	2722	26 718	2411	27 029
Number of hospitalised patients	4	36	≤3	38	5	35
Incidence rates per 1000 person years (age and sex standardized)	6.63 (2.26–19.47)	8.37 (6.03–11.61)	4.50 (1.10–18.40)	8.52 (6.2–11.72)	11.04 (4.47–27.30)	7.88 (5.65–10.98)
Absolute standardized risk at 30 days <sup>a</sup> (%)	0.06 (0.01–0.14)	0.07 (0.04–0.11)	0.04 (0.00–0.11)	0.07 (0.04–0.11)	0.08 (0.02–0.18)	0.07 (0.04–0.10)
Absolute standardized risk difference at 30 days <sup>a</sup> (%)	–0.01 (–0.07–0.06)	—	–0.03 (–0.09–0.04)	—	0.01 (–0.06–0.11)	—
Absolute standardized risk at 60 days <sup>a</sup> (%)	0.11 (0.03–0.24)	0.14 (0.09–0.19)	0.08 (0.00–0.21)	0.14 (0.1–0.19)	0.16 (0.03–0.33)	0.13 (0.09–0.18)
Absolute standardized risk difference at 60 days <sup>a</sup> (%)	–0.03 (–0.13–0.11)	—	–0.07 (–0.16–0.08)	—	0.03 (–0.10–0.20)	—
Adjusted HR <sup>b</sup> time-fixed exposure model	0.81 (0.28–2.33)	1 (Ref.)	0.45 (0.11–1.92)	1 (Ref.)	1.23 (0.46–3.27)	1 (Ref.)
Adjusted HR <sup>c</sup> time-dependent exposure model	0.78 (0.28–2.19)	1 (Ref.)	0.76 (0.23–2.52)	1 (Ref.)	1.22 (0.47–3.15)	1 (Ref.)

HR: hazard ratio; Ref.: reference. <sup>a</sup>Based on Cox model with time-on-study as time scale, adjusted for TNFi/HCQ/glucocorticoid treatment status (time-fixed), age as categorical variable (10-year intervals), sex, cardiovascular disease, diabetes mellitus, lung disease, obesity and treatment with TNFi, HCQ or glucocorticoids if not main exposure variable. <sup>b</sup>Model: Age as underlying time scale, stratified by sex, covariates included TNFi/HCQ/glucocorticoid treatment status (time-fixed), cardiovascular disease, diabetes mellitus, lung disease, obesity and treatment with TNFi, HCQ or glucocorticoids if not main exposure variable. <sup>c</sup>Model: Age as underlying time scale, adjusted for TNFi/HCQ/glucocorticoid treatment status (time-dependent), sex, cardiovascular disease, diabetes mellitus, lung disease, obesity and treatment with TNFi, HCQ or glucocorticoids if not main exposure variable.



**TABLE 4** Characteristics of COVID-19 hospitalised patients with RA and the general population stratified by severeness of COVID-19 infection

Severe outcome	RA, <i>n</i> = 47		General population, <i>n</i> = 2536	
	Yes	No	Yes	No
<i>n</i>	22	25	945	1591
Died	16 (73%)	0 (0%)	567 (60%)	0 (0%)
Stayed in intensive care unit	7 (32%)	0 (0%)	348 (37%)	0 (0%)
Died while in intensive care unit	4 (18%)	0 (0%)	133 (14%)	0 (0%)
Total duration of hospitalization in days, median (interquartile range)	7.5 (1.0–9.8)	2 (1–4)	4 (1–9)	2 (1–5)
Age in years, median (interquartile range)	76.2 (70.4–83.7)	74.1 (59.1–77.7)	75.7 (65.9–83.6)	61.9 (48.4–76.7)
Women, <i>n</i> (%)	16 (73%)	21 (84%)	354 (38%)	796 (50%)
Cardiovascular disease, <i>n</i> (%)	15 (68%)	11 (44%)	518 (55%)	581 (37%)
Lung disease, <i>n</i> (%)	15 (68%)	10 (40%)	261 (28%)	312 (20%)
Diabetes mellitus, <i>n</i> (%)	5 (23%)	4 (16%)	230 (24%)	253 (16%)
History of or concurrent cancer, <i>n</i> (%)	≤3	4 (16%)	201 (21%)	191 (12%)
Diagnosed with obesity, <i>n</i> (%)	≤3	4 (16%)	108 (11%)	188 (12%)
On treatment with HCQ prior to admission, <i>n</i> (%)	≤3	≤3	—	—
On treatment with other csDMARD prior to admission, <i>n</i> (%)	14 (64%)	15 (60%)	—	—
On treatment with glucocorticoid prior to admission, <i>n</i> (%)	≤3	4 (16%)	—	—
On treatment with TNF-inhibitor prior to admission, <i>n</i> (%)	≤3	≤3	—	—
On treatment with IL 6-inhibitor prior to admission, <i>n</i> (%)	0 (0%)	0 (0%)	—	—
On treatment with other biological DMARD prior to admission, <i>n</i> (%)	≤3	≤3	—	—
Age- and sex-adjusted incidence rate of severe outcome per 100 person years	351.7 (208.2–594.2)		327.3 (306.8–349.3)	
Model 1, adjusted for age and sex, HR (95% CI)	1.52 (0.89, 2.59)		1 (Ref.)	
Model 2, adjusted for age, sex and comorbidities <sup>a</sup> , HR (95% CI)	1.43 (0.80, 2.53)		1 (Ref.)	

csDMARD: conventional synthetic disease-modifying antirheumatic drug; HR: hazard ratio. <sup>a</sup>Comorbidities adjusted for included cardiovascular disease, diabetes mellitus, lung disease and cancer.

incidence of hospitalization with COVID-19 compared with the 4.5 million people in the general population. Of the different IRDs, this association was most apparent in patients with RA, who were 72% more likely to be admitted with COVID-19 compared with the general population, but importantly, the absolute risk was low, reflecting that Denmark was not as hard hit by COVID-19 as many other countries during the study period. Increased incidences were also seen in patients with vasculitides and CTDs but with wider confidence intervals including unity. In contrast, the larger SpA group did not have increased rates of hospitalization.

Our findings of increased hospital admission rates in IRDs are largely supported by smaller regional and single-center studies from across Europe and America [5–8, 17, 18]. In three studies from Spain, patients with IRD were also found to have had higher risk of hospitalization [5–7]. However, one of those studies, based on data from seven hospitals in Spain with >26 000 patients with a rheumatic disease, did not

find an excess risk among patients with RA, but rather in patients with polymyalgia rheumatica, giant cell arteritis and most other systemic autoimmune diseases except SLE. In contrast to our findings, there was an excess risk among patients with SpA [5]. Of note, this study presented only unadjusted odds ratios (ORs) and the outcome was a mixture of patients admitted to hospital and patients merely evaluated at a hospital.

The present study suggests similar effect sizes of hospital admission for patients with RA, CTD and vasculitides. A single-center study from Madrid, Spain investigated patients with IRDs once they were admitted, and found that systemic autoimmune conditions including CTD and vasculitides were associated with higher odds of COVID-hospitalization compared with chronic inflammatory arthritis (OR 3.55, 95% CI: 1.30, 9.67). However, this may reflect the pooling of RA, psoriatic arthritis and SpA as well as the cross-sectional setting of the study [7].

We found that RA patients admitted with COVID-19 had a 43% increased hazard rate for a severe outcome compared with non-IRD COVID-19 patients. This is also in accordance with observations from existing studies [9, 17]. D'Silva *et al.* found that rheumatic patients admitted with COVID-19 more often needed to be admitted to an ICU and to have mechanical ventilation compared with age- and sex-matched non-rheumatic COVID-19 patients (11 of 44 vs 7 of 104 patients; OR 2.92, 95% CI: 1.00, 8.49) [17]. On the other hand, Pablos *et al.* did not find that RA was a risk factor for an adverse outcome [18], and so far it is difficult to interpret the conflicting findings due to the diverse settings, low number of patients and outcomes as well as differences in the definition and grouping together of rheumatic diseases.

We did not find that use of TNFi, HCQ nor glucocorticoids for treatment of RA had a substantial effect on the risk of being admitted with COVID-19, but HCQ and TNFi-treated patients did have numerically lower absolute risks compared with non-HCQ and non-TNFi-treated. Of note, the Danish Rheumatism Association sent out an official recommendation on 4 March 2020 as the epidemic started to unfold in Denmark, stating that 'patients should continue their ongoing treatment(s)'. The few other published studies on the effect of RA treatment, do not have consistent findings. For example, Freites Nuñez *et al.* found that patients with autoimmune rheumatic disease admitted with COVID-19 had a lower proportion of HCQ and TNFi-treated patients compared with those not needing admission [7]. Another Spanish study found that treatment with a targeted synthetic or biological DMARD was associated with an OR of 0.45 (95% CI: 0.21, 0.96) for poor COVID-19 outcome, whereas treatment HCQ did not seem protective nor dangerous [18]. Likewise, D'Silva *et al.* did not find any differences in the proportion treated with HCQ or other immunosuppressive DMARDs among admitted and non-admitted COVID-19 patients [17]. In a more recent paper, Gentry *et al.* used data from the Veterans Database in the United States to investigate if patients with various rheumatic conditions and treated with HCQ had a lower risk of acquiring COVID-19 compared with propensity score-matched non-HCQ-treated patients [19]. They found that HCQ treated patients did not have a lower risk of COVID-19 (OR 0.79, 95% CI: 0.52, 1.20) nor COVID-19-related hospital admission. Lastly, a French cohort study of patients with various IRDs found that HCQ-exposed patients had a HR of 1.15 (95% CI: 0.86, 1.55) compared with matched HCQ unexposed patients [20]. To summarize, there are both studies indicating a slight protective effect and no protective effect of HCQ and TNFi treatment on the risk of poor outcomes in COVID-19 hospitalized rheumatic patients, which is in line with the present findings. A cautious interpretation of the current evidence is that any potential protective effect against hospitalization with COVID-19 of these drugs is negligible.

The main strengths of the present study are the follow-up of a nationwide cohort with use of register-based data renowned for its high degree of validity and completeness [21]. The study does, however, have important limitations. First, the observational design of the study makes the findings exploratory and prohibits us from making causal inferences; thus, estimates must be regarded solely as associations, just as the nature of the study was purely exploratory. The intent was not to identify independent risk factors of hospitalization, but rather to investigate if groups of patients with IRDs—regardless of lifestyle, comorbidity and demographic composition and characteristics—were more likely to be hospitalized with COVID-19. Second, with the onset of the COVID-19 epidemic in Denmark, all citizens were advised to keep social distance and several measures were taken to reduce the spread, especially in the case of individuals with chronic diseases. Thus, patients with IRD may have been less exposed relative to the general population. In fact, an Italian survey study reported that >90% of rheumatic patients from their institution 'had adapted a preventive strategy against COVID-19' [10] just as a Dutch survey study found that patients with IRDs had 80% higher odds of taking stricter isolation measures compared with members of their nearest family or closest network [22]. On the other hand, it is possible that patients with IRDs are admitted with a lower threshold due to immunosuppression, although we believe this is less likely as prophylactic admissions were generally not advised by the Danish Health Authority and the outcome definition excluded patients who stayed <24 h in the hospital, and thus outpatients or patients sent for an evaluation at the hospital but deemed fit enough for outpatient treatment or weathering through the infection at home were not counted by the outcome definition. In support of absence of differential outcome misclassification is the fact that the patients with RA had a longer mean and similar median length of hospitalization as the general population. Another potential limitation is the use of ICD-10 codes for the COVID-19 case definition rather than laboratory-verified positive tests; however, a local quality assessment at the University Hospital of Copenhagen showed that 97 of 98 patients with an ICD-10 code for COVID-19 had a laboratory-confirmed RT-PCR test for SARS-CoV-2 [15]. Exposure misclassification was expected to be minimal for patients with RA and SpA registered in DANBIO, both with regard to diagnosis and treatment episodes due to the high validity of the register [23]. In Denmark, all newly diagnosed RA patients are required to be registered in DANBIO, and thus, the RA group is expected to consist of essentially all prevalent RA patients followed in primary and secondary care in Denmark. It is not mandatory to register SpA and PsA patients in DANBIO, but this is often done as the DANBIO platform offers workflow advantages for the physicians, both in primary and secondary care. However, we do acknowledge that there could be a small degree of misclassification in the group of SpA

patients. The CTD and vasculitides groups are exclusively followed in secondary care and were thus identified solely through the DNPR [24]. Consequently, measures known to minimize misclassification in DNPR were taken, e.g. requiring that a diagnosis had to be registered at least twice and restricting ICD-10 codes to those coded by departments of rheumatology or internal medicine [25]. Lastly, even though this study follows a large cohort of patients with IRDs, it is still unclear to what extent the distinct rheumatic diseases are at risk due to the relatively low number of events in some groups and the conflicting results for various diagnoses in the literature as of present. Residual confounding by obesity and smoking is expected to be present and account for at least part of the increased incidence among patients with RA. In support of this is the finding of a general decrease in estimated HRs for the IRDs following adjustments for comorbidities. Further, the number of patients treated with IL-6 inhibitors was too low to analyse the impact of these drugs in the same manner as TNFi, HCQ and glucocorticoids. Importantly the medication data and administration dates in DANBIO have not been formally validated, and we cannot account for non-compliance to the treatments registered.

In conclusion, we found that the incidence of hospitalization with COVID-19 infection in patients with IRD, and in particular patients with RA, was moderately increased compared with the general population, although the absolute risk increase was low in Denmark during the study period. Also, the increased incidence is likely to be explained in part by comorbidities and other risk factors that are associated with IRDs. Among patients with RA, treatment with HCQ, TNFi and glucocorticoids was not associated with neither apparent benefit nor harm concerning hospitalization for COVID-19, although the events were few. While there was a higher proportion of severe outcomes in patients with RA, the number of events were too low to conclude that patients with RA have an increased risk of a severe outcome compared with non-IRD hospitalised COVID-19 patients. While our results do not cause a high degree of concern for these patients, the higher incidence indicate that increased attention on identifying and advising patients at risk due to comorbidities is reasonable.

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## Data availability statement

According to Danish legislation, none of the original data can be shared.

## Supplementary data

Supplementary data are available at *Rheumatology* online.

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