COVID-19 infection and hospitalisation risk according to vaccination status and DMARD treatment in patients with rheumatoid arthritis

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ABSTRACT

Objectives: To investigate the incidence of COVID-19 hospitalisation in unvaccinated and vaccinated patients with rheumatoid arthritis (RA) compared with matched controls, and in patients with RA according to DMARD treatment.

Methods: Danish nationwide matched cohort study from January to October 2021. Patients with RA were identified in the DANBIO register and matched 1:20 with individuals from the general population on age, sex, and vaccination status. Primary and secondary outcomes were COVID-19 hospitalisation (Danish National Patient Register) and first-time positive SARS-CoV2 PCR test (Danish COVID-19 Surveillance Register), respectively. Stratified by vaccination status, incidence rates (IRs) per 1000 person years (PY) and comorbidity-adjusted hazard ratios (aHRs) in cause-specific Cox models were calculated with 95% confidence intervals.

Results: In total, 28 447 unvaccinated patients and 568 940 comparators had Irs for COVID-19 hospitalisation of 10.4 (8.0 to 13.4) and 4.7 (4.3 to 5.1) per 1000 PY, respectively (aHR 1.88, 1.44 to 2.46). When fully vaccinated, corresponding Irs were 0.9 (0.5 to 1.6) and 0.5 (0.4 to 0.6) per 1000 PY (aHR 1.94, 1.03 to 3.66). Unvaccinated RA patients had an aHR of 1.22 (1.09 to 1.57) for testing positive for SARS-CoV2 and 1.09 (0.92 to 1.14) among vaccinated. Vaccinated rituximab-treated patients had increased crude IR of COVID-19 hospitalisation compared with conventional DMARD treated patients.

Conclusion: The incidence of COVID-19 hospitalisation was increased for both unvaccinated and vaccinated patients with RA compared with controls. Importantly, the parallel decreasing risk for patients with RA suggests a comparable relative benefit of vaccination in most patients.

Key words: Rheumatoid arthritis, SARS-CoV2, epidemiology, COVID-19, biologics, rituximab, vaccination

KEY MESSAGES

- Regardless of vaccination, risk of COVID-19 hospitalisation was increased in patients with rheumatoid arthritis.
- The absolute risk of hospitalisation was, however, markedly lower among all vaccinated individuals.
- Less favourable outcomes were observed in rituximab-treated patients regardless of vaccination status but based on few events.

INTRODUCTION

Since the onset of the COVID-19 pandemic, researchers have focused on identifying particular risk groups in terms of contracting SARS-CoV2, being hospitalised with COVID-19 and of experiencing a severe outcome, e.g., death, during COVID-19 hospitalisation. In several studies, patients with rheumatoid arthritis (RA) have been associated with an increased risk of being hospitalised with COVID-19 when compared with the general population or non-RA individuals (1–7), but results have not been uniform when looking at the risk of contracting SARS-CoV2 (8–11) nor of having a severe outcome following hospitalisation (1,11,12).

In Denmark, a national vaccination strategy was implemented at the end of December 2020. The BNT162b2 (Pfizer BioNTech) and mRNA-1273 (Moderna) vaccines, both mRNA vaccines (13,14), were the first available vaccines in Denmark. Considering the immunologic dysregulation intrinsic to RA and the immunosuppressive treatments frequently adopted in these patients, some concerns have arisen regarding vaccine efficacy and safety in this population. In the phase three trials of BNT162b2 by Polack et al. (15) and mRNA-1273 by Baden et al. (14), treatment with immunosuppressive therapy was an exclusion criterion and only few participants suffered from rheumatic disease.

Whether the excess risk of COVID-19 hospitalisation associated with RA has disappeared after introduction of vaccinations, and if patients with RA in general or patients treated with certain disease-modifying antirheumatic drugs (DMARDs) should be prioritised for potential future booster shots is yet to be investigated on a nationwide scale. Thus, the aims of this study were to estimate the incidence of hospitalisation due to COVID-19 in patients with RA according to vaccination status compared with matched individuals from the general population; and as a secondary outcome, the risk of a first-time COVID-19 infection. Lastly, we estimated the

incidence of the primary and secondary outcomes in a subgroup analysis of patients with RA treated with various DMARD regimens.

PATIENTS AND METHODS

Study Design

This was a population-based observational matched cohort study investigating the incidence of COVID-19 hospitalisation in patients with RA from 1 January to 5 October 2021 via linkage of several Danish nationwide registers. Secondarily, we studied the incidence of a first-time positive SARS-CoV2 PCR-test; and, for patients with RA, we explored the rate of COVID-19 hospitalisation and mortality according to vaccination status and type of DMARD treatment. During the study period, the dominant SARS-CoV2 strains were Alpha (start of study period to end of June 2021) and Delta (1 July to end of 5 October 2021)(16,17). According to Danish legislation, no ethics approval is needed for register-based studies. The study has been approved by the Data Protection Committee of Northern Jutland, Denmark (2020-032).

Data Sources

The Danish Civil Registration System contains information on all residents of Denmark including the unique civil registration number, which enables linkage between registers (18). The Civil Registration System was used to identify all Danish individuals above 18 years old and alive on 1 January 2021, and to obtain information on age, sex, and vital status.

DANBIO is a nationwide clinical quality register for inflammatory arthritis, including RA, and used in routine care by all departments of rheumatology in Denmark. The positive predictive value (PPV) of an RA diagnosis in DANBIO has been estimated to 96% (19).

The Danish Vaccination Register (DDV) was used to obtain information on the exact type and date of all first and second COVID-19 vaccine doses (20). From The National Surveillance at The State Serum Institute, Denmark, information was obtained on the date of all first positive PCR-tests for SARS-CoV2 in Denmark during the study period. The Danish National Patient Register (DNPR) is a nationwide administrative register of contacts in the secondary and tertiary health care sector (21). The Danish National Prescription Registry (NPR) holds information on date of redemption and Anatomical Therapeutic Chemical Classification System (ATC) codes on all prescriptions redeemed at pharmacies in Denmark (22).

Study Population and Exposures

Patients with RA were identified in DANBIO with ICD-10 codes M05 and M06 and included in the study if registered before 1 May 2020 and alive on 1 January 2021. The vaccination history of each patient with RA was obtained through linkage with the DDV, thereby obtaining information on the date and exact type of first and second vaccination against COVID-19.

Time-dependent vaccination status, matching ,and follow-up

By 1 January 2021, all patients with RA were unvaccinated and, corresponding to this date, were matched with up to 20 unvaccinated individuals from the general population with no history of inflammatory rheumatic disease. Besides vaccination status, i.e., being unvaccinated, matching parameters were year of birth and sex. Unvaccinated patients and matched comparators were then followed from 1 January 2021 to the date of first COVID-19 hospitalisation, death, date of first vaccination, or 5 October 2021, whichever occurred first.

Those patients who received a first vaccination and had, at that point, not been hospitalised with COVID-19, were then matched with 20 individuals from the general population that also had no history of COVID-19 hospitalisation. The matching parameters were once again vaccination

status (now partially vaccinated), year of birth, sex, and, additionally, the month and year of receiving their first vaccination. The latter matching parameter was included to indirectly minimise temporal variations in the pressure of the epidemic between patients and their matched controls. This stratum of partially vaccinated patients and matched comparators were followed from the date of their first vaccination to the date of first COVID-19 hospitalisation, death, date of second vaccination, or 5 October 2021, whichever occurred first.

Similarly, patients with RA who received a second vaccination and both during their follow-up in the unvaccinated and partially vaccinated strata had not been hospitalised with COVID-19, were matched with 20 individuals with no history of COVID-19 hospitalisation nor inflammatory rheumatic disease. Matching parameters were vaccination status (i.e. fully vaccinated), year of birth, sex, and month and year of receiving their first and second vaccination. Patients and matched comparators were followed-up from the date of their second vaccination to the date of first COVID-19 hospitalisation, death, or 5 October 2021, whichever occurred first.
In all vaccination status strata, individuals were excluded for further follow-up at time of their first COVID-19 hospitalisation. Thus, a patient or comparator could not contribute multiple outcomes in one vaccination stratum, nor could they progress to and contribute with follow-up to the next vaccination status if they had been hospitalised.

Outcome

The primary outcome of COVID-19 hospitalisation was identified through linkage with DNPR and ICD-10 codes created specifically for the pandemic by the Danish Ministry of Health in accordance with the definition established by the World Health Organization (ICD-10 codes B34.2A, B97.2 and B97.2A)(23). COVID-19 hospitalisation was defined as registration with one of the abovementioned ICD-10 codes listed as the primary diagnosis and a hospital-stay lasting > 24 hours. For descriptive purposes, the proportion who had a severe outcome during their

hospitalisation is presented (see Supplementary Table S1, available at *Rheumatology* online, for definition). The secondary outcome was a first-time positive PCR-test for SARS-CoV2 according to the National Surveillance.

Other covariates

Chronic lung disease, cardiovascular disease, diabetes mellitus type I and II, chronic kidney disease, and cancer (except non-melanoma skin cancer) were a priori comorbidities of interest and were identified using ICD-10 codes in the DNPR and/or redeemed prescriptions registered in the NPR of available at *Rheumatology* online). For descriptive purposes, information on redeemed prescriptions of conventional synthetic DMARD (csDMARD) and prednisolone within 1 year prior to start of follow-up, was obtained from NPR using ATC-codes (Supplementary Table S1).

For biological DMARDs (bDMARD) including TNF-inihibitors, rituximab, interleukin-6 inhibitors, and abatacept, as well as certain csDMARDs, SKS-procedure codes in the DNPR were used to obtain information on date of administration for these drugs in the year leading up to start of follow-up (Supplementary Table S1). Unfortunately, neither DNPR nor NPR held information on administration of leflunomide or JAK-inhibitor treatment during the study period.

Statistical Analysis

Age- and sex standardised incidence rates (IRs) of hospitalisation per 1000 person years (PY) were estimated with 95% confidence intervals (95%CI). In each vaccination status stratum, the incidence of hospitalisation with COVID-19 in patients with RA was compared with their matched comparators, using a stratified cause-specific Cox-regression taking into account the competing risk of death (24). RA was considered the main exposure variable and stratification

was done by matched pairs. Additionally, a comorbidity-adjusted model was made (comorbidities: chronic lung disease, diabetes mellitus, cardiovascular disease, chronic kidney disease, and cancer) and hazard ratios (HRs) for COVID-19 hospitalisation and the competing event of death were presented, both with their corresponding 95% CI. The proportional hazards assumption was evaluated by plotting the scaled Schoenfeld residuals against time.

To illustrate the overall absolute risk of first COVID-19 hospitalisation for the RA and comparator groups in the respective vaccination states while taking into account the competing risk of death, the Aalen-Johansen estimated cumulative incidence (in %) was plotted as a function of follow-up time. The x-axis was from time 0 to the 3rd quartile of follow-up within each vaccination stratum.

Following exclusion of patients with a history of COVID-19 prior to start of follow-up, IRs, and cause-specific HR for a first-time positive SARS-CoV2 PCR test were estimated for patients with RA and comparators. Data management and statistical analyses were performed in R 4.0.3. Cause-specific Cox models were fitted using the 'riskRegression' package, and the Aalen-Johansen cumulative incidence functions were estimated using the 'prodlim' package (25,26). The model specifications are shown in the Supplementary Data S1, available at *Rheumatology* online.

Subgroup and exploratory analyses

Considering only patients with RA, the three vaccination strata were split by exposure to DMARDs as ('Any bDMARD treatment except rituximab', 'rituximab', 'csDMARD treatment only' and 'no DMARD treatment'). Patients that had received multiple types of bDMARDs in the year leading up to start of follow-up was allocated to 'Any bDMARD'. The IRs and HRs for first-time infection and hospitalisation with COVID-19, respectively, were estimated The Cox-

regression was adjusted for age (continuous variable) and sex. Within each treatment-stratum we presented both the proportion of patients that had redeemed at least 2 prescriptions of prednisolone in the year leading up to start of follow-up and the proportion of patients with a history of cancer.

Lastly, for exploratory purposes, among rituximab treated patients with RA, we calculated the mean time since last infusion at start of follow-up (date of vaccination) in those with and without COVID-19 infection.

Sensitivity analyses

A sufficient vaccine response is not expected until 7-14 days post-vaccination. Thus, a potential interaction between exposure group (RA vs matched comparators) and time since follow-up was investigated, by calculating HRs for the days 0 to 10 and 10+ post-vaccination. This analysis was repeated using cut-off values for follow-up with days 0 to 14 and 14+.

RESULTS

A total of 28 447 SARS-CoV2 unvaccinated patients with RA started follow-up on 1 January 2021. The median age was 67.7 years, 71.3% were women, 68% were treated with csDMARD and 23.7% treated with a bDMARD (Table 1). During follow-up, 65 unvaccinated patients with RA were hospitalised with COVID-19 corresponding to an IR of 10.4 per 1000 PY (95%CI 8.0 to 13.4), 171 patients died and 96.2% went on to receive the first vaccination (Table 2). Following adjustment for comorbidities, the HR for COVID-19 hospitalisation in the unvaccinated RA group was 1.88 (95%CI 1.44 to 2.46) compared with the matched group (Table 2).

In patients with RA, and thus, also in matched individuals, the first vaccination was predominantly an mRNA vaccine: 89.2% BNT162b2 and 8.4% mRNA-1273. Upon receival of

the first vaccination, the groups were followed for a median of 28 and 30 days and had IRs of COVID-19 hospitalisation of 5.5 (95%CI 3.0 to 10.0) and 2.2 (95%CI 1.8 to 2.7) per 1000 PY, respectively (Table 2).

In Denmark, non-mRNA vaccines were excluded from the state-sponsored COVID-19 vaccination program by mid-April 2021. Thus, 99.9% of patients with RA received an mRNA vaccination as their second dose (91.2% BNT162b2 and 8.7% mRNA-1273). The IR of COVID-19 hospitalisation in patients with RA had decreased to 0.9 (95%CI 0.5 to 1.6) and to 0.5 (95%CI 0.4 to 0.6) per 1000 PY for matched comparators. The adjusted HR for COVID-19 hospitalisation remained increased at 1.94 for fully vaccinated individuals with RA compared to general population comparators (95%CI 1.03 to 3.66).

The absolute risk of hospitalisation was 0.20 % for unvaccinated patients with RA at 60 days and 0.08 % for matched individuals, whereas the absolute risk remained below 0.05 % in both fully vaccinated groups after 180 days of follow-up (Figure 1).

Sensitivity analyses revealed an interaction between exposure and time since vaccination in the partially vaccinated stratum, where the excess risk was exclusively seen from day 10+ (Supplementary Table S2, available at *Rheumatology* online, and Figure 1 Panel B). These patterns remained when changing the cut-off to 14 days.

Among individuals with no history of COVID-19 infection, unvaccinated patients with RA had an adjusted HR of 1.22 (95%CI 1.09 to 1.57) for a first-time positive SARS-CoV2 PCR test (Table 3). Among vaccinated, there was no difference in incidence of first-time SARS-CoV2 infection (Table 3). In patients with RA, bDMARD treated were younger and a higher proportion was women (Table 4). The rituximab treated group had higher proportions of patients with a history of cancer and prednisolone users. For unvaccinated, patients treated with

rituximab had a HR of 4.71 (95%CI 1.98 to 11.18) for hospitalisation with csDMARD treated patients as reference (Table 4). For fully vaccinated, the HR for COVID-19 hospitalisation remained increased for rituximab treated although based on very few (≤ 3) events. The IRs and HRs for a first-time positive PCR-test were also numerically increased for patients receiving rituximab (Supplementary Table S3, available at *Rheumatology* online).

Among unvaccinated rituximab treated patients not hospitalised with COVID-19, the mean number of days since last infusion at start of follow-up was 105 with the corresponding number of days at 124 for those hospitalised during follow-up. Of the latter, none received rituximab infusion between start of follow-up and time of COVID-19 hospital admission, whereas 20% of non-hospitalised patients treated with rituximab received an infusion between start and end of follow-up. The mean number of days since last rituximab infusion at date of second vaccination dose was 120 and 175 for those hospitalised and not hospitalised with COVID-19, respectively.

DISCUSSION

This nationwide matched cohort study showed that the incidence of COVID-19 infection and hospitalisation was markedly lower both among vaccinated patients with RA and matched controls. However, patients with RA had an excess risk of hospitalisation with COVID-19 even when vaccinated, whereas the incidence of SARS-CoV2 infection was only increased in patients with RA up until receiving their first vaccination dose. For rituximab treated patients, the risks of first-time SARS-CoV2 infection and COVID-19 hospitalisation were increased compared with other DMARD regimens, regardless of vaccination status.

Numerous studies from the pre-vaccine era of COVID-19 have shown increased risk of hospitalisation with or death from COVID-19 in patients with RA compared with non-RA individuals (1–7). However, to our knowledge, this study represents the first nationwide study specifically investigating if this excess risk of hospitalisation has remained in the era of the COVID-19 vaccines.

In a pre-vaccine era of COVID-19 study, England et al. used the Veterans Affair in the US to assess the risk of COVID-19 infection found a HR of 1.25 for patients with RA, remarkably similar to the HR of 1.22 for unvaccinated patients with RA in the present study (6). Papagoras et al. compared severity of COVID-19 infection in vaccinated and unvaccinated patients with systemic rheumatic disease, and found that a higher proportion of unvaccinated patients were hospitalised (29% vs 10%) for their COVID-19 (27). In our study, the IR of hospitalisation decreased from 10.4 in unvaccinated to 0.9 per 1000 PY in vaccinated patients with RA. Importantly, the parallel decreasing IR for patients with RA and comparators suggests a comparable relative benefit of vaccination in general. However, other factors than the vaccination contributed to the decrease in both groups: follow-up started at different calendar months for each stratum, i.e., unvaccinated started follow-up in January, whereas vaccinated

strata started follow-up late winter and early spring for partially vaccinated. Even with few calendar months separating the start of follow-up, variations in factors such as which virus strain was dominating; weather conditions; and, importantly, the measures of general restrictions issued by the authorities, surely play a part. Disentangling the effect of vaccination from these factors is impossible in the present study, and thus, the 10-fold decreased in the RA group does not correspond to the effect of vaccination. However, the decreased rate of hospitalisation in vaccinated patients with RA does suggest that the vaccines were effective in most patients with RA. In line with this, studies investigating the immunogenicity of mRNA vaccines in patients with RA found that most patients amounted an antibody response following vaccination, but also, that this response was potentially inferior compared with that of healthy controls (28–32). In addition to the intrinsic dysregulated immune system in RA, there are other potential contributors to this lower antibody response: studies have shown that the RA cornerstone drug, methotrexate, hampers the immunogenicity of the BNT162b2 vaccine (33,34). Also, the case of decreased antibody production is even stronger for patients treated with rituximab (34–36). Among fully vaccinated rituximab treated patients in the present study, although based on few events, there was a numerically increased risk of breakthrough infections and hospitalisation with COVID-19. However, the proportion of rituximab treated patients suffering from previous or ongoing cancer and receiving concomitant glucocorticoids were higher compared to the other DMARD-groups; and both are important confounding factors for which we could not adjust without overfitting the Cox model. There was no clear pattern with regards to time since last rituximab infusion and time to vaccination nor time to hospitalisation; this is in line with what was observed in a Swedish study of rituximab-treated patients with multiple sclerosis (37).
With regards to the specific absolute and relative incidence rates in the present study, it is important to remember two factors putting the results in context: first, the absolute risk of hospitalisation may be considered low, but it is worth noting that Denmark has had one of the lowest SARS-CoV2 infection rates in Europe during the pandemic, and the study period

specifically covered here was when the infection rates were at their lowest from 2020 to 2021.Thus, the absolute risks do not transfer to other countries with different, and likely higher background rates, whereas the relative rates are relevant and of interest to different RA populations in other countries. Second, a Danish study showed that patients with RA were more likely to self-isolate and take stronger measures of social distancing even when federal general restrictions were abandoned. Thus, the HRs for both infection and hospitalisation may be underestimating the true biological difference (38).

We believe that the totality of findings in the existing literature and the results in the present study, constitute a strong argument for prioritising patients with RA high for future booster shots.

There are important limitations that needs mentioning: First, we did not have access to information on incident patients with RA for the period of May 2020 to January 2021. In Denmark, the incidence of RA is roughly 1700 per year, and therefore about 900 patients may have been misclassified as non-RA. The impact of this in a 1:20 general population matching setting is expected to be minimal. Another limitation is that we did not have access to register information on leflunomide and JAK-inhibitor treatment, of which namely the latter could have been of interest to study (7,39). Some of our subgroup analyses were hampered by a low number of events. Lastly, the use of diagnoses in an administrative register could lead to misclassification. However, the high validity of the COVID-19 outcomes is very reassuring, and although we can only speculate, we have very little reason not to think that the sensitivity of these ICD-10 codes is also high given the registration process and incentive to register in DNPR (23).

There are also strengths to our study. Importantly, the validity of the RA diagnosis in DANBIO is very high (19), thus ensuring that the risk estimates provided are in fact for a true RA

population. Also, the vaccination data from DDV has a high validity and carries detailed information, enabling us to match on both temporality as well as exact type of vaccine at each shot.

In conclusion, the results of this study confirm the observed increased risk of hospitalisation with COVID-19 in the pre-vaccination era in patients with RA compared with non-RA individuals. Further, although the absolute risk was low among fully vaccinated individuals, the relative incidence rate has remained increased in patients with RA compared with matched individuals from the general population, but nonetheless underlines the importance of vaccination.

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Concept and design: Cordtz, Pearce, Dreyer.

Acquisition, analyses, or interpretation of data: All authors

Drafting of the manuscript: Cordtz, Westermann, Kristensen, Dreyer

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DATA AVAILABILITY: The dataset generated during the current study is not publicly available. All data were accessed in the research environment of Statistics Denmark where multiple registries can be combined with the limitation that individual data cannot be exported from the re- search environment. Further, individual information is encrypted. Thus, datasets cannot be made available.

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Table 1. Characteristics of patients with rheumatoid arthritis and matched comparators stratified by vaccination status.

	Unvaccinated		Partially vaccinated		Fully vaccinated	
	Rheumatoid arthritis	**General population**	**Rheumatoid arthritis**	**General population**	**Rheumatoid arthritis**	**General population**
N	28 447	568 940	27 154	542 610	26 217	523 826
Women, N (%)	20 286 (71.3%)	405 720 (71.3%)	19 336 (71.2%)	386 384 (71.2%)	18 611 (71.0%)	371 851 (71.0%)
Age in years, median (IQR)	67.7 (34.2-88.3)	67.8 (34.2-88.4)	68.4 (36.4-88.6)	68.4 (36.5-88.6)	68.9 (40.9-88.7)	68.9 (41.0-88.7)
Median (IQR) follow-up time	102 (62-137)	115 (88-146)	28 (22-35)	30 (21-39)	150 (111-189)	150 (111-189)
History of COVID-19, N (%)	534 (1.9%)	11 421 (2.0%)	708 (2.6%)	15 772 (2.9%)	700 (2.7%)	15 890 (3.0%)
History of hospitalisation with COVID-19, N (%)	57 (0.2%)	870 (0.2%)	97 (0.4%)	1567 (0.3%)	96 (0.4%)	1585 (0.3%)
Chronic kidney disease, N (%)	660 (2.3%)	10 890 (1.9%)	662 (2.4%)	15 144 (2.8%)	641 (2.4%)	15 299 (2.9%)
Cardiovascular disease, N (%)	5847 (20.6%)	96 644 (17.0%)	5770 (21.2%)	108 789 (20%)	5692 (21.7%)	107 759 (20.6%)
Use of cardiovascular drugs, N (%)	14 694 (51.7%)	270 220 (47.5%)	14 431 (53.1%)	280 652 (51.7%)	14 281 (54.5%)	278 675 (53.2%)
Hospital-diagnosis of diabetes mellitus (type I or II), N (%)	2266 (8%)	38 267 (6.7%)	2205 (8.1%)	46 636 (8.6%)	2168 (8.3%)	46 493 (8.9%)
Use of anti-diabetic drugs, N (%)	2741 (9.6%)	52 509 (9.2%)	2725 (10.0%)	60 495 (11.1%)	2679 (10.2%)	60 128 (11.5%)
Chronic lung disease, N (%)	2431 (8.5%)	29 188 (5.1%)	2385 (8.8%)	37 909 (7.0%)	2341 (8.9%)	37 844 (7.2%)
Use of inhalation-medicine, N (%)	4545 (16%)	68 846 (12.1%)	4368 (16.1%)	77 422 (14.3%)	4288 (16.4%)	76 669 (14.6%)
History of cancer (except NMSC), N (%)	3608 (12.7%)	72 501 (12.7%)	3563 (13.1%)	88 832 (16.4%)	3534 (13.5%)	89 743 (17.1%)
Methotrexate, N (%)	15 801 (55.5%)	2572 (0.5%)	15 043 (55.4%)	6430 (1.2%)	14 603 (55.7%)	6728 (1.3%)
Sulfasalazine, N (%)	4042 (14.2%)	593 (0.1%)	3726 (13.7%)	1410 (0.3%)	3545 (13.5%)	1407 (0.3%)
Hydroxychloroquine, N (%)	2961 (10.4%)	690 (0.1%)	2787 (10.3%)	4 (0%)	2698 (10.3%)	5 (0%)

Other csDMARD, N (%)	3143 (11.0%)	1019 (0.2%)	2899 (10.7%)	1504 (0.3%)	2771 (10.6%)	1511 (0.3%)
Prednisolone, N (%)	3566 (12.5%)	11 464 (2.0%)	3311 (12.2%)	2775 (0.5%)	3202 (12.2%)	2851 (0.5%)
TNF-inhibitor, N (%)	4799 (16.9%)	612 (0.1%)	4672 (17.2%)	15 974 (2.9%)	4480 (17.1%)	16 071 (3.1%)
Abatacept, N (%)	423 (1.5%)	13 (0%)	410 (1.5%)	2563 (0.5%)	399 (1.5%)	2564 (0.5%)
Tocilizumab, N (%)	843 (3.0%)	66 (0%)	803 (3.0%)	100 (0%)	765 (2.9%)	124 (0%)
Rituximab, N (%)	630 (2.2%)	581 (0.1%)	572 (2.1%)	303 (0.1%)	544 (2.1%)	315 (0.1%)

Abbreviations: IQR, interquartile range; NMSC, non-melanoma skin cancer; csDMARD, conventional synthetic DMARD; TNF, tumour necrosis factor;

Table 2. Incidence rates and hazard ratios for COVID-19 hospitalisation and death stratified by vaccination status.

	Unvaccinated		Partially vaccinated		Fully vaccinated	
	Rheumatoid arthritis	**General population**	**Rheumatoid arthritis**	**General population**	**Rheumatoid arthritis**	**General population**
N	28 447	568 940	27 154	542 610	26 217	523 826
PY of observation	8297	186 493	2370	49 051	10 846	216 529
Median [IQR] days of follow-up	102 (62-137)	115 (88-146)	28 (22-35)	30 (21-39)	150 (111-189)	150 (111-189)
Hospitalised with COVID-19, N	65	727	11	95	11	131
Age and sex standardised COVID-19 hospitalisation rate per 1000 PY, (IQR)	10.4 (8.0-13.4)	4.7 (4.3-5.1)	5.5 (3.0-10.0)	2.2 (1.8-2.7)	0.9 (0.5-1.6)	0.5 (0.4-0.6)
HR for COVID-19 hospitalisation – crude, (IQR)	2.01 (1.54-2.61)	1 (Ref.)	2.36 (1.2-4.66)	1 (Ref.)	1.63 (0.88-3.01)	1 (Ref.)
HR for COVID-19 hospitalisation - adjusted for comorbidities [a], (IQR)	1.88 (1.44-2.46)	1 (Ref.)	2.47 (1.25-4.89)	1 (Ref.)	1.94 (1.03-3.66)	1 (Ref.)
N (%) of COVID-19 hospitalisations with a severe outcome [b]	11 (16.9%)	209 (28.7%)	≤3	26 (27.4%)	4 (36.4%)	42 (32.1%)
Died during follow-up, N	171	2912	69	1273	391	7926
Age and sex standardised mortality rate per 1000 PY, (IQR)	27.7 (23.7-32.4)	21.4 (20.6-22.2)	33.7 (26.6-42.8)	29.2 (27.7-30.9)	29.1 (26.3-32.2)	30.1 (29.4-30.7)
HR for death – crude, (IQR)	1.37 (1.15-1.62)	1 (Ref.)	1.17 (0.88-1.56)	1 (Ref.)	0.98 (0.89-1.09)	1 (Ref.)
HR for death - adjusted for comorbidities [a], (IQR)	1.31 (1.10-1.56)	1 (Ref.)	1.25 (0.94-1.68)	1 (Ref.)	1.05 (0.94-1.16)	1 (Ref.)

Abbreviations: PY, person years; IQR, interquartile range; HR, hazard ratio

[a] Adjusted for history of cancer, cardiovascular disease, diabetes mellitus, chronic kidney disease, and chronic lung disease.

[b] A severe outcome was defined as the composite of either acute respiratory distress syndrome, admission to an intensive care unit, and/or death

Table 3. Incidence rates and hazard ratios for first-time positive SARS-CoV2 PCR test stratified by vaccination status.

	Unvaccinated		Partially vaccinated		Completed vaccination	
	Rheumatoid arthritis	**General population**	**Rheumatoid arthritis**	**General population**	**Rheumatoid arthritis**	**General population**
Number of individuals, N	27 903	557 415	26 444	526 815	25 517	507 926
Median age (IQR)	67.8 (57.4-76.2)	67.9 (57.5-76.2)	68.5 (58.4-76.7)	68.6 (58.5-76.7)	69 (59.4-76.9)	69.1 (59.5-76.9)
Female, N (%)	19 885 (71.3%)	397 314 (71.3%)	18 805 (71.1%)	374 962 (71.2%)	18 088 (70.9%)	360 304 (70.9%)
History of cancer, N (%)	3551 (12.7%)	71 336 (12.8%)	3491 (13.2%)	86 829 (16.5%)	3456 (13.5%)	87 629 (17.3%)
Person years of observation, N	8053	180 804	2290	45 965	10 558	209 456
Median days of follow-up, N (IQR)	102 (62-137)	115 (88-145)	28 (22-35)	29 (21-39)	150 (112-189)	150 (112-189)
First-time COVID-19 infections, N	309	6690	58	1345	107	1942
Age and sex standardised COVID-19 infection rate per 1000 person years (IQR)	37.8 (33.6-42.6)	33.9 (33.1-34.8)	27 (20.7-35.1)	28.5 (27-30.2)	11.3 (9.2-13.9)	10.4 (9.9-10.9)
HR – crude (IQR)	1.24 (1.09-1.41)	1 (Ref.)	0.87 (0.59-1.27)	1 (Ref.)	1.09 (0.9-1.32)	1 (Ref.)
HR - adjusted for comorbidities [a] (IQR)	1.22 (1.09-1.57)	1 (Ref.)	0.87 (0.95-1.74)	1 (Ref.)	1.09 (0.92-1.14)	1 (Ref.)

Died, N	161	2739	62	1187	369	7637
Mortality rate per 1000 PY, N (IQR)	26.8 (22.8-31.4)	20.6 (19.8-21.4)	31.5 (24.5-40.5)	29.3 (27.7-31.1)	28.3 (25.5-31.4)	30 (29.3-30.7)
HR for death – crude (IQR)	1.38 (1.16-1.64)	1 (Ref.)	1.18 (0.88-1.6)	1 (Ref.)	0.96 (0.86-1.06)	1 (Ref.)
HR for death - adjusted for comorbidities [a] (IQR)	1.22 (1.07-1.38)	1 (Ref.)	0.87 (0.59-1.27)	1 (Ref.)	1.09 (0.89-1.32)	1 (Ref.)

Abbreviations: PY, person years; IQR, interquartile range; HR, hazard ratio
[a] Adjusted for history of cancer, cardiovascular disease, diabetes mellitus, chronic kidney disease, and chronic lung disease.

Table 4. Characteristics and rates of COVID-19 hospitalisation in patients with rheumatoid arthritis stratified by DMARD treatment.

	Unvaccinated				Partially vaccinated				Fully vaccinated			
	TNFi, abatacept, or IL6	**Rituximab**	**csDMARD**	**No DMARD**	**TNFi, abatacept, or IL6**	**Rituximab**	**csDMARD**	**No DMARD**	**TNFi, abatacept, or IL6**	**Rituximab**	**csDMARD**	**No DMARD**
N	5768	630	14969	7080	5625	572	14062	6895	5420	544	13626	6627
Median (IQR) age in years	63.3 (53.3-71.7)	66.6 (57-73.1)	69 (58.7-76.8)	69.4 (58.2-78)	63.7 (54.1-71.9)	67 (58-73.7)	69.8 (59.8-77.2)	70.3 (59.4-78.6)	64.3 (55.1-72.2)	67.5 (58.6-74)	70.2 (60.7-77.3)	71 (60.8-78.9)
Female, N (%)	4336 (75%)	485 (77%)	10492 (70%)	4973 (70%)	4214 (75%)	440 (77%)	9856 (70%)	4826 (70%)	4046 (75%)	413 (76%)	9523 (70%)	4629 (70%)
History of cancer, N (%)	337 (6%)	221 (35%)	2011 (13%)	1039 (15%)	342 (6%)	205 (36%)	1952 (14%)	1064 (15%)	349 (6%)	199 (37%)	1924 (14%)	1062 (16%)
Glucocorticoid use, N (%)	769 (13%)	143 (23%)	1719 (11%)	935 (13%)	720 (13%)	136 (24%)	1526 (11%)	929 (13%)	677 (12%)	124 (23%)	1479 (11%)	922 (14%)
PY of observation	1712.6	163.6	4261.6	2159.6	504.9	46.2	1200.1	618.9	2214.4	248.2	5664	2719
Median (IQR) days of follow-up	107 (62-140)	75 (56-122)	101 (62-133)	106.5 (63-143)	28 (22-35)	25 (22-35)	28 (22-35)	28 (22-35)	147 (108-189)	179.5 (135.2-197)	151 (115-189)	148 (108-188)
N hospitalised with COVID-19	5	6	39	15	0	0	5	6	≤3	≤3	4	4

Standardised COVID-19 hospitalisation rate per 1000 PY, N (IQR)	8.3 (2.8-24.4)	44.4 (17.7-111.7)	12.1 (8.6-17.2)	8.0 (4.8-13.4)	-	-	4.8 (2.0-11.6)	8.3 (3.7-18.7)	-	-	0.6 (0.2-1.7)	0.9 (0.3-2.4)
N (%) of COVID-19 hospitalisations with a severe outcome [b]	0	≤3	6 (15.4%)	4 (26.7%)	0	0	≤3	≤3	0	≤3	≤3	≤3
HR for COVID-19 hospitalisation – crude, (IQR)	0.47 (0.19-1.21)	4.71 (1.98-11.18)	1 (Ref.)	0.74 (0.41-1.34)	-	-	1 (Ref.)	1.78 (0.53-5.96)	0.80 (0.09-7.41)	11.69 (2.07-66.06)	1 (Ref.)	1.86 (0.46-7.51)
Died, N (%)	25	5	73	68	≤3	≤3	33	32	41	7	178	165
Mortality rate per 1000 PY, N (IQR)	24.9 (15.4-40.2)	40.9 (15.5-108.4)	20.9 (16.5-26.5)	38.7 (30.4-49.2)	23.3 (4.8-112.7)	38.2 (5.4-271.2)	29.4 (20.9-41.4)	52.0 (36.5-74.1)	22.0 (15.8-30.7)	33.5 (15.6-71.8)	24.3 (20.9-28.2)	42.2 (35.8-49.7)
HR for death – crude, (IQR)	1.48 (0.93-2.34)	2.39 (0.96-5.92)	1 (Ref.)	1.63 (1.17-2.27)	0.39 (0.12-1.29)	0.95 (0.13-7.00)	1 (Ref.)	1.33 (0.81-2.18)	0.95 (0.67-1.34)	1.29 (0.60-2.75)	1 (Ref.)	1.57 (1.27-1.95)

Abbreviations: TNFi, tumour necrosis factor inhibitor; IL6, interleukin 6; csDMARD, conventional synthetic DMARD; IQR, interquartile range; PY, person years; HR, hazard ratio. [b] Severe outcome defined as the composite of either acute respiratory distress syndrome, admission to an intensive care unit, and/or death

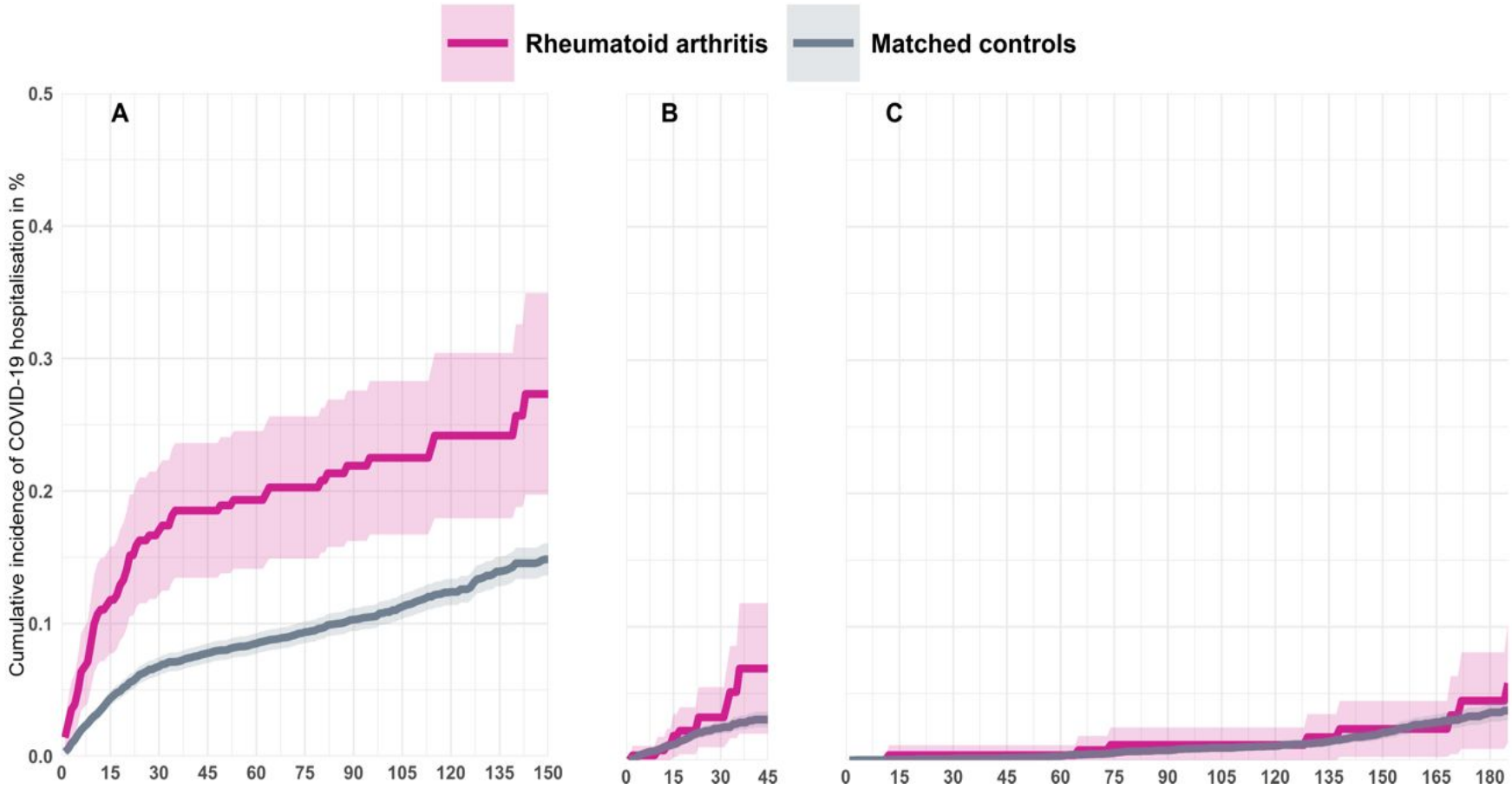

Figure 1. Cumulative incidence (%) of first COVID-19 hospitalisation according to vaccination status. Aalen-Johansen estimated cumulative incidence for (A) unvaccinated, (B) partially vaccinated and (C) fully vaccinated patients with rheumatoid arthritis and matched controls.