









ORIGINAL RESEARCH

TNFi is associated with positive outcome, but JAKi and rituximab are associated with negative outcome of SARS-CoV-2 infection in patients with RMD

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To cite: Regierer AC, Hasseli R, Schäfer M, *et al.* TNFi is associated with positive outcome, but JAKi and rituximab are associated with negative outcome of SARS-CoV-2 infection in patients with RMD. *RMD Open* 2021;7:e001896. doi:10.1136/rmdopen-2021-001896

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Received 25 August 2021
Accepted 24 September 2021

ABSTRACT

Introduction Several risk factors for severe COVID-19 specific for patients with inflammatory rheumatic and musculoskeletal diseases (RMDs) have been identified so far. Evidence regarding the influence of different RMD treatments on outcomes of SARS-CoV-2 infection is still poor.

Methods Data from the German COVID-19-RMD registry collected between 30 March 2020 and 9 April 2021 were analysed. Ordinal outcome of COVID-19 severity was defined: (1) not hospitalised, (2) hospitalised/not invasively ventilated and (3) invasively ventilated/deceased. Independent associations between demographic and disease features and outcome of COVID-19 were estimated by multivariable ordinal logistic regression using proportional odds model.

Results 2274 patients were included. 83 (3.6%) patients died. Age, male sex, cardiovascular disease, hypertension, chronic lung diseases and chronic kidney disease were independently associated with worse outcome of SARS-CoV-2 infection. Compared with rheumatoid arthritis, patients with psoriatic arthritis showed a better outcome. Disease activity and glucocorticoids were associated with worse outcome. Compared with methotrexate (MTX), TNF inhibitors (TNFi) showed a significant association with better outcome of SARS-CoV-2 infection (OR 0.6, 95% CI 0.4 to 0.9). Immunosuppressants (mycophenolate mofetil, azathioprine, cyclophosphamide and ciclosporin) (OR 2.2, 95% CI 1.3 to 3.9), Janus kinase inhibitor (JAKi) (OR 1.8, 95% CI 1.1 to 2.7) and rituximab (OR 5.4, 95% CI 3.3 to 8.8) were independently associated with worse outcome.

Conclusion General risk factors for severity of COVID-19 play a similar role in patients with RMDs as in the normal population. Influence of disease activity on COVID-19 outcome is of great importance as patients with high disease activity—even without glucocorticoids—have a worse outcome. Patients on TNFi show a better outcome of SARS-CoV-2 infection than patients on MTX. Immunosuppressants, rituximab and JAKi are associated with more severe course.

INTRODUCTION

Since the beginning of the SARS-CoV-2 pandemic, increasing evidence about

Key messages

What is already known about this subject?

- ▶ Also in rheumatic and musculoskeletal diseases (RMDs) age, male sex and specific comorbidities are general risk factors for severity of SARS-CoV-2 infection.
- ▶ RMD disease activity and glucocorticoids are specific risk factors.

What does this study add?

- ▶ RMD treatment is associated with SARS-CoV-2 infection severity.
- ▶ While patients under TNFi treatment show better outcome, those under immunosuppressants, Janus kinase inhibitor (JAKi) and rituximab show worse outcome.

How might this impact on clinical practice or further developments?

- ▶ Patients with RMD under treatment with immunosuppressants, JAKi and rituximab need special guidance during the pandemic.

COVID-19 in inflammatory rheumatic and musculoskeletal diseases (RMDs) has been gained. In the general population, age, male sex and certain chronic diseases such as cardiovascular disease (CVD) have been identified as risk factors for severity of COVID-19.^{1,2} In patients with RMD, similar risk factors have been described. In addition, for those patients also RMD-specific risk factors play a role.^{3–6} Disease activity of the underlying RMD, for example, is of utmost importance for the outcome of COVID-19.^{4,6}

Since immunomodulatory treatment can influence the outcome of infectious diseases significantly, the impact of the RMD treatment is also of great interest for patients with RMD



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suffering from SARS-CoV-2 infection. On the one hand, certain immunomodulatory drugs have been proven beneficial in the course of a SARS-CoV-2 infection⁷; on the other hand, immunomodulatory drugs can be detrimental.⁸ Moreover, timing and dosing of the treatment appears to be crucial. For example, dexamethasone is a standard treatment for severe COVID-19⁷ at present, but a long-term glucocorticoid treatment due to RMD is associated with a worse outcome of SARS-CoV-2 infection.^{4,6} The same might be true for Janus kinase inhibitor (JAKi) treatment.⁹

The impact of TNFi on SARS-CoV-2 infection is not completely understood. Use of TNFi in comparison to ‘no disease-modifying anti-rheumatic drug (DMARD)’ was associated with a lower risk of hospitalisation in the first analysis of the data from the Global Rheumatology Alliance (GRA).³ However, it was not significantly associated with lower risk of mortality in a more recent analysis of the GRA in which MTX was used as reference category.⁴ Potential beneficial effects of TNFi have also been described in patients with COVID-19 with inflammatory bowel disease.¹⁰

Due to the lack of interventional studies in patients with RMDs and SARS-CoV-2 infection, the effects of RMD treatment have been evaluated in observational studies only. In this analysis from the German COVID19-RMD registry, we analysed the risk factors for the severity of SARS-CoV-2 infection in patients with RMD, specifically focusing on the impact of RMD treatment.

METHODS

Data source

The German COVID-19 registry for patients with RMDs was founded in March 2020 by the German Society for Rheumatology, together with the Justus-Liebig-University Giessen. Rheumatologists voluntarily entered the data into a web-based registry with implemented plausibility checks (<https://www.covid19-rheuma.de>; for more details, see Hasseli *et al*¹¹).

SARS-CoV-2 infection outcome parameters

The primary outcome of interest was the mutually exclusive ordinal COVID-19 severity outcome:

(1) neither hospitalised, ventilated nor deceased; (2) hospitalised with or without non-invasive ventilation, but neither invasively ventilated nor deceased; and (3) invasively ventilated or deceased. At the time of analysis, all patients were required to have a resolved clinical course.

Statistical analyses

Patient characteristics are shown descriptively, stratified by the three categories of the ordinal outcome. Independent associations between demographic and disease features and the ordinal COVID-19 outcome were estimated by multivariable ordinal logistic regression using the proportional odds model and were reported as OR and 95% CI. In the proportional odds model, an increase in severity is assumed to be equal across

categories: the increase from ‘neither hospitalised, ventilated nor deceased’ to ‘hospitalised with or without non-invasive ventilation, but neither invasively ventilated nor deceased’ is treated in the same way as the increase from the latter category to ‘invasively ventilated or deceased’. Potential deviations from this assumption were assessed graphically and did not show relevant deviation (data not shown). Covariates included in the model were age, sex, key comorbidities (hypertension alone or CVD alone, hypertension combined with CVD, chronic lung disease, chronic kidney disease (CKD) and diabetes), RMD or diagnostic group, rheumatic disease treatment prior to COVID-19 diagnosis (without glucocorticoids), as well as the combined status of disease activity as per the physician’s global assessment (severe/high or moderate disease activity vs minimal/low disease activity or remission), and the prednisolone-equivalent glucocorticoid use (1–10 mg/day and >10 mg/day). The combined status of disease activity and glucocorticoid use represents both their main effects and interaction (in an additive sense) and is analysed to disentangle the effects of both factors.

All patients with confirmed SARS-CoV-2 infection were included in the main analyses. Patients with missing primary outcome (n=2) or missing values for age, sex and DMARDs (n=2) were excluded from analysis. Smoking status was missing in many cases. Therefore, we have not included smoking in the analysis. Missing values for glucocorticoid therapy and disease activity were derived by multiple imputation using full conditional specification.¹² Results of the ordinal logistic regression analyses for 10 imputed data sets were pooled by Rubin’s rules.

For patients listed as having more than one RMD or being treated with more than one of the medications of interest, we created a hierarchy based on clinical expertise to categorise patients. We used the same hierarchy as in Strangfeld *et al*.⁴ This process produces disjoint categories, allowing a clear reference group for interpretation of the regression models and avoiding collinearities. Patients with more than one of the following diseases were grouped according to the following hierarchy: systemic lupus erythematosus >vasculitis>other CTD >rheumatoid arthritis (RA) >psoriatic arthritis (PsA)>(other) spondyloarthritis (SpA) >other non-inflammatory joint diseases (IJDs)/non-CTD rheumatic disease; where ‘X>Y’ means that disease X has priority over disease Y and an individual who has both disease X and disease Y is counted as patient with disease X. Similarly, patients receiving multiple csDMARDs or immunosuppressants (except glucocorticoids) were grouped according to the following hierarchy: immunosuppressants>sulfasalazine>antimalarials>leflunomide>methotrexate. Patients receiving a bDMARD/tsDMARD alone or in combination were considered solely in the bDMARD/tsDMARD group. Patients with an IJD other than RA, PsA or SpA (n=6); patients treated with more than one bDMARD/tsDMARD (n=1); and patients receiving interleukin-1 inhibitors (n=27) or belimumab (n=11) were excluded from analysis due to low numbers.

Table 1 Patient characteristics

Parameter	Not hospitalised, no death	Hospitalised, no invasive ventilation or death	Invasive ventilation or death	Total
N	1771 (77.9)	374 (16.4)	129 (5.7)	2274
General				
Age (years)	55 (18)	67 (19)	71 (19)	57 (19)
66–75	226 (12.8)	90 (24.1)	38 (29.5)	354 (15.6)
>75	137 (7.7)	112 (29.9)	47 (36.4)	296 (13)
Male sex	546 (30.8)	130 (34.8)	67 (51.9)	743 (32.7)
Ever smoker	115 (96.6) n=119 Missing=1652	21 (100) n=21 Missing=353	9 (100) n=9 Missing=120	145 (97.3) n=149 Missing=2125
IJDs				
Rheumatoid arthritis	781 (44.1)	193 (51.6)	76 (58.9)	1050 (46.2)
Spondyloarthritis	251 (14.2)	28 (7.5)	6 (4.7)	285 (12.5)
Psoriatic arthritis	287 (16.2)	19 (5.1)	9 (7)	315 (13.9)
JIA (poly, oligo, not systemic)	6 (0.3)	0	0	6 (0.3)
All IJDs	1313 (74.1)	238 (63.6)	90 (69.8)	1641 (72.2)
CTDs/vasculitis				
SLE	91 (5.1)	12 (3.2)	2 (1.6)	105 (4.6)
CTDs (other than SLE)	134 (7.6)	29 (7.8)	13 (10.1)	176 (7.7)
Vasculitides	145 (8.2)	81 (21.7)	29 (22.5)	255 (11.2)
All CTD/vasculitides	364 (20.6)	121 (32.4)	43 (33.3)	528 (23.2)
Other RMDs				
Total	151 (8.5)	32 (8.6)	11 (8.5)	194 (8.5)
Disease activity	n=1751 Missing=20	n=355 Missing=19	n=109 Missing=20	n=2215 Missing=59
Remission	939 (53.6)	165 (46.5)	37 (33.9)	1141 (51.5)
Minimal/low disease activity	603 (34.4)	112 (31.5)	44 (40.4)	759 (34.3)
Moderate disease activity	169 (9.7)	57 (16.1)	12 (11)	238 (10.7)
Severe/high disease activity	40 (2.3)	21 (5.9)	16 (14.7)	77 (3.5)
Comorbidities				
Hypertension	524 (29.6)	186 (49.7)	83 (64.3)	793 (34.9)
Cardiovascular disease	121 (6.8)	97 (25.9)	51 (39.5)	269 (11.8)
Chronic lung disease	168 (9.5)	72 (19.3)	43 (33.3)	283 (12.4)
Chronic kidney disease	64 (3.6)	71 (19)	35 (27.1)	170 (7.5)
Obesity (BMI ≥30)	355 (20)	87 (23.3)	31 (24)	473 (20.8)
Diabetes	137 (7.7)	67 (17.9)	31 (24)	235 (10.3)
Cancer	50 (2.8)	25 (6.7)	10 (7.8)	85 (3.7)
Number of comorbidities	0 (1)	1.5 (2)	2 (3)	1 (2)
No comorbidity	896 (50.6)	74 (19.8)	15 (11.6)	985 (43.3)
≥3 comorbidities	135 (7.6)	94 (25.1)	53 (41.1)	282 (12.4)
DMARD therapies				
csDMARDs	639 (36.1)	125 (33.4)	37 (28.7)	801 (35.2)
Methotrexate (monotherapy)	381 (21.5)	84 (22.5)	22 (17.1)	487 (21.4)
Leflunomide	76 (4.3)	15 (4)	9 (7)	100 (4.4)
Sulfasalazine	51 (2.9)	12 (3.2)	4 (3.1)	67 (2.9)
Antimalarial	131 (7.4)	14 (3.7)	2 (1.6)	147 (6.5)

Continued

Table 1 Continued

Parameter	Not hospitalised, no death	Hospitalised, no invasive ventilation or death	Invasive ventilation or death	Total
Immunosuppressants	60 (3.4)	36 (9.6)	8 (6.2)	104 (4.6)
bDMARDs	653 (36.9)	102 (27.3)	41 (31.8)	796 (35)
TNF inhibitors	439 (24.8)	43 (11.5)	6 (4.7)	488 (21.5)
Abatacept	21 (1.2)	8 (2.1)	1 (0.8)	30 (1.3)
B cell-targeted bDMARDs	46 (2.6)	29 (7.8)	27 (20.9)	102 (4.5)
Rituximab	37 (2.1)	28 (7.5)	26 (20.2)	91 (4)
Belimumab	9 (0.5)	1 (0.3)	1 (0.8)	11 (0.5)
IL-6 inhibitors	47 (2.7)	9 (2.4)	3 (2.3)	59 (2.6)
IL-1 inhibitors	21 (1.2)	3 (0.8)	3 (2.3)	27 (1.2)
IL-17, IL-23, IL-12/23 inhibitors	79 (4.5)	10 (2.7)	1 (0.8)	90 (4)
tsDMARDs	108 (6.1)	33 (8.8)	14 (10.9)	155 (6.8)
JAK inhibitors	101 (5.7)	32 (8.6)	14 (10.9)	147 (6.5)
Apremilast	7 (0.4)	1 (0.3)	0	8 (0.4)
No DMARD therapies	311 (17.6)	79 (21.1)	29 (22.5)	419 (18.4)
Further therapies				
Glucocorticoids (#)	485 (27.5) n=1759 Missing=12	198 (52.9) n=373 Missing=1	78 (60.5) n=129 Missing=0	761 (33.6) n=2261 Missing=13
0 mg/day<glucocorticoids ≤10 mg/day	453 (25.8)	179 (48)	60 (46.5)	692 (30.6)
Glucocorticoids>10 mg/day	24 (1.4)	18 (4.8)	18 (14)	60 (2.7)
NSAIDs	395 (22.9) (n=1736 Missing=47)	59 (16.3) (n=120 Missing=2)	12 (9.9) n=83 Missing=0	466 (21.1) n=2208 Missing=66

Data are N (column %) for categorical variables or mean (SD) for continuous variables. Table includes all patients with a non-missing outcome and non-missing values for age, sex and DMARDs (four patients excluded). Data refer to patients with non-missing values for the respective variable; total N for patients with non-missing values is given in parentheses for variables with missing values; the total number of missing values is also given in parentheses, for the applicable variables. # denotes patients with a missing glucocorticoid dosage. For csDMARD therapies and immunosuppressants, only patients not simultaneously receiving a bDMARD/tsDMARD are included. For csDMARDs, patients are included who correspond to the specific therapy when applying the hierarchy described in the Methods section. bDMARD, biological disease-modifying antirheumatic drug; BMI, body mass index; csDMARD, conventional synthetic disease-modifying antirheumatic drug; CTD, connective tissue disease; DMARD, disease-modifying anti-rheumatic drug; IJD, inflammatory joint disease; IL, interleukin; JAK, Janus kinase; JIA, juvenile idiopathic arthritis; N, number; NSAID, non-steroidal anti-inflammatory drug; RMDs, rheumatic and musculoskeletal diseases; SLE, systemic lupus erythematosus; TNF, tumour necrosis factor; tsDMARD, targeted synthetic disease-modifying antirheumatic drug.

Regression coefficients were considered statistically significant for p values <0.05. All analyses were conducted in SAS V.9.4 or R V.4.0.4.

RESULTS

Patient characteristics

Baseline characteristics of the patients are shown in table 1. Of the 2274 patients included, 1771 (78%) did not require hospitalisation. Eighty-three patients died, resulting in a case fatality rate of 3.6%.

The mean age of all patients was 57 years; 67% were female. The most common RMD was RA with 46%, followed by PsA (14%), SpA (13%) and vasculitides (11%).

Eighty-six per cent of patients had a PCR-confirmed diagnosis of SARS-CoV-2 infection; 8% had only an antibody-confirmed diagnosis; the remaining patients had an unknown/other type of diagnosis (two patients were diagnosed based on symptoms only). For all patients, the outcome of SARS-CoV-2 infection was known.

RMD treatments

At the time of SARS-CoV-2 infection, 18% did not receive any DMARD treatment (see table 1). Immunosuppressants (mycophenolate mofetil, azathioprine, cyclophosphamide and ciclosporin) were used in 5%, csDMARDs in 35%, bDMARDs in 35% and tsDMARDs in 7%. Methotrexate was the most common csDMARD, and TNFi was

Table 2 Results of the multivariable ordinal logistic regression using the proportional odds model

Ordinal regression (proportional odds model)	OR	95% CI
General		
Age ≤65 years	1.0	Reference
65 years<age≤75	2.6	2.0 to 3.6
Age >75	3.6	3.0 to 5.0
Male sex (vs female)	1.7	1.3 to 2.1
Comorbidities		
Hypertension alone or CVD alone	1.5	1.2 to 2.0
Hypertension and CVD	2.4	1.7 to 3.6
Chronic lung disease	2.0	1.5 to 2.6
Chronic kidney disease	1.8	1.2 to 2.5
Diabetes mellitus	1.3	0.9 to 1.8
Rheumatic disease		
Rheumatoid arthritis	1.0	Reference
Systemic lupus erythematosus	0.5	0.2 to 1.1
Vasculitides	1.1	0.7 to 1.5
Other connective tissue diseases	0.9	0.6 to 1.5
Psoriatic arthritis	0.5	0.3 to 0.7
Spondyloarthritides	0.8	0.5 to 1.3
Other rheumatic diseases (not IJDs/CTDs/vasculitis)	1.0	0.6 to 1.8
Medication*		
Methotrexate (monotherapy)	1.0	Reference
No DMARD therapy	0.9	0.7 to 1.4
Leflunomide	0.8	0.5 to 1.4
Antimalarials	0.7	0.4 to 1.3
Sulfasalazine	1.1	0.6 to 2.1
Immunosuppressants	2.2	1.3 to 3.9
TNF inhibitors	0.6	0.4 to 0.9
Abatacept	1.3	0.5 to 3.0
Rituximab	5.4	3.3 to 8.8
IL-6 inhibitors	0.7	0.3 to 1.5
IL-17/IL-23/IL-12+23 inhibitors	0.9	0.4 to 1.9
JAK inhibitors	1.8	1.1 to 2.7
Disease activity and glucocorticoids		
Remission/low DA, no GCs	1.0	(Reference)
Remission/low DA, GCs 1–10mg/day	1.6	1.2 to 2.0
Remission/low DA, GCs>10mg/day	4.6	1.9 to 11.4
Moderate/high DA, no GCs	2.0	1.3 to 3.1
Moderate/high DA, GCs 1–10mg/day	2.4	1.5 to 3.7
Moderate/high DA, GCs >10mg/day	5.3	2.5 to 10.9

Ordinal outcome of COVID-19 severity was defined as (1) not-hospitalised, (2) hospitalised but not invasively ventilated and (3) invasively ventilated/deceased. Missing values imputed via multiple imputation. Effects significant at level $\alpha=0.05$ are marked in bold. N=2222. Compared with table 1, the following numbers of patients were excluded: 27 patients receiving IL-1 inhibitors, 11 patients receiving belimumab, 8 patients receiving apremilast, 6 patients with non-systemic JIA, 1 patient receiving multiple bDMARDs/tsDMARDs.

*Patients receiving multiple csDMARDs or immunosuppressants (except glucocorticoids) were grouped according to the following hierarchy: immunosuppressants>sulfasalazine>antimalarials>leflunomide>methotrexate. Patients receiving a bDMARD/tsDMARD alone or in combination were considered solely in the bDMARD/tsDMARD group.

bDMARD, biological disease-modifying antirheumatic drug; csDMARD, conventional synthetic disease-modifying antirheumatic drug; CTD, connective tissue disease; CVD, cardiovascular disease; DA, disease activity; DMARD, disease-modifying antirheumatic drug; GC, glucocorticoid; IJD, inflammatory joint disease; IL, interleukin; JAK, Janus kinase; JIA, juvenile idiopathic arthritis; TNF, tumour necrosis factor; tsDMARD, targeted synthetic disease-modifying antirheumatic drug.

the most common bDMARD. Rituximab was used in 91 patients (4%), and JAKi was used in 147 patients (6.5%).

SARS-CoV-2 infection outcome analysis

Age above 65 years was associated with higher COVID-19 severity with an OR of 2.6 (95% CI 2.0 to 3.6) and above 75 years with an OR of 3.6 (95% CI 3.0 to 5.0) (table 2 and figure 1A). Male sex was also associated with greater severity (OR 1.7, 95% CI 1.3 to 2.1).

Arterial hypertension, CVD, chronic lung disease (including chronic obstructive pulmonary disease, asthma and interstitial lung diseases), and CKD showed significant associations with COVID-19 severity (table 2 and figure 1B). The strongest association was found for patients having both comorbidities, arterial hypertension and CVD (OR 2.4, 95% CI 1.7 to 3.6).

With respect to the underlying RMD entity, PsA was associated with less severe COVID-19 course in comparison to RA (OR 0.5, 95% CI 0.27 to 0.74) (table 2 and figure 1C).

Since disease activity and the use of glucocorticoids are usually linked, both factors were analysed jointly. The results are shown in table 2 and figure 1D. Remission/low disease activity *with* low dose GCs (1–10 mg/d) showed a significant association with worse outcome (OR 1.6, 95% CI: 1.2 to 2.0) compared with remission/low disease activity *without* GCs. This effect increased with higher GC doses (OR 4.6, 95% CI 1.9 to 11.4). Moderate/high disease activity but no GCs were also associated with a worse outcome compared with remission/low disease activity with no GCs (OR 1.99, 95% CI 1.28 to 3.11). Moderate/high disease activity with low-dose GC were associated with a worse COVID-19 outcome with an OR of 2.4 (95% CI 1.5 to 3.7), and in case of moderate/high disease activity with high-dose GC, this was even more prominent with an OR of 5.3 (95% CI 2.53 to 10.9).

For the analysis of the impact of RMD treatment on the outcome of SARS-CoV-2 infection, MTX monotherapy was used as reference (table 2 and figure 1E). Treatment with immunosuppressants (mycophenolate mofetil, azathioprine, cyclophosphamide and ciclosporin) was associated with a higher COVID-19 severity (OR 2.2, 95% CI 1.3 to 3.9). JAKis were also associated with a significantly worse severity (OR 1.8, 95% CI 1.1 to 2.7). The strongest association with worse outcome of COVID-19 was found for rituximab with an OR of 5.4 (95% CI 3.3 to 8.8). In contrast, TNFi showed a significant association with a better outcome of SARS-CoV-2 infection with an OR of 0.6 (95% CI 0.4 to 0.9).

DISCUSSION

This analysis adds evidence that medication for RMD has a considerable impact on the course of SARS-CoV-2 infection. Two main results could be retrieved from this analysis: (1) TNFi is not associated with a more severe course of SARS-CoV-2 infection in patients with RMD and, (2) in contrast, immunosuppressants, JAKis and rituximab

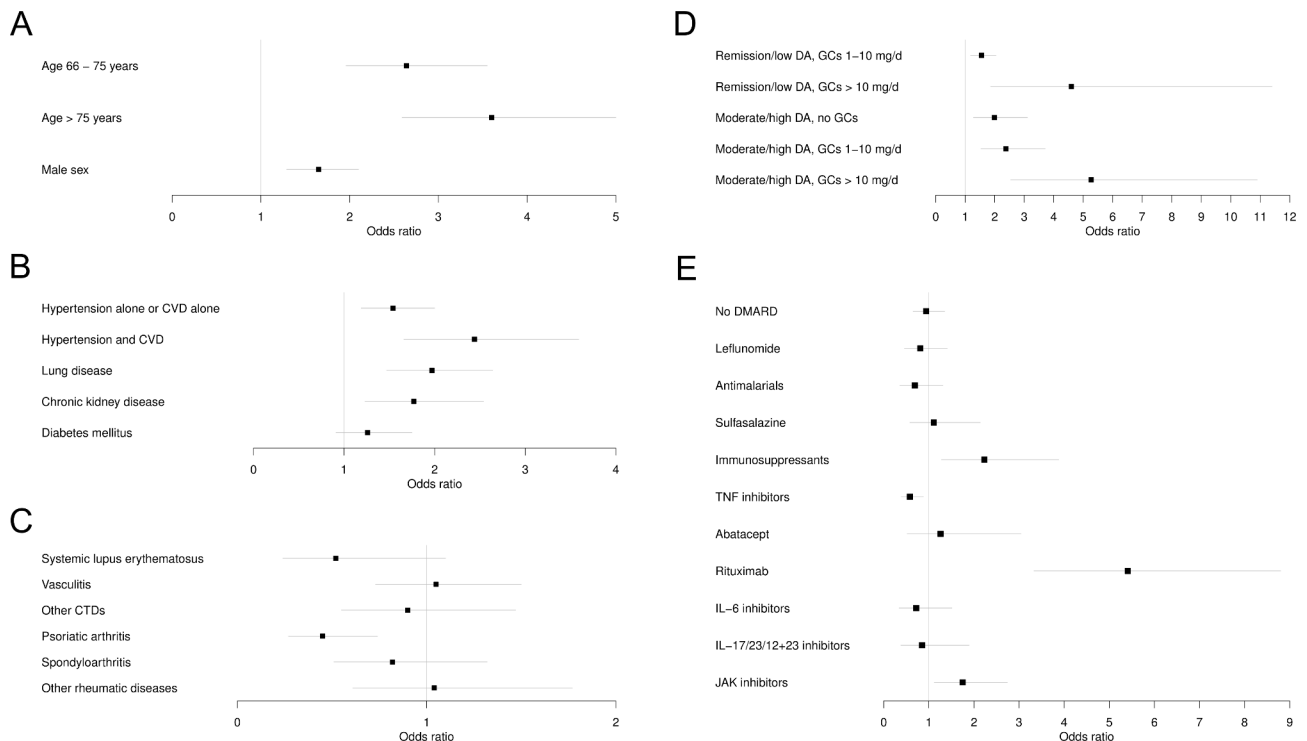


Figure 1 (A–E) Results of the multivariable ordinal logistic regression using the proportional odds model and reported as OR and 95% CI for each regressor variable. Associations with SARS-CoV-2 infection severity are shown with (A) general factors, (B) comorbidities, (C) RMD diagnosis, (D) RMD disease activity and glucocorticoids, (E) RMD treatment (immunosuppressants: mycophenolate mofetil, azathioprine, cyclophosphamide and ciclosporin). The reference categories are as follows: (A) ≤ 65 years, ≤ 65 years, female sex; (B) the non-presence of the specific comorbidity; (C) rheumatoid arthritis; (D) remission/low disease activity, no glucocorticoids; and (E) methotrexate monotherapy. Missing values were imputed via multiple imputation. $N=2222$. Compared with table 1, the following numbers of patients were excluded: 27 patients receiving IL-1 inhibitors, 11 patients receiving belimumab, 8 patients receiving apremilast, 6 patients with non-systemic JIA, one patient receiving multiple bDMARDs/tsDMARDs. bDMARD, biological disease-modifying antirheumatic drug; CVD, cardiovascular disease; CTD, connective tissue diseases; DMARD, disease-modifying anti-rheumatic drugs; DA, disease activity; GC, Glucocorticoids; IL, interleukin; JAK, Janus kinase; TNF, tumour necrosis factor; tsDMARD, targeted synthetic disease-modifying anti-rheumatic drugs.

are associated with a more severe course. Moreover, it could be confirmed that general risk factors like age, male sex and certain chronic conditions are also associated with greater severity of SARS-CoV-2 infection in patients with underlying RMD.¹²

RMD-specific risk factors have been described. The impact of disease activity and GC use are of utmost importance. Disease activity and the use of GC are usually linked. Analysing these effects separately from each other is very difficult because of the known confounding by indication in the setting of observational data. In a correspondence to the COVID-19 mortality analysis of the GRA data set,⁴ this interaction was shown.¹³ Here, we present similar results. However, in this analysis, GC use was associated with worse outcome even in patients in remission or low disease activity.

In this analysis, PsA was associated with a better COVID-19 course compared with RA. In the COVID-19 mortality analysis, PsA was not significantly associated but also showed an OR of less than 1.0 (0.75, 95% CI 0.53 to 1.07). Whether the positive association seen in our analysis is due to true differences between the diseases

or unmeasured confounders is not clear. However, the risk of severe infection in bDMARD-treated patients with psoriasis compared with patients with RA is much lower, which might be a signal of different susceptibility for severe infections.¹⁴

A very important finding of our analysis is the potential beneficial effect of TNFi. This association was not seen in an earlier mortality analysis, although TNFi showed also an OR of less than 1.0 (0.9; 95% CI: 0.5 to 1.4).⁴ This discrepancy might be due to the large heterogeneity in the GRA data set with large differences between the countries regarding the outcomes. In the analysis by Sparks *et al.* TNFi were used as reference medication and therefore, due to methodological reasons, the impact of TNFi could not be estimated in this study.⁵ There are also clinical trials using TNFi in different settings of COVID-19.¹⁵

In the GRA analysis concerning the risk of mortality, sulfasalazine was significantly associated with mortality.⁴ In our analysis, sulfasalazine was not associated with COVID-19 severity, which may be due to more homogeneous data with regard to healthcare system-related factors.

Regarding the influence of rituximab, there is growing evidence for an association with a worse outcome. This has been shown in various settings in RMDs.^{4 5 16–18} In our analysis, we confirmed these results. The influence of B-cell depletion/anti-CD20 antibodies like rituximab on COVID-19 outcome has also been studied in other diseases in which these treatments are used.^{19 20} For example, observational studies from multiple sclerosis showed a similar association of rituximab with severe COVID-19 outcome as in RMD.²¹

Data addressing an influence of JAKis on COVID-19 outcome are still limited. Thus, our analysis adds important knowledge showing an association of JAKi as RMD treatment with a more severe course of COVID-19. A negative association with COVID-19 outcome was also seen in the RA analysis of the GRA data set.⁵ In an analysis from Sweden, an increased risk of COVID-19-related hospitalisation as well as COVID-19-related death has been described for patients under therapy with JAKis.¹⁶ In contrast, owing to their anti-inflammatory potential, JAKis have been approved for the short-term treatment of severe COVID-19.^{9 22} Here, the timing and duration of the treatment seems to play a role, with negative impact in patients with RMD pretreated with JAKis and potential benefits when initiated to treat severe SARS-CoV-2 infection. A pathophysiological explanation could be that type I interferon response is crucial in the initial phase of infection for a good outcome of SARS-CoV2 infection.²³ Therefore, inhibition of the type I interferon pathway by JAKi in the early phase of infection might contribute to more severe COVID-19.

The strengths of this analysis in comparison to the GRA data lie in the fact that our data are more homogenous as they were collected in a single country within one health-care system and similar treatments and chances of care for all included patients.

However, there also are study limitations. Missing data on known confounders like RMD disease duration and number of RMD pretreatments limit the interpretation. Especially for rituximab and JAKi, it is known that they are often used in non-responder to MTX/TNFi.^{24 25} Therefore, the negative impact of those therapies on COVID-19 severity needs to be interpreted carefully. Similarly, we do not have detailed data on RTX dosage and—even more important—time of last infusion to be able to calculate the number of days between RTX treatment and date of SARS-CoV-2 infection. Furthermore, we do not know if the RMD treatment was paused due to acute SARS-CoV-2 infection. Although most patients continue their RMD treatment in the pandemic as stated in the treatment recommendations, in the case of an acute symptomatic infection especially in hospitalised patients, it is recommended to pause the immunomodulating treatment.^{26–28} Differential effects of the RMD treatment might therefore also be explained by different half-lives of these drugs.

In conclusion, risk factors for higher severity of SARS-CoV-2 infection known for the general population, such as age, male sex and certain chronic conditions, play a

similar role in patients with RMDs. In addition, further risk factors need to be taken into account, for example, the influence of higher disease activity with an increased risk of worse outcome even without using GCs on the one hand and association of chronically administered GCs with a similar worse outcome on the other. Regarding RMD medication, our data show that treatment with TNFi was associated with better outcome of SARS-CoV-2 infection than MTX. Moreover, treatment with immunosuppressants, JAKi and rituximab was associated with worse outcome of SARS-CoV-2 infection. These associations may be attributed to residual and unmeasured confounding due to higher burden of comorbidity or cumulative effect of therapies. Taken together, while it is crucial to control RMD disease activity, the medication used to achieve this control needs to be carefully chosen.

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Acknowledgements The authors thank all physicians and personnel involved in the documentation of the cases in our registry: Dr Fredrik Albach, Dr Annette Alberding, Dr Tobias Alexander, Professor Dr Rieke Alten, Dr Susanne Amann, Dr Christopher Amberger, Dr Michaela Amberger, Dr Bianka Andermann, Nils Anders, Ioana Andreica, Dr Jan Andresen, Dr Nikolaos Andriopoulos, Dr Peer Aries, Professor Dr Martin Aringer, Dr Uta Arndt, Sarah Avemarg, Professor Dr Marina Backhaus, Professor Dr Christoph Baerwald, Dr Erich Bärlin, Dr Nora Bartholomä., Dr Hans Bastian, Dr Michael Bäuerle, Dr Jutta Bauhammer, Dr Christine Baumann, Professor Dr Heidemarie Becker, Dr Klaus Becker, Dr Michaela Bellm, Dr Sylvia Berger, Dr Gerhard Birkner, Professor Dr Norbert Blank, Daniel Blendea, Dr Hans Bloching, Dr Stephanie Böddeker, Dr Susanne Bogner, Dr Martin Bohl-Bühler, Sebastian Böltz, Dr Ilka Bösenberg, Nicole Böttcher, PD Dr Jan Brandt-Jürgens, Dr Matthias Braun, Dr Matthias Braunisch, Dr Jan Phillip Bremer, Dr Matthias Broll, Dr Andreas Bruckner, Dr Veronika Brumberger, Dr Martin Brzank, Dr Sahra Büllersfeld, Sandra Burger, Dr Gamal Chehab, Dr Michaela Christenn, Dr Anne Claubnitzer, Professor Dr Kirsten de Groot, Dr Elvira Decker, Dr Frank Demtröder, Dr Jacqueline Detert, Dr Rainer Dörfler, Dr Ines Dornacher, Dr Elke Drexler, Dr Edmund Edelmann, Dr Roman Eder, Dr Christina Eisterhues, Dr Andreas Engel, Dr Joachim Michael Engel, Dr Brigitte Erbslöh-Möller, Dr Miriam Feine, PD Dr Martin Feuchtenberger, Professor Dr Dr Christoph Fiehn, PD Dr Rebecca Fischer-Betz, Professor Dr Martin Fleck, Dr Stefanie Freudenberg, Dr Christian Fräbel, Dr Petra Fuchs, Dr Regina Gaissmaier, Dr Ino Gao, Oliver Gardt, Dr Georg Gauler, Dr Katrin Geißler, Dr Joachim Georgi, Dr Jasmin Gilly, Yannik Gkanatsas, Dr Cornelia Glaser, Agnes Gniezinski-Schwister, Dr Rahel Gold, Dr Norman Görl, Dr Karl-Heinz Götti, Dr Beate Göttele, Dr Anett Gräßler, Dr Ricardo Grieshaber-Bouyer, Dr Gisela Grothues, Dr Mathias Grünke, Dr Elizabeth Guilhon de Araujo, Dr Florian Günther, Mirjam

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Contributors ACR, RH, MS and UM-L had access to the study data, developed the figures and tables, and vouched for the data and analyses. MS performed the statistical analyses and contributed to data quality control, data analysis and data interpretation. ACR, RH, BFH, AK, HM-L, AP, JR, TS, AS, HS-K, REV, CS and UM-L contributed to data collection, data quality control, data analysis and data interpretation. All authors contributed to the intellectual content during the drafting and revision of the work and approved the final version to be published. ACR and RH act as guarantors.

Funding The registry is funded, in part, by the German Society for Rheumatology. RH is funded, in part, by a JLU Career grant of the Justus-Liebig-University Giessen, Germany.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval The study was approved by the ethics committee of the Justus-Liebig-University Giessen (#52–50) and is registered at EuDRAC (2020-001958-21#). For the present analysis, we included data from 30 March 2020 to 9 April 2021.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Applications to access the data should be made to the COVID-19 steering committee of the German Society for Rheumatology.

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