






ORIGINAL RESEARCH

Older age, comorbidity, glucocorticoid use and disease activity are risk factors for COVID-19 hospitalisation in patients with inflammatory rheumatic and musculoskeletal diseases

Rebecca Hasseli ¹, Ulf Mueller-Ladner,¹ Bimba F Hoyer,² Andreas Krause,³ Hanns-Martin Lorenz,⁴ Alexander Pfeil ⁵, Jutta Richter,⁶ Martin Schäfer ⁷, Tim Schmeiser,⁸ Anja Strangfeld,⁷ Hendrik Schulze-Koops ⁹, Reinhard E Voll,¹⁰ Christof Specker,¹¹ Anne Constanze Regierer ⁷

To cite: Hasseli R, Mueller-Ladner U, Hoyer BF, et al. Older age, comorbidity, glucocorticoid use and disease activity are risk factors for COVID-19 hospitalisation in patients with inflammatory rheumatic and musculoskeletal diseases. *RMD Open* 2021;7:e001464. doi:10.1136/rmdopen-2020-001464

CS and ACR contributed equally.

Received 28 September 2020
Revised 6 January 2021

Accepted 10 January 2021



© Author(s) (or their employer(s)) 2021. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

Correspondence to

Dr Anne Constanze Regierer;
Anne.Regierer@drfz.de

ABSTRACT

Introduction Whether patients with inflammatory rheumatic and musculoskeletal diseases (RMD) are at higher risk to develop severe courses of COVID-19 has not been fully elucidated. Aim of this analysis was to describe patients with RMD according to their COVID-19 severity and to identify risk factors for hospitalisation.

Methods Patients with RMD with PCR confirmed SARS-CoV-2 infection reported to the German COVID-19 registry from 30 March to 1 November 2020 were evaluated. Multivariable logistic regression was used to estimate ORs for hospitalisation due to COVID-19.

Results Data from 468 patients with RMD with SARS-CoV-2 infection were reported. Most frequent diagnosis was rheumatoid arthritis, RA (48%). 29% of the patients were hospitalised, 5.5% needed ventilation. 19 patients died. Multivariable analysis showed that age >65 years (OR 2.24; 95% CI 1.12 to 4.47), but even more >75 years (OR 3.94; 95% CI 1.86 to 8.32), cardiovascular disease (CVD; OR 3.36; 95% CI 1.5 to 7.55), interstitial lung disease/chronic obstructive pulmonary disease (ILD/COPD) (OR 2.79; 95% CI 1.2 to 6.49), chronic kidney disease (OR 2.96; 95% CI 1.16 to 7.5), moderate/high RMD disease activity (OR 1.96; 95% CI 1.02 to 3.76) and treatment with glucocorticoids (GCs) in dosages >5 mg/day (OR 3.67; 95% CI 1.49 to 9.05) were associated with higher odds of hospitalisation. Spondyloarthritis patients showed a smaller risk of hospitalisation compared with RA (OR 0.46; 95% CI 0.23 to 0.91).

Conclusion Age was a major risk factor for hospitalisation as well as comorbidities such as CVD, ILD/COPD, chronic kidney disease and current or prior treatment with GCs. Moderate to high RMD disease activity was also an independent risk factor for hospitalisation, underlining the importance of continuing adequate RMD treatment during the pandemic.

Key messages

What is already known about this subject?

- ▶ Due to systemic inflammatory conditions and immunomodulating treatment, rheumatic and musculoskeletal disease (RMD) patients might be at increased risk of a more severe course of SARS-CoV-2 infection.
- ▶ Only limited data on risk factors for a critical course of COVID-19 in patients with RMD are available.

What does this study add?

- ▶ Age, comorbidities (cardiovascular disease, interstitial lung disease/chronic obstructive pulmonary disease and chronic kidney disease), the use of glucocorticoids for the treatment of RMD and RMD disease activity are independent risk factors for COVID-19 hospitalisation.

How might this impact on clinical practice?

- ▶ Adequate treatment of RMD with control of disease activity is crucial for the management of our patients during the pandemic.
- ▶ Patients with RMD with risk factors identified with this analysis should be closely monitored and receive guidance about infection risk minimising behaviour.

INTRODUCTION

In Germany, the first cases of SARS-CoV-2 infection (COVID-19) were reported at the end of January 2020.¹ Similar to other European countries, SARS-CoV-2 spread rapidly in Germany. The course of infection with SARS-CoV-2 ranges from asymptomatic to fatal. In the general population, higher age, male gender and comorbidities are associated with the severity of SARS-CoV-2 infection.^{2,3} Since the outbreak of the pandemic,

concerns have been raised regarding the probability of developing a severe or even life-threatening course in patients with inflammatory rheumatic and musculoskeletal diseases (RMD).⁴⁻⁶ Patients with RMD are characterised by an overall increase in risk of infection due to the autoimmune disease itself and immunomodulatory drugs.⁷⁻⁹ The risk of infection is dependent on age, functional capacity, comorbidities and immunomodulatory treatment with biological disease-modifying antirheumatic drugs (bDMARDs) and glucocorticoids (GC).¹⁰ Immunomodulatory drugs with anti-inflammatory action may limit overwhelming immune responses that appear to be responsible for the severe pulmonary complications in COVID-19.^{11 12} However, not all immunomodulatory treatments seem to influence the risk for a critical course in the same direction. Whereas registry data had shown a beneficial effect of biological DMARDs regarding the development of sepsis and mortality in patients with rheumatoid arthritis (RA) and serious infections, it had also shown a significantly increased risk conveyed with GCs.¹³ Data from the COVID-19 Global Rheumatology Alliance (GRA) physician-reported registry indicate that GC ≥ 10 mg/day are associated with a higher hospitalisation rate with SARS-CoV-2 infection in patients with RMD,¹⁴ which underlines the importance of controlling disease activity with DMARDs in order to decrease GC dose.

Furthermore, the recommendations from EULAR and DGRh (German Society for Rheumatology) state that immunomodulating therapy should be maintained during the SARS-CoV-2 pandemic to avoid RMD relapse.^{15 16}

Limited data are available as for whether and to what extent patients with RMD are at an increased risk for SARS-CoV-2 infection^{11 17 18} and for a more severe course of COVID-19. For this reason, a national registry was established allowing a rapid and timely collection of RMD cases with confirmed SARS-CoV-2 infections in Germany in order to analyse the clinical course of COVID-19 in patients with RMD and to develop guidance for the management of patients with RMD during the COVID-19 pandemic.¹⁹ The aim of this analysis was to identify risk factors for hospitalisation, comparing non-hospitalised patients with RMD to hospitalised patients, stratified by the need for invasive ventilation.

METHODS

Data source

In March 2020, the German Society for Rheumatology, together with the Justus-Liebig-University Giessen, founded a national registry for patients with pre-existing inflammatory rheumatic diseases (RMD) and SARS-CoV-2 infection confirmed by PCR test. Rheumatologists voluntarily enter the data into an online database with implemented plausibility checks (URL <https://www.covid19-rheuma.de>).

The ascertained data include SARS-CoV-2 infection-specific items such as symptoms, duration, treatment and

outcome, RMD specific items such as diagnosis, physician assessed disease activity (categorised into remission, low, moderate or high disease activity), and treatment of RMD, and general items such as sociodemographic information and comorbidities. Missing data on diagnosis and treatment of RMD and outcome of COVID-19 can be queried by contacting participating physicians. Data collection was done retrospectively. Participating centres consist of academic and non-academic rheumatology departments and private practices in Germany.

The German registry's content is harmonised with the EULAR COVID-19 database (https://www.eular.org/eular_covid19_database.cfm) to allow joint analysis. The study is registered at EuDRACt 2020-001958-21#.

Statistical analysis

Descriptive statistics were applied to compare non-hospitalised patients with hospitalised patients, either without or with invasive ventilation.

Multivariable logistic regression was used to estimate odds ratios (OR) and 95% CIs for the main outcome parameter of this analysis, which is hospitalisation due to COVID-19 as indicator for severity of the SARS-CoV-2 infection. Simple logistic regressions with one explanatory variable were performed to determine the set of regressors for the multivariable regression. Variables with a $p < 0.1$ were included in the final model. Covariates included in the model were age group, rheumatic disease group (RA, spondyloarthritis, connective tissue diseases (CTDs) and vasculitis, other rheumatic diseases), inflammatory activity of the rheumatic disease, specific comorbidities (cardiovascular disease (CVD), hypertension without CVD, interstitial lung diseases (ILD) or chronic obstructive pulmonary disease (COPD), diabetes mellitus, chronic kidney disease, cancer), prior and/or current use of GC (none, up to 5 mg/day, over 5 mg/day). Spondyloarthritides included psoriatic arthritis (PsA), axial spondyloarthritis (axSpA) and enteropathic arthritis. CTDs and vasculitis included systemic lupus erythematosus, Sjögren's syndrome, systemic sclerosis, mixed CTDs, overlap syndromes, polymyalgia rheumatica, granulomatosis with polyangiitis (GPA), eosinophilic GPA, microscopic polyangiitis, large vessel vasculitis, Behçet's disease and other types of vasculitis. For patients belonging to more than one rheumatic disease category, we used the following hierarchy for prioritisation: CTD/vasculitis > RA > spondyloarthritides > other rheumatic diseases. In this way, disjoint categories are created, establishing a clear reference group for interpretation of the regression model and avoiding collinearities. In order to avoid collinearity between CVD and hypertension, hypertension in the model refers to patients who had hypertension but not CVD. Missing values for obesity, disease activity state, GC dose and non-steroidal antirheumatic agents were derived by multiple imputation using full conditional specification.²⁰ Results of the logistic regression analyses for 10 imputed datasets were pooled by

Table 1 Patient characteristics stratified for non-hospitalisation, hospitalisation without ventilation and hospitalisation with invasive ventilation

Parameter	Non-hospitalised	Hospitalised without invasive ventilation	Hospitalised with invasive ventilation	Total
N	332 (70.9)	110 (23.5)	26 (5.5)	468
General				
Age (years)	54 (19)	66 (21)	66.5 (15)	57 (19)
Male sex	111 (33.5)	35 (31.8)	13 (50)	159 (34)
Duration of symptoms (days)	12 (9)	17 (13)	32.5 (12)	14 (13)
Smoking	27 (8.1)	10 (9.1)	3 (11.5)	40 (8.5)
Further outcomes				
Death	1 (0.3)	5 (4.5)	13 (50)	19 (4.1)
ARDS	0	1 (0.9)	15 (57.7)	16 (3.4)
Sepsis	0	1 (0.9)	14 (53.8)	15 (3.2)
RMD				
Moderate/high RMD disease activity	35 (10.5)	29 (25.9)	9 (33.5)	72 (15.4)
RA	146 (44)	62 (56.4)	17 (65.4)	225 (48.1)
Spondyloarthritides	105 (31.6)	15 (13.6)	5 (19.2)	15 (26.7)
Connective tissue diseases/vasculitis	65 (19.6)	31 (28.2)	7 (26.9)	103 (22)
Other RMD diagnoses	26 (7.8)	8 (7.3)	1 (3.8)	35 (7.5)
Comorbidities				
No of comorbidities	0 (1)	1 (2)	2 (2)	1 (2)
Arterial hypertension	92 (27.7)	48 (43.6)	16 (61.5)	156 (33.3)
Cardiovascular disease	16 (4.8)	25 (22.7)	8 (30.8)	49 (10.5)
Interstitial lung disease	6 (1.8)	3 (2.7)	2 (7.7)	11 (2.4)
Chronic obstructive pulmonary disease	7 (2.1)	12 (10.9)	6 (23.1)	25 (5.3)
Asthma	31 (9.3)	9 (8.2)	1 (3.8)	41 (8.8)
Chronic kidney disease	9 (2.7)	21 (19.1)	2 (7.7)	32 (6.8)
Cancer	11 (3.3)	11 (10)	1 (3.8)	23 (4.9)
Obesity (BMI ≥ 30 kg/m ²)	59 (17.6)	25 (22.4)	5 (18.5)	88 (18.8)
Diabetes	27 (8.1)	18 (16.4)	3 (11.5)	48 (10.3)
Osteoporosis	19 (5.7)	14 (12.7)	1 (3.9)	34 (7.3)
No comorbidity	154 (46.4)	19 (17.3)	3 (11.5)	176 (37.6)
Therapy				
No DMARD	58 (17.5)	26 (23.6)	5 (19.2)	89 (19)
csDMARD mono	137 (41.3)	49 (44.5)	7 (26.9)	193 (41.2)
tsDMARD	11 (3.3)	6 (5.5)	2 (7.7)	19 (4.1)
bDMARD	126 (38)	29 (26.4)	12 (46.2)	167 (35.7)
TNFi	91 (27.4)	13 (11.8)	2 (7.7)	106 (22.6)
ABA	4 (1.2)	3 (2.7)	1 (3.8)	8 (1.7)
B-cell depletion	10 (3)	7 (6.4)	7 (26.9)	24 (5.1)
IL1i	1 (0.3)	0	0	1 (0.2)
IL6i	6 (1.8)	2 (1.8)	2 (7.7)	10 (2.1)
Other ILi	14 (4.2)	4 (3.6)	0	18 (3.8)
Glucocorticoids	103 (31)	59 (53.6)	18 (69.2)	180 (38.5)
Glucocorticoids ≤ 5 mg/day	91 (27.3)	42 (38.2)	12 (46.2)	145 (30.9)
Glucocorticoids > 5 mg/day	12 (3.7)	17 (15.5)	6 (23.1)	35 (7.6)

Continued

Table 1 Continued

Parameter	Non-hospitalised	Hospitalised without invasive ventilation	Hospitalised with invasive ventilation	Total
N	332 (70.9)	110 (23.5)	26 (5.5)	468
Other RMD medication	6 (1.8)	11 (10)	4 (15.4)	21 (4.5)
NSAID	84 (25.4)	23 (21.3)	3 (11.9)	111 (23.7)
Anti hypertension drugs	67 (20.2)	35 (31.8)	15 (57.7)	117 (25)

For continuous variables, median (IQR) is given, for categorical variables, N (%) is given. The following numbers of missing values exist: 88 (18.8%) for duration of symptoms, 51 (10.9%) for obesity, 31 (6.6%) for disease activity state, 1 for glucocorticoid dose (0.6%, among patients receiving glucocorticoids) and 33 (7.1%) for non-steroidal antirheumatic agents. Absolute numbers may be rounded for some variables due to multiple imputation. Collagenoses include Sjögren syndrome, systemic sclerosis, mixed collagenoses, overlap collagenoses and polymyositis/dermatomyositis/inclusion body myositis. Other RMD include fibromyalgia, sarcoidosis, TRAPS, FMF and adult-onset Still's disease. Other RMD medication include colchicine, mesalazine, and mucofenolate.

ABA, abatacept; ARDS, acute respiratory distress syndrome; bDMARD, biological DMARD; BMI, body mass index; csDMARD, conventional synthetic DMARD; DMARD, disease-modifying antirheumatic drug; IL, interleukin; NSAID, non-steroidal anti-inflammatory drug; RA, rheumatoid arthritis; RMD, rheumatic and musculoskeletal disease; TNFi, tumour necrosis factor inhibitor; tsDMARD, targeted synthetic DMARD.

Rubin's rules. Calculations were carried out with the software packages SAS, V.9.4, and R, V.3.6.3.

RESULTS

Patients characteristics

Between March 30 (first patient in) and 1 November 2020 (database lock), 468 patients with RMD and a PCR-confirmed SARS-CoV-2 infection were documented in the German registry, 309 patients were female. Median age was 57 years. Regarding RMD diagnosis, RA was most common with 48%, followed by 14% PsA, and 12% axSpA.

Patient characteristics are shown in table 1, stratified into the three groups: non-hospitalised patients, hospitalised patients without or with need for invasive ventilation. The following numbers of missing values exist: 88 (18.8%) for duration of COVID-19 symptoms, 51 (10.9%) for obesity, 31 (6.6%) for inflammatory activity state, 1 for GC dose (0.6%, among patients receiving GCs) and 33 (7.1%) for non-steroidal antirheumatic drugs. There was no missing data on outcome of SARS-CoV-2 infection, so all patients either fully recovered or died.

Of the 468 patients, 136 (29%) were hospitalised of whom 26 (5.5%) needed invasive ventilation. 19 patients died, resulting in a case fatality rate of 4%. Eighteen of these patients died in the hospital, 13 had received invasive ventilation.

Most patients with RMD had comorbidities; only 38% did not have any other chronic condition. The most frequent comorbidity was arterial hypertension, followed by obesity, CVD and diabetes.

Regarding RMD treatment, 19% of the patients did not receive any DMARD. Thirty-six per cent were on bDMARDs and 41% on conventional synthetic (cs) DMARD monotherapy. Thirty-nine per cent of the patients were on GC treatment, most of them (81%) received low dose GCs of ≤ 5 mg/day.

Comparison of non-hospitalised patients with hospitalised patients without ventilation and hospitalised patients with invasive ventilation

The percentage of men was larger among hospitalised patients with ventilation (50%) compared with those without ventilation (32%) or non-hospitalised (34%) (table 1).

Forty-four per cent of the non-hospitalised patients suffered from RA, compared with 56% and 65% in the hospitalised groups. According to physicians' assessments, moderate to high RMD disease activity was present in 11% of the non-hospitalised patients, 26% in the hospitalised patients without ventilation and 34% in the ventilated patients.

Regarding RMD treatment, 18% of the non-hospitalised patients did not receive any DMARD compared with 24% and 19% in the hospitalised groups. Tumour necrosis factor inhibitors were documented as RMD treatment in 27% of the non-hospitalised patients, in 12% of the hospitalised group without ventilation and 8% in the ventilated patients. Twenty-seven per cent of the ventilated patients were on B-cell-depletion treatment, whereas only 3% of the non-hospitalised and 6% of the hospitalised patients without ventilation had received B-cell-depleting treatment.

Factors associated with hospitalisation

Results of the univariate analyses comparing non-hospitalised patients with hospitalised patients are shown in table 2.

The results of the multivariable model are shown in figure 1 and online supplemental table 1). Age > 65 years (OR 2.24; 95% CI 1.12 to 4.47), but even more > 75 years (OR 3.94; 95% CI 1.86 to 8.32), CVD (OR 3.36; 95% CI 1.5 to 7.55), lung disease (ILD/COPD) (OR 2.79; 95% CI 1.2 to 6.49) and chronic kidney disease (OR 2.96; 95% CI 1.16 to 7.5) were associated with higher

Table 2 OR of COVID-19 hospitalisation in univariate analyses of patients with RMD

Variable	OR	95% CI	P value
Age 66–75 years	2.470	1.393 to 4.378	0.0020
Age >75 years	7.269	3.983 to 13.263	<0.0001
Gender, male	1.081	0.711 to 1.644	0.7155
Current smoking	1.194	0.596 to 2.390	0.6167
Moderate to high RMD disease activity	3.203	1.879 to 5.461	<0.0001
RMD diagnosis			
spondyloarthritides (reference: RA)*	0.333	0.185 to 0.599	0.0002
CTDs/vasculitis (reference: RA)*	0.882	1.936 to 1.505	0.6438
other RMDs (reference: RA)*	1.283	0.674 to 2.443	0.4473
Comorbidities			
Cardiovascular disease	6.327	3.346 to 11.966	<0.0001
Art. hypertension	1.508	0.975 to 2.331	0.0647
ILD/COPD	4.994	2.448 to 10.191	<0.0001
Asthma	0.771	0.367 to 1.619	0.4916
Chronic kidney disease	7.305	3.283 to 16.255	<0.0001
Obesity (BMI ≥ 30 kg/m ²)	1.283	0.767 to 2.145	0.3419
Diabetes	2.063	1.122 to 3.794	0.0198
Cancer	2.568	1.086 to 6.074	0.0318
RMD treatment			
No DMARD (reference: csDMARDs)	1.308	0.765 to 2.234	0.3264
B/tsDMARD (reference: csDMARD)	0.875	0.558 to 1.373	0.5614
Glucocorticoids ≤ 5 mg/day (reference: no glucocorticoids)†	1.755	1.153 to 2.671	0.0087
Glucocorticoids > 5 mg/day (reference: no glucocorticoids)†	5.250	2.533 to 10.881	<0.0001
NSAID	0.710	0.429 to 1.175	0.1825

For each variable, a separate logistic regression analysis was run containing only an intercept term and the variable in question. For disease activity, obesity, glucocorticoid use and NSAID, missing values were imputed 10 times and the analysis was conducted on each imputation stratum. Subsequently, combined results were obtained following Rubin's rules. Variables presenting a $p < 0.1$ were entered into the multivariable model.

*The variable RMD diagnosis is jointly represented by three dummy regressors.

†The variable glucocorticoid use is jointly represented by two dummy variables.

.BMI, body mass index; COPD, chronic obstructive pulmonary disease; CTD, connective tissue disease; DMARD, disease-modifying antirheumatic drug; ILD, interstitial lung disease; NSAID, non-steroidal anti-inflammatory drug; RA, rheumatoid arthritis; RMD, rheumatic and musculoskeletal disease.

odds of hospitalisation. Patients with spondyloarthritides showed a lower risk of hospitalisation compared with RA (OR 0.46; 95% CI 0.23 to 0.91). Moderate to high RMD disease activity was furthermore significantly associated with hospitalisation (OR 1.96; 95% CI 1.02 to 3.76), as well as treatment with GC in dosages > 5 mg/day (OR 3.67; 95% CI 1.49 to 9.05).

DISCUSSION

In the challenging situation of the SARS-CoV-2 pandemic, physicians and patients need rapid access to the evolving evidence to close the gaps of knowledge which are stressful for patients with chronic conditions. When the pandemic started, it was unclear whether patients with RMD are at an increased risk to get infected or whether

they have a higher risk of a severe course of COVID-19. In this analysis, hospitalisation was used as indicator for a more severe course. Older age, CVD, ILD/COPD, chronic kidney disease, treatment with GC at doses of > 5 mg/day, and moderate to high RMD disease activity were identified as independent risk factors for hospitalisation.

Our results are in line with the recently published analysis of the GRA.¹⁴ In the GRA analysis, the cases from the German registry had not yet been included, so these two cohorts are independent. Similar results have also been found in a meta-analysis on autoinflammatory diseases including RMDs.²¹

Age seems to be the most important factor associated with a more severe course of COVID19^{2 3 22 23} and this

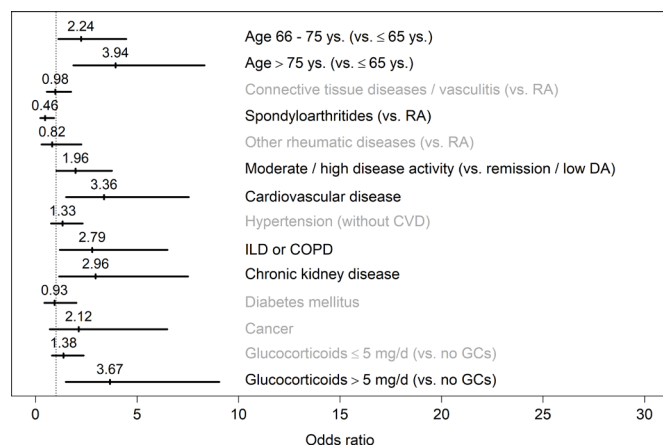


Figure 1 Multivariable logistic regression was used to estimate ORs and 95% CIs for the main outcome parameter of this analysis, hospitalisation due to COVID-19 versus non-hospitalisation as indicator for severity of the SARS-CoV-2 infection. COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; DA, disease activity; GC, glucocorticoid; ILD, interstitial lung disease; RA, rheumatoid arthritis.

holds also true for patients with RMD as described in our analysis and other reports.^{24–28}

Importantly, moderate to high RMD disease activity was identified as an independent risk factor for hospitalisation. This is an important finding, not only in that this is a risk factor specifically related to RMDs but also with implications for the daily management, reaffirming recent recommendations that state the importance of RMD disease control during the pandemic.^{15 16}

The influence of comorbidities is also widely recognised since the first reports of COVID-19.²⁹ In our cohort, CVD, ILD/COPD and chronic kidney disease were significantly associated with hospitalisation. Interestingly, asthma was not associated with an increased risk as was also described in the UK.³ This is in accordance with an asthma-specific analysis where the authors did not find an association of asthma with hospitalisation.³⁰ This effect is in contrast to other pulmonary comorbidities such as ILD and COPD.

In our cohort, prior or current treatment with GC was associated with a high risk of hospitalisation in accordance with the GRA analysis¹⁴ and with previous evidence of an increased infection risk in general.¹⁰

The interpretation of the influence of GC treatment on hospitalisation has to be performed with caution. There is a probability of confounding by indication since GC are given under certain circumstances which may influence the outcome itself like a high disease activity of the RMD. Since uncontrolled RMD activity also enhances the risk of infections, our results should not encourage stopping GC treatment. However, GC should be administered in the lowest possible dose, as recommended by the recently published guidance for the management of COVID-19 in RMD,^{15 16} as already a dose of >5 mg/day was associated with an increased risk of hospitalisation in our study.

Male gender has also been described as an important risk factor for a more severe course and higher mortality.^{3 23} In our analysis, male gender was not associated with hospitalisation. This was also the case in the GRA analysis.¹⁴ However, regarding the results of the descriptive analysis (table 1), male gender was much more common in the group of ventilated patients compared with the other patients. As already described in the general population, male gender might therefore be associated with a worse outcome also in patients with RMD.^{3 23 31}

Comparing the results from RMD with chronic inflammatory bowel disease (IBD), interesting parallels can be found. In the first analysis of the international registry for patients with IBD and confirmed SARS-CoV-2 infection, similar risk factors associated with worse COVID-19 outcome were identified, namely older age, number of comorbidities and use of systemic GC.³²

The strengths of our study include the large sample size with PCR confirmed SARS-CoV-2 infections in patients with RMD. As all patients were treated in Germany, both the healthcare system and treatment strategies for COVID-19 were comparable in all cases, reducing confounding due to differences regarding these factors as might be present in analyses including patients from many countries. The completeness of data is high with only a small percentage of missing values. Particularly, the outcome ‘hospitalisation’ was known in all cases, as all cases were documented after full recovery or death of patient.

A limitation of our study is the observational design, which is prone to confounding by indication. For example, it is possible that patients taking GCs might be hospitalised more often because of the potential risk of a more severe outcome of the infection. Also, a potential influence of the SARS-CoV-2 infection on the course of the RMD cannot be assessed based on our data because of the cross-sectional design. Only few details of the RMD are known, as factors like disease duration, functional capacity or treatment history are not captured in the registry.

Although this is one of the largest RMD COVID-19 cohorts published so far, the number of cases was still too low to include specific RMD treatments into the multivariable analysis. With increasing numbers of patients, these analyses will probably become possible in the near future.

Another limitation is that possibly more severe cases were preferably documented, resulting in a selection bias. However, we believe that the conclusions drawn from our model are robust since there is no indication that the impact of age, disease activity, specific comorbidities or GC treatment is influenced by this bias.

In this large German cohort of patients with RMD with SARS-CoV-2 infection, 29% were hospitalised. Age, RMD disease activity, CVD, ILD/COPD and GC treatment starting at doses of >5 mg/day were independently associated with hospitalisation. These risk factors are similar to those found in general COVID-19 cohorts. However,

to our knowledge, this is the first analysis identifying moderate to high RMD disease activity as independent risk factor for hospitalisation due to COVID-19. It is important to continue the documentation of patients with RMDs and COVID-19 in order to generate more evidence for counselling and to find the best therapeutic management of our patients.

Author affiliations

- ¹Department of Rheumatology and Clinical Immunology, Campus Kerkhoff, Justus-Liebig-University, Giessen, Giessen, Germany
- ²Department of Rheumatology and Clinical Immunology, Clinic for Internal Medicine I, University of Schleswig-Holstein at Kiel, Kiel, Germany
- ³Department of Rheumatology, Clinical Immunology and Osteology, Immanuel Hospital, Berlin, Germany
- ⁴Department of Rheumatology, University Hospital, Heidelberg, Germany
- ⁵Department of Internal Medicine III, Universitätsklinikum Jena, Jena, Germany
- ⁶Department of Rheumatology and Hiller Research Unit, Medical Faculty, Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Nordrhein-Westfalen, Germany
- ⁷Epidemiology Unit, German Rheumatism Research Center Berlin, Berlin, Germany
- ⁸Department of Rheumatology and Immunology, Saint Josef Hospital, Wuppertal, Germany
- ⁹Division of Rheumatology and Clinical Immunology, Department of Internal Medicine IV, University of Munich, Munich, Germany
- ¹⁰Dep. of Rheumatology and Clinical Immunology, University of Freiburg Faculty of Medicine, Freiburg, Germany
- ¹¹Department of Rheumatology and Clinical Immunology, Kliniken Essen-Mitte, Essen, Germany

Acknowledgements The authors would like to thank all physicians (Boeddecker, Stephanie; Kurthen, Reiner; Mattar, Johannes; Anita Viardot; Brandt-Jürgens, Jan; Rühl, Markus; Menne, Hans-Jürgen; Bremer, Jan-Phillip; Bauhammer, Jutta; Maerz, Vanessa; Dörfner, Rainer; Andriopoulos, Nikolaos; Merwald-Fraenk, Helga; Henes, Jörg; Noethe, Matthias; Wiesent, Franziska; Weigelt, Martin; Hauf, Maura-Maria; Riemekasten, Gabriela; Aries, Peer; Bloching, Hans; Reindl, Christiane; Hein, Liane; Herzer, Peter; Decker, Elvira; Gilly, Jasmin; De Groot, Kirsten; Korsten, Peter; Krusche, Martin; Kovacs, Magdolna; Bösenberg, Ilka; Piechalska, Marta; Saar, Petra; Köchel, Katrin; Maus, Sebastian; Krummel-Lorenz, Brigitte; Lantzech, Heiko; Raub, Wolfgang; Kittel, Birgit; Röser, Markus; Sievert, Iris; Weiß, Angela; Ospina, Puschke, Michael; Scholz, Michaela; Anders, Nils; Rossmani, Christoph; Krüger, Klaus; Bruckner, Andreas; Hartmann, Urs; Nerenheim, Anabell; Gniezinski-Schwister, Agnes; Alexander, Tobias; Rockwitz, Karin; Haibel, Hildrun; Schieweck-Güsmar, Andreas; Steinchen, Nicolai; Bender, Nico; Boche, Konrad; Winau, Lea; Bäuerle, Michael; Saech, Jaesmine; Klink, Claudia; Feuchtenberger, Martin; Avemarg, Sarah; Drexler, Elke; Weiner, Stefan; Sonn, Sigrid; Blendea, Daniel; Becker, Klaus; Witt, Matthias; Melzer, Adelheid; Eder, Roman; Fleck, Martin; Löffler, Christian; Hoese, Guido; Schönherr, Jutta; Vallbracht-Ackermann, Inka; Baerwald, Christoph; Sekura, Matthias; Kreutzberger, Rene; Voll, Reinhard; Schiebel, Magnus; Nottarp, Dirk; Zaus, Monika; Wysocki, Nina; Birkner, Gerhard; Krause, Dietmar; Amberger, Christopher; Sensse, Jörg; Grünke, Mathias; Späthling-Mestekemper, Susanna; Werner, Stephanie; Freudenberg, Stefanie; Bellm, Michaela; Willeke, Peter; Röther, Ekkehard; Strunk, Johannes; Veerhoff, Susanne; Welcker, Martin; Schlenker, Ulrike; Karberg, Kirsten; Venhoff, Nils; Schuch, Florian; Alten, Rieke; Hueber, Axel; Albach, Frederik; Hasenkamp, Charlotte; Ochs, Wolfgang; Rudwaleit, Martin; Hein, Reinhard; Büllfeld, Sarah; Jacobi, Annett M.; Becker, Heidemarie; Hallmann-Böhm, Till; Glaser, Cornelia; Sandrock, Eva; Bohl-Bühler, Reckert; Schübler, Anna-Sophia; Pfeil, Alexander; Schnarr, Sebastian; Brzank, Martin; Iburg, Elke; Schmalzing, Marc; Maier, Ingeborg; Weidner, Sven; Mortsch, Markus; Rissom, Viale; Andreica, Ioana; Wisseler, Hans; Schoo, Ulrich; Hübner, Georg; Burger, Sandra; Claußnitzer, Anne; Olk, Jürgen; Günther, Florian; Vogl, Markus; Kirchgässner, Matthias; Vaith, Peter; Weinerth, Jutta; Mörtlbauer, Harald; Wernicke, Dirk; Göttl, Karl Heinz; Aringer, Martin; Grünke, Sabine; Stockdreher, Karin; Hoff, Paula; Kreher, Gabi; Engel, Andreas; Heel, Nicole; Sglunda, Ondrej; Kurzeja, Rolf; Stapfer, Gerald; März, Anette; Thoden, Jan; Georgi, Joachim; Gao, Ino; Pulla, Almut; Reckert, Sabine; Röther, Fabian; Mauf-Etzler, Ursula; Gauler, Georg; Kalthoff, Ludwig; Edelmann, Edmund; Hadjiski, Denitsa; Jandova, Ilona; Grieshaber Bouyer, Ricardo; Metzler, Claudia; Mueche, Burkhard; Pick, Dorothea; Schwarze, Ilka; Vinnemeier-Laubenthal, Lisa; Kapelle, Andreas; Knietz, Christian; Igney-Oertel, Annette; Krieger-Dippel, Eveline; Schmitt-Haendle, Matthias; Hermann, Walter; Tatsis, Stefanie; Arndt, Uta; Schlittenhardt, Daniel; Baumann, Christine; Özden, Filiz; Rösel, Maike; Detert, Jacqueline; Braunisch, Matthias; Demtröder, Frank; Nüvemmann, Dieter; Steinmüller, Mirko; Hornig, Johannes; Sheikh, Naheed; Broll,

Matthias; Meier, Florian; Juche, Aaron; Görl, Norman; Sarholz, Michael; Feine, Miriam; Hendrix, Claudia; Zinke, Silke; Sokoll, Katharina; Blank, Norbert; Surmann, Mechthild; Kaudewitz, Dorothee; Protopopov, Mikhail; Kudela, Holger) and personnel involved in the documentation of the cases in our registry.

Contributors RH and UM-L: Substantial contributions to the conception of the work and the acquisition, analysis and interpretation of data for the work, drafting the work. MS: substantial contributions to the conception of the work, statistical analysis and interpretation of data for the work. BFH, AK, H-ML, AP, JR, TS, AS, HS-K and REV: Substantial contributions to the conception of the work and the interpretation of data for the work. Revising the work critically for important intellectual content. CS and ACR: substantial contributions to the conception and design of the work and the analysis, and interpretation of data for the work. Drafting the work. All authors: final approval of the version to be published. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding RH was supported by the Justus-Liebig University Giessen Clinician Scientist Programme in Biomedical Research (JLU-CAREER) to work on this registry.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The study was approved by the ethics committee of the Justus-Liebig-University Giessen (#52–50).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iDs

Rebecca Hasseli <http://orcid.org/0000-0002-2982-8253>
Alexander Pfeil <http://orcid.org/0000-0002-2709-6685>
Martin Schäfer <http://orcid.org/0000-0001-6487-3634>
Hendrik Schulze-Koops <http://orcid.org/0000-0002-1681-491X>
Anne Constanze Regierer <http://orcid.org/0000-0003-2456-4049>

REFERENCES

- 1 Böhmer MM, Buchholz U, Corman VM, *et al.* Investigation of a COVID-19 outbreak in Germany resulting from a single travel-associated primary case: a case series. *Lancet Infect Dis* 2020;20:920–8.
- 2 Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. *JAMA* 2020;323:1239–42.
- 3 Docherty AB, Harrison EM, Green CA, *et al.* Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. *BMJ* 2020;369:m1985.
- 4 Figueroa-Parra G, Aguirre-Garcia GM, Gamboa-Alonso CM, *et al.* Are my patients with rheumatic diseases at higher risk of COVID-19? *Ann Rheum Dis* 2020;79:annrheumdis-2020-217322–40.
- 5 D'Silva KM, Serling-Boyd N, Wallwork R, *et al.* Clinical characteristics and outcomes of patients with coronavirus disease 2019 (COVID-19) and rheumatic disease: a comparative cohort study from a US 'hot spot'. *Ann Rheum Dis* 2020;79:1156–62.
- 6 Pablos JL, Galindo M, Carmona L, *et al.* Clinical outcomes of hospitalised patients with COVID-19 and chronic inflammatory and autoimmune rheumatic diseases: a multicentric matched cohort study. *Ann Rheum Dis* 2020;79:1544–9.
- 7 Singh JA, Cameron C, Noorbaloochi S, *et al.* Risk of serious infection in biological treatment of patients with rheumatoid arthritis: a systematic review and meta-analysis. *Lancet* 2015;386:258–65.
- 8 Noreña I, Fernández-Ruiz M, Aguado JM. Viral infections in the biologic therapy era. *Expert Rev Anti Infect Ther* 2018;16:781–91.
- 9 Listing J, Gerhold K, Zink A. The risk of infections associated with rheumatoid arthritis, with its comorbidity and treatment. *Rheumatology* 2013;52:53–61.
- 10 Strangfeld A, Eveslage M, Schneider M, *et al.* Treatment benefit or survival of the fittest: what drives the time-dependent decrease in

- serious infection rates under TNF inhibition and what does this imply for the individual patient? *Ann Rheum Dis* 2011;70:1914–20.
- 11 Emmi G, Bettiol A, Mattioli I, *et al.* SARS-CoV-2 infection among patients with systemic autoimmune diseases. *Autoimmun Rev* 2020;19:102575.
 - 12 Mehta P, McAuley DF, Brown M. Hlh across speciality collaboration UK: COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* 2020;395:1033–4.
 - 13 Richter A, Listing J, Schneider M, *et al.* Impact of treatment with biologic DMARDs on the risk of sepsis or mortality after serious infection in patients with rheumatoid arthritis. *Ann Rheum Dis* 2016;75:1667–73.
 - 14 Gianfrancesco M, Hyrich KL, Al-Adely S, *et al.* Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: data from the COVID-19 global rheumatology alliance physician-reported registry. *Ann Rheum Dis* 2020;79:859–66.
 - 15 Schulze-Koops H, Specker C, Iking-Konert C, *et al.* Preliminary recommendations of the German Society of rheumatology (DGRh eV) for the management of patients with inflammatory rheumatic diseases during the SARS-CoV-2/COVID-19 pandemic. *Ann Rheum Dis* 2020;79:840–2.
 - 16 Landewé RB, Machado PM, Kroon F, *et al.* EULAR provisional recommendations for the management of rheumatic and musculoskeletal diseases in the context of SARS-CoV-2. *Ann Rheum Dis* 2020;79:851–8.
 - 17 Michelena X, Borrell H, López-Corbeto M, *et al.* Incidence of COVID-19 in a cohort of adult and paediatric patients with rheumatic diseases treated with targeted biologic and synthetic disease-modifying anti-rheumatic drugs. *Semin Arthritis Rheum* 2020;50:564–70.
 - 18 Pablos JL, Abasolo L, Alvaro-Gracia JM, *et al.* Prevalence of hospital PCR-confirmed COVID-19 cases in patients with chronic inflammatory and autoimmune rheumatic diseases. *Ann Rheum Dis* 2020;79:1170–3.
 - 19 Hasseli R, Mueller-Ladner U, Schmeiser T, *et al.* National Registry for patients with inflammatory rheumatic diseases (IRD) infected with SARS-CoV-2 in Germany (recovery): a valuable mean to gain rapid and reliable knowledge of the clinical course of SARS-CoV-2 infections in patients with IRD. *RMD Open* 2020;6:e001332.
 - 20 van Buuren S. Multiple imputation of discrete and continuous data by fully conditional specification. *Stat Methods Med Res* 2007;16:219–42.
 - 21 Akiyama S, Hamdeh S, Micic D, *et al.* Prevalence and clinical outcomes of COVID-19 in patients with autoimmune diseases: a systematic review and meta-analysis. *Ann Rheum Dis* 2020. doi:10.1136/annrheumdis-2020-218946
 - 22 Grasselli G, Zangrillo A, Zanella A, *et al.* Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy region, Italy. *JAMA* 2020;323:1574–81.
 - 23 Petrilli CM, Jones SA, Yang J, *et al.* Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. *BMJ* 2020;369:m1966.
 - 24 Briggs FBS, Gianfrancesco MA, George MF. More on Covid-19 in immune-mediated inflammatory diseases. *N Engl J Med* 2020;383:796–7.
 - 25 Fredi M, Cavazzana I, Moschetti L, *et al.* COVID-19 in patients with rheumatic diseases in northern Italy: a single-centre observational and case-control study. *Lancet Rheumatol* 2020;2:e549–56.
 - 26 Freitas Nuñez DD, Leon L, Mucientes A, *et al.* Risk factors for hospital admissions related to COVID-19 in patients with autoimmune inflammatory rheumatic diseases. *Ann Rheum Dis* 2020;79:1393–9.
 - 27 Haberman RH, Castillo R, Chen A, *et al.* COVID-19 in patients with inflammatory arthritis: a prospective study on the effects of comorbidities and disease-modifying antirheumatic drugs on clinical outcomes. *Arthritis Rheumatol* 2020;72:1981–9.
 - 28 Montero F, Martínez-Barrio J, Serrano-Benavente B, *et al.* Coronavirus disease 2019 (COVID-19) in autoimmune and inflammatory conditions: clinical characteristics of poor outcomes. *Rheumatol Int* 2020;40:1593–8.
 - 29 Chen N, Zhou M, Dong X, *et al.* Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020;395:507–13.
 - 30 Chhiba KD, Patel GB, Vu THT, *et al.* Prevalence and characterization of asthma in hospitalized and nonhospitalized patients with COVID-19. *J Allergy Clin Immunol* 2020;146:307–14.
 - 31 Scirè CA, Carrara G, Zanetti A, *et al.* COVID-19 in rheumatic diseases in Italy: first results from the Italian registry of the Italian Society for rheumatology (CONTROL-19). *Clin Exp Rheumatol* 2020;38:748–53.
 - 32 Brenner EJ, Ungaro RC, Gearry RB, *et al.* Corticosteroids, but not TNF antagonists, are associated with adverse COVID-19 outcomes in patients with inflammatory bowel diseases: results from an international registry. *Gastroenterology* 2020;159:481–91.