

Identification of Risk Factors for COVID-19 Hospitalization in Patients With Anti-Rheumatic Drugs: Results From a Multicenter Nested Case Control Study

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Patients with inflammatory rheumatic diseases (IRDs) do not have an increased risk for coronavirus disease 2019 (COVID-19) compared with the general population. However, it remains uncertain whether subgroups of patients with IRD using different immunosuppressive antirheumatic drugs carry a higher risk for severe COVID-19 compared with other patients with IRD. The aim of this study is to identify risk factors for severe COVID-19, requiring hospitalization in patients with IRD. This is a multicenter nested case control study conducted in the Netherlands. Cases are hospital known patients with IRD requiring hospitalization for COVID-19 between March 1, 2020, and May 31, 2020. Controls are hospital known patients with IRD not requiring hospitalization for COVID-19 in this period, included at a 4:1 ratio. Patient, disease, and treatment characteristics were extracted from electronic medical records and a questionnaire. Potential risk factors were analyzed using unconditional logistic regression, corrected for confounders and multiple testing. Eighty-one cases and 396 controls were included. General risk factors of older age and obesity apply to patients with IRD as well (odds ratio (OR) for age ≥ 75 3.5, 95% confidence interval (CI) 1.9–6.3, OR for body mass index ≥ 40 4.5, 95% CI 1.5–14). No significantly increased ORs for COVID-19 hospitalization were found for any antirheumatic agent or IRD. A protective effect was found for use of methotrexate (OR 0.53, 95% CI 0.31–0.92). In conclusion, similar to the general population, elderly and obese patients with IRD have a higher risk for hospitalization for COVID-19. We did not identify a specific antirheumatic agent or IRD to increase the risk of COVID-19 hospitalization in patients with IRD, except for a possible protective effect of methotrexate.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

✓ The majority of the studies performed on coronavirus disease 2019 (COVID-19) risk in inflammatory rheumatic diseases (IRDs) show no increased risk for severe COVID-19 in these patients, who often receive immunosuppressive antirheumatic drugs. Case-control studies are, however, a scarce commodity and most of the data is derived from registry-based studies.

WHAT QUESTION DID THIS STUDY ADDRESS?

✓ In this study, we aimed to determine whether certain patients with IRD carry a higher risk for COVID-19-related hospitalization, for example, due to the use of antirheumatic agents.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

✓ The overall finding that no specific antirheumatic drugs or IRD enhances the risk of severe COVID-19, requiring hospitalization, is reassuring for patients and medical personnel. Additionally, the finding that methotrexate has a possible protective effect for severe COVID-19 is of high interest in an enduring pandemic and still imperfect protection by vaccination.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

✓ Our finding might spark interest in further investigations into methotrexate as an avenue for prospective clinical investigation in COVID-19 treatment and prevention.

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In 2020, coronavirus disease 2019 (COVID-19) developed into a worldwide pandemic. Risk factors for hospitalization for COVID-19 in the general population include older age, male sex, obesity, and cardiovascular and pulmonary comorbidities.¹⁻³ Important questions are whether these generic risk factors apply for patients with inflammatory rheumatic diseases (IRDs) as well, and whether these patients carry a higher risk due to the use of antirheumatic immunomodulatory agents (IAs).

Patients with IRD have a modest increased risk of infections,^{4,5} possibly due to the IRD itself, general risk factors (e.g., smoking and comorbidities) that are more prevalent in this population,⁶ or IA use. Although proven to be safe and effective, some IAs are associated with a slightly enhanced infection risk.^{5,7} Data on COVID-19 risk and course in patients with IRD is still quite scarce, but seems to support the fact that these patients do not have a substantially increased risk for hospitalization due to COVID-19 as compared with the general population. However, use of (high dose) glucocorticoids and possibly rituximab (RTX) may be associated with a higher risk for severe COVID-19.^{3,7-9}

The majority of studies on risk factors for COVID-19 hospitalization in patients with IRD are based on (online) registry data, introducing bias due to low quality of data, no correction for the improvement of care, and other second order effects (social distancing) for patients with COVID-19 during the pandemic. Additionally, these data lack detailed information on potentially important co-mediators. For example, a possible moderating effect in COVID-19 severity might be cross-vaccination effects, as BMR vaccinations have been suggested to be associated with less severe cases of COVID-19.^{10,11} Other indirect evidence indicates that patients with vitamin D deficiency might experience more severe cases of COVID-19.¹² Additional potential risk modifiers that remain uncharted include lifestyle, certain medication (including ACE-inhibitors and proton pump inhibitors (PPIs)⁹), and compliance with social distancing measures.

To further elucidate which patients with IRD are at higher risk for hospitalization due to COVID-19 and to avoid biases often present in registry studies, we performed an in-depth nested case-control study during a fixed span of time in the beginning of the pandemic.

METHODS

Study design

Multicenter, nested case control study conducted in four rheumatology centers in the Netherlands (Máxima Medical Centre Eindhoven, Elizabeth TweeSteden Hospital Tilburg, Bernhoven Uden, and Amphia Hospital Breda) in a region heavily affected by COVID-19 by a first wave in the spring of 2020. This study's cohort exists of patients treated for an IRD in one of the participating hospitals. Ethical approval was not required, as assessed by the local ethics committee (Commissie Mensgebonden Onderzoek region Arnhem-Nijmegen, 2020-6689). Written informed consent was obtained from all patients, except for seven patients that gave oral consent and for the case patients who died. The STROBE checklist for case control studies was used (Table S3).

Participants

Case patients were defined as patients with IRD with COVID-19 requiring hospitalization, between March 1, 2020, and May 31, 2020. Controls

were defined as patients with IRD who did not require hospitalization for COVID-19 within this period. They were randomly selected at the outpatient clinic (at physical visits as well as during telephonic consultations and recruited by different healthcare professionals, such as rheumatologists and physician assistants) and were included at a 4:1 ratio. IRDs included were rheumatoid arthritis (RA), psoriatic arthritis, axial spondylarthritis (SpA), unspecified arthritis, gout, polymyalgia rheumatica (PMR), and systemic inflammatory diseases (e.g., systemic lupus erythematosus (SLE), Sjögren). We selected cases early in the pandemic to minimize bias due to different COVID-19 measures over time, and after this initial episode we commenced our in-depth analysis and no additional cases were included.

Data collection

Patient, disease, and treatment characteristics were extracted from the electronic health records (EHRs). In addition to this, patients received a questionnaire in order to collect additional data.

Outcomes

Primary outcomes are the odds ratio (OR) point estimates of potential risk factors on COVID-19 hospitalization in patients with IRD.

Analyses

Categorical variables are expressed as numbers (percentage) and numerical variables as mean (\pm SD) or median (interquartile range (IQR)), depending on the distribution. To calculate crude and adjusted ORs for (potential) risk factors for hospital admission for COVID-19, unconditional logistic regression was used. Due to the explorative nature of this study, there was no correction for multiple testing. If relevant, the analyses were corrected for one or more confounders (Table S1). All analyses were performed using Stata 13 for Windows.

RESULTS

Patient characteristics

Eighty-one cases and 396 controls were included. Cases overall were older, more often men, and had more comorbidities than controls (Table 1). Twenty-six patients with COVID-19 died, of which 7 were on the intensive care unit, 18 in the general hospital ward, and 1 at home.

Risk factors for hospitalization due to COVID-19

Adjusted ORs are displayed in Table 2, unadjusted ORs can be found in Table S2. Age \geq 75 years was significantly associated with hospitalization (OR 3.5, 95% confidence interval (CI) 1.9–6.3). ORs for (morbid) obesity (OR for obesity 2.1, 95% CI 1.2–3.8, OR for morbid obesity 4.5, 95% CI 1.5–14) and use of ACE-inhibitors were increased as well (OR 2.0, 95% CI 1.1–3.8).

We did not find a significantly increased risk for certain IRDs or use of a particular IA. We did observe that patients with IRD using methotrexate (MTX) had a significantly lower OR for COVID-19-related hospitalization (OR 0.53, 95% CI 0.31–0.92).

DISCUSSION

In the current study, we established that risk factors for severe COVID-19 previously described in the general population apply to patients with IRD as well. Older age and a high body mass index (BMI) were identified as a risk factor for hospitalization due to COVID-19. We did not find a significantly

Table 1 Patient characteristics

	Cases (n = 81)	Controls (n = 396)
Sex, n (% male)	47 (58%)	158 (40%) ^a
Age, years, median (IQR)	74 (67–79)	64 (56–72) ^a
BMI, kg/m ² , median (IQR) [18.5–25]	28 (25–32)	26 (24–29) ^a
Smoker, including current and ex-smokers, n (%)	49 (60%)	200 (51%)
Inflammatory rheumatic disease, n (%)		
RA ^b	44 (54%)	117 (58%)
SpA	9 (11%)	119 (30%)*
Gout	17 (21%)	14 (3.5%)*
PMR	7 (8.6%)	31 (7.8%)
Systemic inflammatory diseases	6 (7.4%)	15 (3.8%)
Comorbidities, n (%)		
Diabetes mellitus	17 (21%)	49 (12%)
Cardiac disease ^c	42 (52%)	125 (32%)*
Renal impairment	19 (23%)	24 (6.1%)*
Pulmonary disease	28 (35%)	49 (12%)*
Malignancy	7 (8.6%)	4 (1.0%)*
One or more comorbidities	62 (77%)	182 (46%)*
Immunomodulatory agents, n (%)		
Conventional synthetic DMARDs	47 (58%)	287 (75%)*
Methotrexate	34 (42%)	218 (55%)*
Hydroxychloroquine	8 (9.9%)	59 (15%)
Others	16 (20%)	71 (18%)
Biological DMARDs	13 (16%)	120 (30%)*
TNF-inhibitors	9 (11%)	90 (23%)*
Abatacept	0 (0.0%)	10 (2.5%)
IL6R-blockers	1 (1.2%)	10 (2.5%)
RTX	1 (1.2%)	2 (0.51%)
Targeted synthetic DMARDs	0 (0.0)	13 (3.3%)
Glucocorticoids ≥10 mg/day	7 (8.6%)	15 (3.8%)
Other medication, n (%)		
NSAIDs	13 (16%)	121 (31%)*
ACE-inhibitors	22 (27%)	39 (9.9%)*
PPIs	51 (63%)	184 (46%)*
Vitamin D status, n (% sufficient) ^c	59 (73%)	265 (67%)
Environmental characteristics, n (%)		
Healthcare worker	7 (8.4%)	45 (11%)
Living with two or more persons	10 (12%)	91 (23%)*
Living in a nursing home	2 (2.5%)	3 (0.76%)
Receiving home care	13 (17%)	22 (5.6%)*

BMI, body mass index; DMARDs, disease modifying antirheumatic drugs; IQR, interquartile range; NSAIDs, nonsteroidal anti-inflammatory drug; PMR, polymyalgia rheumatica; PPI, proton-pump inhibitor; RA, rheumatoid arthritis; RTX, rituximab; SpA, axial spondylarthritis.

^aIncluding unspecified arthritis.

^bIncluding hypertension, cardiac failure, and myocardial infarction.

^cDefined as sufficient vitamin D level (> 50 nmol/L if age ≥ 70 years and > 30 nmol/L if age < 70 years) and/or receiving vitamin D supplementation.

*P ≤ 0.05

Table 2 Adjusted ORs for COVID-19 hospitalization

Potential risk factor	Adjusted OR (95% CI)
Generic risk factors	
Age 65–75 years	1.1 (0.63–1.8)
Age ≥ 75	3.5 (1.9–6.3)*
Obesity, BMI 30–40	2.1 (1.2–3.8)*
Morbid obesity, BMI ≥ 40	4.5 (1.5–14)*
Male sex	1.7 (0.96–2.9)
Presence of ≥ 1 comorbidity ^b	1.8 (0.97–3.4)
Smoker, current or exsmoker	1.3 (0.74–2.2)
IRD	
RA ^c	1.3 (0.70–2.4)
SpA	0.59 (0.27–1.3)
Gout	2.2 (0.83–5.8)
Polymyalgia	0.37 (0.13–1.1)
Systemic diseases	1.7 (0.54–5.4)
Immunomodulatory agents	
csDMARDs (any)	0.67 (0.33–1.4)
Methotrexate	0.53 (0.31–0.92)*
HCQ	0.55 (0.23–1.3)
Other	1.5 (0.72–3.1)
bDMARDs (any)	0.72 (0.35–1.5)
TNF-inhibitors	0.60 (0.26–1.4)
IL6R-blockers	0.53 (0.065–4.3)
RTX	7.8 (0.55–110)
Glucocorticoids ≥ 10 mg/day	1.4 (0.50–3.8)
Other medication	
NSAIDs	0.94 (0.46–1.9)
ACE-inhibitors	2.0 (1.1–3.8)*
PPIs	1.3 (0.79–2.3)
Other	
Vitamin D sufficient ^c	1.2 (0.64–2.3)
Healthcare worker	1.7 (0.67–4.2)
Received BMR vaccination	0.35 (0.10–1.2)
Receiving home care	1.8 (0.75–4.3)
Living in a nursing home	0.75 (0.064–8.7)
Living with two or more other persons	1.4 (0.61–3.1)

bDMARDs, biological disease modifying antirheumatic drugs; BMI, body mass index; CI, confidence interval; COVID-19, coronavirus disease 2019; csDMARDs, conventional synthetic disease modifying antirheumatic drugs; HCQ, hydroxychloroquine; IQR, interquartile range; IRD, inflammatory rheumatic disease; NSAIDs, nonsteroidal anti-inflammatory drug; OR, odds ratio; PMR, polymyalgia rheumatica; PPI, proton-pump inhibitor; RA, rheumatoid arthritis; RTX, rituximab; SpA, axial spondylarthritis.

*P < 0.05.

^aIncluding cardiac disease, pulmonary disease, malignancy, diabetes mellitus, and renal impairment.

^bIncluding unspecified arthritis.

^cDefined as sufficient vitamin D level (> 50 nmol/L if age 70 years and > 30 nmol/L if age < 70 years) and/or receiving vitamin D supplementation.

increased risk for COVID-19 hospitalization for any IRD or IA, except for a possible protective effect for MTX. However, our study may be underpowered to detect differences between

some IRDs and IAs, as others report increased risks for severe COVID-19 in patients with IRD that use RTX and/or glucocorticoids > 10 mg/day.^{8,13,14}

We did find an increased OR for COVID-19-related hospital admission in patients with IRD using ACE-inhibitors. Evidence on this topic was mixed in the beginning of the pandemic, however, several meta-analyses show no increased risk for the use of ACE-inhibitors in the general population.^{15,16} Therefore, this finding might be a spurious finding or due to residual confounding. Intriguingly, a lower risk for MTX use is seen. MTX is one of the most frequently used IAs in the treatment of various IRDs.¹⁷ MTX has various anti-inflammatory effects, and is, for example, known to influence T cells and cause decrease of TNF- α and IL-6 levels.¹⁸ These immunomodulatory effects could be beneficial in COVID-19 as they may suppress the hyperinflammatory response observed in COVID-19.¹⁹

Strengths of this study include low bias by second order effects due to inclusion of cases only early in the pandemic. By selecting only the “early cases,” the effects of (unbalanced) adaption of behavior, differences between COVID-19 measures in the Netherlands (e.g., lockdowns, vaccination, and testing capacity), and evolving treatment strategies have been minimized. Another strength is the completeness of the determinants, not only of those present in the EHRs but also of determinants collected from the questionnaires. However, these questionnaires could not be sent to deceased patients. Information was looked up in the EHRs (admission reports often contain information on smoking status, receiving home care, etc.).

Due to the collaboration of four rheumatology centers and inclusion of all IRDs, we expect our results to be generalizable to the IRD population. However, vaccination programs and lockdown measures may vary between countries, so results may only apply to countries comparable to the Netherlands. Other limitations could be residual confounding and the relatively small sample size, possibly explaining the observed increased OR for severe COVID-19 for use of ACE-inhibitors and the nonsignificant trend toward a higher risk that is seen in patients with gout. Even though we did correct for the most likely confounders (including comorbidities, age, BMI, and sex), there may be other factors that play a role in the risk of severe COVID-19. Finally, there may be “missed cases” (e.g., patients that were admitted to other hospitals due to capacity problems or patients that did require hospitalization but were not admitted; e.g., because of old age or comorbidities). However, information on admission in other hospitals is expected to be complete and any case patient that was identified during the enrollment period was asked to participate. Ultimately, there could be a small bias regarding the controls as no deceased controls were included.

In conclusion, risk factors for COVID-19 hospitalizations studied in the general population, such as older age and high BMI, apply to patients with IRD as well. In this study, no specific IRD or IA was identified as a risk factor for severe COVID-19. On the other hand, use of MTX might protect patients with IRD from hospitalization due to COVID-19.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

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CONFLICTS OF INTEREST

M.O. reports received grants (to the institution) from Gilead Sciences. A.d.B. has received consultancy honoraria, congress invitations, and research grants (to the institution) from Abbvie, Amgen, Cellgene, Roche, Biogen, Lilly, Novartis, Celltrion Sanofi, and Gilead. Is coinventor on a rituximab related patent (pending). J.B. has received consultancy fees from Novartis, UCB, Gilead, and Galapagos. All other authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

All authors wrote the manuscript. M.O., S.B., L.V., R.T., A.d.B., and J.B. designed the research. M.O., S.B., J.B., S.v.B., F.L., and P.V. performed the research. M.O., A.d.B., and J.B. analyzed the data.

DATA AVAILABILITY STATEMENT

De-identified data obtained, used, and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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1. Ho, F.K. *et al.* Modifiable and non-modifiable risk factors for COVID-19, and comparison to risk factors for influenza and pneumonia: results from a UK Biobank prospective cohort study. *BMJ Open* **10**, e040402 (2020).
2. Pijls, B.G. *et al.* Demographic risk factors for COVID-19 infection, severity, ICU admission and death: a meta-analysis of 59 studies. *BMJ Open* **11**, e044640 (2021).
3. Williamson, E.J. *et al.* Factors associated with COVID-19-related death using OpenSAFELY. *Nature* **584**, 430–436 (2020).
4. Listing, J., Gerhold, K. & Zink, A. The risk of infections associated with rheumatoid arthritis, with its comorbidity and treatment. *Rheumatology* **52**, 53–61 (2013).
5. Singh, J.A. *et al.* Risk of serious infection in biological treatment of patients with rheumatoid arthritis: a systematic review and meta-analysis. *Lancet* **386**, 258–265 (2015).
6. Ziade, N. *et al.* Prevalence and pattern of comorbidities in chronic rheumatic and musculoskeletal diseases: the COMORD study. *Sci. Rep.* **10**, 7683 (2020).
7. Sepriano, A. *et al.* Safety of synthetic and biological DMARDs: a systematic literature review informing the 2019 update of the EULAR recommendations for the management of rheumatoid arthritis. *Ann. Rheum. Dis.* **79**, 760–770 (2020).
8. FA12R/SFR/SNFMI/SOFREMIP/CRI/IMIDIATE consortium and contributors. Severity of COVID-19 and survival in patients with rheumatic and inflammatory diseases: data from the French RMD COVID-19 cohort of 694 patients. *Ann. Rheum. Dis.* **80**, 527–538 (2021).
9. Charpiat, B., Bleyzac, N. & Tod, M. Proton pump inhibitors are risk factors for viral infections: even for COVID-19? *Clin. Drug Investig.* **40**, 897–899 (2020).
10. Anbarasu, A., Ramaiah, S. & Livingstone, P. Vaccine repurposing approach for preventing COVID 19: can MMR vaccines reduce morbidity and mortality? *Hum. Vaccine Immunother.* **16**, 2217–2218 (2020).
11. Gold, J.E. *et al.* Analysis of Measles-Mumps-Rubella (MMR) titers of recovered COVID-19 patients. *MBio* **11**, e02628-20 (2020).

12. Isaia, G. & Medico, E. Associations between hypovitaminosis D and COVID-19: a narrative review. *Aging Clin. Exp. Res.* **32**, 1879–1881 (2020).
13. Gianfrancesco, M. *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.* **79**, 859–866 (2020).
14. Strangfeld, A. *et al.* Factors associated with COVID-19-related death in people with rheumatic diseases: results from the COVID-19 Global Rheumatology Alliance physician-reported registry. *Ann. Rheum. Dis.* **80**, 930–942 (2021).
15. Lo, K.B. *et al.* Angiotensin converting enzyme inhibitors and angiotensin II receptor blockers and outcomes in patients with COVID-19: a systematic review and meta-analysis. *Expert Rev. Cardiovasc. Ther.* **18**, 919–930 (2020).
16. Ssentongo, A.E. *et al.* Renin-angiotensin-aldosterone system inhibitors and the risk of mortality in patients with hypertension hospitalised for COVID-19: systematic review and meta-analysis. *Open Heart* **7**, e001353 (2020).
17. Smolen, J.S. *et al.* EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Ann. Rheum. Dis.* **73**, 492–509 (2014).
18. Safavi, F. & Nath, A. Silencing of immune activation with methotrexate in patients with COVID-19. *J. Neurol. Sci.* **415**, 116942 (2020).
19. Mehta, P., McAuley, D.F., Brown, M., Sanchez, E., Tattersall, R.S. & Manson, J.J. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* **395**, 1033–1034 (2020).
20. Opdam, M. *et al.* Pos1197 in depth identification of risk factors for severe COVID-19, requiring hospitalization, in patients with inflammatory rheumatic diseases: results of a Dutch nested case control study (preliminary results). *Ann. Rheum. Dis.* **80**, 880–881 (2021).