

## ORIGINAL RESEARCH

# High levels of immunosuppression are related to unfavourable outcomes in hospitalised patients with rheumatic diseases and COVID-19: first results of ReumaCoV Brasil registry

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**To cite:** Marques CDL, Kakehasi AM, Pinheiro MM, *et al*. High levels of immunosuppression are related to unfavourable outcomes in hospitalised patients with rheumatic diseases and COVID-19: first results of ReumaCoV Brasil registry. *RMD Open* 2021;**7**:e001461. doi:10.1136/rmdopen-2020-001461

Received 27 September 2020  
Revised 1 December 2020  
Accepted 24 December 2020



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## ABSTRACT

**Objectives** To evaluate risk factors associated with unfavourable outcomes: emergency care, hospitalisation, admission to intensive care unit (ICU), mechanical ventilation and death in patients with immune-mediated rheumatic disease (IMRD) and COVID-19.

**Methods** Analysis of the first 8 weeks of observational multicentre prospective cohort study (ReumaCoV Brasil register). Patients with IMRD and COVID-19 according to the Ministry of Health criteria were classified as eligible for the study.

**Results** 334 participants were enrolled, a majority of them women, with a median age of 45 years; systemic lupus erythematosus (32.9%) was the most frequent IMRD. Emergency care was required in 160 patients, 33.0% were hospitalised, 15.0% were admitted to the ICU and 10.5% underwent mechanical ventilation; 28 patients (8.4%) died. In the multivariate adjustment model for emergency care, diabetes (prevalence ratio, PR 1.38; 95% CI 1.11 to 1.73;  $p=0.004$ ), kidney disease (PR 1.36; 95% CI 1.05 to 1.77;  $p=0.020$ ), oral glucocorticoids (GC) (PR 1.49; 95% CI 1.21 to 1.85;  $p<0.001$ ) and pulse therapy with methylprednisolone (PR 1.38; 95% CI 1.14 to 1.67;  $p=0.001$ ) remained significant; for hospitalisation, age  $>50$  years (PR 1.89; 95% CI 1.26 to 2.85;  $p=0.002$ ), no use of tumour necrosis factor inhibitor (TNFi) (PR 2.51; 95% CI 1.16 to 5.45;  $p=0.004$ ) and methylprednisolone pulse therapy (PR 2.50; 95% CI 1.59 to 3.92;  $p<0.001$ ); for

ICU admission, oral GC (PR 2.24; 95% CI 1.36 to 3.71;  $p<0.001$ ) and pulse therapy with methylprednisolone (PR 1.65; 95% CI 1.00 to 2.68;  $p<0.043$ ); the two variables associated with death were pulse therapy with methylprednisolone or cyclophosphamide (PR 2.86; 95% CI 1.59 to 5.14;  $p<0.018$ ).

**Conclusions** Age  $>50$  years and immunosuppression with GC and cyclophosphamide were associated with unfavourable outcomes of COVID-19. Treatment with TNFi may have been protective, perhaps leading to the COVID-19 inflammatory process.

## INTRODUCTION

Patients with immune-mediated rheumatic diseases (IMRD) are at increased risk of infections, with significant morbidity associated with serious infections, constituting one of the main causes of mortality in these patients.<sup>1</sup> Although previously published studies that evaluated patients with IMRD with COVID-19 did not demonstrate an increased risk of more severe infections in these groups when compared with the general population,<sup>2-4</sup> these studies do not fully clarify whether patients with IMRD are at an increased risk

## Key messages

## What is already known about this subject?

- ▶ Patients with immune-mediated rheumatic diseases (IMRD) are at increased risk of infections.
- ▶ There are uncertainties as to whether patients with IMRD are at an increased risk of developing more severe forms of COVID-19.

## What does this study add?

- ▶ Patients with IMRD with COVID-19 did not demonstrate an increased risk of more severe infection in previous studies.
- ▶ High levels of immunosuppression with methylprednisolone or cyclophosphamide pulse therapy and chronic oral GC were associated with unfavourable outcomes of the SARS-CoV-2 infection.
- ▶ Tumour necrosis factor inhibitor (TNFi) had an association with a lower prevalence of hospitalisation and need for intensive care unit admission.

## How might this impact on clinical practice?

- ▶ Immunosuppressed patients should be routinely and even more carefully evaluated for SARS-CoV-2 infection, as they may have unfavourable outcomes.
- ▶ In countries where the COVID-19 epidemic is on the rise, high-grade immunosuppression and GC should be stopped or reduced, as long disease activity allows.
- ▶ TNFi can be continued, as it appears to protect against severe forms of the disease.

of developing more severe forms of COVID-19.<sup>5,6</sup> Moreover, Brazil is a country of continental dimensions, with important regional differences in relation to socioeconomic status, basic sanitation and access to health, and the evolution of patients with COVID-19 and IMRD may assume a different behaviour from other parts of the world.

The primary aim of this paper was to describe the patients included in the first 8 weeks of the ReumaCoV Brasil register, evaluating the factors associated with the following outcomes: (1) need for emergency care (patients who went to the hospital, except those who were seen in an outpatient clinic), (2) hospitalisation (more than 24 hours of hospital permanence), (3) intensive

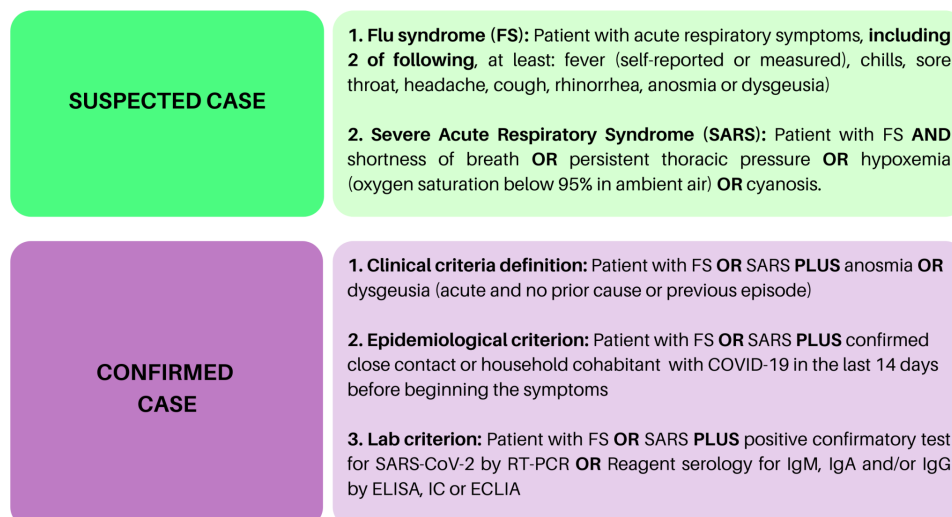
care unit (ICU) admission, (4) mechanical ventilation and (5) death. Our hypothesis was that patients with IMRD and high-grade immunosuppression could have an unfavourable evolution compared with those with less immunosuppression.

## METHODS

The complete study methodology was previously published.<sup>7</sup> Briefly, the ReumaCoV Brasil is a multicentre, observational, prospective cohort study carried out to monitor adult IMRD patients with COVID-19 diagnosis, using a convenience sample, whose data collection began 20 May 2020, with inclusion scheduled until December 2020, with 43 participating research centres.<sup>8</sup> This paper will present the analysis of data for the first 8 weeks of inclusion in the study.

Eligible patients were selected based on the identification of a case of COVID-19 by the researcher, through telephone contact, outpatient consultation or during hospitalisation for COVID-19. Inclusion criteria were: (1) age over 18, (2) COVID-19 diagnosis, according to the Brazilian Health Minister (BMH) (figure 1) and (3) prior diagnosis of IMRD, according to the American College of Rheumatology or the European League against Rheumatism criteria. Exclusion criteria were other immunodeficiency diseases, past organ or bone marrow transplantation, neoplasms within the last 5 years, current chemotherapy, HIV diagnosis and thymus diseases.

Demographic data such as age, sex, work situation and social isolation during the pandemic, as well diagnosis and treatment of IMRD, comorbidities (<https://www.who.int/classifications/icd/icdonlineversions/en/>), clinical characteristics, treatment and evolution of COVID-19 were collected using a Research Electronic Data Capture (REDCap) database (<https://www.project-redcap.org/>), through telephone call or face-to-face interview, if permitted by local health recommendations. In case of hospitalisation, the data were collected directly



**Figure 1** COVID-19 diagnosis established by the Brazilian Ministry of Health during the pandemic period. FS, flu syndrome.

with the patient, if possible, or from medical records. In cases where death was notified, data were collected directly from a family member, who authorised the inclusion of the data in the register.

For data analysis, a database was built using the REDCap database, which was exported to the SPSS program, V.21, where the analysis was performed. To characterise the profile of the patients, the percentage of frequencies were calculated, and the frequency distribution of the evaluated factors was constructed. For the quantitative variables, the median and IQR statistics were calculated. In order to verify which factors influenced the outcomes, the contingency table was constructed and the Chi-square test for the independence sample was applied. In cases where the assumptions of the  $\chi^2$  test were violated, Fisher's exact test was applied. In addition, prevalence ratios (PR) and the respective CI were calculated. Since the objective of the study was to assess the evolution of the most severe forms of COVID-19 in patients with IMRD, the IUC and death outcomes were analysed only among patients who were hospitalised.

All conclusions were drawn considering the significance level of 5%. The variables that showed statistical significance of up to 20% in the bivariate analysis were included in the Poisson multivariate adjustment. Variables with a 5% significance remained in the final model. The OR was calculated to assess the chance of a COVID-19 symptom occurring in patients with laboratory confirmed disease.

This study was registered at the Brazilian Registry of Clinical Trials—REBEC, RBR-33YTQC. All patients read and signed the informed consent form before inclusion.

## RESULTS

Results are reported in accordance with STROBE guidelines. Between 20 May 20 and 24 July 2020, 334 IMRD patients with a diagnosis of COVID-19 were included in the register. The median age was 45 years (IQR=31–57) and 81.4% were female. In regard to their work situation, 186 (55.0%) patients were active at the time of SARS-CoV-2 infection; among the inactive, most were retired or on work leave due to rheumatic disease (69.0%); 126 (37.3%) patients reported a profession that dealt directly with the public (public attendance, health, security, education); 159 (47.0%) patients reported no social isolation during the pandemic; 159 (47.0%) reported close contact with a confirmed case of COVID-19, with 104 (30.8%) events occurring at home. The most common comorbidities were hypertension (35.8%), obesity (15.7%) and diabetes (11.5%); smoking was reported by 4.4% of patients. Regarding rheumatic disease diagnosis, systemic lupus erythematosus (SLE) (32.9%) and rheumatoid arthritis (RA) (28.4%) were the most frequent. Hydroxychloroquine (HCQ) (118/338; 34.9%), oral glucocorticoids (GC) (116/338; 34.2%), tumour necrosis factor inhibitor (TNFi) (75/338; 22.2%) and methotrexate (68/338; 20.1%) were the

most common rheumatic disease treatments. All patients included were COVID-19 confirmed cases, according to BMH recommendations (figure 1), most of them classified according to lab criterion (76.8%), mostly through RT-PCR (n=175; 51.8%). Table 1 describes demographic and clinical data of the sample.

In regard to COVID-19 symptoms, the most frequent were headache (58.0%), cough (56.5%) and fever (51.2%). Twelve asymptomatic patients (3.6%) were included because they presented a positive RT-PCR for SARS-CoV-2, collected due to contact with a confirmed case of COVID-19.

The median duration of symptoms was 12 days (IQR=10) and 102 patients (30.2%) still had symptoms at study entry. The most common medications used to treat COVID-19 were analgesics (n=166, 49.6%) and azithromycin (n=165, 49.3%), HCQ (n=66, 19.7%) and oral GC (n=71, 20.6%), at a dosage above >30 mg/day in 44.1% of patients. Pulse therapy with GC was used by 14 (4.2%) patients.

Regarding the main outcomes, emergency care was required in 160 patients (48%); 110 (33.0%) patients were hospitalised, 50 (15.0%) were admitted to the ICU, 35 (10.5%) underwent mechanical ventilation and 28 (8.4 %) died. Among the 28 patients who died, 24 (85.7%) were women, and the median age was 53 years (IQR 36–69). The diagnosis was SLE in 11 patients, 4 were RA, 2 axial spondyloarthritis, 5 systemic sclerosis and 6 had other diseases; 5 (17.9%) patients were using pulse therapy with methylprednisolone and 5 (17.9%) patients were using pulse therapy with cyclophosphamide.

Table 2 describes the binary associations between the need for emergency care and explanatory variables only in the COVID-19 lab confirmed group. There was a statistically significant difference in relation to being inactive at work (PR 1.42, 95% CI 1.13 to 1.78; p=0.002), the presence of diabetes (PR 1.49, 95% CI 1.18 to 1.87; p=0.008), and having hypertension (PR 1.30, 95% CI 1.05 to 1.62; p=0.020), hypothyroidism (PR 1.52, 95% CI 1.17 to 1.98; p=0.030), kidney disease (PR 1.49, 95% CI 1.13 to 1.97; p=0.046), using oral corticosteroids (PR 1.60, 95% CI 1.30 to 1.97; p<0.001) and methylprednisolone pulse therapy (PR 1.86, 95% CI 1.65 to 2.08; p=0.018). Not using TNFi was associated with an increased prevalence rate for hospitalisation (PR 1.53; 95% CI 1.07 to 2.18; p=0.007). No differences were observed regarding age, gender, social isolation, heart and lung disease, obesity, smoking, HCQ, methotrexate, leflunomide or rheumatic disease diagnosis.

In the multivariate adjustment using the Poisson model for emergency care, diabetes, kidney disease, use of oral GC and pulse therapy with methylprednisolone remained significant (table 3).

Table 4 shows the binary associations between the primary outcomes: hospitalisation, ICU, mechanical ventilation, death and explanatory variables. For hospitalisation, a statistically significant association was observed with age >50 years (PR 1.91; 95% CI 1.26 to

**Table 1** Demographic and clinical characteristics of 334 patients with confirmed or suspected COVID-19 and rheumatic diseases

Variables	n	%
Female	275	81.4
Age, median (IQR)	45 (31–57)	
Professions that deal with the public	126	37.3
Active at work	186	55.0
Retired/ work leave due rheumatic disease*	230	69.0
Social isolation	159	47.0
Close contact with a confirmed case of COVID-19	159	47.0
Comorbidities		
Hypertension	121	35.8
Obesity	53	15.7
Diabetes	39	11.5
Hypothyroidism	20	5.9
Lung disease	32	9.4
Heart disease	25	7.4
Dyslipidaemia	22	6.5
Fibromyalgia	12	3.6
Kidney disease	21	6.2
Smoking	15	4.4
Alcoholism	8	2.4
Depression	7	2.1
Rheumatic diseases diagnostic		
Systemic lupus erythematosus	110	32.9
Rheumatoid arthritis	95	28.4
Axial Spondyloarthritis	45	13.5
Systemic sclerosis	23	6.9
Psoriatic arthritis	23	6.9
Vasculitis	10	3.3
Others	28	8.3
Rheumatic disease treatment		
Hydroxychloroquine	118	34.9
Oral corticosteroids	116	34.3
Methotrexate	68	20.1
Azathioprine	42	12.4
Leflunomide	23	11.8
Mycophenolate mofetil	21	6.2
TNFi	75	22.2
Non-TNFi	41	12.1
Rituximab	13	3.8
Anti-IL-17	12	3.6
Tocilizumab	9	2.7
Belimumab	3	0.9
Abatacept	3	0.9

Continued

**Table 1** Continued

Variables	n	%
Anti-IL12-23	1	0.3
JAK-inhibitors	12	3.6
Cyclophosphamide (pulse therapy)	10	3.0
Methylprednisolone (pulse therapy)	8	2.4
COVID-19 symptoms		
Cough	195	56.7
Shortness of breath	160	46.5
Headache	200	58.0
Asthenia	165	47.9
Fever	176	51.2
Anosmia	153	44.4
Rhinorrhoea	111	32.2
Joint pain	72	21.0
Myalgia	140	40.8
Dysgeusia	146	42.3
COVID-19 lab confirmation		
RT-PCR	175	51.8
SARS-CoV-2 Serology (IgM or IgG)	98	29.3
Unknown	30	8.9
Emergency care		
Hospitalised	110	33.0
Discharge alive	66	19.8
Intensive unit care	50	15.0
Mechanical ventilation	35	10.5
Death	28	8.4

\*Among 148 inactive at work

GC, glucocorticoids; IL-17, interleukin 17; JAK, Janus kinase; TNFi, tumour necrosis factor inhibitor.

2.91;  $p=0.002$ ), not using TNFi (PR 2.69; 95% CI 1.26 to 2.91;  $p=0.005$ ), oral GC (PR 1.82; 95% CI 1.1 to 2.74;  $p=0.005$ ), oral GC dose above 20 mg/day (PR 2.18; 95% CI 1.29 to 3.66;  $p=0.007$ ) and methylprednisolone pulse therapy to treat rheumatic disease (PR 2.90; 95% CI 1.73 to 4.87;  $p=0.014$ ). In multivariate analysis using the Poisson model, age >50 years, and not using TNFi and methylprednisolone pulse therapy remained statistically significant (table 3).

Regarding admission to the ICU, a statistically significant association was observed with oral GC (PR 2.15, 95% CI 1.32 to 3.48;  $p=0.001$ ), not using TNFi (PR 2.59; 95% CI 0.88 to 7.57), pulse therapy with methylprednisolone or cyclophosphamide for rheumatic disease treatment (PR 2.26, 95% CI 1.33 to 3.85;  $p=0.042$ ), with these last two also associated with increased risk of death (PR 2.86, 95% CI 1.59 to 5.14;  $p=0.018$ ) (table 4). In multivariate analysis using the Poisson model, oral CE and pulse therapy with methylprednisolone remained statistically significant SLE was shown to have a possible protective effect for IUC in the multivariate (table 3). None of the

**Table 2** Associations between the need for emergency care with explanatory variables (255) patients with laboratory confirmed COVID-19

Variables	Emergency care		p-value	PR 95% CI	
	Yes (n, %)	No (n, %)			
<b>Age</b>					
Up to 50 years	81 (52.9)	72 (47.1)	0.429*	1.00;	–
>50 years	58 (58.0)	42 (42.0)		1.10;	0.88 to 1.37
<b>Sex</b>					
Male	25 (53.2)	22 (46.8)	0.769*	1.00;	–
Female	115 (55.6)	92 (44.4)		1.04;	0.78 to 1.40
<b>Work situation</b>					
Inactive	73 (65.2)	39 (34.8)	0.002*	1.42;	1.13 to 1.78
Active	63 (46.0)	74 (54.0)		1.00;	–
<b>Skin colour</b>					
White	78 (56.9)	59 (43.1)	0.529*	1.07;	0.86 to 1.34
Non white	62 (53.0)	55 (47.0)		1.00;	–
<b>Geographic distribution</b>					
Non-southeast	58 (49.6)	59 (50.4)	0.101*	1.00;	–
Southeast	82 (59.9)	55 (40.1)		1.21;	0.96 to 1.52
<b>Hypertension</b>					
No	81 (49.7)	82 (50.3)	0.020*	1.00;	–
Yes	59 (64.8)	32 (35.2)		1.3	1.05 to 1.62
<b>Obesity</b>					
No	113(53,6)	98(46,4)	0.267*	1.00;	–
Yes	27(62,8)	16(37,2)		1.17	0.90 to 1.52
<b>Diabetes</b>					
No	116 (52.0)	107 (48.0)	0.008*	1.00;	–
Yes	24 (77.4)	7 (22.6)		1.49	1.18 to 1.87
<b>Lung disease</b>					
No	121 (54.3)	102 (45.7)	0.461*	1.00;	–
Yes	19 (61.3)	12 (38.7)		1.13	0.83 to 1.53
<b>Cardiovascular disease</b>					
No	124 (53.7)	107 (46.3)	0.144*	1.00;	–
Yes	16 (69.6%)	7 (30.4)		1.3	0.96 to 1.74
<b>Dyslipidaemia</b>					
No	129 (54.4)	108 (45.6)	0.411*	1.00;	–
Yes	11 (64.7)	6 (35.3)		1.19	0.82 to 1.72
<b>Hypothyroidism</b>					
No	127 (53.4)	111 (46.6)	0.030*	1.00;	–
Yes	13 (81.3)	3 (18.8)		1.52	1.17 to 1.98
<b>Kidney disease</b>					
No	128 (53.6)	111 (46.4)	0.046*	1.00;	–
Yes	12 (80.0)	3 (20.0)		1.49	1.13 to 1.97
<b>Smoking</b>					
No	136 (56.0)	107 (44.0)	0.228†	1.54	0.70 to 3.39
Yes	4 (36.4)	7 (63.6)		1.00;	–
<b>Fibromyalgia</b>					

Continued

Table 2 Continued

Variables	Emergency care		p-value	PR 95% CI	
	Yes (n, %)	No (n, %)			
No	133 (54.5)	111 (45.5)	0.519†	1.00;	–
Yes	7 (70.0)	3 (30.0)		1.28	0.84 to 1.96
Alcoholism					
No	137 (55.9)	108 (44.1)	0.049†	3.91	0.64 to 24.11
Yes	1 (14.3)	6 (85.7)		1.00;	–
Depression					
No	137 (55.2)	111 (44.8)	1.000†	1.1	0.49 to 2.48
Yes	3 (50.0)	3 (5.,0)		1.00;	–
TNFi					
No	119 (59.5)	81 (40.5)	0.007*	1.53	1.07–2.18
Yes	21 (38.9)	33 (6.1)		1.00;	–
HCQ					
No	86 (51.2)	82 (48.8)	0.079*	1.00;	–
Yes	54 (62.8)	32 (37.2)		1.23	0.98 to 1.53
Oral GC					
No	80 (46.2)	93 (53.8)	<0.001	1.00;	–
Yes	60 (74.1)	21 (25.9)		1.6	1.30 to 1.97
GC dosage					
<20mg/day	43 (69.4)	19 (30.6)	0.133†	1.00;	–
≥20mg/day	17 (89.5)	2 (10.5)		1.29	1.03 to 1.62
Intravenous GC					
No	133 (53.8)	114 (46.2)	0.018†	1.00;	–
Yes	7 (100.0)	0 (0,0)		1.86	1.65 to 2.08
CYC					
No	133 (54.3)	112 (45.7)	0.193†	1.00;	–
Yes	7 (77.8)	2 (22.2)		1.44	1.00 to 2.09

\*P value of the  $\chi^2$  test for independence;

†P value of Fisher's exact test.

CYC, cyclophosphamide pulse therapy; GC, glucocorticoids; HCQ, hydroxychloroquine; Methyl, methylprednisolone e pulse therapy; PR, prevalence ratio; TNFi, tumour necrosis factor inhibitor.

tested variables were associated with mechanical ventilation (table 4).

Before including the use of TNFi in the binary analysis, it was tested whether there was an association with the use of biologicals of all classes as a group, and an association was observed with the ICU outcome ( $p=0.001$ ). However, when we separated the groups into biological TNFi ( $p=0.006$ ) and non TNFi ( $p=0.089$ ), the difference remained only for the TNFi group. For this reason, only this group was included in the binary analysis and Poisson model.

## DISCUSSION

Brazil is the country with the third highest number of cases of COVID-19 in the world, with the first case confirmed 26 February 2020, and counting 4123000 cases and 126203 deaths through 6 September 2020.<sup>9</sup>

To the best of our knowledge, ReumaCoV Brasil is the largest cohort of patients with COVID-19 and underlying IMRD from a single country. Our results demonstrate that age over 50, diabetes, kidney disease, use of oral GC, not using TNFi, pulse therapy with methylprednisolone and cyclophosphamide were associated with a higher prevalence of worse outcomes of COVID-19 in patients with IMRD. We did not find any association between the variables and the need for mechanical ventilation.

The first published report regarding COVID-19 in patients with rheumatic diseases suggested that there would be no greater risk in relation to the general population or with other comorbidities.<sup>3 10</sup> Since then, some studies addressed the risk and severity of COVID-19 infection in people with IMRD, confirming this initial impression, except for hospitalisation in patients exposed to high GC doses.<sup>11</sup> However, evidence on COVID-19 risk

**Table 3** Multivariate adjustment using the Poisson model for emergency care, hospitalisation and intensive unit care admission

Variables	PR	95% CI	P value*
<b>Emergency care</b>			
<b>Diabetes</b>			
No	1.00	–	
Yes	1.38	1.11 to 1.73	0.004
<b>Kidney disease</b>			
No	1.00	–	
Yes	1.36	1.05 to 1.77	0.020
<b>Oral GC</b>			
No	1.00	–	
Yes	1.49	1.21 to 1.85	<0.001
<b>Intravenous GC</b>			
No	1.00	–	
Yes	1.38	1.14 to 1.67	0.001
<b>Hospitalisation</b>			
<b>Age</b>			
Up to 50	1.00	–	–
>50	1.89	1.26 to 2.85	0.002
<b>TNFi</b>			
No	2.51	1.16 to 5.45	0.020
Yes	1.00	–	–
<b>Intravenous GC</b>			
No	1.00	–	–
Yes	2.50	1.59 to 3.92	<0.001
<b>Intensive care unit admission</b>			
<b>Oral GC</b>			
No	1.00	–	–
Yes	2.24	1.36 to 3.71	0.002
<b>Intravenous GC</b>			
No	1.00	–	–
Yes	1.65	1.0 to 2.68	0.043
<b>SLE</b>			
No	1.00	–	
Yes	1.72	1.04 to 2.88	0.036

\*P value of the Wald test  
PR, prevalence ratio; TNFi, tumour necrosis factor inhibitor; GC, glucocorticoids; SLE, systemic lupus erythematosus.

and outcome in patients with systemic autoimmune diseases is limited and conflicting and should be interpreted with great caution.

Almost half of the patients in our study required emergency care, being more prevalent among patients with diabetes, kidney disease and chronic users of corticosteroids, either oral or in the form of pulse therapy. Among those who sought emergency care, there was the need for hospitalisation in two thirds of cases, especially in

older patients, those who were treated with methylprednisolone pulse therapy and those who did not use TNFi. The prevalence is higher than those reported in most published studies,<sup>11–16</sup> and similar to that reported in an Italian cohort by Fredi *et al.*<sup>17</sup> One possible explanation for these differences is the lower social conditions in Brazil, which makes patients more susceptible to more severe conditions, besides the difference in the patient's disease profile and medications, raising the need for greater concern for patients in developing countries. In accordance with ReumaCov Brazil, most of the studies have found advanced age associated with a higher risk of hospitalisation.<sup>13 15–18</sup>

Chronic GC use, both oral and pulse therapy, was associated with all outcomes, except mechanical ventilation. Other previous studies describe similar results with oral GC, with doses ranging from 5 to 10 mg<sup>11 12 14 19</sup>; however, none of these studies described the impact of pulse therapy with methylprednisolone to treat IMRD in COVID-19 outcomes. Although recent studies have shown that the use of GCs in the moderate to severe acute phase of COVID-19 has led to a benefit,<sup>20 21</sup> the effect seems to be deleterious in patients on chronic use, probably associated increased risk of infection with higher dose of GC,<sup>22</sup> due to impairment of innate immune responses with a reduction in neutrophil recruitment and a delay in viral clearance.<sup>23</sup>

The result that associated lower prevalence of hospitalisation and ICU admission in patients using TNFi therapy is similar to that described in other studies<sup>12–14</sup> and could not be demonstrated to all classes of biologicals. We must also consider that the number of patients using non-TNFi biologicals was lower (12.1%), therefore, the data should be interpreted with caution. However, other studies, including populations with different diseases, have shown similar results, which demonstrates that there must be a biological plausibility for this effect.<sup>11 24 25</sup> Gianfrancesco *et al* also reported that TNFi use was associated with reduced odds of hospitalisation (OR 0.40, 95% CI 0.19 to 0.81), a finding that was not seen with conventional DMARDs alone or in combination with biologics or Janus kinase inhibitors.<sup>11</sup>

A possible explanation for the TNFi effect on COVID-19 could be inflammation control, based on the evidence that patients with more severe COVID-19 have higher levels of cytokines as TNF and IL-6,<sup>26–28</sup> and the TNF inhibition in animal models has led to a protection against SARS-CoV-2 infection,<sup>29</sup> induces a rapid decrease of IL-6 and IL-1 concentrations in patients with active RA,<sup>30</sup> triggers a reduction of adhesion molecules and vascular endothelial growth factor, which is partly responsible for capillary leak,<sup>31</sup> with a consequence of less leucocyte traffic to inflamed tissues.<sup>32</sup> A similar effect was also observed in other viral infections, such as Chikungunya fever, where the use of TNFi was associated with better outcomes.<sup>33</sup>

Twenty-eight patients died, accounting for 8.4% of the total of our series and 17.5% of hospitalised

**Table 4** Associations between the primary outcomes (hospitalisation, ICU, mechanical ventilation and death) with explanatory variables

Variables	Hospitalisation				ICU*				Death*						
	Yes		No		Yes		No		Yes		No				
	(n, %)	(n, %)	P value	RP	95% CI	(n, %)	(n, %)	P value	RP	95% CI	(n, %)	(n, %)	P value	RP	95% CI
Age															
Up to 50 years	29	125	0.002	1.91;	1.91;	23	58	0.111†	1.46;	1.46;	13	33	0.949†	1.02;	1.02;
	-18.8	-81.2		1.26 to 2.91	1.26 to 2.91	-28.4	-71.6		0.92 to 2.31	0.92 to 2.31	-28.3	-71.7		0.54 to 1.91	0.54 to 1.91
>50 years	36	64				24	34				15	37			
	-36	-64				-41.4	-58.6				-28.8	-71.2			
SLE															
No	46	132	0.982	1.01;	1.01;	33	55	0.200†	1.39;	1.39;	17	50	0.352†	1.35;	1.35;
	-25.8	-74.2		0.64 to 1.58	0.64 to 1.58	-37.5	-62.5		0.83 to 2.35	0.83 to 2.35	-25.4	-74.6		0.72 to 2.55	0.72 to 2.55
Yes	20	57				14	38				11	21			
	-26	-74				-26.9	-73.1				-34.4	-65.6			
Anti-TNF															
No	60	141	0.005	2.69;	2.69;	44	75	0.042†	2.59;	2.59;	26	64	1.000‡	1.30;	1.30;
	-29.9	-70.1		1.23 to 5.88	1.23 to 5.88	-37	-63		0.88 to 7.57	0.88 to 7.57	-28.9	-71.1		0.37 to 4.60	0.37 to 4.60
Yes	6	48				3	18				2	7			
	-11.1	-88.9				-14.3	-85.7				-22.2	-77.8			
Oral GC															
No	36	138	0.006	1.82;	1.82;	18	62	0.001†	2.15;	2.15;	13	37	0.610†	1.18;	1.18;
	-20.7	-79.3		1.21 to 2.74	1.21 to 2.74	-22.5	-77.5		1.32 to 3.48	1.32 to 3.48	-26	-74		0.63 to 2.21	0.63 to 2.21
Yes	30	51				29	31				15	34			
	-37	-63				-48.3	-51.7				-30.6	-69.4			
Oral GC															
<20 mg/day	18	44	0.007	2.18;	2.18;	18	25	0.111†	1.55;	1.55;	10	23	1.000‡	1.03;	1.03;
	(29.0)	-71		1.29 to 3.66	1.29 to 3.66	-41.9	-58.1		0.94 to 2.54	0.94 to 2.54	-30.3	-69.7		0.42 to 2.52	0.42 to 2.52
≥20 mg/day	12	7				11	6				5	11			
	-63.2	-38.8				-64.7	-35.3				-31.3	-68.8			
HCC															

Continued



**Table 4** Continued

Variables	Hospitalisation				ICU*				Death*			
	Yes		No		Yes		No		Yes		No	
	(n, %)	(n, %)	(n, %)	(n, %)	(n, %)	(n, %)	(n, %)	(n, %)	(n, %)	(n, %)	(n, %)	
No	46	122	0.448	1.19;	32	54	0.250†	1.34;	18	48	0.752†	1.11;
	-27.4	-72.6		0.75 to 1.88	-37.2	-62.8		0.80 to 2.23	-27.3	-72.7		0.58 to 2.13
Yes	20	67			15	39			10	23		
	-23	-77			-27.8	-72.2			-30.3	-69.7		
<b>CYC</b>												
No	62	184	0.196	1.76;	42	91	0.042‡	2.26;	23	69	0.018‡	2.86;
	-25.2	-74.8		0.82 to 3.78	-31.6	-68.4		1.33 to 3.85	-25	-75		1.59 to 5.14
Yes	4	5			5	2			5	2		
	-44.5	-55.6			-71.4	-28.6			-71.4	-28.6		
<b>Methyl</b>												
No	61	187	0.0142	2.90;	42	91	0.042‡	2.26;	23	69	0.018‡	2.86;
	-24.6	-75.4		1.73 to 4.87	-31.6	(68.4)		1.33 to 3.85	-25	-75		1.59 to 5.14
Yes	5	2			5	2			5	2		
	-71.4	-28.6			-71.4	-28.6			-71.4	-28.6		

\*Calculated only for hospitalised patients

†P value of the  $\chi^2$  test for independence;

‡P value of Fisher's exact test.

anti-TNF, tumour necrosis factor inhibitor; CYC, cyclophosphamide pulse therapy; GC, glucocorticoids; HCQ, hydroxychloroquine; ICU, intensive care unit; Methyl, methylprednisolone pulse therapy; RP, prevalence ratio; SLE, systemic lupus erythematosus.

patients, which is quite similar to the data found in other cohorts.<sup>11–13 17 19</sup> The factors associated with mortality in these various studies were variable, but the use of oral GC was the common factor for most of them. In our study deaths were associated with pulse therapy with methylprednisolone and cyclophosphamide. The impact of these medications on both hospitalisation and mortality may be due to the greater number of patients with SLE included in our cohort when compared with others, but also the greater number of SLE among the deaths. It is noteworthy that patients treated with these medications have more severe disease, especially in SLE. This fact calls attention to the evaluation of treatment alternatives during the COVID-19 pandemic, with lower doses of GC and other immunosuppressants than cyclophosphamide, once this is possible.

HCQ was not protective against COVID-19. Despite some initial promising *in vitro* results,<sup>34 35</sup> this hypothesis was not supported by our results or by the results of other studies performed in pre-exposed and postexposure prophylaxis using HCQ, as well as more recent randomised clinical trials, including mild-moderate and severe forms of COVID-19.<sup>36–39</sup> More recently, Gianfrancesco *et al* reported no association of antimalarial use (OR 0.94, 95% CI 0.57 to 1.57) with hospitalisation.<sup>11</sup>

Patients with rheumatic diseases had greater need for ICU hospitalisation and presented over a threefold increased risk of requiring mechanical ventilation.<sup>15</sup> Here, we report that 35 out of 50 patients in the ICU required invasive mechanical ventilation, corresponding to 70% of the patients in the ICU. This represents a need for ventilatory assistance in a higher proportion than described in other cohorts of IMRD patients and in the general population.<sup>40</sup>

Other important points addressed by our study deserve to be highlighted, as they demonstrate a different profile from other data previously published. As in the other series, there was a predominance of females, probably reflecting the higher prevalence of IMRD in women.<sup>11 17</sup> However, different from other studies, our patients were younger<sup>11 17 19</sup> and most of those who died were women under the age of 60 (median 53 years). Considering the median age of 45 years of patients in our cohort, and the mean age of the patients that died, it suggests that immunosuppression is a relevant factor associated with mortality in COVID-19. The immunosuppressed, younger patients can be more vulnerable, and should be considered as a group for shielding. Although our patients were younger, more than two-thirds were not working, and among those who were active at work, most performed activities involving care or contact with the public, which may have favoured infection by SARS-CoV-2. Less than half reported social isolation, suggesting a lack of confidence in social distancing measures or for being considered as breadwinners. Compared with other cohorts, in which SLE patients comprise 6.5%–19.0%, we have found a higher proportion (32.9%).<sup>11–13 15 17</sup> Some cohorts that evaluated only SLE patients demonstrated a higher rate

of hospitalisation<sup>41 42</sup> with no difference between those who used or did not use HCQ and also with no difference in relation to the need for mechanical ventilation or extracorporeal membrane oxygenation.<sup>41 43</sup>

Although the most recent systematic review and meta-analysis<sup>44</sup> has shown the IMRD patients are more susceptible to the COVID-19, including unfavourable outcomes, when SLE patients are separately analysed, particularly in case–control studies, this finding does not seem to be an absolute true. It probably reflects a selection bias, frequently reported by observational studies, similar to our findings, since most research centres have a great number of SLE patients, with easy access to the researcher and to hospital. In addition, these patients could have been more frequently hospitalised because the clinician may have considered the potential severity of the disease in the COVID-19 scenario. In the multivariate analysis, having a diagnosis of SLE was considered as a possible protective effect for ICU. Nonetheless, it is worth emphasising that SLE patients may have the combination of infection and disease activity in the context of immunosuppression and the rheumatologist needs to individualise the treatment weighing benefits and risks. Interestingly, the current reports have not shown reactivation of underlying IMRD after the COVID-19.<sup>45 46</sup> Thus, large and longitudinal studies are necessary to address this relevant issue.

In the 74 Latin American patients with rheumatic diseases and COVID-19 reported from the COVID-19 Global Rheumatology Alliance Physician-Reported Registry there were more RA patients (35%) than SLE patients (22%), while in our sample the proportion of SLE patients (32,9%) was greater than the RA (28,4%).<sup>47</sup>

Although hypertension and diabetes were the most frequent comorbidities, as described in other cohorts, we observed that diabetes and renal diseases were the two diseases associated with emergency care at the final model. Of interest, we found 15.7% of obesity, which was not frequently described in other cohorts, but almost the same to one multicentric cohort.<sup>13 15 18</sup>

A strength of our study is that we included patients from different states of Brazil, a continental country, with most of the patients with confirmed diagnosis of COVID-19 based on positive COVID-19 RT-PCR testing. In addition, the 8-week interim analysis is related to the first weeks of community viral transmission, a relevant finding simulating the pandemic epidemiological curve in Brazil.<sup>48</sup>

As a limitation of the study, many cases may be not included in the cohort because they were not tested or have not been confirmed, usually for presenting a benign evolution of the disease. Since in the Brazilian public health system only hospitalised patients were being tested, this may have become a selection bias, including only the most severely ill patients. Because this is a national register, patients were treated in different services, possibly with different physical and personnel characteristics—a fact that may have interfered with the

results. The availability of healthcare in Brazil can be different when it comes to the public or private health system. Regarding treatment, it was not possible to evaluate the association between COVID-19 with the combination use of different immunosuppressants or DMARDs combination.

Another limitation is related to main endpoints, including hospitalisation, need of mechanical ventilation and death, because they could not be adjusted for potential bias, such as access to healthcare systems, availability of hospital beds, strategies to mitigate the community viral transmission, heterogeneous expertise of medical team.<sup>49 50</sup> Physicians' beliefs on the risk of poor outcome in IMRD patients, especially those under immunosuppression, could have driven decision making, such as the need of ICU and medications given earlier. However, it is also important to consider that some patients enrolled in our registry had active and severe underlying IMRD. Therefore, the unfavourable evolution of them could occur itself, regardless of COVID-19.

Brazil is a country with a heterogeneous population, with variations in socioeconomic, cultural, ethnic and health status. The fact that we included representative patients from all Brazilian geographic regions allows our results to be generalised to Brazil and possibly to Latin American countries, with the same population pattern. Future studies comparing the different populations are needed to confirm whether these data occur similarly or not in the rest of the world.

In conclusion, the results of first 8 weeks of the ReumaCoV Brazil registry showed that aspects related to the patients with IMRD (age >50 years), and those related to their treatment (immunosuppression with GC and cyclophosphamide) were associated with unfavourable outcomes of the SARS-CoV-2 infection. Treatment with TNFi, on the other hand, may have been protective, perhaps leading to the control of COVID-19 inflammatory process, but randomised controlled trials to prove this effect are needed.

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**Acknowledgements** The authors would like to thank the Brazilian Society of Rheumatology for technical support and rapid nationwide mobilisation and all Collaborators on behalf of the ReumaCoV Brasil register

**Contributors** All authors have contributed to study conception and design. CDLM, AMK, LMHM, ETR-N and ESP drafted the manuscript, which was critically reviewed by all authors. All authors have read and approved the final version of the manuscript.

**Funding** This work is supported by Research Funding of the Brazilian Society of Rheumatology and National Council for Scientific and Technological Development (CNPq).

**Competing interests** CDLM reports grants from National Council for Scientific and Technological Development (CNPq) and from Brazilian Society of Rheumatology, personal fees from Janssen, Novartis, Abbvie. AMK reports personal fees from Abbvie, Janssen, Pfizer, Lilly and Roche. MMP reports personal fees from Abbvie, Janssen, UCB, Novartis, Pfizer and Lilly. LMHM reports personal fees from Abbvie, Janssen, Pfizer, Roche, Boehringer Ingelheim, GSK, Libbs and Lilly. CRS reports personal fees from Pfizer, Abbvie and Novartis. AD reports personal fees from Boehringer Ingelheim. RDG reports personal fees from Janssen, Eli Lilly, Roche, Boehringer Ingelheim, Amgen Brasil, Pfizer, Sandoz, Novartis Brasil. LDAH reports personal fees from Janssen, Novartis and UCB. AKGM reports grants from Brazilian Society of Rheumatology, personal fees from Janssen and UCB. MAY reports personal fees from Novartis, Abbvie, Lilly and, UCB. RADT reports personal fees from ABBVIE, GSK, JANSSEN, NOVARTIS, LILLY, PFIZER, ROCHE and UCB. RX reports grants and personal fees from Abbvie, Eli-Lilly, Pfizer, Janssen and Roche, personal fees from Novartis, UCB.

**Patient consent for publication** Not required.

**Ethics approval** This study was approved by Brazilian Committee of Ethics in Human Research (CONEP), on 5 April 2020, CAAE 30186820.2.1001.8807

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** All data relevant to the study are included in the article.

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## Correction: High levels of immunosuppression are related to unfavourable outcomes in hospitalised patients with rheumatic diseases and COVID-19: first results of ReumaCoV brasil registry

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Marques CDL, Kakehasi AM, Pinheiro MM, *et al.* High levels of immunosuppression are related to unfavourable outcomes in hospitalised patients with rheumatic diseases and COVID-19: first results of ReumaCoV Brasil registry. *RMD Open* 2021;7:e001461. doi: 10.1136/rmdopen-2020-001461

The article has been corrected since it was published online. The authors want to alert the readers on missing to include co-author Felipe Omura in the authors' list. He has been identified one of the authors who had a vital contribution towards the preparation of the paper.

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*RMD Open* 2021;7:e001461corr1. doi:10.1136/rmdopen-2020-001461corr1

